

## References: A Weighty Issue: The Tricky GLP-1 Questions

Apovian, C. M., Aronne, L. J., Bessesen, D. H., McDonnell, M. E., Murad, M. H., Pagotto, U., Ryan, D. H., & Still, C. D. (2015). Pharmacological management of obesity: An Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism*, 100(2), 342–362. <https://doi.org/10.1210/jc.2014-3415>

- Science Note 4: Overweight vs Obesity and GLP-1 Eligibility

Aronne, L. J. (2024, July 3). *Obesity and the new science of weight loss*. ZOE.

<https://zoe.com/learn/obesity-with-dr-louis-j-aronne>

- On paper, overweight and obesity are separate categories.
- We're still waiting for time and data to answer that one.
- According to set-point theory, the brain and appetite-regulation ...
- hunger may increase, energy expenditure may remain lower and the body may continue defending a higher weight
- Approximately one in six people maintain at least 80% of their weight loss after discontinuing a GLP-1
- Remaining healthier than before treatment
- GLP-1 therapy for conditions such as Parkinson's disease, dementia, addiction and other neurological disorders
- The most common are nausea, vomiting, diarrhoea, constipation and indigestion
- Science Note 2: What Conditions Are GLP-1 Medications Used to Treat?
- Science Note 3: Are GLP-1s Treating the Root Cause or Just the Symptoms?
- Science Note 4: Overweight vs Obesity and GLP-1 Eligibility
- Science Note 7: Should we be worried about the long-term use of GLP-1s?

Bayat, Z., Daya, R., & Mahyoodeen, N. G. (2021). Cardiovascular outcome trials of GLP-1 receptor agonists and SGLT2 inhibitors. *South African General Practitioner*, 2(3), 100–104.

<https://doi.org/10.36303/SAGP.2021.2.3.0073>

- Help regulate blood sugar by improving insulin function and reducing glucagon release
- Slow the rate at which food leaves the stomach
- GLP-1 medications are used alongside lifestyle interventions to improve weight loss and reduce the health risks associated with excess adiposity
- Several GLP-1 medications have also been shown to reduce cardiovascular risk in people with obesity, overweight or Type 2 diabetes
- GLP-1 therapy for conditions such as Parkinson's disease, dementia, addiction and other neurological disorders
- Science Note 1: How Do GLP-1 Medications Work?
- Science Note 2: What Conditions Are GLP-1 Medications Used to Treat?
- Science Note 6: Side Effects and Safety Considerations

Bikman, B. (2025, February 28). 92: *Natural ways to boost GLP-1 with Dr. Ben Bikman* [Video]. YouTube.

<https://www.youtube.com/watch?v=vdqHQMJBW>

- chronic insulin dysregulation
- Help regulate blood sugar by improving insulin function and reducing glucagon release
- Slow the rate at which food leaves the stomach

- Science Note 1: How Do GLP-1 Medications Work?
- Science Note 3: Are GLP-1s Treating the Root Cause or Just the Symptoms?

The Metabolic Link. (2025, July 14). *Ben Bikman, PhD | Are We Using GLP-1 Medications All Wrong? | The Metabolic Link* [Video]. YouTube. [https://www.youtube.com/watch?v=vM78Mb\\_VNcU](https://www.youtube.com/watch?v=vM78Mb_VNcU)

- should we not be treating insulin resistance before we reach the stage where GLP-1 medication becomes necessary?
- The message is still there, but its impact may gradually weaken
- using GLP-1s as a temporary support whilst building healthier lifestyle habits
- Would you put control of those 10 kilograms in the hands of a needle?
- If GLP-1 medications reduce the reward value of food, could they also reduce the reward value of other pleasurable activities
- She also raised a concern about the reports of irreversible neurological blindness that may be associated with GLP-1 use
- Slow the rate at which food leaves the stomach
- Science Note 5: GLP-1 Medications Are Not the Whole Treatment
- Science Note 6: Side Effects and Safety Considerations

Drucker, D. J. (2018). Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metabolism*, 27(4), 740–756. <https://doi.org/10.1016/j.cmet.2018.03.001>

- Help regulate blood sugar by improving insulin function and reducing glucagon release
- Slow the rate at which food leaves the stomach
- Help regulate blood pressure and cholesterol
- GLP-1 medications improve blood sugar control and reduce the risk of several diabetes-related complications
- Victoza
- The most common are nausea, vomiting, diarrhoea, constipation and indigestion
- low dose and gradually increase
- Long-term GLP-1 use has also been associated with small increases in heart rate in some people
- Science Note 1: How Do GLP-1 Medications Work?
- Science Note 2: What Conditions Are GLP-1 Medications Used to Treat?
- Science Note 6: Side Effects and Safety Considerations

Drucker, D. J. (2022). GLP-1 physiology informs the pharmacotherapy of obesity. *Molecular Metabolism*, 57, Article 101351. <https://doi.org/10.1016/j.molmet.2021.101351>

- For Type 2 diabetes, the answer is relatively straightforward
- If you were taking a GLP-1 medication to treat a chronic disease such as Type 2 diabetes (T2D) or obesity
- Unlike the approved dosing schedules studied in clinical trials
- Help regulate blood sugar by improving insulin function and reducing glucagon release
- Slow the rate at which food leaves the stomach
- GLP-1 medications improve blood sugar control and reduce the risk of several diabetes-related complications
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- Science Note 1: How Do GLP-1 Medications Work?

- Science Note 2: What Conditions Are GLP-1 Medications Used to Treat?
- Science Note 3: Are GLP-1s Treating the Root Cause or Just the Symptoms?
- Science Note 7: Should we be worried about the long-term use of GLP-1s?

Drucker, D. J. (2024). The GLP-1 journey: From discovery science to therapeutic impact. *Journal of Clinical Investigation*, 134(2), e175634. <https://doi.org/10.1172/JCI175634>

- Unlike the approved dosing schedules studied in clinical trials
- Slow the rate at which food leaves the stomach
- Help regulate blood pressure and cholesterol
- GLP-1 medications improve blood sugar control and reduce the risk of several diabetes-related complications
- GLP-1 therapy for conditions such as Parkinson's disease, dementia, addiction and other neurological disorders
- Saxenda
- Wegovy
- Tirzepatide acts on both GIP and GLP-1 receptors
- Long-term GLP-1 use has also been associated with small increases in heart rate in some people
- Science Note 1: How Do GLP-1 Medications Work?
- Science Note 2: What Conditions Are GLP-1 Medications Used to Treat?
- Science Note 6: Side Effects and Safety Considerations

Egefjord, L., Gudbergesen, H., & Holm, J.-C. (2024, May). *Is coming off semaglutide slowly the key to preventing weight regain?* [Conference presentation abstract]. European Congress on Obesity (ECO 2024), Venice, Italy.

- 2024 European Congress on Obesity

Garvey, W. T. (2022). Is obesity or adiposity-based chronic disease curable: The set point theory, the environment, and second-generation medications. *Endocrine Practice*, 28(2), 214–222. <https://doi.org/10.1016/j.eprac.2021.11.081>

- According to set-point theory, the brain and appetite-regulation
- Treating disease versus treating appearance is where much of the current ethical and medical debate sits
- Science Note 3: Are GLP-1s Treating the Root Cause or Just the Symptoms?

Gelfand, S. T., Tveit, M. C., & Simon, J. A. (2025). Clinical review of how glucagon-like peptide-1 agonist obesity medications decrease sexual desire, and a biopsychosocial model for why we don't 'see' it. *Obesity Pillars*, 17, 100233. <https://doi.org/10.1016/j.obpill.2025.100233>

- Possibly. But we don't know yet

Green, A. (2023, May 3). *In-depth: SA's obesity problem and the promise of new weight loss medicines.* Spotlight. <https://www.spotlightnsp.co.za/2023/05/03/in-depth-sas-obesity-problem-and-the-promise-of-new-weight-loss-medicines/>

- The challenge is that scientists still do not fully understand why some people gain weight more easily than others

- Researchers argue that if it were causing some large, previously unnoticed problem, we would probably have seen signs of that by now
- Researchers argue that if it were causing some large, previously unnoticed problem, we would probably have seen signs of that by now
- losing "those last few kilograms" to finally button up your jeans from 2018
- Help regulate blood sugar by improving insulin function and reducing glucagon release
- Slow the rate at which food leaves the stomach
- Help regulate blood pressure and cholesterol
- Victoza
- Wegovy
- The most common are nausea, vomiting, diarrhoea, constipation and indigestion
- low dose and gradually increase
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- Science Note 6: Side Effects and Safety Considerations
- Science Note 7: Should we be worried about the long-term use of GLP-1s?

Gudzune, K. A., & Kushner, R. F. (2024). Medications for obesity: A review. *JAMA*, 332(7), 571–584.  
<https://doi.org/10.1001/jama.2024.10816>

- GLP-1 medications are used alongside lifestyle interventions to improve weight loss and reduce the health risks associated with excess adiposity
- The most common are nausea, vomiting, diarrhoea, constipation and indigestion
- Science Note 2: What Conditions Are GLP-1 Medications Used to Treat?
- Science Note 3: Are GLP-1s Treating the Root Cause or Just the Symptoms?
- Science Note 6: Side Effects and Safety Considerations

Kushner, R. F. (2023, May 1). *A promising obesity drug with Robert Kushner, MD* [Audio podcast episode]. In *Breakthroughs Podcast*. Northwestern University Feinberg School of Medicine.  
<https://www.feinberg.northwestern.edu/research/podcast/a-promising-obesity-drug-with-robert-kushner-md.html>

- Slow the rate at which food leaves the stomach
- Science Note 1: How Do GLP-1 Medications Work?

Kushner, R. (2025, January 13). *Weight loss drugs with Robert Kushner, MD* (No. 47) [Audio podcast episode]. In *Off the Chart: A Business of Medicine Podcast*. American Medical Association.

- Approximately one in six people maintain at least 80% of their weight loss after discontinuing a GLP-1
- Several GLP-1 medications have also been shown to reduce cardiovascular risk in people with obesity, overweight or Type 2 diabetes
- low dose and gradually increase
- eat smaller meals, eat more slowly, stay hydrated, get enough fibre and limit alcohol

Kushner, R. F., Almandoz, J. P., & Rubino, D. M. (2025). Managing adverse effects of incretin-based medications for obesity. *JAMA*. Advance online publication. <https://doi.org/10.1001/jama.2025.11737>

- tirzepatide is approved for the treatment of moderate-to-severe obstructive sleep apnoea
- Zepbound
- The injection was intended to be one component of treatment, not the entire treatment plan.
- Adequate protein intake, fruit, vegetables, whole grains and healthy fats remain essential.
- Exercise also remains a cornerstone of care
- The most common are nausea, vomiting, diarrhoea, constipation and indigestion
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- Science Note 3: Are GLP-1s Treating the Root Cause or Just the Symptoms?
- Science Note 5: GLP-1 Medications Are Not the Whole Treatment
- Science Note 6: Side Effects and Safety Considerations

Luks, H. (2025, December 8). *Thinking about starting a GLP-1 medication? Read this first: The weight loss is pleasant, but it's a side effect. The metabolic correction is lifesaving.* Substack.

<https://howardluksmd.substack.com/p/thinking-about-starting-a-glp-1-medication>

- Exercise also remains a cornerstone of care
- If the answer is type 2 diabetes, obesity, cardiovascular risk, fatty liver disease, chronic inflammation, or one of the other conditions for which these medications are proving beneficial, then the risk-benefit equation starts to make sense.
- known side effects and the unknowns that still remain
- Science Note 2: What Conditions Are GLP-1 Medications Used to Treat?
- Science Note 3: Are GLP-1s Treating the Root Cause or Just the Symptoms?
- Science Note 5: GLP-1 Medications Are Not the Whole Treatment

Novo Nordisk A/S. (2025). *Wegovy (semaglutide) injection prescribing information* (Rev. 2025). U.S. Food and Drug Administration.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/215256s024lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/215256s024lbl.pdf)

- They are approved for obesity, or for overweight when there is at least one weight-related health condition
- Science Note 4: Overweight vs Obesity and GLP-1 Eligibility

Rivelland, J. Personal communication. June 16, 2026.

- As one GP I spoke to pointed out
- After all, some people report that their appetites are no longer suppressed or that they stop losing weight after they have been on the medication for a while
- When people lose weight on a GLP-1, they do not lose only fat.
- Unlike the approved dosing schedules studied in clinical trials, there is currently no standard definition of a microdose.
- If GLP-1 medications reduce the reward value of food, could they also reduce the reward value of other pleasurable and normal activities, including sex?
- Even so, anyone with a history of mental health challenges should be appropriately monitored while taking these medications.
- raised by the GP I consulted with
- She also raised a concern about the reports of irreversible neurological blindness that may be associated with GLP-1 use
- prescribed and monitored by healthcare professionals

- Science Note 2: What Conditions Are GLP-1 Medications Used to Treat?
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Rubino, F., Cummings, D. E., Eckel, R. H., Cohen, R. V., Wilding, J. P. H., Brown, W. A., Stanford, F. C., Batterham, R. L., Farooqi, I. S., Farpour-Lambert, N. J., le Roux, C. W., Sattar, N., Baur, L. A., Morrison, K. M., Misra, A., Kadowaki, T., Tham, K. W., Sumithran, P., Garvey, W. T., ... Mingrone, G. (2025). Definition and diagnostic criteria of clinical obesity. *The Lancet Diabetes & Endocrinology*, 13(3), 221–262.  
[https://doi.org/10.1016/S2213-8587\(24\)00316-4](https://doi.org/10.1016/S2213-8587(24)00316-4)

- If you were taking a GLP-1 medication to treat a chronic disease such as Type 2 diabetes (T2D) or obesity
- Science Note 2: What Conditions Are GLP-1 Medications Used to Treat?

Salamah, H. M., Marey, A., Abugdida, M., Abualkhair, K. A., Elshenawy, S., Elhassan, W. A. F., Naguib, M. M., Malnev, D., Durrani, J., Bailey, R., Tsyunchyk, A., Ibrahim, L., Zavgorodneva, Z., & Sherazi, A. (2024). Efficacy and safety of glucagon-like peptide-1 receptor agonists on prediabetes: A systematic review and meta-analysis of randomized controlled trials. *Diabetology & Metabolic Syndrome*, 16, Article 129.  
<https://doi.org/10.1186/s13098-024-01371-3>

Sexual Medicine Society of North America. (n.d.). *What effects do GLP-1 agonists have on sexual health?* Retrieved June 8, 2026, from <https://www.smsna.org/patients/did-you-know/what-effects-do-glp-1-agonists-have-on-sexual-health>

- Some people taking GLP-1 medications have reported a reduced libido or difficulty achieving orgasm ...

Schoretsanitis, G., Weiler, S., & Barbui, C. (2024). Disproportionality analysis from World Health Organization data on semaglutide, liraglutide, and suicidality. *JAMA Network Open*, 7(8), e2423385.  
<https://doi.org/10.1001/jamanetworkopen.2024.23385>

- depression, anxiety and suicidal thoughts
- Science Note 6: Side Effects and Safety Considerations

U.S. Food and Drug Administration. (2025, September 12). *FDA requests removal of suicidal behavior and ideation warning from glucagon-like peptide-1 receptor agonist (GLP-1 RA) medications.*  
<https://www.fda.gov/drugs/drug-safety-communications/fda-requests-removal-suicidal-behavior-and-ideation-warning-glucagon-peptide-1-receptor-agonist-glp>

- regulatory reviews have not established a causal link
- Science Note 6: Side Effects and Safety Considerations

Wang, W., Volkow, N. D., Berger, N. A., Davis, P. B., Kaelber, D. C., & Xu, R. (2024). Association of semaglutide with risk of suicidal ideation in a real-world cohort. *Nature Medicine*, 30, 168–176.  
<https://doi.org/10.1038/s41591-023-02672-2>

- larger studies have not confirmed a clear increase in risk
- Science Note 6: Side Effects and Safety Considerations

Wilding, J. P. H., Batterham, R. L., Davies, M., Van Gaal, L. F., Kandler, K., Konakli, K., Lingvay, I., McGowan, B. M., Oral, T. K., Rosenstock, J., Wadden, T. A., Wharton, S., Yokote, K., & Kushner, R. F. (2022). Weight regain and

cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. *Diabetes, Obesity and Metabolism*, 24(8), 1553–1564. <https://doi.org/10.1111/dom.14725>

- hunger may increase, energy expenditure may remain lower and the body may continue defending a higher weight
- weight regain after stopping the medication may tell us more about the biology of the condition than about any failure of the drug itself