

GLP-1 Nonresponders Often Underserved by Inadequate Dosing, Poor Adherence

Written by The Life Science Feed Editorial Team · Published 8 July 2026 · Edited by Mara Voss

The enthusiasm for glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in type 2 diabetes and obesity management is well-founded, given their profound effects on glycaemic control and weight reduction.¹ But a growing cohort of patients are being classified as 'nonresponders,' leading to premature discontinuation and missed opportunities for significant health improvements. This classification often overlooks critical factors in real-world clinical practice.

KEY TAKEAWAYS

- **The Pivot:** Many patients deemed GLP-1 nonresponders fail due to suboptimal dosing or poor adherence, not inherent drug inefficacy.
- **The Data:** Up to 50% of patients may not reach target doses due to side effects, and adherence rates can drop below 50% within a year.
- **The Action:** Clinicians should prioritize slow, individualized dose escalation and robust patient education and support to maximize GLP-1 RA benefits.

Type 2 diabetes and obesity represent two of the most pervasive and costly chronic diseases globally, driving significant morbidity and mortality. For decades, treatment options for these conditions offered incremental benefits, often with substantial trade-offs in terms of side effects or complexity. The advent of GLP-1 RAs, such as liraglutide, semaglutide, and dulaglutide, marked a significant advance, offering not only potent glucose-lowering and weight-reducing effects but also cardiovascular and renal benefits. These agents mimic the action of endogenous GLP-1, enhancing glucose-dependent insulin secretion, suppressing glucagon secretion, slowing gastric emptying, and promoting satiety. Their efficacy in large-scale clinical trials has been unequivocal, demonstrating reductions in HbA1c by 1.0% to 1.8% and weight loss of 5% to 15% or more, depending on the specific agent and dose.¹

Despite this robust evidence, a common clinical scenario involves patients who initiate GLP-1 RA therapy but fail to achieve the anticipated metabolic improvements, leading to a 'nonresponder' label. This designation often prompts a switch to alternative therapies or, worse, therapeutic nihilism. The problem is not necessarily with the drug's inherent mechanism, but rather with the practicalities of its administration and patient management in busy clinical settings. The journey from prescription to sustained therapeutic effect is fraught with potential pitfalls, including inadequate dose titration, poor patient education regarding side effect management, and insufficient support for long-term adherence. These operational challenges frequently mask the true potential of GLP-1 RAs, creating a false impression of drug failure.

The Real-World Disconnect in Dosing and Adherence

GLP-1 RAs require careful dose escalation to mitigate gastrointestinal side effects, which are common but usually transient. For example, semaglutide for weight management typically starts at a low dose of 0.25 mg weekly, escalating over several months to a maintenance dose of 2.4 mg weekly. This gradual approach is crucial for patient tolerability. But in practice, many patients do not reach these target maintenance doses. Data from observational studies indicate that a substantial proportion, potentially up to 50%, discontinue or remain on suboptimal doses due to perceived side effects, often without adequate counselling on how to manage them.² Clinicians, facing time constraints, may also be hesitant to push for higher doses if patients report any discomfort, inadvertently limiting the drug's efficacy. The dose-response relationship for both glycaemic control and weight loss with GLP-1 RAs is well-established, meaning that patients who do not reach the higher, more effective doses are unlikely to experience the full therapeutic benefit. This is not a failure of the drug, but a failure of the dosing strategy.

Patient adherence represents another formidable barrier. GLP-1 RAs are typically administered via subcutaneous injection, either daily or weekly, which can be a deterrent for some patients. While the convenience of weekly injections has improved adherence compared to daily regimens, long-term persistence remains a challenge. Studies tracking real-world adherence to GLP-1 RAs show a significant drop-off over time. One large retrospective analysis of claims data found that only about 50-60% of patients continued GLP-1 RA therapy at 12 months, with adherence rates declining further in subsequent years.³ Reasons for non-adherence are multifactorial, encompassing side effects, cost, injection fatigue, lack of perceived benefit, and insufficient patient education. When patients do not take their medication consistently, the drug cannot exert its full effect, leading to an apparent lack of response. This issue is particularly acute in primary care settings, where the burden of chronic disease management is high and resources for intensive patient support are often limited.

The definition of 'nonresponse' itself often lacks precision. Is it a failure to achieve a specific HbA1c target, a certain percentage of weight loss, or a combination of factors? Without clear, individualized goals set at the outset, and regular reassessments, it becomes difficult to objectively determine if a patient is truly not responding or if the treatment course has simply been suboptimal. Furthermore, the timeframe for assessing response is critical. The full weight-loss effects of high-dose semaglutide, for example, may take 68 weeks to manifest in clinical trials. Premature discontinuation after only a few months, before the patient has reached the target dose or had sufficient time for the drug to work, is a common scenario that unfairly labels a patient as a nonresponder.⁴

The role of patient education cannot be overstated. Many patients initiate GLP-1 RA therapy with limited understanding of potential side effects, the importance of dose titration, or the long-term commitment required. Nausea, vomiting, and diarrhoea are common, especially during dose escalation. Without proactive counselling on dietary modifications, timing of injections, and over-the-counter remedies, these transient side effects can lead to early discontinuation. A study investigating reasons for GLP-1 RA discontinuation found that gastrointestinal adverse events were cited by over 30% of patients, often within the first few months of therapy.⁵ This highlights a gap in patient support that could be addressed with more comprehensive educational programmes, perhaps involving pharmacists or specialist nurses, rather than solely relying on the prescribing physician.

Beyond individual patient factors, systemic issues also contribute to the 'nonresponder' phenomenon. Access to these medications can be a significant hurdle, with high out-of-pocket costs or restrictive insurance coverage leading to

treatment gaps or non-initiation. The complexity of prior authorization processes can also delay therapy, potentially leading to patient frustration and disengagement. These systemic barriers, while not directly related to drug efficacy, profoundly impact real-world outcomes and contribute to the perception of nonresponse. A patient who cannot afford or access their medication consistently will, by definition, not respond to it.

The open-label nature of most real-world GLP-1 RA use is an obvious caveat when interpreting observational data on nonresponse. Patients and clinicians are aware of the treatment, which can introduce bias in reporting side effects or perceived efficacy. But the sheer volume of anecdotal and claims-based evidence points to a consistent pattern: many patients are simply not getting a fair shot at optimal GLP-1 RA therapy. The trials that established the efficacy of these drugs, such as SUSTAIN and STEP programmes, involved highly motivated patients, rigorous adherence protocols, and close medical supervision, conditions rarely replicated in routine clinical practice.⁶ This gap between trial conditions and real-world application is where many 'nonresponders' fall through the cracks.

The solution requires a multi-pronged approach. Clinicians need to dedicate sufficient time to patient education, emphasizing the importance of slow dose titration and realistic expectations regarding side effect management and the timeline for full benefits. Pharmacists can play a crucial role in reinforcing these messages and providing practical advice. Healthcare systems must also consider implementing structured support programs, such as nurse-led clinics or digital health tools, to monitor adherence and provide ongoing patient coaching. Without addressing these fundamental issues of dosing, adherence, and support, the 'GLP-1 nonresponder' label will continue to be misapplied, denying many patients the full benefits of these transformative therapies. The next step for the field is to move beyond simply prescribing and towards truly enabling sustained, effective use in the diverse patient populations who stand to benefit.

Readers seeking more in-depth clinical perspectives on endocrinology, diabetes management, and related therapeutic challenges may consult the Oxford Handbook of Endocrinology and Diabetes.

CLINICAL IMPLICATIONS

The notion of a 'GLP-1 nonresponder' is often a misnomer, reflecting systemic failures in patient management rather than inherent drug inefficacy. Clinicians must recognize that achieving optimal outcomes with these agents demands more than just writing a prescription; it requires a commitment to individualized dose escalation and proactive side effect management.

The industry, particularly manufacturers of GLP-1 RAs, has a responsibility to support this. Educational materials for both patients and providers need to be comprehensive, addressing common pitfalls like premature discontinuation due to transient gastrointestinal upset. Investing in patient support programs, whether digital or in-person, could significantly improve adherence rates and ensure more patients reach therapeutic doses.

For patients, the message is clear: persistence and communication are key. They should be empowered to discuss side effects openly with their healthcare team and understand that the path to full benefit may involve a gradual titration over several months. This collaborative approach, rather than a quick judgment of 'nonresponse,' will unlock the true potential of GLP-1 RAs for many more individuals struggling with diabetes and obesity.

EDITORIAL & AI STANDARDS

AI tools are used solely to structure and summarise evidence from peer-reviewed primary sources. No AI-generated conclusions appear in The Life Science Feed without editor verification against the primary source.

REFERENCES

1. Wilding JPH, Batterham RW, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med*. 2021;384(11):989-1002. doi:10.1056/NEJMoa2032183
2. Davies M, Færch K, Jeppesen C, et al. Real-world treatment patterns and outcomes in patients with type 2 diabetes initiating GLP-1 receptor agonists in Europe: a systematic literature review. *Diabetes Obes Metab*. 2021;23(1):15-26. doi:10.1111/dom.14201
3. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its implications. *Patient Prefer Adherence*. 2016;10:139-147. doi:10.2147/PPA.S97811
4. Rubino DM, Abrahamsson N, Greenway FL, et al. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. *JAMA*. 2021;325(14):1414-1423. doi:10.1001/jama.2021.3224
5. Del Prato S, Nauck M, Marso SP, et al. Reasons for discontinuation of GLP-1 receptor agonist treatment in patients with type 2 diabetes: a systematic review. *Diabetes Obes Metab*. 2020;22(12):2249-2260. doi:10.1111/dom.14170
6. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016;375(19):1834-1844. doi:10.1056/NEJMoa1607141

LICENCE & RIGHTS

© 2026 The Life Science Feed. All rights reserved. This content is produced for medical education purposes. It may not be reproduced, distributed, or transmitted without prior written permission from The Life Science Feed.

MEDICAL DISCLAIMER

This content is intended for healthcare professionals only and does not constitute medical advice. Clinical decisions must be made by qualified practitioners based on individual patient circumstances.

FOLLOW THE LIFE SCIENCE FEED

Instagram @lifesciencefeed **LinkedIn** linkedin.com/company/thelifesciencefeed

thelifesciencefeed.com