GLP-1 Receptor Agonists and the Path to Sustainable Obesity Care

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As of 2024, more than 1 billion people are estimated to be living with obesity worldwide.[1] The glucagon-like peptide-1 receptor agonist (GLP-1RA) and closely related glucose-dependent insulinotropic polypeptide (GIP/GLP-1) dual agonist medication classes offer a promising strategy to treat obesity and prevent its downstream health complications. However, the optimal use of these medications is currently hindered by many unanswered questions, ranging from how best to select the optimal patients for treatment to their long-term effects to how to manage their costs. Among these is an increasingly urgent concern about the coverage and optimal treatment duration of GLP-1RAs at obesity dosing and evidence-based approaches to off-ramping, defined as the tapering or withdrawal of a GLP-1RA after this treatment period and its replacement by an alternative approach to weight maintenance.

The science behind obesity care begins with the acknowledgment that obesity is a chronic disease. Although not a single entity, obesity therefore often requires some form of lifelong intervention, much like hypertension or diabetes. Several studies have shown that complete withdrawal of an obesity treatment dose of a GLP-1RA without other structured care leads to weight regain in most people.[2] However, it remains unclear whether lifelong treatment of obesity should always consist of GLP-1RAs at full obesity dosing or whether a range of alternative strategies can enable some subset of people with obesity to maintain their weight loss after a limited duration of initial treatment, followed by tapering, discontinuing, or off-ramping these agents.

Off-ramping strategies may include, alone or in various combinations: (1) prescribing lower or less frequent doses of a GLP-1RA until achieving a regimen that allows for weight maintenance; (2) continuing older, cheaper, well-tolerated weight loss medications; and (3) offering lifestyle support programs with a focus on structured physical activity or diet.[3] There are preliminary data that support the possible efficacy of these off-ramping approaches and several early studies that are being pursued to test them. First, a 2024 meta-analysis of more than 48 000 people from 132 clinical trials showed that phentermine-topiramate was among the most effective medications for obesity for achieving sustained weight loss of 5% or more, even as GLP-1RAs led to a greater overall magnitude of weight loss; this effectiveness suggests

a potential role for phentermine-topiramate in off-ramping.[4] Second, a small 2024 randomized clinical trial compared weight regain following cessation of several weight maintenance strategies. This study from Denmark began with an 8-week lifestyle intervention for all, after which participants were randomized to one of four 52-week regimens (placebo, GLP-1RA alone, supervised exercise alone, and GLP-1RA plus supervised exercise). This study showed that 52 weeks after cessation of all treatment (ie, 52 weeks of therapy plus 52 weeks without any further treatment), more than 63% of the GLP-1RA plus supervised exercise combination group had maintained 5% or more weight loss and 45% of those had maintained greater than 10% weight loss.[5] Far fewer (33% and 16%, respectively) in the GLP-1RA alone group sustained this weight loss. Thus, exercise may be an important component of treatment itself and may play a role in off-ramping. Finally, interventions targeting dietary behaviors and food environments, such as Food is Medicine, in which healthy food is provided with the goal to prevent, manage, or treat specific clinical conditions, or group-based nutrition education, have been suggested as additional lifestyle approaches that warrant testing in off-ramping strategies.[3]

There are both health and economic motivations to study off-ramping. First, not all people with obesity will be able to tolerate or adhere to long-term GLP-1RA therapy. Additionally, loss of lean muscle mass alongside weight loss on GLP-1RAs may not maximize health in all patients and little is known about the long-term effects of changes in body composition. Moreover, the economic implications of off-ramping are significant. For most people with obesity, long-term therapy with GLP-1RAs is anticipated to remain inaccessible due to high medication pricing and strong patent protections.[6] Even in the wealthiest nations, such as Denmark, insurers have been forced to limit coverage of GLP-1RAs for people with obesity due to high costs. In the US, if all eligible adults received a GLP-1RA, the cost would approximately equal that of all other prescription drug spending combined. Hence, the ability to treat some people for shorter periods and then maintain weight loss via a lower-cost strategy could have significant budget implications; however, future decreases in drug prices may affect this economic motivation for off-ramping.

Thus, a range of important questions remain that define a clear research agenda for the optimal duration of GLP-1RA therapy and these activities should be prioritized by public funders, such as the National Institutes of Health and the Patient-Centered Outcomes Research Institute. Such studies will lead to a better understanding of the possible approaches and health consequences of off-ramping (Table).

Table. Key Questions and Research Needs in Tapering Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs)

Key question	Research needs
Which patients with obesity can safely off-ramp from GLP-1RAs?	• RCTs of off-ramping strategies that enroll diverse populations • Heterogeneity analyses in both RCTs and observational databases to determine in whom off-ramping allows for sustained weight loss
If off-ramping is feasible in some people, at what point in therapy is this appropriate or optimal for sustained weight reduction?	RCTs to compare varied treatment durations (eg, until weight loss plateaus or until a threshold of weight loss) with GLP-1RAs prior to initiating off-ramping
Given the benefits of GLP-1RAs for cardiometabolic risk reduction, what are the health implications of off-ramping and how will possible fluctuations in body weight affect those benefits?	• Include detailed collection of cardiometabolic risk markers and body composition in RCTs of off-ramping strategies • Include collection of older medications for obesity that lack sufficient data on cardiometabolic effects in all relevant off-ramping RCTs • Collect and analyze cardiometabolic outcomes in observational studies of those who discontinue or interrupt GLP-1RAs
What is the most effective way to maintain weight loss after off-ramping from a GLP-1RA?	• RCTs of off-ramping strategies, including use of older medications for obesity or exercise with lower or less frequent doses of GLP-1RAs • RCTs of permutations of these strategies with complete withdrawal of GLP-1RAs • RCTs that compare weight training with aerobic exercise vs a combination of these activities • RCTs that incorporate Food is Medicine as another potential off-ramping strategy

Abbreviation: RCT, randomized clinical trial.

This research agenda must include diverse populations, the presence of various social determinants of health that may hinder scalability or contextual adaptation, and the presence of medical comorbidities, such as chronic HIV infection or use of weight gain–inducing medications like antipsychotics. These trials should assess not only weight and cardiometabolic measures but also general health indicators, such as body composition (particularly lean muscle mass and visceral fat), physical function, and quality-of-life end points.[7] Implementation science research will be needed to translate trial results into feasible clinical algorithms. Finally, for those people in whom lifelong treatment of obesity with a GLP-1RA is the best or only reasonable treatment option, there is a pressing need to increase affordability and access and support adherence.

Although we remain far from a world in which obesity care is available to all who need it, GLP-1RAs have given us a novel tool to make that vision a reality. Although this landscape is fast moving, evidence to define the appropriate duration of therapy and optimal strategy for tapering, discontinuing, or off-ramping GLP-1RAs where able will be a critical next step on this path to sustainable, global access to obesity care.

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