Residency Review

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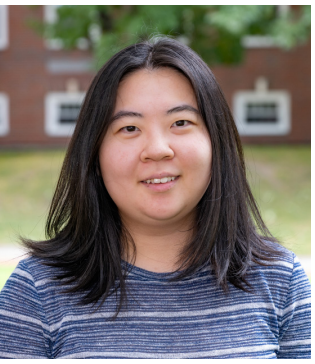

A Shot at Something Different: Exploring Alternative GLP-1 Dosing

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Obesity remains one of the most prevalent chronic health conditions in the United States and is associated with substantial morbidity and mortality. It is also strongly associated with numerous comorbid conditions, including type 2 diabetes, cardiovascular disease, multiple types of cancer, infectious complications, and poorer surgical outcomes.[1] With more than 40% of U.S. adults meeting criteria for obesity (BMI ≥ 30 kg/m^2), the condition continues to impose a considerable clinical and economic burden, with annual medical costs exceeding $170 billion.[2,3] In response, a new wave of weight-loss medications has transformed the treatment landscape, with the widespread use of GLP-1–based therapies playing a major role in this shift.

In the 2026 American Diabetes Association (ADA) Standards of Care, glucagon-like peptide-1 (GLP-1) receptor agonists and the dual-glucose dependent insulinotropic peptide (GIP)/GLP-1 are recommended as preferred pharmacologic therapies for people living with diabetes and obesity. The guidelines recommend prioritizing glucose-lowering therapies that are weight neutral or associated with weight loss. Semaglutide and tirzepatide are identified as preferred options because they provide greater weight-loss efficacy than other glucose-lowering therapies.[10] However, patient access to these agents remains challenging. Supply shortages have disrupted access for some patients, while high out-of-pocket costs, often exceeding $1,000 per month without insurance, make these medications unattainable for many who may benefit from them.[4]

As concerns about access, costs and long-term treatment burden persist, interest in alternative dosing regimens has grown, particularly as patients and clinicians consider strategies to support sustained weight loss over time. Given the growing discussion surrounding alternate approaches, it is important to examine the limited but emerging evidence on alternative dosing strategies for continued weight loss and weight maintenance. Several recent studies have begun to explore whether dose reduction, dose spacing, or other nontraditional regimens may help maintain weight loss and improve accessibility for patients. In this newsletter, alternative dosing refers broadly to off-label regimens that differ from manufacturer-recommended dosing, including reduced doses and extended dosing intervals. Findings of weight regain after discontinuation of GLP-1 therapy have further increased interest in alternative maintenance strategies as possible ways to sustain treatment benefit over time.

Emerging Evidence for Alternative Dosing Strategies

Available evidence on alternative GLP-1 dosing strategies includes pharmacokinetic modeling and small patient-based studies examining whether nontraditional regimens can help preserve weight-loss effects over time. Collectively, these reports offer early insight into the potential role of reduced frequency and lower-dose maintenance approaches.

Rather than evaluating patient outcomes directly, Cengiz and colleagues used mathematical modeling to estimate whether less frequent GLP-1 receptor agonist dosing could preserve weight-loss benefit at a lower cost.[5] Using prior clinical trial data, they modeled how alternative semaglutide and tirzepatide dosing schedules might affect weight loss and projected how broader use of these regimens could influence obesity prevalence and mortality in the U.S. population. For semaglutide 2.4 mg, dosing every 2 weeks instead of weekly was predicted to reduce average weight loss from 17% to 12%, suggesting retention of about 72% of the benefit despite half the total drug exposure. Similar findings were observed with tirzepatide, with approximately 75% of the weight-loss benefit retained across the 5 mg, 10 mg, and 15 mg doses.[5]

Beyond theoretical modeling, small clinical reports have also explored whether less frequent GLP-1 receptor agonist dosing may help preserve weight loss. Wu and colleagues described two patients who maintained substantial weight reduction despite less frequent dosing.[6] In the first case, a man in his 30s with prediabetes and a baseline weight of 285 pounds (BMI 37.6 kg/m^2) experienced medication shortages and began spacing tirzepatide doses every 10 to 14 days. His weight decreased to 212 pounds and was later maintained at 210 to 212 pounds on this schedule. In the second case, a woman in her 50s with type 2 diabetes, obesity, and multiple comorbidities had a baseline weight of 180 pounds (BMI 32.9 kg/m^2). After intermittent dosing related to shortages, she reached a lowest weight of 126 pounds and later maintained a weight of 134 to 139 pounds while also sustaining improved glycemic outcomes.

Taken together, these earlier reports suggest that reduced-frequency dosing may be feasible in select patients. Wong et al later provided additional clinical data in the retrospective case series *Reduced-Frequency GLP-1 Therapy Maintains Weight, Body Composition, and Metabolic Syndrome Improvements*, offering a broader evaluation of reduced-frequency dosing outcomes.[7] This retrospective case series evaluated whether patients who had reached a weight-loss plateau on weekly semaglutide or tirzepatide could maintain their weight loss after transitioning to reduced-frequency dosing. Maintenance dosing included injection intervals of every 10 to 14 days, every 2 weeks, and greater than every 2 weeks. Thirty adults were evaluated after transitioning from weekly GLP-1 therapy to reduced-frequency dosing once a weight-loss plateau was reached. During weekly GLP-1 dosing, patients' mean body weight decreased from 193.4 pounds before treatment to 161 pounds at the plateau time point, representing an average 17.2% reduction. After transitioning to reduced-frequency maintenance dosing, patients generally maintained this weight loss over follow-up, with mean body weight remaining stable at 159.3 pounds.[7]

Limitations

Current evidence on alternative GLP-1 dosing remains preliminary and should be interpreted with caution. The available literature includes mathematical modeling, isolated case reports, and retrospective case series rather than prospective, randomized trials, limiting the ability to determine whether reduced-frequency dosing itself is responsible for maintained weight loss. Across the published reports, dosing schedules are also highly variable, ranging from every 10 to 14 days to every 2 weeks or longer, and patients often differ in medication type, dose, duration of therapy, and reasons for de-escalation. The interpretation of these findings is further limited by the presence of concurrent dietary, exercise, and behavioral changes, which make it challenging to isolate the independent effect of alternative dosing on weight loss outcomes. Another limitation is that the current literature focuses mainly on short-term maintenance in selected patients who had already responded well to GLP-1 therapy. It remains unclear how broadly these findings can be applied or whether reduced-frequency regimens can reliably sustain weight loss over longer periods.

Alternative GLP-1 dosing regimens fall outside current FDA-approved labeling and are not endorsed by major clinical organizations (see Table 1). The American Association of Clinical Endocrinologists (AACE) does not recommend reduced doses or extended dosing intervals that fall outside manufacturer-recommended labeling, emphasizing that current support for these practices remains largely anecdotal and that there is insufficient peer-reviewed evidence to establish safety or efficacy. AACE recommends adherence to FDA-approved dosing guidance and considers these alternative regimens to fall outside standard evidence-based prescribing recommendations.[8] In contrast, the American Diabetes Association (ADA) notes that individualized dose adjustment outside standard titration may be considered in select patients to improve tolerability, particularly when slower dose escalation is needed because of gastrointestinal adverse effects or other barriers to standard titration. However, the ADA presents this as a patient-specific, off-label strategy requiring careful selection, counseling, and monitoring rather than a broadly recommended alternative dosing approach.[9]

Although alternative GLP-1 dosing strategies have attracted growing interest in the setting of persistent barriers to long-term treatment, their place in obesity management remains uncertain. Their emergence highlights an important challenge in contemporary weight management. Even highly effective therapies may have limited impact if patients cannot maintain them over time. Early findings suggest that reduced-frequency dosing may help some patients preserve weight-loss benefits after an initial response to therapy, but the evidence remains preliminary and these strategies should still be approached cautiously. At present, alternative dosing is best understood not as a replacement for standard therapy, but as a sign of the growing demand for treatment approaches that balance clinical benefit with long-term practicality. As GLP-1–based therapies continue to reshape obesity management, further study is needed to clarify whether alternative maintenance strategies may have a safe and appropriate role in select patients. This will be especially important as clinicians work to reconcile the substantial benefits of these agents with the practical challenges that can limit long-term use in everyday care.

Table 1. Professional and Regulatory Positions on Alternative GLP 1 Dosing

Organization	Standard (Approved) Use	Position on Alternative Dosing
American Diabetes Association (ADA)[9,10]	Recommended pharmacotherapy in appropriate patients; semaglutide and tirzepatide emphasized due to superior weight-loss efficacy.	May consider individualized dose adjustment in select patients; not recommended as routine practice.
American Association of Clinical Endocrinologists (AACE)[8]	Supports evidence-based prescribing of FDA-approved GLP-1 therapies.	Does not support routine alternative dosing; recommends adherence to labeled dosing.
U.S. Food and Drug Administration (FDA)[11]	Approved GLP-1 products should be used according to labeled indications and dosing.	Use according to FDA-approved labeling; does not support alternative doses or dosing intervals outside the prescribing information.

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