Pharmacotherapy for obesity management

Clinical Practice Guideline for the Management of Obesity in Adults in South Africa

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SOUTH AFRICAN METABOLIC MEDICINE AND SURGERY SOCIETY

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KEY MESSAGES FOR HEALTHCARE PROVIDERS

- Pharmacological treatments are an effective and scalable approach to treating people living with obesity (PLWO). As with any chronic disease, such as type 2 diabetes (T2DM) or hypertension, pharmacotherapy is an important pillar in the management of obesity.
- The focus of management of PLWO should be the improvement of health parameters (metabolic, mechanical, mental, and/or quality of life), not solely weight reduction, and should include outcomes that PLWO identify as important. Obesity is defined by body mass index (BMI) in clinical trials, but BMI itself does not adequately reflect the burden of adiposity-related disease.
- There are four medications indicated for long-term management of PLWO in South Africa (SA) as adjuncts to health behaviour changes: liraglutide (Saxenda®), naltrexone/bupropion (Contrave®) in a combination tablet, orlistat (Xenical®) and semaglutide (Wegovy®). All four medications are effective in producing clinically significant weight loss and health benefits greater than placebo over a duration of at least 1 year.
- The individual response to pharmacotherapy for management of PLWO is heterogeneous. Efficacy (both for weight and management of obesity-related health issues), mechanism of action, safety, potential side-effects/tolerability, contraindications, medication interactions, mode of administration and cost are important considerations in choosing the most appropriate obesity pharmacotherapy.
- Obesity medications are intended as part of a long-term treatment strategy. Clinical trials of pharmacotherapy for management of PLWO consistently demonstrate regain of weight when treatment is stopped.
- Medications that are not approved as pharmacotherapy for obesity management should not be used for this purpose.

KEY MESSAGES FOR PEOPLE LIVING WITH OBESITY

- Obesity medications are effective for managing weight and weight-related health issues, often in combination with healthy behaviour changes and/or psychological interventions.
- The goals in management for individuals living with obesity should include improvement in health and should include discussing outcomes that are important to you.
- There are four medications approved by the South African Health Products Regulatory Authority (SAHPRA) for long-term obesity management in South Africa: liraglutide 3.0 mg (Saxenda®), naltrexone/bupropion in a combination tablet (Contrave®), orlistat (Xenical®) and semaglutide 2.4 mg (Wegovy®). These medications can help you to achieve and maintain improvements in weight and in the health complications associated with excess weight. These medications have been proven to be safe and effective for obesity management. Phentermine is registered for short-term use only (less than 3 months).
- Medications that are not approved for treatment of individuals living with obesity may not be safe or effective for obesity management and should be avoided.

RECOMMENDATIONS

1. Pharmacotherapy for obesity management can be used for individuals with a BMI ≥30 kg/m^2, or ≥27 kg/m^2 with adiposity-related complications, in conjunction with medical nutrition therapy, physical activity and psychological interventions (semaglutide 2.4 mg weekly [Level 1a, Grade A],[1] liraglutide 3.0 mg daily [Level 2a, grade B],[2-4] naltrexone/bupropion 16 mg/180 mg twice a day [BID] [Level 2a, Grade B],[5] orlistat 120 mg three times a day [TID] [Level 2a, Grade B]).[6]

2. Pharmacotherapy may be used to maintain weight loss and to prevent weight regain (liraglutide 3.0 mg daily [Level 2a, Grade B],[4] orlistat 120 mg TID [Level 2a, Grade B]).[7]
3. Pharmacotherapy for obesity management in conjunction with health behaviour changes for people living with prediabetes and overweight or obesity (BMI ≥27 kg/m^2) can be used to delay or prevent T2DM (liraglutide 3.0 mg daily [Level 2a, Grade B],[3] orlistat 120 mg TID [Level 2a, Grade B]).[8]
4. Obesity pharmacotherapy can be used in conjunction with health behaviour changes in people living with T2DM and a BMI ≥27 kg/m^2, for weight loss and improvement in glycaemic control (semaglutide 2.4 mg weekly [Level 1a, Grade A],[9] liraglutide 3.0 mg daily [Level 1b, Grade A],[10] naltrexone/bupropion 16 mg/180 mg BID [Level 2a, Grade B],[11] orlistat 120 mg TID [Level 2a, Grade B]).[12]
5. Pharmacotherapy can be considered in conjunction with health behaviour changes in treating people with obstructive sleep apnoea and a BMI ≥30 kg/m^2, for weight loss and associated improvement in the apnoea-hypopnoea index (liraglutide 3.0 mg daily [Level 2a, Grade B]).[13]
6. Pharmacotherapy can be considered in conjunction with health behaviour changes in treating people living with metabolic dysfunction-associated steatohepatitis (MASH) and overweight or obesity, for weight loss and improvement of MASH parameters (liraglutide 1.8 mg daily [Level 3; Grade C],[14] semaglutide 2.4 mg [Level 4 Grade D]).[15]
7. Metformin and psychological treatment (such as cognitive behavioural therapy) should be considered for prevention of weight gain in people with severe mental illness who are treated with antipsychotic medications associated with weight gain (Level 1a, Grade A).[16]
8. For people living with overweight or obesity who require pharmacotherapy for other health conditions, we suggest choosing medications that are not associated with weight gain (Level 4, Grade D, Consensus).
9. We do not suggest the use of prescription or over-the-counter medications other than those approved in SA for obesity management (Level 4, Grade D, Consensus).

Introduction

Sustained weight loss is associated with improvements in comorbidities associated with obesity.[17-19] Healthy eating and physical activity are fundamental to successful weight management; however, these changes alone are often not sufficient for achieving sustained weight loss. Healthy behaviour changes alone generally achieve only a 3 - 5% weight loss, which is most often not sustained over the long term.[20] Pharmacotherapy for management of people living with obesity (PLWO) should be considered to decrease weight and optimise health in addition to healthy eating, physical activity and other behavioural interventions.

Despite the high prevalence of obesity,[21] obesity medications are prescribed far less frequently than medications for other chronic medical conditions, such as type 2 diabetes (T2DM).[22] The adoption rate of novel diabetes medications is greater and more rapid than the adoption rate of new pharmacotherapies for weight management.[22] This may be due to the reluctance of public health and medical organisations to recognise obesity as a chronic disease, which in turn affects reimbursement. Provider inexperience, and/or misperceptions about the efficacy and safety of available treatments, may also contribute to this gap.

This chapter provides a review of the literature pertaining to the efficacy of the obesity medications currently approved by the South African Health Products Regulatory Authority (SAHPRA). It is intended to inform primary care practitioners and specialists on the appropriate use of obesity pharmacotherapy. **As this is a rapidly developing field, the chapter will be updated when required.**

International regulatory authorities have established the following criteria that must be satisfied for a pharmacotherapeutic agent to receive regulatory approval for long-term weight management:

- The agent must be studied in clinical trials of at least 1 year in duration.
- The agent must produce a placebo-adjusted mean weight loss of ≥5% or demonstrate a ≥5% weight loss in at least 35% of participants, with this proportion being more than double that in placebo.
- The agent should demonstrate an improvement in obesity-related comorbidities.

Pharmacotherapy is indicated for long-term weight management in South Africa (SA) for PLWO with a body mass index (BMI) ≥30 kg/m^2, or ≥27 kg/m^2 with comorbidities associated with excess body fat (e.g. T2DM, hypertension, dyslipidaemia, obstructive sleep apnoea [OSA]).

There are four medications approved for long-term management of PLWO in SA: orlistat (Xenical®) 120 mg three times a day (TID), liraglutide (Saxenda®) 3.0 mg subcutaneously daily, naltrexone/bupropion (Contrave®) 16 mg/180 mg twice a day (BID), and semaglutide (Wegovy®) 2.4 mg subcutaneously weekly. It is recognised that other medications, available in SA but not approved for management of PLWO, are used off-label for this purpose. Our literature search therefore employed an open strategy to capture all pharmacotherapeutic agents that have been studied for management of PLWO. However, except for metformin for prevention of antipsychotic medication-induced weight gain, we discourage healthcare providers (HCPs) from using agents solely for obesity management if the agents do not have regulatory approval for this indication, or do not have evidence-based recommendations for their use. We have recommended the use of metformin for prevention of antipsychotic medication-induced weight gain, given the high-quality data supporting this intervention. (See the chapter 'The role of mental health in obesity management'.)

This chapter addresses clinical questions pertaining to the efficacy of pharmacotherapy in PLWO, and summarises existing evidence for use of pharmacotherapy for obesity in persons with obesity-related comorbidities, including prediabetes, T2DM, metabolic dysfunction-associated steatotic liver disease (MASLD), dyslipidaemia, hypertension, polycystic ovary syndrome (PCOS), OSA, osteoarthritis (OA), gastro-oesophageal reflux disease (GORD), depression, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), chronic kidney disease (CKD) and atherosclerotic vascular disease.

A structured literature search was conducted using PubMed and Google Scholar to identify relevant studies in these subpopulations. The search included trials where weight loss was the primary endpoint, as well as those evaluating approved pharmacotherapies for obesity with disease-specific outcomes, regardless of whether weight loss was explicitly assessed. Studies exploring the effects of pharmacotherapy on cravings and quality of life (QoL) – two important patient-centred outcomes – were also included. The search was restricted to randomised controlled trials (RCTs) and meta-analyses of at least 6 months' duration, published between the last literature review and May 2025. While obesity is now understood

as a complex chronic disease characterised by excess or abnormal adiposity that impairs health – rather than strictly defined by BMI – this chapter presents evidence using BMI-based criteria, in keeping with the eligibility criteria of most clinical trials to date. Future trials incorporating alternative diagnostic criteria may shift this framework.

Considerations in the use of pharmacotherapy for obesity management

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

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

Individualised goals of treatment are important in evaluating the success of pharmacotherapy. If goals of therapy have not been achieved, factors contributing to a suboptimal response such as adequacy of dosing, challenges in adherence and barriers to health behaviour change, as well as psychosocial and medical issues, should be reassessed. There is considerable heterogeneity in the response to any pharmacotherapeutic agent, and consideration should be given to adding or substituting another obesity medication or intervention if treatment goals have not been achieved after 3 - 6 months on the maximum tolerated dose.

We do not currently have the ability to predict which medication will be most effective for PLWO, although preliminary data suggest that phenotypes of obesity may be helpful in guiding the choice of pharmacotherapy in the future,[23] especially with the evolution of hormonal and genetic profiling.

Pharmacotherapy for management of PLWO can be used not only to facilitate weight loss, but also for weight loss maintenance and to improve health. Regulatory agencies have traditionally recommended discontinuing pharmacotherapy for weight management if weight loss of ≥5% has not been achieved after 3 months on therapeutic dose. However, substantial health improvements may be realised without a weight loss of ≥5%. Pharmacotherapy can also assist in the maintenance of weight loss achieved with a prior health behaviour change or a very low-energy diet.[4,7]

Pharmacotherapy for management of PLWO should be considered early in the natural history of obesity, as weight and obesity-related health complications tend to increase and progress with time. (See the chapter 'Assessment of people living with obesity'.) Obesity medications are intended as part of a long-term treatment strategy. Clinical trials of pharmacotherapy for obesity management consistently demonstrate regain of weight when treatment is stopped.[6]

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

BMIs and waist circumferences that correlate with comorbidities vary by ethnicity.[24] The BMI criteria for inclusion in pharmacotherapy studies are in accordance with the BMI criteria for overweight and obesity in Caucasian, Europid and North American ethnicity, which are higher than the BMI criteria in South, Southeast or East Asian ethnicity. The prescribing physician may elect to interpret the recommendations in this chapter with ethnicity-specific BMI criteria in mind. Ethnic minorities are under-represented in clinical trials of pharmacotherapy for weight management, as well as in data from Africa; having balanced ethnic representation is important for future pharmacotherapy trials.

Approved pharmacotherapy for obesity management (Table 1)

Orlistat 120 mg TID

Orlistat, a semisynthetic derivative of lipstatin, was approved as pharmacotherapy for management of PLWO in SA in 1997. It is a potent and selective inhibitor of pancreatic lipase, thereby inhibiting the breakdown of dietary triglycerides into absorbable free fatty acids. As a result, approximately 30% of ingested triglycerides are excreted, primarily in the faeces, creating a caloric deficit.[25] Orlistat does not target appetite or satiety mechanisms.

Orlistat at a dose of 120 mg TID (taken during or up to 1 hour after meals) is approved by the SAHPRA for weight reduction or reducing the risk of weight regain after prior weight loss in individuals with a BMI ≥30 kg/m^2, or ≥27 kg/m^2 in the presence of comorbidities (e.g. hypertension, T2DM, dyslipidaemia, excess visceral fat).[26]

A systematic review and meta-analysis of RCTs of orlistat 120 mg TID reported a mean placebo-subtracted weight loss of –2.9% at 1 year.[27] Additionally, 54% and 26% of participants achieved ≥5% and ≥10% weight loss, respectively, compared with 33% and 14% for placebo.[27] Orlistat has been shown to be effective in maintaining weight loss after a very low-energy diet for 8 weeks, with less weight regain in the orlistat arm compared with placebo over 3 years (4.6 kg v. 7.0 kg).[7]

Orlistat therapy is associated with gastrointestinal side-effects, including oily spotting and loose stools, flatus with discharge, faecal urgency and increased defaecation.[27] These adverse effects may cause PLWO who do not lower their dietary fat intake to discontinue therapy. A long-term analysis of obesity medications in Canada demonstrated 6-month, 1-year and 2-year persistence rates with orlistat therapy of 18%, 6% and 2%, respectively.[28] Orlistat therapy may interfere with the absorption of fat-soluble vitamins (A, D, E and K), and patients should therefore be counselled to take a multivitamin at least 2 hours before or after taking orlistat.[27,29] Orlistat is contraindicated in PLWO with chronic malabsorption syndrome or cholestasis. Some PLWO may develop increased levels of urinary oxalate on orlistat; cases of oxalate nephropathy with renal failure have been reported.[30] There have also been rare cases of severe liver injury or acute liver failure.[31]

As orlistat may interfere with vitamin K absorption, the international normalised ratio (INR) should be monitored closely when oral anticoagulants are co-administered. Orlistat may affect absorption of levothyroxine and/or iodine salts; PLWO on levothyroxine should be monitored for changes in thyroid function. A reduction in plasma cyclosporine levels has been observed when orlistat is co-administered, and it is therefore recommended to monitor cyclosporine levels frequently. Orlistat may affect absorption of anticonvulsant medications, so PLWO on anticonvulsants and orlistat should be monitored for possible changes in the frequency and/or severity of seizures.[29]

Table 1. Pharmacotherapy for obesity (currently registered in South Africa)

	Orlistat	Liraglutide	Naltrexone/bupropion	Semaglutide
Mode of administration	Oral	SC	Oral	SC
Dose/frequency	120 mg TID	3.0 mg daily	16/180 mg BID	2.4 mg weekly
Effect on % weight loss at 1 year, placebo subtracted	−2.9%[27]	−5.4%[3]	−4.8%[5]	−12.5%[1]
Effect on weight over longer term, placebo subtracted	−2.8 kg at 4 years[8]	−4.2% at 3 years[3]	Not studied	Not available
% of patients achieving ≥5% weight loss at 1 year	54% (v. 33% for placebo)[27]	63.2% (v. 27.1% for placebo)[2]	48% (v. 16% for placebo)[5]	86.4% (v. 31.5% for placebo)[1]
% of patients achieving ≥10% weight loss at 1 year	26% (v. 14% for placebo)[27]	33.1% (v. 10.6% for placebo)[2]	25% (v. 7% for placebo)[5]	69.1% (v. 12% for placebo)[1]
% of patients achieving ≥15% weight loss at 1 year	Not studied	14.4% (v. 3.5% for placebo)[3]	13.5% (v. 2.4% for placebo)[34]	50.5% (v. 4.9% for placebo)[1]
% of patients achieving ≥20% weight loss at 1 year	Not studied	Not studied	Not studied	32% (v. 1.7% for placebo)[1]
Effect on maintenance of previous lifestyle-induced weight loss	2.4 kg less weight regain v. placebo over 3 years[7]	−6.0% additional placebo-subtracted weight loss at 1 year[4]	Not studied	Not studied
Cost	$$	$$$$	$$$	$$$$
Contraindications	Cholestasis Chronic malabsorption syndrome Pregnancy, attempting conception, breastfeeding	Personal or family history of medullary thyroid cancer Personal history of MEN2 syndrome Pregnancy, attempting conception, breastfeeding	Uncontrolled hypertension Any opioid use History of, or risk factors for, seizures Abrupt discontinuation of alcohol Concomitant administration of monoamine oxidase inhibitors Severe hepatic impairment End-stage renal failure Pregnancy, attempting conception, breastfeeding	Personal or family history of medullary thyroid cancer Personal history of MEN2 syndrome Pregnancy, attempting conception, breastfeeding
Common side-effects	Loose, oily stools, flatus	Nausea, constipation, diarrhoea, vomiting	Nausea, constipation, headache, dry mouth, dizziness, diarrhoea	Nausea, diarrhoea, constipation, vomiting
Rare side-effects	Liver failure Nephrolithiasis Acute kidney injury	Cholelithiasis Pancreatitis	Seizures Worsening of depression	Cholelithiasis Pancreatitis
Medication interactions	Fat-soluble vitamins Levothyroxine Cyclosporine Oral anticoagulants Anticonvulsants	May affect absorption of medications due to slowing of gastric emptying	Yes: See chapter text	May affect absorption of medications due to slowing of gastric emptying

SC = subcutaneously; TID = three times a day; BID = twice a day; MEN2 = multiple endocrine neoplasia type 2.

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

Liraglutide 3.0 mg subcutaneously daily

Liraglutide is a daily, subcutaneously administered, human glucagon-like peptide-1 receptor agonist (GLP-1 RA) that acts centrally on the pro-opiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons to improve satiation and satiety and reduce hunger, with a transient effect to decrease gastric emptying.[32,33]

Liraglutide increases insulin release and suppresses glucagon during times of glucose elevation. Liraglutide is approved in SA for the management of T2DM at a dose of 1.2 mg or 1.8 mg daily, with near-maximal therapeutic efficacy for glycated haemoglobin (HbA1c) lowering at the 1.8 mg dose. Liraglutide was approved in SA in 2020 for long-term obesity management at a dose of 3.0 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 3.0 mg target dose is achieved.

Among people with normoglycaemia or prediabetes, liraglutide 3.0 mg with health behaviour modification resulted in −8.0% weight

loss at 1 year, compared with –2.6% with placebo (health behaviour modification alone).[2] In terms of categorical weight loss, 63.2% of PLWO on liraglutide lost ≥5% body weight at 1 year, compared with 27.1% of PLWO in the placebo group; 33.1% and 10.6% of participants lost >10% of their body weight on liraglutide 3.0 mg and placebo, respectively.[2]

Patients with prediabetes were followed for 3 years, with sustained weight loss of –6.1% in the liraglutide group versus –1.9% in placebo.[3] In addition to intensive behavioural therapy, liraglutide 3.0 mg resulted in –7.5% weight loss at 1 year versus –4.0% with placebo.[45]

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 1 year compared with 0.2% in the placebo group (ongoing health behaviour counselling alone).[4] More participants 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 with placebo (17.5%).[4]

The most common side-effect of liraglutide is nausea.[2-4,45] There are likely to be many causes for the nausea, both central and peripheral, which may include a transient delay in gastric emptying.[33] PLWO may also experience constipation, diarrhoea, 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 with placebo.[10]

There is a small increased risk of pancreatitis compared with placebo, with about half of the cases seen in association with gallstones.[3] Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid cancer or a personal history of multiple endocrine neoplasia type 2 because of an increased risk of medullary thyroid cancer in rodent studies. There have been no cases of medullary thyroid cancer in human studies of liraglutide. Liraglutide delays gastric emptying, which may affect absorption of concomitantly administered oral medications.

Naltrexone/bupropion 16 mg/180 mg BID

Naltrexone hydrochloride/bupropion hydrochloride is a combination of two medications. Naltrexone is an opioid receptor antagonist that has been used for decades for the treatment of alcohol and opioid dependence. Bupropion is a widely used antidepressant that inhibits the reuptake of dopamine and norepinephrine. The naltrexone/bupropion sustained-release formulation was approved for long-term obesity management in SA in 2020, at a dose of 16 mg naltrexone and 180 mg bupropion given twice daily. Bupropion induces satiety centrally by enhancing production and release of α-melanocyte-stimulating hormone and β-endorphin from the POMC cells in the arcuate nucleus of the hypothalamus. Naltrexone disrupts the auto-inhibitory effect of β-endorphin on the POMC cells by blocking the μ-opioid receptors. Naltrexone/bupropion also influences the mesolimbic reward system, resulting in a reduction in cravings.[46] This synergistic mode of action is supported by evidence that the use of bupropion or naltrexone alone does not lead to clinically meaningful weight loss.[47]

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

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

Naltrexone/bupropion has been demonstrated to reduce cravings.[5,34] Results from the Control of Eating Questionnaire (CoEQ) demonstrated reductions in eating in response to food cravings, and increased ability to resist food cravings and control eating.[5] A combined analysis of three naltrexone/bupropion trials found that early improvements in cravings were predictive of greater weight loss.[47]

The most common side-effects of naltrexone/bupropion include nausea, constipation, headache, vomiting, insomnia, dry mouth, dizziness and diarrhoea. Most nausea events occur during the dose escalation period and are transient.

Naltrexone/bupropion is contraindicated in patients with uncontrolled hypertension. Any opioid use is an absolute contraindication to the use of naltrexone/bupropion. Opioid therapy should be discontinued for 7 - 10 days prior to initiation of naltrexone/bupropion to prevent the precipitation of opioid withdrawal.[48] As bupropion is associated with a slightly increased risk of seizures, naltrexone/bupropion is contraindicated in seizure disorders, anorexia nervosa, bulimia, and PLWO undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates or antiepileptic medications. Naltrexone/bupropion should be dosed with caution with any medications that lower the seizure threshold. Monoamine oxidase inhibitors can increase the risk of hypertensive reactions, and naltrexone/bupropion should therefore not be used within 14 days of taking monoamine oxidase inhibitors. Naltrexone/bupropion should not be taken with a high-fat meal, as this significantly increases systemic exposure to the medication.[49]

There are multiple potential medication interactions with naltrexone/bupropion, which stem from the effect of bupropion and its metabolites to inhibit the hepatic CYP2D6 enzyme system. Physicians and pharmacists must be aware of the importance of evaluating potential medication interactions prior to initiating naltrexone/bupropion. Among PLWO 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, antipsychotic agents, type 1C antiarrhythmic agents, and many tricyclic antidepressants, such as citalopram, metoprolol, risperidone, propafenone and desipramine).[50] For patients already receiving these medications, dose reduction should be considered 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. Naltrexone/bupropion dosing should therefore 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 medications (e.g. levodopa, amantadine).

Semaglutide 2.4 mg subcutaneously weekly

Semaglutide is a once-weekly, subcutaneously administered, human GLP-1 RA that acts centrally on the POMC/CART neurons to improve satiation and satiety, reduce hunger and reduce cravings.[44]

Semaglutide increases insulin release and suppresses glucagon during times of glucose elevation. Semaglutide was approved in SA in 2020 for

the management of T2DM at a dose of 0.5 mg or 1.0 mg weekly, with near-maximal therapeutic efficacy for HbA1c lowering at the 1.0 mg dose. Semaglutide was approved in SA in 2024 for long-term 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 up-titration every 4 weeks to 0.5 mg weekly, 1 mg weekly, 1.7 mg weekly, and then the maximum dose of 2.4 mg weekly.

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

In addition to a low-calorie diet for 8 weeks followed by intensive behavioural therapy for 68 weeks, semaglutide 2.4 mg resulted in −16.0% weight loss versus −5.7% with placebo.[52] Among 803 adults with overweight or obesity who completed a 20-week run-in period with semaglutide 2.4 mg weekly (with a mean weight loss of 10.6%), maintaining treatment with semaglutide resulted in continued weight loss of −7.9% over the following 48 weeks versus +6.9% weight gain with switch to placebo.[53]

In a study of semaglutide 2.4 mg weekly versus liraglutide 3 mg daily in 338 people with overweight or obesity without diabetes, mean weight loss at 68 weeks was −15.8% with semaglutide versus −6.4% with liraglutide.[54] Gastrointestinal adverse events (side-effects) were seen in similar proportions of patients with semaglutide and liraglutide, although more events occurred with semaglutide than liraglutide. Proportions of participants discontinuing treatment for any reason were 13.5% with semaglutide and 27.6% with liraglutide.

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

There is a small increased risk of pancreatitis compared with placebo.[55] Semaglutide is contraindicated in PLWO with a personal or family history of medullary thyroid cancer or a personal history of multiple endocrine neoplasia type 2 because of an increased risk of medullary thyroid cancer in rodent studies.[55] There have been no cases of medullary thyroid cancer in human studies of semaglutide 1.0 mg or 2.4 mg.[55]

Semaglutide may delay gastric emptying, which could potentially influence absorption of concomitantly administered oral medications. However, in a pharmacodynamic study, no clinically relevant effect on the rate of gastric emptying was observed with semaglutide 2.4 mg at 20 weeks.[44]

Phentermine

Phentermine is registered in SA for treatment of PLWO in doses of 15 mg daily or 30 mg daily. It is registered for short-term (maximum 3 months) treatment only and therefore falls outside the scope of this guideline. Phentermine has been withdrawn from the market in Europe and Canada owing to safety concerns.

Phentermine is a sympathomimetic amine that increases levels of norepinephrine, dopamine and serotonin in several hypothalamic nuclei. Activating these nuclei suppresses appetite, and this is the dominant mechanism of action.[56] Weight loss with phentermine use for 12 weeks was modest, with approximately 3.6% of total body weight. A recent study by Lewis *et al*.[57] showed that a longer duration of phentermine use was associated with clinically significant greater weight loss up to 2 years after initiating medication, with no observed increase in risk for incident cardiovascular events or death over 3 years of follow-up. Long-term use of phentermine is currently being investigated in the LEAP trial, and results are expected in 2027. Discontinuation of phentermine consistently resulted in weight regain.[56,57] Phentermine has shown benefit in reducing hepatic fat content in the immediate preoperative period in patients undergoing bariatric surgery.[58] Phentermine use should be avoided in PLWO with serious cardiovascular disease, serious psychiatric disease, or a history of substance abuse.

Efficacy of pharmacotherapy on health parameters (Table 2)

Prevention of type 2 diabetes mellitus

T2DM is a common complication in PLWO, and prevention of diabetes is an important goal in long-term obesity management. People with prediabetes are at high risk of developing T2DM, with about 25% of individuals with either impaired fasting glucose or impaired glucose tolerance progressing to T2DM over 3 - 5 years.[59] Among individuals with prediabetes, one kilogram of weight loss is associated with a 16% relative risk reduction in the development of T2DM.[59]

Pharmacotherapy for PLWO can prevent or delay the development of T2DM. Orlistat was evaluated for diabetes prevention in a trial of 3 305 people with obesity and either normal (79%) or impaired (21%) glucose tolerance. Patients were randomised to health behaviour changes plus either orlistat or placebo.[8] After 4 years of treatment, the cumulative incidence of diabetes was 6.2% in the orlistat group compared with 9.0% for placebo, with a corresponding 37.3% decrease in risk of progression to T2DM. Participants with impaired glucose tolerance derived the greatest benefit in terms of decreased rate of progression to T2DM, compared with those with normoglycaemia. A secondary analysis demonstrated greater weight loss to be the primary reason for diabetes prevention.[8]

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

An analysis of 3 375 adults with overweight/obesity across the STEP 1, 3 and 4 trials evaluated whether more participants with prediabetes had normoglycaemia after 68 weeks' treatment with semaglutide 2.4 mg weekly.[52,53,60] Significantly more participants with baseline prediabetes had normoglycaemia at week 68 versus placebo (STEP 1: 84.1% v. 47.8%; STEP 3: 89.5% v. 55.0%; STEP 4: 89.8% v. 70.4%; all p<0.0001). Among participants with obesity and prediabetes, the results of the STEP 10 trial showed that 81% of patients treated with semaglutide 2.4 mg weekly subcutaneously reverted to normoglycaemia after 52 weeks of treatment versus only 9% of patients treated with placebo.[35]

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

Our literature review identified one RCT evaluating the efficacy of exenatide (a short-acting GLP-1 RA) versus placebo on body weight and glucose tolerance among people with obesity with normoglycaemia, impaired glucose tolerance or impaired fasting

Table 2. Pharmacotherapy for obesity in South Africa: Effects on adiposity-related comorbidities

	Orlistat 120 mg TID	Liraglutide 3.0 mg daily SC	Naltrexone/ bupropion 16/180 mg BID	Semaglutide 2.4 mg weekly SC
Effect on prediabetes	37.3% reduction in risk of developing T2DM over 4 years[8]	79% reduction in risk of developing T2DM over 3 years[3]	Not studied	81% reverted to normoglycaemia[5]
Effect on BP at 1 year, placebo subtracted	–1.7 mmHg SBP –0.71 mmHg DBP[36]	–2.87 mmHg SBP –0.73 mmHg DBP[37]	Not significantly different[36]	–5.1 mmHg SBP –2.4 mmHg DBP[1]
Effect on lipids at 1 year, placebo subtracted (only statistically significant changes in lipid parameters listed)	LDL –0.22 mmol/L HDL +0.03 mmol/L[36]	LDL –0.08 mmol/L[37]	HDL +0.06 mmol/L[36]	Total cholesterol –0.22 mmol/L LDL –0.1 mmol/L HDL +0.1 mmol/L Triglycerides –0.22 mmol/L[1, 38]
Effect on HR at 1 year, placebo subtracted	No change	+2.4 bpm[2]	+1.1 bpm[5]	+4.2 bpm[1]
Effect on HbA1c in patients with diabetes at 1 year, placebo subtracted	–0.4%[12]	–1.0%[10]	–0.5%[11]	–1.2%[9]
Effect on MACEs	Not studied	Cardiovascular safety demonstrated[39]	Not studied	Improved[40]
Effect on MASLD	No change	Resolution of MASH and improvement in steatosis (39% with liraglutide 3 mg v. 9% with placebo)[14]	Not studied	Resolution of MASH (59% with semaglutide 0.4 mg daily v. 17% with placebo)[15]
Effect on PCOS	Not studied	Not sufficiently studied	Not studied	Not studied
Effect on OA	Not studied	No benefit	Not studied	Improved[41]
Effect on OSA (placebo subtracted)	Not studied	Reduces AHI by 6/hour[13]	Not studied	Not studied
Effect on physical function	Not studied	SF-36: improvement[42] IWQOL: improvement[42]	IWQOL: improvement[5]	SF36: improvement[1] IWQOL: improvement[1]
Effect on QoL	Not studied	SF36: improvement[42] IWQOL: improvement[42]	IWQOL: improvement[5]	SF36: improvement[1] IWQOL: improvement[1]
Effect on CoEQ (cravings)	Not studied	Not studied	Improvements in craving control, positive mood, craving for sweet and savoury food[43]	Improvements in craving control, positive mood, craving for sweet and savoury food[44]

TID = three times a day; SC = subcutaneously; BID = twice a day; T2DM = type 2 diabetes; BP = blood pressure; SBP = systolic BP; DBP = diastolic BP; LDL = low-density lipoprotein; HDL = high-density lipoprotein; HR = heart rate; bpm = beats per minute; HbA1c = glycated haemoglobin; MACEs = major adverse cardiovascular events; MASLD = metabolic dysfunction-associated steatotic liver disease; MASH = metabolic dysfunction-associated steatohepatitis; PCOS = polycystic ovary syndrome; OA = osteoarthritis; OSA = obstructive sleep apnoea; AHI = apnoea-hypopnoea index; SF-36 = 36-Item Short Form Survey; IWQOL = Impact of Weight on Quality of Life; QoL = quality of life; CoEQ = Control of Eating Questionnaire.

glucose, on a background of health behaviour intervention over a 24-week period.[61] The exenatide group demonstrated a –5.1 kg weight loss compared with –1.6 kg for placebo. Impaired glucose tolerance or impaired fasting glucose normalised in 77% of exenatide-treated participants compared with 56% in the placebo group. Exenatide is not indicated for obesity management or for the prevention of T2DM.

Type 2 diabetes mellitus

Obesity in T2DM is associated with poorer glycaemic control, blood pressure (BP) and lipid profiles, and increased use of lipid-lowering and antihypertensive medications, compared with people with diabetes who do not have obesity.[62]

The effect of glucose-lowering pharmacotherapy on weight should be considered in choosing the most appropriate medication(s) for glycaemic control. GLP-1 RAs and sodium/glucose cotransporter-2 inhibitors are associated with weight loss in addition to improving glycaemic control. Metformin, dipeptidyl peptidase-4 inhibitors and acarbose are typically weight neutral. Insulin, insulin secretagogues and thiazolidinediones are associated with weight gain.[63] Pharmacotherapy for obesity can be of benefit for weight management, improved diabetes control, and reduction in the need for other glucose-lowering medication.

Orlistat has been demonstrated to improve glycaemic control in PLWO with T2DM. A meta-analysis comprising 2 550 people with

T2DM and obesity randomised 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 v. 0.47 mmol/L and 0.74% v. 0.31%, respectively).[12] Weight loss in the orlistat group was –3.8 kg compared with –1.4 kg on placebo. The primary reason for improvement in glycaemic control with orlistat is weight loss, although orlistat may provide beneficial metabolic effects independent of weight loss.

In the SCALE diabetes trial, liraglutide 3.0 mg subcutaneously daily was compared with liraglutide 1.8 mg subcutaneously daily and placebo, in addition to health behaviour changes, in PLWO and T2DM managed with oral agents or health behaviours alone.[10] At 1 year, liraglutide 3.0 mg reduced weight by –6.0% (*n*=423) compared with –4.7% among those receiving liraglutide 1.8 mg (*n*=211) and –2.0% with placebo (*n*=212). A clinically significant weight loss of ≥5% was achieved by 54.3% of patients on liraglutide 3.0 mg, versus 40.4% with liraglutide 1.8 mg and 21.4% with placebo. Weight loss of ≥10% occurred in 25.2% of patients on liraglutide 3.0 mg, 15.9% of those on liraglutide 1.8 mg, and 6.7% of those receiving placebo. HbA1c was reduced by –1.3% in the liraglutide 3.0 mg group, –1.1% in the liraglutide 1.8 mg group and –0.3% in those receiving placebo. In addition, more participants treated with liraglutide 3.0 mg and 1.8 mg reduced their net use of oral glucose-lowering agents compared with placebo.[10] In the SCALE insulin trial, 396 participants with T2DM and obesity treated with basal insulin and two or more oral glucose-lowering agents were randomised to receive liraglutide 3 mg daily or placebo, combined with intensive behavioural therapy.[64] At 56 weeks, mean weight change was –5.8% with liraglutide 3 mg versus –1.5% with placebo. Liraglutide 3 mg was associated with significantly greater reductions in HbA1c and less need for insulin compared with placebo.[64]

The Contrave Obesity Research (COR) diabetes trial evaluated the safety and efficacy of naltrexone/bupropion 16 mg/180 mg BID in addition to health behaviour changes in adults with a BMI of 27 - 45 kg/m^2 and T2DM managed with oral agents or diet.[11] Naltrexone/bupropion-treated participants achieved a –5.0% weight reduction compared with –1.8% in the placebo group. Additionally, 44.5% of patients achieved ≥5% weight loss compared with 18.9% in the placebo arm, and 18.5% of patients had ≥10% weight loss compared with 5.7% of patients receiving placebo. Participants treated with naltrexone/bupropion demonstrated a –0.5% greater improvement in HbA1c compared with placebo and were more likely to achieve an HbA1c <7% (44.1% in the naltrexone/bupropion group v. 26.3% for 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 glucose-lowering agents compared with placebo (22.3% v. 35.2%, respectively).

In the STEP 2 study,[9] 1 210 people with overweight or obesity and T2DM managed with oral agents or health behaviours alone were randomised to semaglutide 2.4 mg weekly, semaglutide 1.0 mg weekly or placebo, in addition to health behaviour modification. Semaglutide 2.4 mg resulted in a superior weight loss of –9.6% at 68 weeks compared with –7.0% for semaglutide 1.0 mg and –3.4% for placebo. More participants achieved weight reductions of at least 5% with semaglutide 2.4 mg (68.8%) than with semaglutide 1.0 mg (57.1%) or placebo (28.5%). Weight loss ≥10% occurred in 45.6% of patients in the semaglutide 2.4 mg group, 28.7% in the semaglutide 1.0 mg group and 8.2% in the placebo group. Weight loss ≥15% occurred in 25.8% of participants in the semaglutide 2.4 mg group, 13.7% in the semaglutide 1.0 mg group and 3.2% in the placebo group. Reduction in HbA1c was similar at both doses of semaglutide, with –1.6% for semaglutide 2.4 mg, –1.5% for semaglutide 1.0 mg and –0.4% for placebo. A decrease in use of concomitant glucose-lowering medication was reported in 28.6% of participants receiving semaglutide 2.4 mg, 25.1% receiving semaglutide 1.0 mg and 7.1% receiving placebo.

Other cardiovascular risk factors: Hypertension and lipids

Pharmacotherapy-induced weight loss can be of benefit in improving cardiovascular risk factors.

A systematic review assessed the effect of long-term obesity pharmacotherapy (at least 1 year's duration) on various aspects of cardiometabolic risk, including blood glucose, cholesterol profile, BP and visceral adiposity.[36] Studies from inception of databases until 2017 were included. RCTs were included that evaluated adults with a BMI of ≥30 kg/m^2, or 25 - 29.9 kg/m^2 with and without obesity-associated comorbidities (hypertension, hyperlipidaemia, diabetes mellitus, impaired glucose tolerance or OSA); treated with obesity management pharmacotherapy for at least 1 year; compared with another active agent or placebo; and reporting at least one prespecified cardiometabolic outcome in addition to a primary weight loss outcome (5% of baseline weight loss or mean weight loss). There were 17 trials of orlistat versus placebo (*N*=10 702), three trials of liraglutide versus placebo (*N*=4 557) and four trials of naltrexone/bupropion versus placebo (*N*=3 953).

In this systematic review,[36] orlistat, liraglutide and naltrexone/bupropion demonstrated modest effects on cholesterol profiles. Although the effects of some of these medications on the lipid profile were statistically significant, they were of doubtful clinical significance. Orlistat, liraglutide and naltrexone/bupropion had minimal effects on BP, with very small declines in systolic and diastolic BP. As naltrexone/bupropion can increase BP on initiation, it is contraindicated in patients with uncontrolled hypertension.[61]

In PLWO and prediabetes, liraglutide reduced systolic BP by –2.8 mmHg compared with placebo over 3 years, with modest improvements in lipid parameters. A heart rate increase of two beats per minute (bpm) was observed, in keeping with what is seen in the GLP-1 RA class.[3]

Semaglutide reduced systolic BP by –6.1 mmHg versus –1.1 mmHg with placebo at 68 weeks, with modest improvement in lipid parameters, in a study of PLWO without T2DM (see Table 2). A heart rate increase of +3.5 bpm was noted versus –0.7 bpm with placebo, in keeping with what is seen in the GLP-1 RA class.[1]

Atherosclerotic cardiovascular disease

Regulatory requirements for obesity pharmacotherapy do not include a standard requirement for cardiovascular outcome trials to assess the cardiovascular safety of these medications. However, cardiovascular outcome studies may be required by regulatory agencies, particularly if there is any concern for potential adverse effects on any cardiovascular risk factor. Sibutramine was studied in a cardiovascular outcome trial because of reported increases in BP and heart rate.[65] This study found an increased risk of cardiovascular events in people with pre-existing cardiovascular disease.

In patients with T2DM, liraglutide 1.2 - 1.8 mg has been shown to reduce cardiovascular events and mortality.[39] These data have been accepted as sufficient safety data by the US Food and Drug Administration (FDA) to give reassurance on the cardiovascular safety of liraglutide in people with obesity without T2DM, at the therapeutic dose of 3.0 mg. The cardiovascular safety of liraglutide 3.0 mg was evaluated *post hoc* using data from five randomised, double-blind, placebo-controlled clinical trials comprising 5 908 participants, the

majority (97%) of whom did not have diabetes. Liraglutide 3.0 mg was not associated with excess cardiovascular risk, with a hazard ratio (HR) of 0.42 (95% confidence interval [CI] 0.17 - 1.08) versus pooled comparators (*n*=1 941 receiving placebo, *n*=95 receiving orlistat).[66]

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 (MACEs) occurred, compromising the integrity of the trial.[67] Although the trial was terminated on the recommendation of the lead investigator, the results of the preplanned 50% interim analysis were released and demonstrated an HR for the time to the first MACE of 0.88 (95% CI 0.57 - 1.34).[67] These results could not be used to establish non-inferiority owing to the compromise of the trial.

A subsequent meta-analysis including 12 RCTs comprising 19 176 patients was conducted to evaluate the relationship of bupropion, naltrexone or naltrexone/bupropion in combination with MACEs.[68] The additive network meta-analysis model for random effects showed no significant effect of bupropion (odds ratio [OR] 0.90; 95% CI 0.65 - 1.25), naltrexone (OR 1.08; 95% CI 0.71 - 1.63) or naltrexone/bupropion (OR 0.97; 95% CI 0.75 - 1.24) on MACEs.

Semaglutide 0.5 - 1 mg has been shown to decrease cardiovascular events in people living with T2DM with established cardiovascular disease or at high risk of cardiovascular disease compared with placebo.[55] The SELECT trial enrolled 17 604 patients with overweight/obesity and pre-existing cardiovascular disease but without diabetes. Of these patients, 8 803 received treatment with semaglutide 2.4 mg.[40] It was a primary cardiovascular event-driven trial. Of the 8 803 participants in the group treated with semaglutide 2.4 mg, 569 (6.5%) developed a primary cardiovascular event compared with 701/8 891 (8.0%) in the placebo group (HR 0.80; 95% CI 0.72 - 0.90; $p<0.001$).

There are no cardiovascular outcome trials for orlistat.

Heart failure with preserved ejection fraction

Over 80% of people with HFpEF have overweight or obesity.[69] As weight loss has been shown to improve HFpEF,[70] it is of interest whether pharmacotherapy for obesity management may be of benefit in people with HFpEF.

In adults with HFpEF and obesity, once-weekly treatment with semaglutide was associated with greater reductions in HF-related symptoms and physical limitations and greater weight loss than placebo over 52 weeks.[71]

Heart failure with reduced ejection fraction

The effect of the GLP-1 RA liraglutide was studied in three small trials enrolling patients with HFrEF. Liraglutide was used in two trials and albiglutide in the third.[72] The FIGHT trial enrolled PLWO with severely symptomatic HFrEF who had recently been hospitalised for worsening heart failure (HF), and the LIVE trial enrolled patients with stable HFrEF.[73,74] Patients were randomly assigned to treatment with liraglutide or placebo. Both trials showed an increased risk of adverse cardiac events in the groups treated with liraglutide.

A meta-analysis of the EXSCEL and FIGHT trials suggested an increased risk of HF hospitalisations with GLP-1 RAs in patients with left ventricular ejection fraction <40%, with little heterogeneity across studies: meta-analysed OR 1.49 (95% CI 1.05 - 2.10) (overall treatment effect $p=0.02$ and heterogeneity $I^2=0\%$).[75]

These results suggest that GLP-1 RAs may be associated with an increased risk of HF hospitalisations in patients with HFrEF. Until further randomised studies are available, GLP-1 RAs should be avoided in this patient group.

The use of GLP-1 RAs must be individualised, and active screening for HF is advised. Before starting GLP-1 RAs, all patients should be evaluated for symptoms and signs of HF and have natriuretic peptide levels measured. If natriuretic peptides are elevated (>35 pg/mL for BNP and >125 pg/mL for NT-pro-BNP), an echocardiogram should be performed, as recommended by international guidelines.[76,77]

Metabolic dysfunction-associated steatotic liver disease

MASLD (previously known as non-alcoholic fatty liver disease [NAFLD] and non-alcoholic steatohepatitis [NASH]) is currently recognised as the most prevalent chronic liver disease, and globally affects approximately 25% of the adult population.[78] Metabolic comorbidities associated with MASLD include obesity (51.3%), T2DM (22.5%), hyperlipidaemia (69.1%), hypertension (39.3%) and metabolic syndrome (42.5%).[79] Weight loss is recognised as the cornerstone of treatment of people with MASLD and overweight or obesity.[80] Fifty participants who were overweight (BMI ≥27) with biopsy-proven NASH were randomised to receive a 1 400 kcal/day diet plus vitamin E (800 IU) daily with or without orlistat (120 mg TID) for 36 weeks.[81] The primary study endpoint was improvement in steatosis, NAFLD activity score and fibrosis score on follow-up liver biopsy obtained at 36 weeks. Twenty-three participants in the orlistat/diet/vitamin E group and 18 in the diet/vitamin E group completed the study. Orlistat did not enhance weight loss or improve liver enzymes, measures of insulin resistance or histopathological features compared with placebo. However, participants in either group who lost ≥5% body weight had improved insulin resistance and steatosis, and participants who lost ≥9% also achieved improved hepatic histological changes.

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

The effect of semaglutide in patients with NASH was evaluated in a 72-week, phase 2, double-blind trial involving 320 participants with BMI >25 and biopsy-confirmed NASH and liver fibrosis of stage F1, F2 or F3.[15] Patients received subcutaneous semaglutide at a dose of 0.1 mg, 0.2 mg or 0.4 mg once daily, or placebo. The proportion of participants who experienced NASH resolution with no worsening of fibrosis was 40% in the 0.1 mg group, 36% in the 0.2 mg group, 59% in the 0.4 mg group and 17% in the placebo group ($p<0.001$ for semaglutide 0.4 mg daily v. placebo). Weight loss was –5%, –9%, –13% and –1% in the semaglutide 0.1 mg, 0.2 mg and 0.4 mg and placebo groups, respectively. Semaglutide 2.4 mg weekly was studied in people with MASH in the ESSENCE trial.[82-84] This showed that semaglutide is the first GLP-1 RA to demonstrate efficacy in a phase 3 MASLD trial, with superiority confirmed for semaglutide versus placebo with regard to MASLD resolution with no worsening of fibrosis, improvement in liver fibrosis with no worsening of steatohepatitis, and resolution of steatohepatitis with improvement in liver fibrosis.

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

Although data are conflicting, some small studies have suggested that metformin may cause a small decrease in BMI of –0.5 kg/m² to –1.3 kg/m² with an improvement in aminotransferases and/or liver histological features in patients with NAFLD.[85,86]

Current literature suggests that GLP-1 RAs are likely to be the optimal choice for obesity management in a person with MASLD. Medications in this class have consistently demonstrated reductions in liver fat and have frequently also shown benefits in terms of reducing serum markers of liver injury.

Polycystic ovary syndrome

Among women with PCOS, liraglutide 1.8 mg daily has been shown in a small study to induce placebo-subtracted weight loss of –5.2 kg and reduce liver fat content, visceral fat and the presence of NAFLD over 26 weeks.[87] A meta-analysis of six studies (randomised and non-randomised) with 401 women evaluated the effect of liraglutide monotherapy and add-on pharmacotherapy on weight, BMI, waist circumference and homeostatic model assessment for insulin resistance (HOMA-IR) among women with a diagnosis of PCOS.[88] Weight, BMI and waist circumference were significantly reduced in comparison with placebo by –4.33 kg (95% CI –6.05 - –2.61), –2.53 kg/m² (95% CI –2.79 - –2.27) and –6.28 cm (95% CI –7.89 - –4.67), respectively. Follicle-stimulating hormone and luteinising hormone showed a decline in the liraglutide group, and there was a moderate decline in HOMA-IR. These studies did not evaluate menstrual frequency, fertility or hirsutism.

There are no studies of sufficient quality evaluating orlistat, naltrexone/bupropion or semaglutide in patients with PCOS. Semaglutide 0.5 mg weekly subcutaneously was evaluated in one small study, and almost 80% of PCOS participants with obesity who were unresponsive to a lifestyle plan achieved an at least 5% decrease in their body weight. This was associated with a significant improvement in basal glucose and insulin resistance (calculated by HOMA-IR).[89]

Metformin with health behaviour changes may be associated with a small reduction in BMI (–0.73 kg/m²) and improved menstruation in women with PCOS over 6 months compared with health behaviour alone, according to one systematic review and meta-analysis.[90] However, another systematic review and meta-analysis showed no effect of metformin on weight in this population.[91]

In a small study comparing exenatide, metformin and the combination of exenatide and metformin in women with PCOS and overweight, weight loss in both exenatide arms was superior to metformin, with weight loss of –6.0 kg on the combination of exenatide and metformin, –3.2 kg with exenatide alone and –1.6 kg on metformin alone. The combination of exenatide and metformin was superior to either medication as monotherapy to improve menstrual cyclicity and ovulation rate.[92]

A small open-label study (*N*=119) compared the effect of once-weekly exenatide, exenatide and dapagliflozin in combination, dapagliflozin and metformin in combination, and phentermine/topiramate (a weight management pharmacotherapy not available in SA) on weight and metabolic health parameters in women with PCOS and obesity without diabetes.[93] Phentermine/topiramate and the combination of exenatide and dapagliflozin resulted in the greatest weight loss of –9.0 kg and –6.0 kg, respectively. Testosterone and free androgen index were significantly improved in all treatment groups. Exenatide/dapagliflozin and exenatide resulted in significant improvements in mean blood glucose and insulin sensitivity. Improvements in menstrual cyclicity were not assessed.

Obstructive sleep apnoea

The only obesity pharmacotherapy available in SA that has been specifically studied in patients with OSA is liraglutide. Among PLWO with moderate or severe OSA 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 apnoea-hypopnoea index events by –12.2 events per hour, compared with a reduction of –6.1 events per hour with health behaviour modification alone.[13]

Osteoarthritis

In a trial of 156 adults with BMI ≥27 and knee OA, participants were randomised to receive liraglutide 3.0 mg or placebo, following 5% weight loss with an 8-week dietary intervention.[94] At week 52, there was a significant difference in body weight between the liraglutide and placebo group (–2.8 kg v. +1.2 kg, respectively), but no difference in knee OA pain as assessed by the Knee Injury and Osteoarthritis Outcome Score. The lack of benefit in this trial is likely to be due to insufficient magnitude of weight loss; weight loss goals of ≥10% of body weight are advised for symptomatic and functional improvement among people with overweight or obesity and OA of weight-bearing joints.[95]

In the STEP 9 trial, 407 patients with OA of the knees were enrolled.[41] The mean age was 56 years and mean BMI 40.3 kg/m². The mean WOMAC pain score was 70.9. At week 68 the mean change in body weight was –13.7 % in the group treated with semaglutide and –3.2 % in the placebo group. The mean change in WOMAC pain score at week 68 was –41.7 points in the semaglutide-treated group versus –27.5 points in the placebo group (estimated treatment difference 14.1; $p<0.001$). The SF-36 (36-Item Short Form Survey) physical function score improved by 12 points in the semaglutide-treated group at week 68 versus 6.5 points in the placebo group ($p<0.001$).

Chronic kidney disease

Elevated BMI has consistently been associated with an increased risk of CKD and kidney failure.[96,97] Consideration of efficacy and safety of any medication is important in people with chronic kidney disease.

Liraglutide and semaglutide are endogenously metabolised without a specific organ as a major route of elimination. The efficacy and safety of liraglutide and semaglutide at T2DM treatment doses have been established in patients with T2DM and CKD.[39,55] Liraglutide and semaglutide resulted in lower rates of development and progression of albuminuria compared with placebo. Semaglutide 1.0 mg weekly in patients with T2DM and CKD reduced the risk of important kidney outcomes and death from cardiovascular disease.[98] Semaglutide 2.4 mg weekly for 24 weeks resulted in a clinically meaningful reduction in albuminuria in patients with overweight/obesity and non-diabetic CKD.[99]

Dose adjustment is not required for liraglutide 3 mg in patients with mild/moderate renal insufficiency. Liraglutide 3.0 mg is not recommended in people with severe renal insufficiency, including end-stage renal disease, owing to very limited or no clinical experience in this population.[100]

For semaglutide 2.4 mg weekly, no dosage adjustment is required for PLWO with renal insufficiency. Semaglutide 2.4 mg is not recommended in people with end-stage renal disease.[101]

Naltrexone/bupropion has not been studied in PLWO with renal impairment. Based on data available for the individual constituents, systemic exposure is significantly higher for bupropion, naltrexone and metabolites in patients with moderate to severe renal impairment. The maximum recommended daily maintenance dose for naltrexone/bupropion is one tablet (8 mg/90 mg) BID in patients with moderate

or severe renal impairment. Naltrexone/bupropion is contraindicated in patients with end-stage renal disease. There is a lack of adequate information to guide naltrexone/bupropion dosing in patients with mild renal impairment. All patients with renal impairment should be closely monitored for possible adverse effects.

Orlistat has not been studied in PLWO with renal impairment. There are no dosage adjustments provided in the manufacturer's labelling. However, the need for dosage adjustment in renal insufficiency is unlikely owing to low systemic absorption. The major route of excretion is in the faeces, with <2% excretion in the urine.[102]

Gastro-oesophageal reflux disease

GORD is common in people with overweight and obesity,[103] and can improve with weight loss.[104] Onset of GORD, or exacerbation of pre-existing GORD, can occur with obesity pharmacotherapy, in particular with the GLP-1 RAs liraglutide and semaglutide. This is typically transient and mild to moderate in severity.[1,3]

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

Mental health

HCPs should consider the impact on weight when prescribing medication for treatment of mental health concerns such as depression or psychosis. (See the chapter 'The role of mental health in obesity management'.) Pharmacotherapy for binge-eating disorder and attention deficit hyperactivity disorder may also affect weight.

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

There has been a long-standing concern that in rare cases antidepressants can, 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 PLWO, 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 participants treated with placebo compared with one (0.03%) of 3 239 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.

Liraglutide 3.0 mg has demonstrated neuropsychiatric safety.[105]

Neuropsychiatric concerns have not been identified with semaglutide.[106]

Weight gain is a common side-effect of some antipsychotic medications. A systematic review and meta-analysis were conducted to assess the effect of metformin on preventing weight gain associated with mental health medications.[107] Twelve double-blind, randomised, placebo-controlled trials of 12 weeks' to 24 weeks' duration, including a total of 743 participants with schizophrenia or schizoaffective disorder, were included in the study. 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.[107]

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

Craving and control of eating

Food craving is the intense desire to eat a particular food, and can be distinguished from hunger, as cravings occur spontaneously, whereas hunger increases in intensity over the time spent without food. Food craving has been shown to contribute to adherence difficulties with health behaviour interventions; reducing and managing food cravings is a key component in the management of PLWO and successful weight loss maintenance.[7,108]

An integrated analysis of four RCTs with naltrexone/bupropion assessed food craving using the CoEQ. The study demonstrated that early improvements in craving control and reductions in craving for sweet throughout the 56-week trial period were greater in the patients treated with naltrexone/bupropion, and these scores were predictive of greater reductions in BMI at the end of the trial.[43]

In a study of 72 patients over 20 weeks, semaglutide 2.4 mg weekly improved control of eating and reduced cravings, based on the results from the CoEQ. The study found overall better control of eating, fewer food cravings, less hunger and, subsequently, less energy intake with semaglutide 2.4 mg versus placebo.[44]

Orlistat and liraglutide 3.0 mg have not been evaluated with regard to control of eating or cravings. Orlistat would not be expected to have a benefit in this regard, as it does not have a central nervous system mechanism of action.

Quality of life

Quality of life (QoL) broadly encompasses how an individual measures the 'goodness' of multiple aspects of their life.[109] Obesity has a negative impact on many aspects of health-related QoL (HRQoL).[110] Measuring QoL for weight loss interventions has been challenging, as the SF-36 is the traditional tool used for assessment, but it is not specific to PLWO. The recently developed Impact of Weight on Quality of Life (IWQOL)-Lite Clinical Trials (CT) version, which is more specific to PLWO, is now being utilised in many clinical trials.[111]

Weight loss is associated with improved QoL in most studies and is a component of the FDA submission for approval.[112]

The SCALE 3-year extension study evaluated the effect of liraglutide 3.0 mg daily on HRQoL versus placebo in participants with overweight or obesity and prediabetes.[42] The IWQOL-Lite questionnaire and SF-36 survey were used. Both tools demonstrated long-term, statistically significant improvement in HRQoL and physical function with liraglutide versus placebo.

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

Semaglutide 2.4 mg has been shown to improve QoL and physical functioning.[1,9,52] The STEP 1 trial assessed QoL changes from baseline to week 68 using the IWQOL-Lite CT version. Significantly greater improvements in IWQOL-Lite CT were reported with semaglutide versus placebo for all composite and total scores. Semaglutide-treated participants were more likely to achieve clinically meaningful improvements from baseline to week 68 in physical function, physical, psychosocial and total scores versus placebo.

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 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 randomised, placebo-controlled trials evaluated the efficacy of topiramate on weight loss among PLWO 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 group, respectively, compared with weight losses of 1.7 - 2.5% in the placebo groups.[113,114] While topiramate is not intended as pharmacotherapy for obesity, it could be considered in PLWO who require topiramate for other indications (e.g. antiseizure or migraine therapy) and for whom weight gain is a clinically relevant concern.

A systematic review and meta-analysis evaluating the metabolic effects and weight loss of fluoxetine 60 mg/day in 215 adults with overweight or obesity and T2DM demonstrated a –4.3 kg weight loss compared with placebo.[115] These patients did not have depression. Follow-up was 6 - 12 months in four studies, but only 2 months in the fifth study included. Fluoxetine should not be prescribed for weight loss but could be considered in PLWO who require it for other indications, such as depression, and for whom weight gain is a clinically relevant concern.[115]

A review summarises medications available in Canada that cause weight gain, as well as alternative choices.[116]

Emerging obesity pharmacotherapy

Tirzepatide is a once-weekly, subcutaneously administered, dual gastric inhibitory polypeptide (also known as glucose-dependent insulinotropic polypeptide) (GIP)/GLP-1 RA that is approved in SA as a treatment for T2DM. In the SURPASS clinical trial programme, tirzepatide 5 mg, 10 mg and 15 mg once weekly, administered subcutaneously, were evaluated as monotherapy, with metformin in comparison with semaglutide 1 mg, in comparison with basal insulin, and as an add-on to basal insulin therapy.[117-120] Superior and robust HbA1c reduction was seen with tirzepatide versus comparators, with most tirzepatide arms achieving HbA1c reduction >2%. Weight loss with tirzepatide 15 mg weekly ranged from –9.5% to –12.9% and was superior to comparator arms. In the SURPASS-4 trial, which evaluated tirzepatide in comparison with open-label insulin glargine, study completion was driven by the accrual of MACEs.[120] Adjudicated MACEs were not increased on tirzepatide compared with glargine (HR 0.74; 95% CI 0.51 - 1.08).

In the SURMOUNT-1 study, 2 539 participants with overweight or obesity, without diabetes, were randomised to receive tirzepatide 5 mg, 10 mg, 15 mg or placebo.[121] Prediabetes was present in 40.6% of participants at baseline. At 72 weeks, weight loss was –15%, –19.5% and –20.9% with tirzepatide 5 mg, 10 mg and 15 mg, respectively, versus –3.1% with placebo. The proportions of patients achieving at least 5% weight loss were 85%, 89% and 91% for tirzepatide 5 mg, 10 mg and 15 mg, respectively, versus 35% of participants receiving placebo. The proportions of participants achieving at least 20% weight loss were 30%, 50% and 57% with tirzepatide 5 mg, 10 mg and 15 mg, respectively, versus 3% of participants receiving placebo. Over 95% of participants with prediabetes at baseline converted to normoglycaemia versus 62% with placebo. Significant improvements were seen in systolic and diastolic BP. The most common adverse events were gastrointestinal side-effects, of mild to moderate severity and transient, occurring primarily during dose escalation.

Tirzepatide lowered the risk of worsening HF and death from cardiovascular causes and improved health status in patients with HFpEF compared with placebo.[122]

Treatment with tirzepatide (52 weeks) in patients with MASLD and moderate/severe fibrosis was more effective than placebo with regard to resolution of MASLD without worsening of fibrosis.[123]

The approval of tirzepatide by SAHPRA as an obesity treatment in SA occurred after the finalisation of this document; nonetheless, it represents a notable milestone that will be reflected in future guideline updates.

Cagrilintide is a long-acting, once-weekly, subcutaneously administered amylin RA under investigation for obesity management in combination with semaglutide 2.4 mg weekly. In the phase 2 trial of cagrilintide monotherapy, 706 participants with a BMI ≥30 kg/m^2 or ≥27 kg/m^2 with hypertension or dyslipidaemia were randomly assigned various doses of once-weekly cagrilintide, once-daily liraglutide 3.0 mg or placebo for 26 weeks.[124] Mean percentage weight reductions were greater with all doses of cagrilintide versus placebo, and superior for the highest dose of cagrilintide studied (4.5 mg weekly) versus liraglutide 3.0 mg daily (–10.8% v. –9.0%, respectively). The most frequent adverse events were gastrointestinal, predominantly nausea, constipation and diarrhoea.

Setmelanotide has been granted marketing authorisation in Canada, the USA and the EU for long-term obesity management in PLWO caused by POMC, proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency. Obesity due to POMC, PCSK1 or LEPR deficiency is extremely rare. Variants in POMC, PCSK1 or LEPR genes impair the MC4R pathway, causing extreme, insatiable hunger beginning at a young age and resulting in early-onset, severe obesity.[125,126] As an MC4R agonist, setmelanotide is designed to restore impaired MC4R pathway activity arising as a result of genetic deficits upstream of the MC4 receptor.[127] Adults and children with POMC deficiency (homozygous or compound heterozygous variants in POMC or PCSK1) were treated with open-label setmelanotide, with adult dosing starting at 1.0 mg subcutaneously once daily, then titrated to achieve weight loss of 2 kg/week to 3 kg/week, with a maximum dose of 3 mg/day.[128] Of 10 participants enrolled in the trial (including four adults), 80% achieved ≥10% weight loss at approximately 1 year, and mean weight loss was –25.6%. Hunger scores decreased by –27.1%. In a study of 11 patients (including eight adults) with LEPR deficiency (homozygous or compound heterozygous variants in LEPR), using the same dosing protocol described above,[128] 45% of participants achieved ≥10% weight loss at 1 year, and mean weight loss was –12.5%. Hunger score decreased by –43.7%. The most common adverse events were injection site reactions, skin disorders (including hyperpigmentation) and nausea.

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

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