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ARTICLE

Beyond weight loss: the gap in current drug development for obesity

Current obesity drug development remains overly focused on short-term weight reduction, despite obesity being a chronic, multifactorial disease. Broader, mechanism-driven approaches are needed to ensure durable efficacy, safety and accessibility.

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There is a somewhat narrow focus on relative weight loss when it comes to drug development for obesity. Obesity treatment requires far more than

achieving short-term rapid weight loss. Obesity is a chronic disease, similar to hypertension and type 2 diabetes, but is also heterogenous and multifactorial to a greater extent than other metabolic diseases.

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The development of incretin-based therapies has revolutionised obesity treatment, offering unprecedented efficacy. There are currently six approved anti-obesity medications (AOMs) which have been shown to decrease weight (compared to placebo) in the range of three to 17 percent (Table 1). Similar or greater weight loss seems to be achievable with future products that may be on the market in the next few years. However, it is important to look beyond the relative weight loss observed in clinical trials. Most patients will not have access to the same support as those in clinical trials, and as treatment will be long-term it must be affordable, safe and improve overall health.

Table 1. Approved¹ medications, sorted according to overall mechanism of action.

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Medication	Placebo adjusted relative weight loss	The most prevalent side-effects (prevalence) ²
Targeting CNS specifically		
Phentermine-topiramate (oral)	7.8%	Paresthesia (tingling, 20%) Dry mouth (19%) Constipation (16%)
Naltrexone-bupropion (oral)	6.4%	Nausea (33%) Constipation (19%) Headache (18%)

Targeting the gut-brain axis (eg, GLP-1 and GIP receptor agonists)		
Liraglutide (injectable)	4.5%	Nausea (39%) Diarrhoea (21%) Constipation (19%)
Semaglutide (injectable ³)	12.4%	Nausea (44%) Diarrhoea (30%) Vomiting (24%)
Tirzepatide (injectable)	17.8%	Nausea (32%) Diarrhoea (23%) Vomiting (13%)
Targeting local gastrointestinal systems		
Orlistat (oral)	3%	Oily spotting (27%) Flatus with discharge (24%) Faecal urgency (22%)

¹ Approved by FDA and EMA except phentermine-topiramate, which is approved by FDA and a few European countries

² FDA label

³ Oral semaglutide for weight management is under review by the FDA.

The main problem with obesity is not yet solved

The majority of patients that initiate medical treatment (some form of glucagon-like peptide-1 (GLP-1) receptor agonist-related therapy), discontinue treatment within the first year¹ – mainly due to cost, but also side-effects and lack of treatment effect. External and internal weight stigma alongside insufficient insight regarding obesity are likely also important factors.

When obesity treatment is withdrawn, the underlying pathophysiology reasserts itself with regained weight,^{2,3} predominantly as increased fat mass.⁴ This is identical to when patients discontinue antihypertensive or lipid-lowering medications, ie, blood pressure and cholesterol levels typically return to pathological ranges. Aside from the psychological burden of multiple failed attempts to achieve sustained weight loss and considering it as an impossible mission,⁵ this regain has detrimental metabolic consequences beyond the simple return of weight. There is often a higher fat-to-muscle ratio than before the start of treatment⁶ and weight cycling (repeated loss/regain or 'yo-yo

dieting') is associated with metabolic dysfunction, an increased risk of type 2 diabetes and cardiovascular disease.^{7,8}

Cost – the main barrier for treatment discontinuation

Although prices for AOMs have dropped significantly, incretin mimetics such as the peptide drugs semaglutide and tirzepatide still cost around \$500 per month. Generic versions of the GLP-1 receptor agonist liraglutide have started to be launched, but without any major changes in price. The high cost of treatment is partly driven by expenses related to clinical development and manufacturing and is further amplified by sustained high demand and limited supply of GLP-1 receptor agonist drugs on the market. Despite the expectation that more products would lead to lower prices, there are no clear indications that future launched products will be dramatically cheaper. Thus, the treatment cost for most current and coming AOMs will likely be beyond reach for most patients with obesity.

Side effects and lack of efficacy as important additional obstacles

Recent clinical trials using incretin-based therapies, where dose-titration is regulated and there is limited room for individualisation, have seen a substantial portion of participants experience side-effects such as nausea, vomiting and constipation – despite the intense lifestyle support provided. In clinical practice, where the possibility of more intense lifestyle support is limited, one can stretch out the dose-escalation and decrease the prevalence of at least nausea and vomiting, but still a fair number of patients cannot overcome the side effects. Furthermore, as obesity is a heterogenous disease, a sizeable minority experiences no or minimal treatment effect, even with the coming highly effective treatments or with bariatric surgery.

Long-term safety –uncertainties for most treatments

Despite incretin-based therapy (DPP4-inhibitors and GLP-1 receptor analogues) having been used for diabetes treatment for a long time, the doses employed in obesity treatment are far higher, with clinical use only dating back to [late 2014 with the approval of Saxenda](#). Furthermore, prior to the launch of Wegovy the prescription rate of AOMs was very low. Now, as AOM use is more prevalent, side effects that were not picked up in clinical trials are emerging. Less frequent side effects will only be detected after launch, such as the [increased suicide rate observed with rimonabant](#) or the [increased cancer rate seen with lorcaserin](#). Of the approved products, orlistat (Table 1), has the longest clinical experience as it was launched globally almost 30 years ago. Probably due to its negligible systemic uptake, the occurrence of serious adverse events is rare.

The treatment gap in obesity

Using hypertension as an example of another chronic metabolic disease, there are currently 61 approved drugs, distributed in seven different classes of medications (Figure 1).

This affords the possibility of various combinations to maximise treatment effects and minimise side effects; it also enables more personalised treatment. The treating physician can adjust medication depending on achieved treatment effect but also side-effect profile; usually a combination of different medications is used. In contrast, there are around 56 medications in late-stage development for obesity, which are unevenly distributed in around seven different classes. More than 75 percent of projects are in the class 'Gut-brain axis' (Figure 1).

This skewed distribution of approved and coming medications is associated with specific problems:

1. The medications within the 'gut-brain axis' have an overlapping side-effect profile, with a substantial portion of patients suffering from initial nausea/vomiting as well as persistent constipation. Changing to another medication within the same class will most likely not improve tolerability. Unfortunately, there is also some side-effect overlap with approved non-gut-brain medications, namely constipation and nausea (Table 1). However, combining drugs with agents that have different side-effect profiles (eg, locally acting agents or medications targeting other pathways) may be a solution.
2. Given that a fair percentage of patients do not respond to gut-brain medications, changing to another medication within the same class is unlikely to improve efficacy. However, combining or replacing with agents targeting other pathways may increase treatment success. In addition, companion diagnostics and personalised treatment approaches are being developed to identify likely responders earlier to reduce time spent on ineffective therapies.⁹
3. A reduction in appetite typically leads to a decrease in overall food quantity; however, for many patients, this does not necessarily translate into improved meal quality. Consequently, the risk of malnutrition and micronutrient deficiencies may increase. Locally acting enzyme inhibitors – such as the approved lipase inhibitor orlistat (marketed as Xenical) and the late-stage investigational combination EMP16 (orlistat and acarbose) – may encourage patients to select higher-quality, more nutrient-dense meals. They also have a different route of action and different side effects, enabling combination with other classes to improve efficacy and minimise side effects.

Essentially, the lack of diversity will severely limit the ability to individualise treatment, eg, by combining different medications, as it will be problematic to combine medications within the same class.

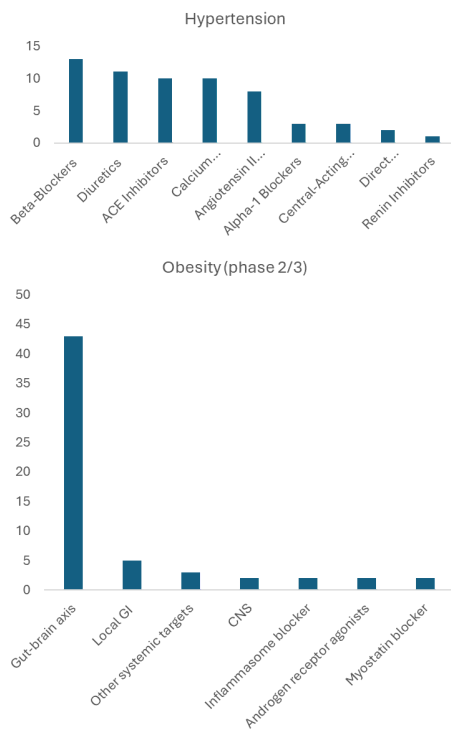


Figure 1: Hypertension and obesity, distribution of medications depending on overall mechanism of action.

Future perspectives

As obesity is a chronic and heterogenous disease, there is a need to expand the treatment toolbox to provide different medications for different patients. The current emphasis on incretin-based therapies and novel chemical entities, while transformative, does not fully address the core challenge of obesity: the need for inclusive, sustainable and broadly accessible treatment strategies. Incretin-based drugs have demonstrated remarkable efficacy in weight reduction, yet they are not suitable or tolerable for all patients.

We suggest that a substantial 'zone of development' exists beyond incretin-based therapies that warrants far greater scientific and clinical investment. Expanding research into alternative mechanisms, innovative delivery systems and reformulations of established drugs will be essential to building a more resilient therapeutic landscape. Combining therapies (such as Wegovy (semaglutide), gut-brain, and EMP16 (orlistat and acarbose), local GI) – either to lower treatment costs (lower dose of expensive peptide drug), improve efficacy or mitigate adverse events – should be more widely employed. With a diversified pipeline – spanning both established and novel approaches – effective, safe and with diverse side effects, sustainable treatments can be made available to the full spectrum of individuals living with obesity.

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Meet the authors



Ulf Holmbäck is Associate Professor in Clinical Nutrition and Metabolism at Uppsala University. He has been in the nutrition and obesity fields as a researcher and educator for almost 30 years.



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Conflicts of Interest

Ulf Holmbäck, Stefan Grudén and Anders Forslund have equity interests in Empros Pharma AB, which develops the anti-obesity medication EMP16, and have acted as consultants for the company. Ulf Holmbäck, Stefan Grudén and Anders Forslund are patent holders for EMP16.

