glp1 studies on 2 or 3 doses per week vs 1 weekly dose, use only animal, preclinical, clinical studies published in reputable journals, NO influencers, NO youtube, NO clinics

There are essentially no head-to-head trials directly comparing 1×/week vs 2–3×/week dosing of the *same* GLP-1 agonist, so current evidence is indirect and mostly models or observational data rather than classic RCTs answering your exact question.[1] [2] [3]

What has actually been studied

- Classical GLP-1 RAs (exenatide BID vs QW, liraglutide QD vs exenatide QW, etc.) compare *different molecules and half-lives* rather than different dosing schedules of the same drug.
    - DURATION-1 and DURATION-5 showed exenatide once weekly produced greater HbA1c reductions and similar weight loss to exenatide twice daily, consistent with the idea that a long-acting exposure profile is at least as good as, and often better than, multiple short-acting doses.[1]
- Long-acting analogs (dulaglutide, semaglutide, etc.) have been developed specifically so that a *single* weekly injection maintains therapeutic concentrations over 7 days (half-lives ~5–7 days), and all pivotal phase 2/3 programs used once-weekly schedules, not 2–3×/week.[4] [1]
- In preclinical work with newer long-acting GLP-1/glucagon or GLP-1/GIP/glucagon co-agonists, daily vs less-frequent dosing is often explored, but again this is comparing *short-acting daily* exposure to *long-acting once-weekly* exposure, not splitting a weekly long-acting dose into multiple injections.[5] [6]

The “alternative dosing” paper

- Cengiz et al., Diabetes Obesity and Metabolism 2025 (“Alternative dosing regimens of GLP-1 receptor agonists may reduce costs and maintain weight loss efficacy”) analyzes less-frequent GLP-1 RA use, primarily by modeling and real-world data, to ask whether you can extend the interval (e.g., q2wk) while preserving most efficacy.[2] [7] [3]
- The emphasis is on interval *extension* (weekly → every 2 weeks or longer) to reduce cost and burden, not on fractionating the weekly dose into 2–3 injections per week; there is no controlled clinical dataset of 2–3×/week vs 1×/week for the same molecule in this paper.[3] [2]

Clinical de-escalation data (less frequent than weekly)

These are useful only as context for how far you can stretch intervals, not for your specific 2–3×/week question.

- A small Scripps Clinic study (published in Obesity) followed patients who voluntarily reduced GLP-1 dose frequency after achieving target weight (q1wk → q2wk or even q6wk). Most maintained the majority of their weight loss and metabolic benefits on extended-interval dosing over ~36 weeks, though the study is small, non-randomized, and subject to selection bias.[8] [9]
- Again, this is every-other-week or less, not 2–3×/week; it suggests a *buffer* in exposure where you can drop frequency without immediate loss of effect, but it does not support any specific superiority of higher-frequency micro-dosing.[9] [8]

Pharmacology and what it implies about 2–3×/week

- Long-acting GLP-1 RAs like semaglutide and dulaglutide have flat PK with half-lives ~5–7 days; a single weekly injection already provides near-steady-state receptor exposure across the week.[1]
- Splitting a 1 mg weekly semaglutide dose into, say, 0.33 mg three times a week at the **same total weekly dose** is unlikely to materially increase time-above-threshold or AUC; it mainly alters the minor peaks and troughs, which are already modest with long-acting formulations.[4] [1]
- For short-acting exenatide, moving from BID to QW with an extended-release depot improved glycemic control, which argues that a smoother, more sustained exposure can outperform spikier multiple-daily dosing at similar or lower total dose.[1]

Taken together, the mechanistic and clinical data support that for long-acting GLP-1 RAs, 1×/week dosing at the approved weekly dose is already effectively "continuous," and there is no evidence that cutting that weekly dose into 2–3 injections improves weight loss, HbA1c, side-effect profile, or anything else.[4] [1]

Animal / preclinical evidence on dosing schedules

- Preclinical GLP-1 and co-agonist studies in DIO mice and rats usually compare once-daily vs less-frequent injections according to half-life, not 1×/week vs 2–3×/week for the same long-acting construct.[6] [10] [5]
- For example, NN1177 (long-acting GLP-1/glucagon co-agonist) and NN1706 (GLP-1/GIP/glucagon tri-agonist) regimens were designed so that each injection produces protracted exposure; efficacy is driven by *total* exposure and steady state, not by more frequent smaller doses.[5] [6]
- Liraglutide rodent work uses once-daily dosing (shorter half-life), showing strong effects on weight and glucose, but there are no robust rodent datasets where the *same* weekly exposure is divided into 2–3 injections vs one.[10]

Practical takeaways based on current literature

- For existing long-acting GLP-1 RAs (semaglutide, dulaglutide, exenatide QW, tirzepatide, etc.), the evidence base, including head-to-head trials and PK, is built around once-weekly dosing; there are no RCTs or high-quality preclinical studies demonstrating any advantage to 2–3×/week dosing at equivalent weekly exposure.[11] [4] [1]
- Limited clinical and modeling work suggests you can sometimes *lower* frequency (e.g., every 2 weeks) after weight loss without major regression in the short–medium term, but this is preliminary and not randomized.[2] [8] [3] [9]
- Given the long half-life and existing data, if anything, future trials are more likely to test *less* frequent than weekly maintenance dosing rather than more frequent micro-dosing of currently weekly drugs.[11] [2] [1]

Would you want me to focus next on PK modeling papers that simulate different semaglutide or tirzepatide schedules (e.g., same weekly AUC split into multiple injections) to see if anyone has done a formal exposure–response comparison, even if not tested clinically yet?

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# <q>no evidence that cutting that weekly dose into 2-3 injections improves weight l
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Tirzepatide's PK is dominated by its long half-life (~5 days) and slow absorption, so 2.0 mg once weekly and 0.5 mg four times weekly (same 2.0 mg/week) would have very similar weekly exposure and steady-state concentrations; there is no evidence that splitting the dose meaningfully improves efficacy or tolerability.[27] [28] [29]

Key PK facts for tirzepatide

- Half-life ≈ 5 days, supporting once-weekly dosing; after a single SC dose it absorbs over many hours and declines slowly.[27]
- Steady state is reached after about 4 weeks of once-weekly dosing, with relatively flat concentrations between injections thanks to this long half-life.[28] [29]
- Label and clinical program are built entirely around once-weekly administration, with no approved or trial-tested 3–4×/week regimens at the same weekly dose.[30] [28]

Conceptual PK comparison: 2.0 mg weekly vs 0.5 mg four times weekly

If total weekly dose is the same (2.0 mg):

- **AUC (total exposure per week):** AUC is largely proportional to total dose divided by clearance; four 0.5 mg injections and one 2.0 mg injection in the same week will yield essentially the same weekly AUC at steady state, because clearance and half-life are unchanged.[29] [27]
- **Cmax / trough:**
  - 2.0 mg once weekly gives a higher single Cmax and a slightly deeper trough before the next dose.

    - 0.5 mg four times weekly yields four smaller peaks with slightly higher troughs, but the amplitude of peaks and troughs is already modest due to the long half-life, so the difference in fluctuation is small.
- **Steady-state profile:** Because the dosing interval (weekly) is shorter than the half-life and you are at steady state, concentration-time curves overlap strongly; splitting to 4×/week adds minor smoothing but does not create a fundamentally different exposure pattern. [29] [27]

In other words, on a long-half-life drug like tirzepatide, changing from 2.0 mg once weekly to 0.5 mg four times weekly mainly trades one slightly higher peak for four slightly lower peaks; weekly AUC and average concentration $\bar{C}$ remain nearly identical.

Evidence base: what is and is not known

- Regulatory PK documents and reviews (e.g., StatPearls and label summaries) only evaluate once-weekly dosing; they do not report modeled or observed PK for 3–4×/week schedules at the same weekly dose.[28] [29]
- Clinical trials and systematic reviews focus on once-weekly regimens at different dose levels (5–15 mg), and compare tirzepatide against other once-weekly GLP-1 RAs, not against more frequent micro-dosing at equal weekly dose.[31] [32] [30]
- I could not find any animal, preclinical, or clinical study in a reputable journal that specifically reports PK curves for tirzepatide 2.0 mg once weekly versus 0.5 mg four times weekly; any comparison is therefore PK-theoretical, based on half-life and linear PK, rather than trial data.[30] [28]

Expected clinical implications from the PK

Given the similar AUC and average concentrations:

- **Weight and HbA1c:** With linear PK and PD, similar steady-state exposure implies similar efficacy for weight and glycemia at equal weekly dose; there is no reason from the PK alone to expect superior outcomes with 4×/week dosing.[28] [30]
- **GI side effects:** More frequent smaller doses might theoretically blunt the *very* early peak-related nausea, but tirzepatide's absorption is already slow, and clinical practice uses low-dose once-weekly titration rather than splitting maintenance doses; no data show that 4×/week at the same weekly dose improves tolerability.[30] [28]
- **Adherence and logistics:** Four injections per week versus one, with no proven benefit, would likely worsen adherence and goes against all current labeling and trial experience. [28]

If you want, next I can sketch an explicit one-compartment PK model (using the known half-life) to show approximate concentration–time curves for 2.0 mg weekly vs 0.5 mg four times weekly over several weeks.

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