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BRIEF CUTTING EDGE REPORT

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Less frequent dosing of GLP-1 receptor agonists as a viable weight maintenance strategy

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Abstract

Objective: Incretin mimetics are revolutionizing obesity treatment, but high prices and supply shortages limit patient access. Some clinicians have suggested less frequent dosing as an off-ramping strategy to maintain weight loss, but this approach lacks published evidence regarding its weight loss efficacy. We aim to provide such clinical evidence and to rationalize these results with mathematical modeling.

Methods: We present a real-world case series of two patients who took their incretin mimetic less frequently than recommended. We complement this case report with a pharmacokinetic-pharmacodynamic model of virtual patients that simulates long-term weight change with semaglutide and tirzepatide administered at various frequencies.

Results: Both real-world and virtual patients maintained significant weight loss under reduced dosing frequencies. Our results indicate that reducing frequency does not commensurately reduce efficacy. The majority of weight loss persists even when patients wait 2, 3, or perhaps even 4 weeks between doses.

Conclusions: Our findings support the hypothesis that less frequent administration of incretin mimetics can be a viable and cost-saving long-term weight maintenance strategy in conjunction with sustained lifestyle modification. Further research is warranted to validate the effectiveness of this off-label approach, define optimal dosing regimens to meet individual patient needs, and evaluate the cost–benefit implications.

INTRODUCTION

The incretin mimetics semaglutide and tirzepatide (also referred to as glucagon-like peptide-1 [GLP-1] receptor agonists) have upended the treatment paradigm of obesity. Meta-analyses of randomized controlled trials have indicated that semaglutide and tirzepatide facilitate an average placebo-adjusted body weight (BW) loss of 15.0% and 19.2% [1], respectively, compared with the 5% to 10% of older generation antiobesity medications (AOMs) [2].

These benefits must be weighed against their high cost, which can exceed $1000 monthly. Demand for these incretin mimetics has frequently outstripped their supply, leaving patients uncertain as to whether they will be able to fill their next prescription. Some have had to switch to alternative AOMs or stop entirely, whereas others have rationed their remaining supply. Although high costs and supply shortages might eventually subside, both issues still impede patient access to incretin mimetics.

We present two patients who maintained their BW loss despite less frequent dosing of their incretin mimetic to illustrate the potential

viability of such a strategy and then provide a pharmacokinetic-pharmacodynamic (PK/PD) model as a mathematical basis for why this may have been successful.

METHODS AND RESULTS

Case 1

A gentleman in his 30s presented initially with class II obesity and newly diagnosed prediabetes. Despite intermittent fasting and daily walks, his BW had risen to 285 lb (BMI = 37.6 kg/m^2) as of August 2021. Semaglutide was initiated in September 2021, which helped him reduce portion sizes and lose 40 lb over the next 6 months. Because of mild nausea and his desire to not overly suppress his appetite, he stayed on a low dose of 0.5 mg of semaglutide weekly for 9 months before increasing it to 1 mg weekly. With the BW loss, he reported a corresponding improvement in mood, energy levels, and snoring.

By midyear 2022, he began having difficulty reliably filling his semaglutide because of pharmacy supply shortages. At one point, he went 4 months without medication and avoided weighing himself so as not to focus on his weight. New stressors at work and in his personal life were also negatively impacting his mental health, eating habits, and exercise regimen. He benefited from a temporary switch to tirzepatide 5 mg weekly and, later, an increase in his semaglutide dose up to 1.7 mg once weekly, but the availability of both medications remained intermittent and unpredictable. His weight continued to fluctuate between 255 and 273 lb over the next year. By August 2023, he was taking tirzepatide at a higher dose of 7.5 mg, but he began self-administering it every 10 to 14 days to extend his limited supply of medication. Importantly, he felt his cravings were adequately suppressed between doses. Meanwhile, he resolved most of his prior stressors, managed to resume his daily walks and gym workouts three to four times per week, and started cooking at home more consistently to cut down further on his calorie intake. His BW steadily declined thereafter, dropping from 249 lb in September 2023 to 212 lb (BMI = 28.0) in April 2024. At his most recent follow-up in August 2024, he was confidently maintaining his BW at 210 to 212 lb.

Case 2

A woman in her 50s presented initially in March 2020 for management of uncontrolled type 2 diabetes. Her baseline hemoglobin A1c was 11.1%, and her medical history included class I obesity, hypertension, postpartum cardiomyopathy, and depression. She was previously on a Medtronic insulin pump between 2008 and 2017, but her mental health and glycemic control both deteriorated after a family tragedy in 2018. With renewed motivation, she worked closely with our diabetes care team to optimize her diet and insulin regimen and, within 2 months, was achieving excellent glycemic control on the Tandem t:slim X2 insulin pump (Tandem Diabetes Care, Inc.).

Study Importance

What is already known?

- Semaglutide and tirzepatide confer robust weight-lowering benefits, but their high cost greatly limits broader access and long-term affordability.
- Optimal strategies for weight loss maintenance to follow an initial period of incretin therapy are needed, but there is hitherto a lack of published literature to support the specific approach of dosing an incretin mimetic less frequently.

What does this study add?

- To our knowledge, this is the first case series to describe the clinical course and weight outcomes of two patients who self-administered their incretin mimetic less frequently than recommended.
- We provide a pharmacokinetic-pharmacodynamic model to explain why this off-label dosing strategy might have been successful for our patients and predict how patients might respond to a variety of alternative dosing frequencies.

How might these results change the direction of research or the focus of clinical practice?

- Our findings provide both anecdotal and mathematical evidence to suggest that reduced-frequency dosing of incretin mimetics is worth exploring further as an effective and cost-saving approach to long-term weight loss maintenance after an initial period of incretin mimetic therapy.

She started semaglutide in July 2021; we later switched to tirzepatide and gradually increased the dose to 15 mg weekly. Although she initially weighed 180 lb (BMI = 32.9) and required 90 to 110 units of insulin per day, her BW steadily dropped to 126 lb (BMI = 23.0), and we successfully weaned her off insulin entirely by January 2024. Unfortunately, ensuing supply shortages left her frequently managing without medication for weeks at a time while the "food noise" resurfaced. Even with only intermittent dosing, she has maintained her BW at 134 to 139 lb through October 2024 by also keeping to a reduced-carbohydrate diet and smaller portion sizes. Her latest hemoglobin A1c was 5.8%, and she remains off insulin.

Mathematical evidence

We now present results from a PK/PD model [3] to explain why less frequent dosing may be effective for long-term weight loss maintenance with incretin mimetics.

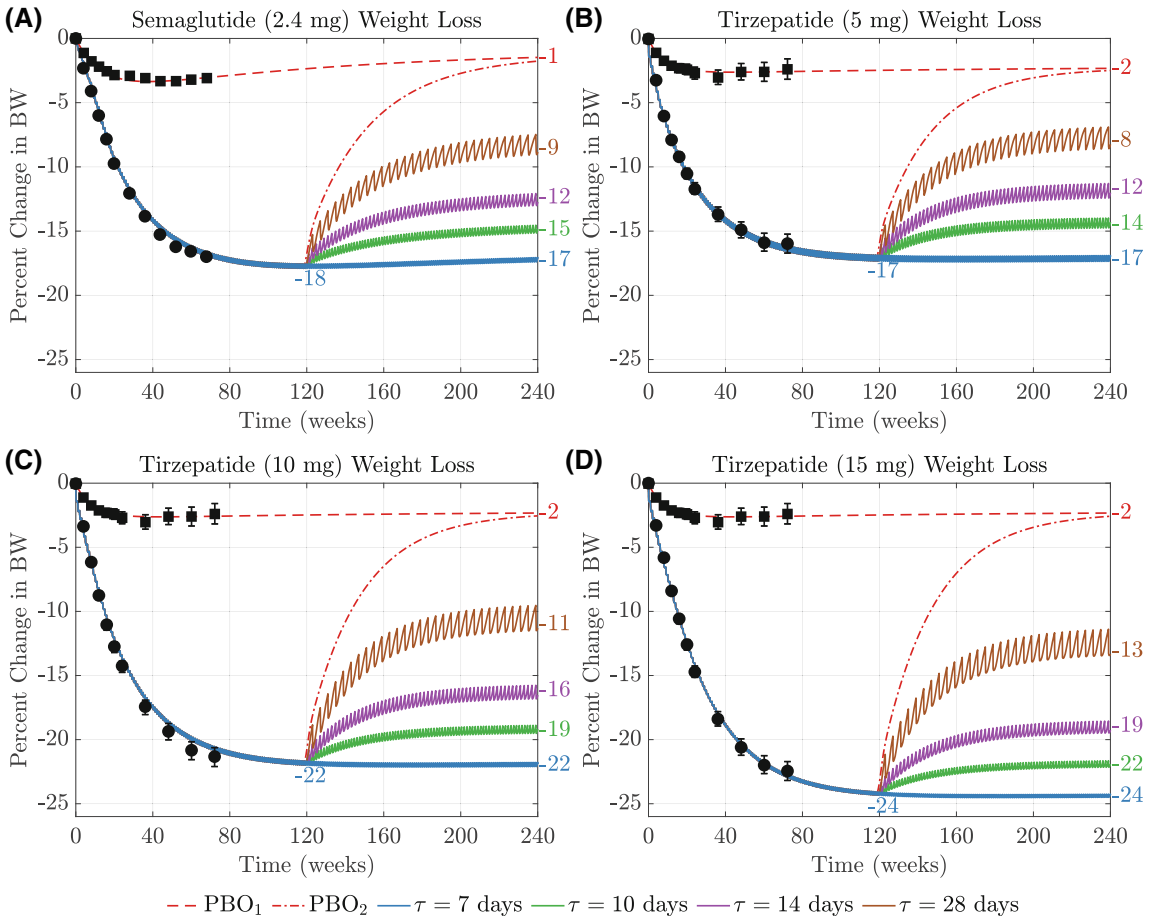

FIGURE 1 BW loss remains high after reducing dose frequency. After weight loss plateaus with once-weekly dosing, virtual patients increase their dosing interval (denoted τ) from 7 days to 10 days (green), 14 days (purple), or 28 days (brown) or retain a 7-day dosing interval (blue). The red dashed curve depicts a patient who is always on the placebo (PBO_1), and the red dot dashed curve depicts a patient who switches from once-weekly dosing to the placebo after weight loss plateaus (PBO_2). Black markers show weight loss data from Jastreboff et al. [7] (semaglutide in panel A) and Wilding et al. [6] (tirzepatide in other three panels) for the placebo (square markers) and the drug (circle markers). BW, body weight; PBO_1, patient always takes placebo; PBO_2, patient switches to placebo after 120 weeks on the drug. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Reducing dose frequency does not commensurately reduce BW loss.

Dosing interval	7 d	10 d	14 d	21 d	28 d
Dose frequency relative to once weekly, %	100	70	50	33	25
2.4-mg semaglutide BW loss relative to once weekly, %	100	86	72	58	50
5-mg tirzepatide BW loss relative to once weekly, %	100	84	68	54	46
10-mg tirzepatide BW loss relative to once weekly, %	100	88	74	59	50
15-mg tirzepatide BW loss relative to once weekly, %	100	90	78	63	54

Note: The final four rows indicate how the steady-state weight loss for various reduced-frequency dosing regimens compares to once-weekly dosing for different drugs and dose sizes. These percentages are calculated from Figure 1 by comparing the weight loss achieved at 240 weeks for a given dosing interval with that achieved at 240 weeks for a 7-day dosing interval. These percentages are notably higher than how their dose frequency compares with a 7-day dosing interval (first row).
Abbreviation: BW, body weight.

The PK parameters are from Strathe et al. [4] for semaglutide and from the US Food and Drug Administration [5] for tirzepatide. The PD parameters are estimated using data from Wilding et al. [6] for semaglutide and from Jastreboff et al. [7] for tirzepatide. See our previous study [3] for model details. Following previous studies [3–5], PK parameters do not change over time as the patient loses weight. We show in the online Supporting Information that incorporating such time-varying PK parameters only slightly affects model predictions. In the Supporting Information, we also discuss the effects of dose adjustments after a patient loses BW.

Semaglutide simulations assume once-weekly doses of 2.4 mg for 120 weeks (including the dose escalation in Wilding et al. [6]). After 120 weeks, various reduced dosing frequencies are implemented as follows: every 7, 10, 14, and 28 days, plus the placebo. Similarly, tirzepatide simulations assume once-weekly doses of 5 mg, 10 mg, or 15 mg for 120 weeks (including the dose escalation in Jastreboff et al. [7]), after which dosing matches the reduced frequencies used for semaglutide.

Figure 1 predicts the change in BW for these regimens. For each drug and dose size, BW initially decreases and then levels off after 120 weeks of once-weekly dosing. At 120 weeks, BW increases for virtual patients who reduce dosing frequency and plateaus by 240 weeks. As expected, lower dose frequencies reduce BW loss at 240 weeks. However, the reduction in BW loss is not proportional to the reduction in dose frequency. For instance, switching from one dose per week to one dose every 2 weeks reduces the steady-state BW loss from 17% to 12% for a 2.4-mg dose of semaglutide (Figure 1A). That is, switching from one dose per week to one dose every 2 weeks reduces the dose frequency by 50% but maintains 72% of the BW loss for semaglutide.

The percentages of BW loss maintained under various reduced frequencies are given in Table 1. Notice that high levels of BW loss are maintained when dose frequency is reduced. Indeed, even one dose per month may maintain half of the BW loss attained with one dose per week.

DISCUSSION

To our knowledge, this is the first case series to describe the clinical outcomes of patients taking incretin mimetics with extended intervals between doses to maintain weight loss. This was a strategy born out of desperation amid drug shortages, yet these patients maintained a large proportion of their weight loss with fewer overall doses. Our first patient deliberately self-administered tirzepatide 7.5 mg every 10 to 14 days and experienced an additional 13.7% reduction in BW over 7 months with maintenance thereafter. Incretin mimetic therapy enabled our second patient to lose 30% of BW and safely discontinue insulin; even when limited supplies of tirzepatide forced her to dose intermittently, she retained an overall 22.8% reduction in BW from baseline. Naturally, a larger case series is needed to determine how the success of these two individuals extends to other patients.

We believe a plausible explanation for their clinical response lies in the PK/PD models, which predict that less frequent dosing does not proportionally diminish treatment outcomes. Although more frequent dosing regimens lead to greater initial weight loss, our findings suggest that substantial long-term weight loss maintenance might still be achieved with reduced dosing frequencies. Naturally, this strategy does not lessen the importance of adhering to a hypocaloric diet and increased physical activity, and further clinical studies are needed to validate our findings and optimize dosing regimens for individual patient needs.

Incretin mimetics are indeed groundbreaking weight loss therapies, but, unless their costs come down substantially, our healthcare system cannot afford their indefinite use for weight maintenance in all people with obesity. Few may adequately maintain their weight loss through lifestyle modification alone; many others will need to consider alternative AOMs or incretin mimetic booster periods over time [8]. Although lacking broad clinical validation of long-term efficacy and tolerability, we propose that patients and providers also explore off-label reduced-frequency dosing of incretin mimetics as they navigate disruptions to the pharmaceutical supply chain and the financial burdens of prolonged incretin mimetic therapy. Indeed, for patients who cannot maintain once-weekly dosing indefinitely (perhaps because of financial constraints), reduced-frequency dosing is very likely preferable to discontinuing treatment altogether, which tends to erase most of the weight loss achieved with treatment [9, 10]. Investigating reduced-frequency dosing in clinical trials, such as one dose every 14 days, is a natural next step to validate this approach. Future studies are also needed to identify patient factors that predict a more favorable response to less frequent dosing of incretin mimetics and to examine the long-term clinical outcomes achieved through this approach compared with other off-ramping options (e.g., switching to alternative AOMs) [11].O

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in GitHub at https://github.com/seanlawley/glp1.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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