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Review

Obesity pharmacotherapy: 2026 update recommendations for the care of persons with obesity in Romania

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Abstract

This article presents the 2026 update of the FORO (Romanian Obesity Forum) recommendations for the pharmacological management of persons with obesity. The update focuses on the three incretin-mimetic anti-obesity medications (AOMs) currently approved by the European Medicines Agency and available in Romania: liraglutide, semaglutide (including the newly approved 7.2 mg weekly dose), and tirzepatide, a dual GLP-1/GIP receptor agonist. In addition, agents with limited use — orlistat, naltrexone/bupropion, and setmelanotide — are briefly reviewed. A novel risk stratification tool, the RO score (Obesity Risk), is proposed to guide prioritization of pharmacotherapy. The score integrates anthropometric criteria (body mass index [BMI], waist circumference, waist-to-height ratio), Edmonton Obesity Staging System disease stage, and cardiovascular risk category. AOM selection is primarily guided by the presence or absence of obesity-associated complications, with therapeutic decisions supported by evidence from landmark phase 3 trials addressing cardiovascular outcomes, heart failure with preserved ejection fraction, metabolic steatohepatitis, prediabetes, obstructive sleep apnea, and knee osteoarthritis. Practical guidance is provided on contraindications, adverse effects, nutritional monitoring, perioperative management, and use in special circumstances including pregnancy planning. An updated treatment algorithm is included to aid clinicians' decisions, aligned with current international obesity pharmacotherapy guidelines.

Keywords: obesity, anti-obesity agents, incretin-mimetics, guideline

Introduction

Obesity pharmacotherapy is part of the interventional methods for weight loss and long-term weight maintenance, alongside lifestyle modification and metabolic surgery. This update focuses on the incretin-mimetic molecules approved in Europe: liraglutide, semaglutide (including 7.2 mg) and tirzepatide. These recommendations are based on the authors' expert opinion after an extensive review of international guidelines and relevant scientific literature.

Indications for pharmacotherapy

Before initiating pharmacotherapy, the medical team and the person with obesity (PwO) should establish clear goals, including reducing cardiometabolic risk, improving or achieving remission of complications, maintaining weight loss, managing appetite and improving quality of life [1, 2].

General indications for pharmacotherapy in adults

Pharmacotherapy is indicated in combination with non-pharmacological methods, for weight loss and maintenance of the new weight, in adult patients with either a body mass index (BMI) ≥30 kg/m^2 or a BMI ≥27 kg/m^2 with complications associated with excess adiposity [1–6]. For indications in children and adolescents, the Summary of Product Characteristics (SmPC) should be consulted for each molecule.

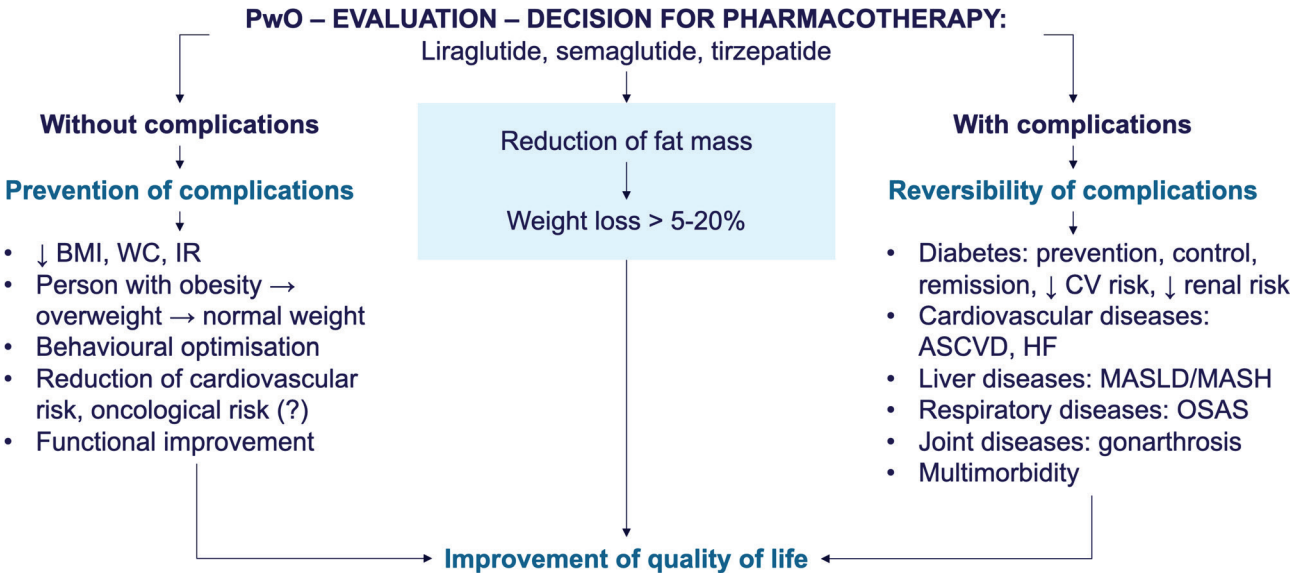

Figure 1: AOM selection based on the absence or presence of complications.

Classification/categories of anti-obesity medication (AOM) approved in Europe

For the purpose of these recommendations, AOMs are classified into incretin-mimetic medication, with weekly administration- semaglutide, tirzepatide, or with daily administration- liraglutide, and other classes of AOM (with limited use) which include orlistat, naltrexone/bupropion, and setmelanotide

AOM selection

AOM selection will be primarily made based on the absence or presence of complications [3, 4]. When complications are present, selection is based on available evidence for each complication. When absent, effects on anthropometric parameters, quality of life and prevention of complications should be considered (Figure 1).

Anthropometric criteria (A) BMI (kg/m²); WHtR, waist-to-height ratio	Edmonton criteria: disease stages (B)	**C**ardiovascular criteria (ESC)
30– 34.9 + WHtR ≥ 0.5 ***1 point***	Stage 1 ***1 point***	Moderate CV risk ***1 point***
35 – 39.9 ***2 points***	Stage 2 ***2 points***	High CV risk ***2 points***
≥ 40 ***3 points***	Stages 3 and 4 ***3 points*** *OR* ***> 3 points*** *in the presence of additional factors*	Very high CV risk ***3 points***

- The three criteria are graded into three risk levels.
- Each level is scored as 1, 2, or 3 points, or >3 points when additional factors are present, under the Edmonton criteria.
- Each person with obesity is classified within the **ABC system**.
- The **RO score** (obesity risk score) is calculated as the sum of the highlighted points.
- **Maximum score:** 3 × 3 = **9 points** (or **>9 points** in the presence of additional factors for the Edmonton criteria).
- **Minimum score:** 3 × 1 point

Stratification of the RO score
- **Low:** < 3 points
- **Moderate:** 3-5 points
- **Severe:** 6-9 points
- **Very severe:** > 9 points

Figure 2: Obesity risk assessment using the ABC system: sum of Anthropometric criteria (A), Edmonton/Disease Stage Criteria (B), Cardiovascular Criteria (C).

PwO, person with obesity; BMI, body mass index; WC, waist circumference, IR, insulin-resistance; CV, cardiovascular; ASCVD, atherosclerotic cardiovascular diseases; HF, heart failure; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, Metabolic dysfunction-associated steatohepatitis; OSAS, obstructive sleep apnea syndrome

AOM prioritization criteria – the RO score

Given the high prevalence of obesity, a novel risk stratification system is proposed to guide prioritization of pharmacotherapy, in particular in settings where coverage is in place – the RO score (Obesity Risk), based on anthropometric criteria (BMI, waist circumference [WC], waist-to-height ratio), Edmonton staging and European Society of Cardiology (ESC) cardiovascular risk (Figure 2).

Incretin-mimetic medication

Incretin-mimetic medication. General mechanisms of action

Incretin-mimetic medication approved for the treatment of obesity includes GLP-1 receptor agonists (GLP-1 RA) — liraglutide and semaglutide — and the dual GLP-1/GIP agonist tirzepatide.

GLP-1 RAs induce weight loss through central effects (appetite reduction, increased satiety, modification of food preferences) and peripheral effects (delayed gastric emptying, glucose-dependent insulin secretion, adipose tissue modulation, cardiovascular and renal protection, reduction of hepatic steatosis and systemic anti-inflammatory effects). The dual GLP-1/GIP agonist combines these effects with those mediated by GIP on appetite, insulin secretion and lipogenesis [7].

Incretin-mimetic medication – agents, administration

Three incretin-mimetic AOMs are approved by the European Medicine Agency (EMA) and available in Romania (Table 1).

Incretin-mimetic medication – effects on anthropometric parameters and risk factors

As semaglutide and tirzepatide are the most widely used AOM, they are discussed in detail (Tables 2A and 2B); for liraglutide, only comparative data are presented. For efficacy data, Semaglutide Treatment Effect in People with Obesity (STEP)-1, STEP-UP, and A Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight (SURMOUNT-1) trials were considered the most relevant. All included patients with obesity, or overweight and at least one complication and used semaglutide up to 2.4 mg, semaglutide up to 7.2 mg and tirzepatide up to 15 mg, respectively [8–10]. Data on quality of life, behavioral regulation and physical functioning for semaglutide and tirzepatide were obtained after reviewing relevant studies [8, 11–14].

Incretin-mimetic medication – effects on obesity complications

An important aspect in AOM selection is the effect on obesity complications, including prevention, remission or improvement. Table 3 summarizes the evidence for semaglutide and tirzepatide and includes phase III trials with obesity complications as primary outcome [15–25].

Incretin-mimetic medication – contraindications, adverse effects and precautions; lifestyle adaptation to reduce adverse effects

Contraindications of incretin-mimetics are personal or family history of medullary thyroid carcinoma, personal history of MEN2 syndrome (multiple endocrine neoplasia) and pregnancy, women planning to become pregnant, or breastfeeding [1].

The most common adverse effects are gastrointestinal (nausea, diarrhea, constipation, dyspepsia, vomiting), generally dose-dependent and diminishing during treatment. Initiating with low doses and slow titration reduces these effects. Rarer adverse effects: gallstones and acute pancreatitis. Patients should seek emergency care in case of severe abdominal pain. Rare reports of suicidal ideation have been noted but not confirmed in large studies [1, 2].

Renal and hepatic impairment

Table 4 presents treatment with semaglutide and tirzepatide in patients with renal and hepatic impairment.

Muscle and bone effects

Marked and rapid weight loss (>4 kg/month) is associated with reduction in muscle mass and bone density. Resistance exercise, adequate protein intake (1.2–1.5 g/kg/day) and regular assessment of muscle mass/muscle strength are recommended [26].

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Table 1: Main characteristics, SmPC indications and mode of administration of incretin-mimetic medication.

A. Characteristics and indications according to the SmPCs		
Molecule	**Formulation**	**SmPC indications**
Liraglutide (Saxenda®)	Solution for injection in a pre-filled pen; one pre-filled pen contains 18 mg of liraglutide in 3 mL	**Adults** Saxenda is indicated as an adjunct to a hypocaloric diet and increased physical activity for weight loss in adult patients with a BMI of: • ≥30 kg/m² (obesity), or • ≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity, including impaired glycaemic control (prediabetes or type 2 diabetes mellitus), arterial hypertension, dyslipidaemia, or obstructive sleep apnoea. Treatment with Saxenda should be discontinued after 12 weeks of treatment at a dose of 3.0 mg/day if patients have not achieved a weight loss of at least 5% of their initial body weight. **Adolescents (≥12 years)** Saxenda may be used as an adjunct to a healthy diet and increased physical activity for weight loss in adolescent patients aged 12 years and older with: • Obesity, defined as a BMI corresponding to ≥30 kg/m² in adults, according to international cut-off points*, and • Body weight above 60 kg. Treatment with Saxenda should be discontinued and re-evaluated if patients have not lost at least 4% of their BMI score or BMI z-score after 12 weeks of treatment at a dose of 3.0 mg/day or at the maximum tolerated dose. https://www.ema.europa.eu/en/documents/product-information/saxenda-epar-product-information_en.pdf

Table 1: Continued.

A. Characteristics and indications according to the SmPCs		
Molecule	**Formulation**	**SmPC indications**
Semaglutide (Wegovy®)	Wegovy FlexTouch solution for injection in a pre-filled pen; each pen contains 4 doses (ranging from 0.5 to 2.4 mg per dose, according to the dose-escalation steps)	**Adults** Wegovy is indicated as an adjunct to a hypocaloric diet and increased physical activity for body weight management, including weight loss and weight maintenance, in adults with an initial BMI of: • ≥30 kg/m² (obesity), or • ≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity, such as dysglycemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia, obstructive sleep apnoea, or cardiovascular disease. For study results regarding cardiovascular risk reduction, obesity-related heart failure, and the studied populations, see section 5.1 of SmPC. **Adolescents (≥12 years)** Wegovy is indicated as an adjunct to a hypocaloric diet and increased physical activity for body weight management in adolescents aged 12 years and older with: • Obesity* and • Body weight above 60 kg. Treatment with Wegovy should be discontinued and re-evaluated if adolescent patients have not achieved a reduction in BMI of at least 5% after 12 weeks of administration at a dose of 2.4 mg, or at the maximum tolerated dose. *Obesity (BMI ≥95th percentile), as defined in sex- and age-specific BMI growth charts (CDC.gov) https://www.ema.europa.eu/en/documents/product-information/wegovy-epar-product-information_en.pdf
Tirzepatide (Mounjaro®)	Solution for injection in a pre-filled pen (KwikPen); each pen contains 4 doses (ranging from 2.5 to 15 mg per dose, according to the dose-escalation steps)	Mounjaro is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial body mass index (BMI) of: • ≥30 kg/m² (obesity) or • ≥27 kg/m² to <30 kg/m² (overweight) with at least one weight-related comorbidity (*e.g.* arterial hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus). https://www.ema.europa.eu/en/documents/product-information/mounjaro-epar-product-information_en.pdf

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Table 1: Continued.

B. Incretin-mimetic medication administration	
Molecule	**Doses and method of administration**
Liraglutide (Saxenda®)	Saxenda is administered subcutaneously only. It must not be administered intravenously or intramuscularly. Saxenda is administered once daily, at any time of the day, independent of meals. It should be injected into the abdomen, thigh, or upper arm. The injection site and timing may be changed without dose adjustment. However, it is preferable that Saxenda be injected at approximately the same time each day, once the most convenient time of day has been chosen. The starting dose is 0.6 mg once daily. The dose should be increased to 3.0 mg once daily in increments of 0.6 mg, with intervals of at least one week between dose escalations, in order to improve gastrointestinal tolerability. If escalation to the next dose level is not tolerated for two consecutive weeks, discontinuation of treatment should be considered. A daily dose higher than 3.0 mg is not recommended. If a dose is missed within 12 hours of the usual time of administration, the patient should administer the dose as soon as possible. If there are less than 12 hours until the next scheduled dose, the missed dose should not be administered, and the patient should resume the once-daily dosing regimen with the next scheduled dose. A double dose should not be taken, and the dose should not be increased to compensate for a missed dose. https://www.ema.europa.eu/en/documents/product-information/saxenda-epar-product-information_en.pdf
Semaglutide (Wegovy®)	Wegovy is administered subcutaneously. Wegovy is administered once weekly, at any time of the day, with or without food. It is injected subcutaneously into the abdomen, thigh, or upper arm. The injection site may be rotated. Wegovy must not be administered intravenously or intramuscularly. The weekly dosing day may be changed, if necessary, provided that the interval between two doses is at least 3 days (>72 hours). After selecting a new dosing day, once-weekly administration should be continued. The maintenance dose of 2.4 mg semaglutide once weekly is reached starting from an initial dose of 0.25 mg. To reduce the likelihood of gastrointestinal adverse events, the dose should be escalated over a 16-week period to the maintenance dose of 2.4 mg once weekly (dose-escalation steps: 0.25–0.5–1.0–1.7–2.4 mg). In the event of significant gastrointestinal symptoms, delaying dose escalation or reducing the dose to the previous level until symptoms improve should be considered. Weekly doses greater than 2.4 mg are not recommended. Optional higher dose: 7.2 mg once weekly, after ≥4 weeks on 2.4 mg (adults with BMI ≥30 kg/m^2 at treatment initiation). Administer as 3 consecutive SC injections of 2.4 mg into the same body area, separated by ≥5 cm. https://www.ema.europa.eu/en/documents/product-information/wegovy-epar-product-information_en.pdf

Table 1: Continued.

B. Incretin-mimetic medication administration	
Molecule	**Doses and method of administration**
Tirzepatide (Mounjaro®)	Mounjaro is administered by subcutaneous injection into the abdomen, thigh, or upper arm. The dose may be administered at any time of the day, with or without food. Injection sites should be rotated with each dose. If the patient also administers insulin, Mounjaro should be injected at a different injection site. The initial dose of tirzepatide is 2.5 mg once weekly. After 4 weeks, the dose should be increased to 5 mg once weekly. If necessary, doses may be increased in 2.5 mg increments after a minimum of 4 weeks at the current dose. The recommended maintenance doses are 5 mg, 10 mg, and 15 mg. The maximum dose is 15 mg once weekly. If a dose is missed, it should be administered as soon as possible, within 4 days of the missed dose. If more than 4 days have elapsed, the missed dose should not be administered, and the next dose should be given on the scheduled day. In all cases, patients may subsequently resume the usual once-weekly dosing schedule. https://www.ema.europa.eu/en/documents/product-information/mounjaro-epar-product-information_en.pdf

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Table 2A: Benefits on anthropometric parameters and effects on cardiovascular risk factors for semaglutide and tirzepatide.

Parameter	Semaglutide (STEP-1 trial) [8]	Semaglutide (STEP UP trial) [9]	Tirzepatide (SURMOUNT-1 trial) [10]
% body weight reduction	-14.9% *vs.* 2.4% placebo at 68 weeks	-17.5% (2.4 mg) -20.7% (7.2 mg) *vs.* -2.4% placebo at 72 weeks	-15.0% (5 mg) -19.5% (10 mg) -20.9% (15 mg) *vs.* 3.1% placebo at 72 weeks
% of patients achieving ≥10% body weight reduction	69.1% *vs.* 12% with placebo	75.1% (2.4 mg) 82.4% (7.2 mg) *vs.* 20.5% with placebo	68.5% (5 mg) 78.1% (10 mg) 83.5% (15 mg) *vs.* 18.8% with placebo
Waist circumference	–13.54 cm *vs.* –4.13 cm with placebo	-14.6 cm (2.4 mg) -17.5 cm (7.2 mg) *vs.* -5.9 cm with placebo	-14.0 (5 mg) -17.7 (10 mg) -18.5 (15 mg) *vs.* -4.0 with placebo
Change in total fat mass	–3.48 *vs.* -0.19 with placebo (percentage points) –8.36 kg *vs.* –1.37 kg	-25.1% (pooled semaglutide) *vs.* -0.9% with placebo -24.3% (percentage points)	-33.9% *vs.* -8.2% with placebo (absolute values)
Change in lean body mass	+3.04 *vs.* +0.09 with placebo (percentage points) –5.26 kg *vs.* –1.83 kg	Lean body volume change by -6.7% with pooled semaglutide *vs.* 0.2% with placebo	Fat mass/lean mass ratio decreased more with tirzipatide *vs.* placebo
Systolic and diastolic blood pressure (SBP and DBP) – values adjusted for placebo effect	SBP -5.1 mm Hg DBP -2.4 mm Hg	SBP (*mm Hg*) -8.7 (2.4 mg) -9.9 (7.2 mg) DBP (*mm Hg*) -3.0 (2.4 mg) -4.5 (7.2 mg)	SBP (*mm Hg*) -5.8 (5 mg) -7.0 (10 mg) -6.4 (15 mg) DBP (*mm Hg*) -4.2 (5 mg) -4.5 (10 mg) -3.6 (15 mg)
Lipid parameters – values adjusted for placebo effect	Total cholesterol: -5.93% LDL: -6.55% Triglycerides: -18.34%	Total cholesterol: -5% (both 2.4 and 7.2 mg) LDL: -7% (both 2.4 and 7.2 mg) HDL: +6% (2.4 mg) and +8% (7.2 mg) Triglycerides: -16% (2.4 mg) and -23% (7.2 mg)	Total cholesterol: -3.1% LDL: -4.2% HDL: +8.8% Triglycerides: -20.3%

Note: In SURMOUNT-5 [14] open-label trial a direct comparison between semaglutide and tirzepatide showed that after 72 weeks, the weight loss was –20.2% with tirzepatide 10 or 15 mg and –13.7% with semaglutide at maximum tolerated dose (1.7 or 2.4 mg). No direct comparison is available with semaglutide 7.2 mg.

Nutritional disorders

Nutritional deficiencies (vitamins D, B12; iron, calcium, magnesium) can occur in patients treated with AOM due to lower food intake. No routine monitoring is recommended for all users of AOMs. Clinical orientation should be used to guide the type and frequency of micronutrient testing. Supplementation should be recommended in case of proven deficiency [26, 27].

Lifestyle adaptation

Includes caloric and qualitative adjustment of diet – with an adequate protein intake (1.2–1.5 g/kg/day), adequate hydration, daily aerobic and resistance

Table 2B: Benefits on quality of life, behavioral regulation and physical functioning for semaglutide and tirzepatide.

Parameter	Semaglutide	Tirzepatide
Quality of life	SF36 – improvement IWQOL-Lite-CT – improvement [8]	SF36 – improvement (all doses) IWQOL-Lite-CT – improvement (all doses) [11]
Physical functioning	SF36 – improvement IWQOL-Lite-CT – improvement [8]	SF36 v2 – improvement (all doses) IWQOL-Lite-CT – improvement (all doses) [11]
Effects on food craving	Improvement [12]	Improvement [13]

Note: SF-36 – 36-Item Short Form Health Survey; IWQOL-Lite-CT – Impact of Weight on Quality of Life-Lite Clinical Trials Version.

exercise, restful sleep, self-monitoring of weight, waist circumference, blood glucose, blood pressure and bowel habits, and periodic quality of life assessment [26, 27].

Special circumstances: anesthesia, planning of a pregnancy

For surgical interventions under general anesthesia, there is an additional aspiration risk due to delayed gastric emptying. Consensus recommendations include stopping GLP-1 RAs at least one week before elective surgery, or longer if GI symptoms are present. Post-anesthesia, treatment can be resumed. For details, consult the AGA-ASMBS-ASA guidelines [28]. Post-anesthesia, treatment can be resumed, but no clear duration can be specified before medication is restarted. For details, refer to the Multisociety clinical practice guidance for the safe use of glucagon-like peptide-1 receptor agonists in the perioperative period [28].

Table 3: Effects on obesity complications semaglutide and tirzepatide.

Complication	Semaglutide	Tirzepatide
MACE risk	20% reduction in MACE in patients with established atherosclerotic CVD after 40 months of treatment [15]	Under evaluation SURMOUNT-MMO trial: https://clinicaltrials.gov/study/NCT05556512 (phase 3 trial)
HFpEF	KCCQ-CSS score (-placebo) +7.8 points [16]	KCCQ-CSS score (-placebo) +9.8 points 38% reduction in HF worsening events or CV death at 104 weeks [17]
Prediabetes	81% reversion to normoglycaemia *vs.* 14% with placebo after 52 weeks [18]	93% reduction in T2DM risk after 176 weeks [19]
Diabetes (HbA1c)	-1.2% (-placebo) [20]	–1.6% (10 mg) (-placebo) –1.6% (15 mg) (-placebo) [21]
MASH (metabolic steatohepatitis)	MASH remission without worsening of fibrosis: 62.9% *vs.* 34.3% placebo Fibrosis improvement without worsening of steatohepatitis: 36.8% *vs.* 22.4% placebo [22]	Phase 2 trial showing improvements [23]
OSA: change in AHI (-placebo)	No studies available	Patients not using PAP: –20.0 events/hour Patients using PAP: –23.8 events/hour [24]
Knee osteoarthritis: WOMAC pain score (-placebo)	Improvement of 14.2 points [25]	No studies available

Note: MACE – major adverse cardiovascular events (CV death, non-fatal MI, non-fatal stroke); OSA – obstructive sleep apnoea; AHI – Apnea Hypopnea Index; PAP – positive airway pressure; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index.

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Table 4: Semaglutide and tirzepatide in patients with renal and hepatic impairment.

Semaglutide	Tirzepatide
No dose adjustment is required in patients with mild or moderate renal impairment and in those with mild or moderate hepatic impairment. Semaglutide is not recommended in patients with severe renal impairment (eGFR<30 ml/min/1.73 m^2), including patients with end-stage renal disease and in patients with severe hepatic impairment (due to limited experience) and should be used with caution in patients with mild or moderate hepatic impairment. https://www.ema.europa.eu/en/documents/product-information/wegovy-epar-product-information_en.pdf	No dose adjustment is required in patients with renal impairment, including end-stage renal disease (ESRD) but experience with the use of tirzepatide in patients with severe renal impairment and ESRD is limited. Caution is recommended when treating these patients with tirzepatide. No dose adjustment is required in patients with hepatic impairment. Experience in patients with severe hepatic impairment is limited and caution is recommended when treating these patients with tirzepatide. https://www.ema.europa.eu/en/documents/product-information/saxenda-epar-product-information_en.pdf

Women of childbearing potential should use contraceptive methods during treatment with AOM. If a patient attempts a pregnancy, or pregnancy occurs, semaglutide and tirzepatide should be discontinued. Semaglutide should be discontinued at least 2 months and tirzepatide at least 1 months before a planned pregnancy due to their long half-life [29].

Other classes of AOM limited use

Orlistat is a specific inhibitor of gastrointestinal lipases and is approved in combination with diet in patients with a BMI ≥30 kg/m^2 or BMI ≥28 kg/m^2 with associated risk factors. The contraindications are hypersensitivity, chronic malabsorption syndrome,

Table 5: Obesity pharmacotherapy: effects on weight loss.

Medication	Mean reduction from initial weight (%)	Percentage of patients losing ≥5% of body weight *vs.* placebo
Liraglutide 3 mg	5.4	63.2 *vs.* 27.1
Orlistat	3.8	50.5 *vs.* 30.7
Naltrexone/bupropion combination	4.8	48 *vs.* 16
Setmelanotide	12.5–25 (depending on genetic variant)	64–90 (depending on genetic variant)

Table 6: AOM selection based on obesity complications [3, 4].

Complication	Molecules with evidence (randomized trials)
Prediabetes	Liraglutide, semaglutide, tirzepatide
Diabetes remission	Liraglutide, semaglutide, tirzepatide
MACE	Semaglutide (pre-existing established atherosclerotic CVD)
HFpEF	Semaglutide, tirzepatide
MASH	Semaglutide, (tirzepatide – phase 2 trial only)
SAS	Tirzepatide
Knee osteoarthritis pain remission	Semaglutide

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Algorithm: Selection of Anti-Obesity Medications

PwO (BMI ≥30 or ≥27 + comorbidities) → **EVALUATION** → **DECISION FOR PHARMACOTHERAPY**

WITHOUT COMPLICATIONS

Goals: ↓ fat mass, BMI, WC • Prevention • ↓ CV risk • ↑ QoL

Parameter	Liraglutide	Semaglutide	Tirzepatide
Weight loss ↓	Modest	High (>20%)	High (>20%)
↓ WC, ↓ fat mass	✓	✓	✓
↓ Blood pressure	✓	✓	✓
↓ Lipid parameters	✓	✓	✓
↑ Quality of life	—	✓	✓
↑ Physical function	—	✓	✓
Craving regulation	—	✓	—

Order reflects EMA approval sequence for obesity treatment

WITH COMPLICATIONS OF OBESITY

Goal: Reversibility / improvement • Select by evidence per complication

Complication	Liraglutide	Semaglutide	Tirzepatide
Prediabetes	✓	✓	✓
T2DM (HbA1c ↓)	✓	✓	✓
MACE / ASCVD	—	✓	—
HFpEF	—	✓	✓
MASH	—	✓	—
OSA	—	—	✓
Knee osteoarthritis	—	✓	—

In PwO with multiple complications, prioritise the most severe prognosis

Evidence colour coding: ✓ Phase III RCT | Phase II RCT | Under evaluation | — No dedicated studies

FORO = Romanian Obesity Forum Only incretin-mimetic molecules included, other AOM classes are of restricted use. Molecules listed by EMA approval order for ob esity treatment.

ASCVD, atherosclerotic CV disease; BMI, body mass index; CV, cardiovascular; HFpEF, heart failure with preserved EF; MACE, ma jor adverse CV events; MASH, metabolic dysfunction -associated steatohepatitis; OSA, obstructive sleep apnoea; PwO, person with obes ity; QoL, quality of life; RCT, randomised controlled trial; T2DM, type 2 diabetes; WC, waist circumference

Figure 3: Treatment algorithm for persons with obesity, according to FORO.

cholestasis, breastfeeding. Treatment discontinuation is recommended if at least 5% of prior weight has not been lost after 12 weeks [30].

Naltrexone/bupropion combination inhibits appetite through naltrexone, a mu-opioid receptor antagonist, and bupropion, a weak inhibitor of neuronal reuptake of dopamine and norepinephrine. It is indicated in combination with diet in adult patients with a BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with associated risk factors (type 2 diabetes mellitus, dyslipidaemia or controlled hypertension). It is contraindicated in case of hypersensitivity, uncontrolled hypertension, seizures, neuropsychiatric instability, monoamine oxidase (MAO) inhibitor use, and pregnancy. Treatment discontinuation is recommended if at least 5% of prior weight has not been lost after 16 weeks [31].

Setmelanotide is a melanocortin-4 receptor agonist associated with increased satiety signaling in the central nervous system. It is approved for the treatment of obesity and hunger control associated with biallelic pro-opiomelanocortin (POMC) deficiency, confirmed by genetic testing, including PCSK1 deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children aged ≥6 years. It is contraindicated in case of hypersensitivity. Setmelanotide is administered in daily subcutaneous injections, in doses starting at 0.5 mg and up-titrated to 3 mg, according to age, weight, clinical response, and tolerability [32].

The mean reduction from initial weight and the percentage of patients losing ≥5% of body weight is presented in Table 5, as reported in SmPC [30–32].

Evidence synthesis and AOM choice based on the presence/absence of complications

A. PwO with complications

Selection will be made based on existing evidence for each molecule regarding its effect on each complication (Table 6). In POB with multiple complications, the complication with the most severe prognosis should be considered. Figure 3 presents the algorithm for selecting incretin-based AOM according to the available phase III randomized-controlled studies (RCTs).

B. PwO without complications

For PwO without complications, the choice will be guided by effects on anthropometric parameters, quality of life, physical functioning, prevention of complications and the safety profile (Figure 3). Weight loss effects correspond to the maximum approved doses – liraglutide 3 mg, semaglutide 7.2 mg and tirzepatide 15 mg.

C. PwO pre- or post-metabolic surgery

AOM can be used pre-operatively to reduce body weight and post-operatively in case of weight regain. Given the existence of gastrointestinal changes, close monitoring is required [2–4].

D. Pharmacotherapy during the maintenance period and for complication management

AOMs can also be administered to maintain the new weight. Since obesity is a chronic disease, treatment should be considered long-term; discontinuation can lead to weight regain [2–4].

Conclusion

These recommendations are intended to aid clinicians' decision in the selection of PwO who might benefit from AOM and to guide the use of these medications. They are in line with current international guidelines addressed to pharmacotherapy of obesity and will be updated periodically according to new evidence that will be published regarding existing and newly-approved molecules for the treatment of obesity.

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Conflict of interest

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