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Framework for the pharmacological treatment of obesity and its complications from the European Association for the Study of Obesity (EASO)

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Obesity and associated complications can be managed by obesity medications, prompting the revision of criteria for the diagnosis and staging of this disease.

Obesity is a multifactorial, chronic, relapsing, non-communicable disease marked by dysfunctional and/or excessive accumulation of body fat[1]. Obesity has direct negative effects on the functioning of individual organs, the whole body, or both[2], and serves as a gateway to a wide range of obesity-related complications[3,4]. Complications can be broadly classified into two categories: those that result from altered and pathological mechanical forces, referred to as 'fat mass disease', and those associated with dysregulated metabolic, endocrine, inflammatory and immune responses, known as 'sick fat disease'[3].

The management of obesity should not be limited to weight loss alone but should instead adopt a holistic approach that includes the prevention, resolution or improvement of complications, enhanced mental well-being, physical fitness, social functioning, and overall health and quality of life[1]. Pillars of obesity management are represented by behavioral modifications (including therapeutic nutrition, therapeutic physical activity, stress reduction and sleep improvement), with the possible addition of psychological support, obesity management medications, and metabolic or bariatric (surgical and endoscopic) procedures[1].

The number of medications available to treat obesity has been steadily increasing in recent years and is expected to continue growing, offering clinicians a wider selection of agents with distinct modes of action to be used alongside lifestyle interventions[5]. As different medications vary in their efficacy for total weight loss and their effects on obesity-related complications, personalized therapy based on individual patient characteristics has become both feasible and necessary. Following a synthesis of scientific evidence about the effects of medications on total weight loss and complications, the algorithm proposed here is intended to assist clinicians in guiding obesity disease treatment by aligning each patient's health background with the action profiles of the available medications[6].

Any treatment algorithm inevitably involves simplification and is limited by the available evidence at a given point in time. In line with the new European Association for the Study of Obesity (EASO) framework for defining obesity[1], we used the presence or absence of complications as the primary factor to guide the strategy for selecting the treatment (Fig. 1). Each individual medication was therefore evaluated based on its effectiveness in promoting total weight loss, its impact on complications, and its safety profile.

Although the proposed treatment algorithm reflects the shared expert opinions and clinical experience of the authors, it is firmly grounded in current scientific evidence, synthesized through formal meta-analyses of all relevant randomized controlled trials that assess the effectiveness of obesity management medications, following rigorous methodological standards. It is important to highlight that the present treatment algorithm incorporates scientific evidence published up to 31 January 2025[6]. Given the rapid evolution of evidence-based treatments for obesity, periodically updating this algorithm based on new and robust data is essential to ensure that the treatment strategy remains aligned with the most current scientific understanding.

Body weight management in obesity

In individuals without established complications, total weight loss remains an important primary goal of treatment to reduce the risk of incident complications[7]. All approved medications significantly reduce body weight in comparison with placebo, which is a regulatory requirement for their approval by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). However, the efficacy in total weight loss is different across medications. In available trials, both tirzepatide and semaglutide resulted in a total weight loss of >10% versus placebo, whereas orlistat, naltrexone–bupropion, liraglutide, and phentermine–topiramate had smaller effects[6] (Table 1).

Available data on the long-term safety of medications is also heterogeneous; specific data on cardiovascular safety are available, at present, only for naltrexone–bupropion and semaglutide. In addition, data are still insufficient on more rare serious adverse events (such as some forms of cancer[8]) in the longer term. Tolerability also differs across medications. Because the main side effects are different for each class (diarrhea for orlistat[9], nausea, vomiting and constipation for GLP-1 and dual GLP-1/GIP receptor agonists[10], and so on), a formal meta-analysis comparing non-serious adverse events could not be performed.

On the basis of the results of clinical trials included in the traditional and network meta-analyses[6], tirzepatide and semaglutide should be considered the medications of choice when a substantial total body weight loss is required. By contrast, a broader range of agents may be

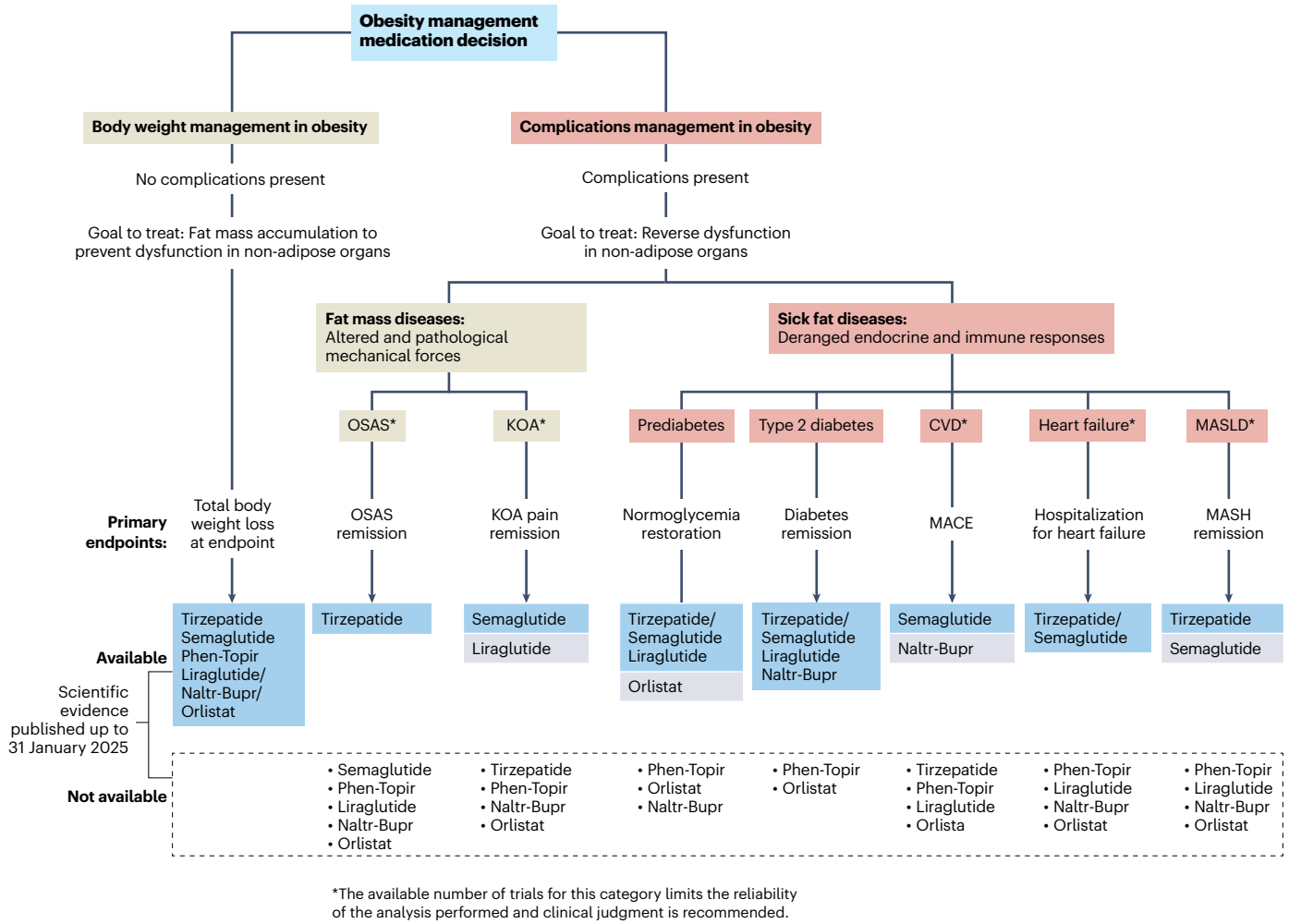

Fig. 1 | Treatment algorithm from the EASO for individuals with obesity. The treatment algorithm is based on the presence or absence of relevant obesity-related medical conditions. The algorithm is grounded in scientific evidence available up to 31 January 2025. Obesity management medications are listed in order of efficacy. Medications with equivalent or comparable efficacy are listed in the same position. Asterisks indicate that the available number of trials for this category limits the reliability of the analysis performed and clinical judgment is recommended. Color coding reflects statistical significance: blue shading indicates statistically significant effects; gray shading denotes obesity medications tested without significant effects. CVD, cardiovascular disease; KOA, knee osteoarthritis; Naltr-Bupr, naltrexone–bupropion; Phen-Topir, phentermine–topiramate.

appropriate for individuals whose treatment goal involves a more moderate degree of weight loss. It is important to highlight that the evidence supporting the use of medications is very limited for individuals with a body mass index (BMI) over 40 kg m^{-2} and entirely lacking for those with a BMI below 27 kg m^{-2}.

Management of complications in obesity

In individuals with established complications, the selection of the most appropriate medications should be guided by the demonstrated improvement or remission of complications. The effect of medications on obesity-related complications is heterogeneous and not always proportional to the degree of total weight loss, potentially reflecting direct pharmacological actions beyond weight reduction alone. Therefore, the present treatment algorithm has been developed based on a synthesis of scientific evidence on the effects of medications on specific complications[6], incorporating data available up to 31 January 2025, and aligned with the conceptual distinction between fat mass disease and sick fat disease.

1. Fat mass diseases

1.1 Obstructive sleep apnea syndrome (OSAS)

Data from randomized controlled trials (RCTs) specifically designed for the assessment of the effects on OSAS in individuals with obesity ($n = 1$) are available only for tirzepatide[6]. Tirzepatide is associated with a higher resolution of OSAS[6] (Table 1) and induced a clinically significant reduction in the apnea–hypopnea index. Tirzepatide should be considered as the first-line treatment for patients with obesity and OSAS (Fig. 1).

1.2 Knee osteoarthritis

Two RCTs were performed specifically in individuals with obesity and knee osteoarthritis examining liraglutide and semaglutide, respectively[6]. Our meta-analysis[6] showed that semaglutide

Table 1 | Primary endpoints for each subgroup of patients

			Primary endpoint	Orlistat	Naltr-Bupr	Liraglutide	Phen-Topir	Semaglutide	Tirzepatide
Obesity management medication decision	**Body weight management in obesity**	**No complications present**	Total body weight loss (%)						
			At endpoint	3.0[a]	4.8[a]	4.2[a]	8.8[a]	8.7[a]	16.5[a]
			At 52 weeks	2.1	4.8[a]	7.0[a]	8.8[a]	10.7[a]	14.8[a]
			At 53–104 weeks	2.8[a]	4.8[a]	4.3[a]	8.8[a]	10.1[a]	16.5[a]
	Complications management in obesity	**Fat mass diseases**							
		OSAS	OSAS remission (OR)	NA	NA	NA	NA	NA	2.9[a]
		KOA	KOA improvement (WMD)	NA	NA	NA	NA	−8.6[a]	NA
		Sick fat diseases							
		Pre-diabetes	Normoglycemia restoration (OR)	NA	NA	3.25[a]	NA	19.6[a]	8.3[a]
		Type 2 diabetes	Diabetes remission (OR)	NA	2.3[a]	6.8[a]	NA	12.3[a]	15.6[a]
		Cardiovascular disease	MACE incidence (OR)	A	0.88	NA	NA	0.78[a]	NA
		Heart failure	Hospitalization for heart failure (OR)	NA	NA	NA	NA	0.23[a]	0.45[a]
		MASLD	MASH remission (OR)	NA	NA	NA	NA	2.0	11.8[a]

Data obtained from the network metanalysis[6]. KOA improvement refers to a reduction in knee pain and/or improvement in physical functioning assessed using any validated questionnaire. NA, information not available; OR, subtracted-placebo Mantel–Haenszel odds ratio; WMD, subtracted-placebo weighted mean difference. [a]Statistically significant result ($P < 0.05$).

resulted in greater pain reduction than liraglutide (Table 1). Semaglutide should be considered as the first-line treatment for patients with obesity and knee osteoarthritis (Fig. 1).

2. Sick fat diseases

2.1 Prediabetes and type 2 diabetes

We retrieved three and eleven trials specifically designed in patients with prediabetes and diabetes, respectively[6]. Tirzepatide, semaglutide, liraglutide, and, to a lesser extent, naltrexone–bupropion provided significant improvement in glycemic parameters and variable rates of type 2 diabetes remission[6] (Table 1). Tirzepatide, semaglutide and liraglutide also reduced the incidence of progression to type 2 diabetes in individuals with overweight/obesity and pre-diabetes[6] (Table 1). Tirzepatide and semaglutide should be prescribed as first-choice medications and liraglutide and naltrexone–bupropion as second-line treatments in individuals with obesity and glycemic alterations (Fig. 1).

2.2 Cardiovascular disease

There are two RCTs available specifically designed to examine cardiovascular outcomes using semaglutide and naltrexone–bupropion, respectively[6]. Our meta-analysis[6] has shown a significant reduction in the incidence of major adverse cardiovascular events (MACE) in individuals with previous cardiovascular events treated with semaglutide; whereas naltrexone–bupropion did not show any significant cardiovascular benefits[6]. Semaglutide should be recommended in individuals with previous cardiovascular disease (Fig. 1).

2.3 Heart failure

There are three trials performed in patients with previous heart failure (two with semaglutide and one with tirzepatide)[6]. Our meta-analysis[6] suggests that these two medications reduce the risk of hospitalizations caused by heart failure (Table 1) in patients with both preserved and reduced ejection fraction[6]. Data collected are, however, still insufficient to provide individual recommendations for these two distinct conditions. Tirzepatide and semaglutide should be considered first-line treatments in patients with heart failure (Fig. 1).

2.4 Metabolic dysfunction associated steatotic liver disease

Only two trials have been retrieved on individuals with metabolic dysfunction associated steatotic liver disease (MASLD) (one with semaglutide and one with tirzepatide)[6]. Only tirzepatide (Table 1) has demonstrated a significant effect on resolution of metabolic dysfunction-associated steatohepatitis (MASH) and liver fibrosis improvement (that is, resolution of MASH without worsening of fibrosis and a reduction of at least one fibrosis stage without worsening of MASH). Semaglutide has shown a reduction in liver fat content, but not a statistically significant improvement in liver fibrosis or remission of MASH[6]. Notably, the phase 3 ESSENCE trial, not included in the present algorithm because it was published after 31 January, 2025, showed that semaglutide was associated with a significant improvement in MASH and liver fibrosis[11] similar to tirzepatide. At present, we recommend the use of tirzepatide for individuals with obesity and MASLD (Fig. 1).

Economic considerations

Obesity medications are generally considered expensive and have limited insurance coverage, making them less affordable for many individuals. In fact, some medications, such as tirzepatide and semaglutide, are effective but costly, with significant effect on healthcare budgets[12]. However, despite their high cost, medications can lead to cost savings in direct medical expenses per patient per year[13]. Recent policies have aimed to improve affordability and access to medications, such as capping out-of-pocket payments and allowing government negotiation of drug prices[14]. However, these efforts are still evolving and may not fully address affordability. In this context, the cost of not treating obesity and adipose tissue dysfunction at early stages — thus enabling the progression to complications and end-organ damage — should be weighed equally in health policy and clinical decision-making.

Future considerations

It is important to note that most medications have not been specifically evaluated for the treatment of individual complications, resulting in gaps in our understanding of their full therapeutic potential. Although some benefits may be inferred based on the degree of total body weight loss – given the well-documented positive effect of total weight loss on various complications – direct evidence for many conditions remains limited. Nevertheless, there is growing potential for medications to positively influence a broader range of complications, including chronic kidney disease, neurodegenerative disorders, polycystic ovary syndrome, certain cancers, and mental health conditions[15].

In the context of personalized medicine and the evolving understanding of obesity as both a fat mass disease and a sick fat disease, the framework for the use of medications proposed by EASO in this Comment reinforces the importance of tailoring therapy to address obesity and obesity-related medical conditions. It provides guidance to clinicians based on the current scientific evidence, developed from a systematic review and network meta-analysis of published clinical trials[6]. This approach aligns with the concept of obesity as an adiposity-based chronic disease, distinguishing between factors primarily associated with fat mass and those linked to dysfunctional (or 'sick') fat[3].

Tailoring treatment to the individual is a complex task that must consider several factors, including the severity of adiposity, the presence and extent of complications, comorbidities and concurrent therapies. Socioeconomic context, patient values, expectations, and personal goals must also be considered. Although no treatment algorithm can replace the nuanced clinical judgment required for such comprehensive assessments, this tool can serve to support therapeutic decision-making in obesity. Given the rapid advances in the field of medications, EASO intends to update the present treatment algorithm regularly to incorporate the latest available evidence.

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