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Rates of, Reasons for, and Reactions to Discontinuation of GLP-1 Receptor Agonists: A Narrative Review

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ABSTRACT

GLP-1RAs are increasingly used for their glucose-lowering and weight-management effects, but many patients discontinue them. In this narrative review we aim to review real-world, quantitative and qualitative GLP-1RA discontinuation, adherence, and persistence evidence as it aligns with an established conceptual framework for understanding medication adherence in noncommunicable chronic disease. Many inconsistencies exist in how discontinuation, adherence, and persistence are studied in this literature. Few qualitative studies have focused on discontinuation of GLP-1RAs. Quantitative approaches often focus on medication-related factors and more superficial aspects of socioeconomic and condition-related factors. Very few studies encompass all 5 dimensions of the medication adherence conceptual framework. Patient-related factors, especially related to patient behaviors, are understudied in relation to GLP-1RA discontinuation. Patients treated for type 2 diabetes mellitus or weight management with GLP-1RAs often discontinue the medication, but this is often nonpermanent. Improving adherence to and persistence on GLP-1RAs will require nuanced attention to care trajectories as well as an integrated understanding of GLP-1RA tolerability, expectations, and the understudied role of patient behaviors and the healthcare system. To clarify relevant mechanisms and guide targeted intervention for highest-risk individuals, further study should standardize definitions of persistence and discontinuation and implement patient-centered qualitative work, especially related to health behaviors.

1 | Introduction

There has been exponential growth in the use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in recent years [1], with semaglutide and tirzepatide dominating the market since late 2023. Despite their popularity and clinical efficacy, real-world observational studies suggest that many patients discontinue GLP-1RAs early in treatment [2–4]. Given their high cost [5] and evidence that benefits may diminish upon discontinuation [6, 7], understanding reasons for early discontinuation is important.

Patterns of discontinuation of, or adherence and persistence to prescription medicine are shaped by a complex interplay of pharmacologic, illness-centered, social, health system, and behavioural factors. An established conceptual model for medication adherence has previously been described for noncommunicable illnesses like type-2 diabetes mellitus (T2DM) and obesity. While many factors outlined in that model have been addressed in real-world studies of GLP-RA adherence, many others have not yet been considered, and reviews have not assembled existing literature into such a framework. We

aim to clarify established and emerging factors associated with real-world adherence (dose-taking behaviour), persistence (time on therapy), or discontinuation of GLP-1RAs across T2DM or weight management (WM) indications and to situate these findings within an established conceptual model for medication adherence.

2 | Study Design

This narrative review synthesizes recent evidence on discontinuation, persistence, and adherence to GLP-1RAs, focusing on the most recent and popular agents, semaglutide and tirzepatide. We follow a narrative rather than systematic approach, prioritizing conceptual synthesis over formal study appraisal, because real-world studies comprising this review are not only numerous and represent a rapidly evolving body of literature but also encompass substantial heterogeneity across study designs, patient populations, healthcare settings, and qualitative analytic frameworks. Quantitative and qualitative findings are mapped onto an established conceptual model of medication adherence, updated to reflect the unique aspects of discontinuing or adhering to GLP-1RAs.

3 | Conceptual Framework

The 2001 World Health Organization (WHO) adherence framework describes 5 interacting dimensions: social/economic, therapy-related, patient-related, condition-related, and healthcare system/healthcare team-related factors, as reproduced in Figure 1 [8]. Subsequent work by Peh and colleagues expanded the framework by mapping numerous general and specific factors within each dimension relevant to chronic noncommunicable diseases such as T2DM [9]. Across these dimensions and factors, adherence may be shaped by medication complexity, cost, and side effects; disease severity and comorbidity burden; socioeconomic barriers including stigma and social support; healthcare system factors such as insurance coverage, continuity of care, and provider communication; and patient-specific beliefs, expectations, cognitive characteristics, and behavioral patterns. The framework is broadly applicable to GLP-1RAs used in T2DM and WM, both chronic conditions requiring sustained self-management, while also providing flexibility to examine emerging influences unique to contemporary incretin therapies.

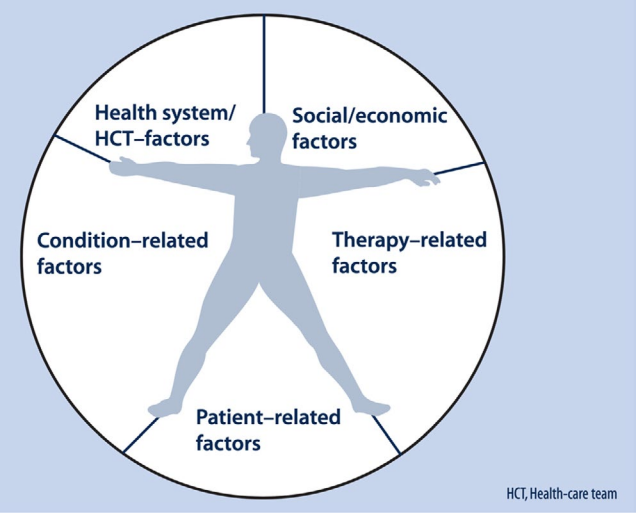

FIGURE 1 | Five Dimensions of Adherence from the Noncommunicable Diseases and Mental Health Cluster of the WHO [8].

4 | Quantitative Evidence on Adherence and Persistence

4.1 | Medication-Related Factors

Medication-related characteristics play a central role in adherence to and discontinuation of GLP-1RAs. A substantial body of literature addresses dosing frequency, tolerability, drug class comparison, and formulation. Medication cost has also historically been classified as a medication-related factor [9], even as cost is intrinsically linked with multiple other dimensions of adherence. Real-world adherence data appear to be shaped by cost as well as practical aspects of medication delivery and patient experience.

Medication cost is a critical component of the broader adherence landscape for GLP-1RAs. High out-of-pocket costs for GLP-1RA have consistently been associated with reduced adherence [10] and increased discontinuation [11, 12]. Across studies tracking reasons for GLP-1RA discontinuation, high cost is frequently the most common [13]. When medication cost rises with dose, patients have identified affordability as a key consideration in dose maintenance, underscoring the potential value of flexible dosing strategies to support sustained treatment engagement [14]. These cost-related dynamics highlight the importance of considering other modifiable treatment attributes, including dosing frequency, as determinants of sustained GLP-1RA use.

Dose frequency is an extensively studied determinant of GLP-1RA adherence, reflecting evolution of the drug class from twice-daily to once-weekly injectable agents [15–18]. A meta-analysis of clinical trials found greater adherence with weekly injections than with daily injectables [19], and this appears consistent whether treating T2DM [20–22] or WM [23, 24]. Although semaglutide users appear to discontinue less than users of other GLP-1RAs in these cohorts, a median 43.5% (range 27.8%–60.0%) of semaglutide users discontinue the medication within the first year in real-world studies involving comparison to other GLP-1RAs, regardless of indication [2, 20, 22–28], underscoring that dosing convenience alone does not eliminate adherence challenges.

Drug-specific design and tolerability have been targeted as potentially modifiable barriers to persistence. Gastrointestinal (GI) side-effects (e.g., nausea, vomiting, diarrhoea) are the most frequent patient-reported triggers for discontinuation, often occurring early in therapy and undermining persistence [29–32]. Recent innovations to improve tolerability include molecular modifications, development of oral formulations and exploration of small-molecule alternatives to peptide-based therapies [33]. Tirzepatide, approved by the U.S. Food and Drug Administration (FDA) in 2023 for both T2DM and WM, combines glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonism; the initial hypothesis was that it improved tolerability [34]. However, head-to-head trials have not demonstrated lower GI adverse-effect burden than with semaglutide in

TABLE 1 | Discontinuation of newer GLP-1RAs due to adverse events in Phase 3 trials for T2DM.

Interventional agent (formulation)	Trial	Follow-up duration	Discontinuation of study drug (adjusted)[a]	Discontinuation of placebo (adjusted)[a]
Orforglipron (PO)	ACHIEVE-1 [58]	40 weeks	4.4%–7.8% (4.4%–7.8%)	1.4% (1.4%)
Tirzepatide (SQ)	SURPASS-1 [59]	40 weeks	3.3%–6.6% (3.3%–6.6%)	2.6% (2.6%)
Semaglutide (PO)	PIONEER-1 [60]	26 weeks	2.3%–7.4% (3.5%–11.4%)	2.2% (3.4%)
Semaglutide (SQ)	SUSTAIN-1 [61]	30 weeks	5.4%–6.3% (7.2%–8.4%)	2.3% (3.1%)

[a]Given variability in follow-up duration across studies, discontinuation percentages were transformed to a common 40-week period to roughly facilitate cross-study comparison. Adjusted discontinuation percent was derived by standardizing discontinuation rates to a 40-week follow-up period. Specifically, the raw discontinuation percent was divided by the study's follow-up duration (in weeks) and multiplied by 40 weeks, corresponding to the maximum duration among studies presented in this table.

either T2DM [35] or WM populations [36]. Nevertheless, a meta-analysis of 17 RCTs found that discontinuation risk was similar for tirzepatide and placebo [37].

Early comparative studies suggested lower adherence to GLP-1RAs than other classes of glucose-lowering agents [38]. This gap appears to have narrowed with the introduction of once-weekly injectable agents and oral semaglutide [39]. More recent direct comparisons between sodium-glucose transport proteins-2 inhibitors and GLP-1RAs demonstrate similar rates of discontinuation [40] and adherence [41], suggesting that GLP-1RA persistence may be converging with that of other glucose-lowering medications.

Medication formulation, particularly oral versus injectable delivery, represents another salient medication-related factor. The approval of oral semaglutide for T2DM in 2019 may have reshaped expectations regarding adherence by offering a noninjectable option; but uptake has remained modest, accounting for a relatively small share of GLP-1RA spending [42]. Following FDA approval for WM in December 2025, oral semaglutide may be an option for more patients. Nevertheless, to ensure absorption of the medication, the specialized delivery system for oral semaglutide may represent a nontrivial burden for its use, as it must be taken on an empty stomach, with no more than 4 oz. of water, and at least 30 min before consuming other food, drink, or medications [43, 44]. Such a burden may prevent prescriptions for the oral formulation, as physicians seek treatments that facilitate patient self-management [45]. To date, real-world adherence and persistence data for oral semaglutide are limited to the T2DM indication and show mixed results [46–54]. A U.S.-based cohort demonstrated adherence and persistence comparable to oral dipeptidyl peptidase-4 inhibitors, despite higher out-of-pocket costs associated with oral semaglutide's specialized peptide delivery system [55]. In contrast, European studies report lower persistence with oral semaglutide. In a matched cohort, persistence with injectable semaglutide was significantly longer [49]; and an Italian cohort similarly favoured weekly injectable over the daily oral semaglutide [29]. Conversely, a Japanese cohort reported higher adherence and persistence with oral, rather than injectable, semaglutide [56]. Collectively, these findings suggest that medication formulation may interact with contextual factors, perhaps along geocultural boundaries encompassing healthcare systems, prescribing norms and patient preferences, ultimately shaping adherence patterns.

Emerging small-molecule GLP-1RAs may further reshape medication-related adherence determinants. Orforglipron received FDA approval [57] in April 2026 for WM and offers theoretical advantages related to oral bioavailability without requiring specialized delivery systems. Phase 3 trial data suggest its discontinuation profile may be similar to that of other GLP-1RAs (Table 1), highlighting the potential for formulation simplicity to influence long-term adherence by reducing administration complexity and cost-related barriers.

4.2 | Condition-Related Factors

Condition-related factors encompass aspects of disease control, such as condition severity and response to the medication, as well as patient-specific disease characteristics, including presence and number of comorbid conditions. Additionally, the treatment indication may bring about unique adherence and discontinuation trajectories.

The severity of illness can set the stage for a discontinuation event. In T2DM, people with very high baseline haemoglobin A1c (≥9%) may be 15% (9%–20%) more likely to discontinue than those with baseline A1c ≤6.5%; in contrast, those with more moderate baseline A1c elevations between 6.5% and 8% may be 10% (5%–14%) less likely to discontinue than those with baseline A1c ≤6.5% [40]. An early therapeutic response to GLP-1RA therapy (i.e., clinically significant reduction in A1c or body weight within 3 to 6 months) is associated with significantly higher adherence at 18 months and a lower likelihood of treatment discontinuation [62]. On the other hand, a dramatic initial effect can be burdensome, as the odds of achieving 12-month adherence were 26% lower for those in the highest tier of weight loss (7.5%–10% weight loss in 1 month) for a WM cohort than those who had lost only 2.51%–5% [63].

Comorbidity burden also appears to influence adherence and discontinuation behaviour. When T2DM is the primary condition being treated, higher BMI is associated with lower risk of discontinuation compared to normal BMI [63]. Beyond T2DM and WM, a higher *number* of comorbid conditions [64], as well as certain specific comorbidities, have been associated with increased risk of GLP-1RA discontinuation [7, 40, 65–68]. Frequently reported comorbidities associated with discontinuation include ischemic heart disease, stroke, and heart failure [7, 40, 65, 67]. Heterogeneity in the comorbid conditions

examined across studies may limit identification of additional relevant conditions.

Different treatment indications may be expected to be associated with distinct adherence patterns [8, 9]. Adherence challenges have been reported across glucose-lowering therapies [69], as well as pharmacologic treatments for WM [24]. Relative to people treated for T2DM alone, people treated for obesity alone (no T2DM) had 79% higher odds of discontinuation, and people treated for both conditions had 9% lower odds of discontinuation [68].

4.3 | Socioeconomic Factors

Quantitative studies have identified demographic and socioeconomic factors associated with GLP-1RA persistence and/or discontinuation. While evidence is robust for treatment costs/copays and patient demographics such as age and sex, other characteristics are less frequently reported. Among demographic characteristics, patient age and sex are consistently relevant.

Adherence patterns appear to vary across the lifespan and, to a lesser extent, by sex. Middle adulthood frequently predicts greater adherence, whether for T2DM [7, 15, 40, 66] or WM [12]; while early adulthood [3, 12, 15, 40] and advancing age [12, 16, 36, 52, 67] are often associated with lower adherence or higher discontinuation rates. Differences by sex are modest but directionally consistent across multiple studies in T2DM; women tend to discontinue more frequently than men [40, 66, 67]. Adherence differences by sex have been either nonsignificant or absent in studies of WM [24, 68]. Socioeconomic disparities are also evident: lower adherence and persistence have been observed among Black and Hispanic patients [7, 64, 68], patients in the United States with noncommercial insurance [64, 68], and patients with lower educational attainment [12, 40].

Economic factors provide essential context for discontinuation events. High out-of-pocket costs represent the strongest and most consistent predictor of nonadherence or early discontinuation of GLP-1RAs [12, 13, 15, 66]. Similarly, low income is often associated with a higher risk of discontinuation [12, 40, 64, 70]; and, among commercially insured patients and those on Medicare, higher copayment tiers are associated with higher discontinuation risk and reduced 1-year adherence [12, 66]. Geographic disparities in healthcare access also influence adherence patterns; paralleling broader geographic disparities in healthcare access [71], patients in the Southern United States may show lower GLP-1RA adherence than those in other regions [15, 65].

4.4 | Healthcare System-Related Factors and Provider-Reported Reasons for Discontinuation

Healthcare-system and healthcare-personnel factors associated with GLP-1RA adherence are understudied, except for insurance. Insurance and medication costs are deeply interconnected, but cost may be best characterized as medication-related, while insurance is a structural determinant of healthcare access. Out-of-pocket cost reflects the patient-facing financial burden tied to a specific therapy and may directly influence comparisons between alternative medications or devices. In contrast, insurance-related factors were categorized as healthcare system-associated because they are determined by broader payer, policy, and formulary structures that shape healthcare access at the systems level.

In the United States, patients on Medicare and Medicaid are more likely to discontinue [68] GLP-1RAs and less likely to adhere [64] to them than patients with private insurance. Unfortunately, patients may sometimes discontinue medications under the mistaken perception that medication may no longer be needed if coverage ends [72]. Nevertheless, insurance coverage restrictions, prior authorization requirements [13], and supply shortages can involve termination in coverage despite ongoing need [73]. Even among healthcare system employees, the loss of GLP-1RA coverage from employer based insurance for WM has been linked to reduced employee satisfaction, increased burnout, and greater turnover [74]. Although cost-reduction policies may increase affordability and improve adherence to GLP-1RAs [11], insurance coverage for GLP-1RAs in the United States has been restricted, particularly for the WM indication [75].

These and many other potentially important system- and provider-level factors remain insufficiently examined. Healthcare personnel characteristics, such as the ability to relate to patients, provide education, ensure effective follow-up, establish trust, and implement shared-decision making, have been identified as important contributors to adherence in noncommunicable chronic disease [9]; but they do not appear to have been empirically studied in relation to GLP-1RA adherence.

A few studies have examined physicians' and other prescribers' perceptions pertinent to their patients' adherence to or discontinuation of GLP-1RAs. In a Canadian survey of 50 physicians prescribing semaglutide, discontinuation was most commonly attributed to GI side-effects or treatment affordability, with fewer respondents citing failure to meet treatment goals [76]. In contrast, a survey of prescribers identifying as "lifestyle practitioners" suggested that GLP-1RAs are often continued in patients with T2DM even after lifestyle interventions successfully reduce the need for pharmacotherapy, implying that these prescribers may place greater emphasis on risks of discontinuation than risks of long-term use [77]. Discordance between provider perceptions and clinical reality has also been reported. In Japan, 330 physicians prescribing oral semaglutide were significantly more likely to overestimate patient discontinuation risk [78]. Similarly, in a U.S. survey of family practice and internal medicine physicians, physicians overestimated established discontinuation rates while underestimating weight-loss efficacy and side-effect burden, all perhaps representing opportunities for education that could influence patient counselling and the setting of appropriate clinical expectations [79].

4.5 | Patient-Related Factors and Patient-Reported Reasons for Discontinuation

Factors categorized in the framework as social, systemic, economic, or condition-related are nevertheless experienced

by individual patients, underscoring the interrelatedness of these dimensions. A patient's uniquely dynamic experience with restarting or switching GLP-1RA medications may also be considered patient related. Importantly, discontinuation may often be temporary. Within a year of discontinuing, approximately 25%–50% of patients reinitiate therapy or switch to an alternate GLP-1RA [40, 67, 70, 80]. Many patients navigate periods of interruption followed by re-engagement. The evolving landscape of GLP-1RA access and availability likely contributes to these patterns. Those who switch may be seeking newer options offering greater efficacy, improved convenience, and/or lower side-effect burden [81]. Switching may also be driven, at least in part, by changes in insurance coverage. To the extent that agents have comparable efficacy, intra-class switching may more appropriately reflect ongoing persistence and treatment optimization rather than nonadherence, highlighting the need for the literature to differentiate permanent discontinuation from temporary or shorter-term discontinuation.

Patient-reported factors are also highly relevant in this context. The decision to discontinue a GLP-1RA likely reflects a combination of patient-related, medication-related, and socioeconomic reasons, not typically captured in large clinical or administrative database cohorts. Survey findings suggest that GLP-1RA discontinuation is driven by a complex interaction of medication tolerability, practical barriers (including healthcare system and socioeconomic factors), and the patient's perceptions of benefit [31]. These patient-reported insights complement epidemiologic studies by describing the subjective experiences administrative data do not capture.

Within the patient-reported literature, medication-related factors emerge as a dominant theme, especially adverse reactions. However, patients have been clear that healthcare provider-related factors can mitigate these challenges, as more supportive care pathways may *prevent* discontinuation [82], particularly given that GI side-effects often decrease in severity with continued use [83]. Risk of discontinuation also increases when patients perceive insufficient treatment efficacy or encounter challenges related to medication formulation, including preferences for oral therapy, inconvenience or discomfort with injections, or needle-related anxiety [29, 30, 32]. Patients have also confirmed that socioeconomic and healthcare system-related barriers add further strain to GLP-1RA adherence efforts, particularly with high costs, insurance denials, and drug shortages [29, 30, 32].

Questionnaire-based findings largely corroborate observations from clinical and administrative data. However, future survey-based research could further explore specific patient behaviours (e.g., orderliness and planning), perceived impacts on quality of life or mental health, and ways these factors relate to GLP-1RA use and discontinuation [9]. Notably, potential psychological or mental health-related reasons for discontinuation remain underexplored, representing an important evidence gap, given the growing interest in neuropsychiatric effects of these agents [84, 85]. Studies have also not examined how patient-reported factors cluster within individuals, how patients prioritize these factors, or how they correlate with objectively measurable clinical variables. Moreover, substantial heterogeneity and limited methodological consistency characterize the few studies examining patient-reported factors [29–32, 82, 83].

The breadth of patient-reported reasons for discontinuation and the inherent limitations of quantitative approaches underscore the need for qualitative research. Such work is essential to elucidate the psychological, social, economic, and healthcare system-related contextual factors that shape discontinuation and nonadherence. Qualitative inquiry offers critical insight into the lived experiences underlying real-world treatment trajectories, particularly as survey instruments cannot fully capture the complex and evolving meanings that patients attach to GLP-1RA use and discontinuation.

5 | Qualitative Evidence on Discontinuation and Non-Adherence

Qualitative reports have highlighted a variety of psychological and motivational influences shaping how individuals engage with GLP-1RA therapy. Narratives suggest that a decision to discontinue or continue treatment often reflects a dynamic intersection among expectations, lived experiences, and personal associations with medication use, rather than an isolated event or linear causal pathway [86–88].

A central theme across narratives is the intertwining of physiological and emotional responses. Physical changes like decreased waist circumference with weight loss often carry symbolic value, representing regained control over eating behaviours or confirmation that efforts were "working." Motivation to initiate a GLP-1RA is often anchored in powerful hopes for weight reduction or improved metabolic control, expectations often entangled with broader aspirations for renewed identity and social acceptance [87]. Early experiences of appetite suppression or visible weight change can affirm these expectations [86], while slower or subtler results may exacerbate self-blame and frustration. For some, acceptance of negative side effects becomes possible with promise of physical health benefits [89]. For others, GI discomfort erodes a subjective sense of progress and deteriorates resiliency. Discontinuation may emerge not solely from side effects but rather, also, from a shifting sense of whether the treatment experience aligned with the patient's self-image or personal goals [86].

Perceptions of GLP-1RA convenience or burden also appear prominently in patient narratives [90]. Some patients describe once-weekly injections as simple, finding the regimen to be less intrusive than daily pills or insulin; others underscore the emotional and logistical toll of managing side-effects and coordinating the timing of injections. Given these accounts, persistence may hinge on the extent to which treatment can be easily incorporated into pre-existing routines without amplifying feelings of illness or dependency [88]. Insulin-injection stigma has long been a challenge in T2DM management, and conflicting perspectives exist regarding how daily and weekly injectable GLP-1RAs fit into this schema. Some perceive any self-injection as a

marker of disease progression; others emphasize the liberating or empowering aspects of GLP-1RA use as a modern, acceptable tool that sheds many burdens associated with insulin [86]. Such divergent viewpoints illustrate how adherence decisions reflect personal identity as much as clinical reasoning and practical circumstances.

Clinical encounters can represent pivotal moments for medication persistence trajectories. By reassuring patients that side-effects tend to dissipate within a few weeks of continued use, healthcare professionals may be able to support GLP-1RA adherence. They can also validate struggles, guide appropriate adjustment of expectations, and redefine what constitutes treatment "success." [90] On the other hand, clinical encounters also become a context for patients to feel isolated or shamed through a clinician's dismissive attitude or moralizing language, particularly when discontinuation is interpreted as a lack of willpower [87]. Such encounters may increase the likelihood of discontinuation and intensify reluctance to re-initiate following discontinuation.

Discontinuation of GLP-1RAs seldom appears to be a complete rejection of pharmacologic treatment. Some patients describe intentional "pauses" that help manage costs, regain bodily comfort, and reassess priorities, with the possibility of restarting therapy later [87]. Others pause to switch agents or recalibrate dose requirements. Leverage of treatment flexibility suggests that patients conceptualize adherence as a fluid process responsive to changing circumstances, rather than as a fixed behavioural trait. Moreover, insurance coverage or changes also represent a dynamic influence on persistence and discontinuation. Qualitative accounts ultimately reinforce that GLP-1RA persistence reflects a negotiation among perceived benefit, personal identity, treatment burden, and the healthcare environment. Table 2 lists real-world, quantitative and qualitative studies regarding factors related to adherence, discontinuation, or persistence with GLP-1RAs, organized by the WHO Five Dimensions of Adherence.

6 | Synthesis and Discussion

6.1 | Overview of Main Findings

Adherence persistence and discontinuation of GLP-1RAs arise from medication-related, patient-related, healthcare system-, socioeconomic, and condition-related influences. Across diverse data sources, discontinuation of GLP-1RAs is common within the first 1 to 2 years of treatment; although estimates vary by population, agent, indication and operational definition. Discontinuation frequently represents a temporary interruption rather than permanent cessation, with many individuals restarting therapy or switching within the drug class. Third, drivers of nonadherence reflect a convergence of influences spanning all 5 dimensions of the medication adherence framework, shown in Figure 2.

Although the WHO framework offers a broad structure for organizing determinants of treatment engagement, its application to GLP-1RAs exposed important gaps and emerging influences not captured in the original model. Peh and colleagues' listing of general and specific factors within the dimensions in the original WHO model resulted in an expansive list generated from pertinent literature [9]. We collapsed several of these specific factors to avoid redundancy. Additionally, many specific factors identified by Peh and colleagues as relevant from past literature were not explicitly addressed in literature about GLP-1RAs. While many factors are well accommodated by the framework, other considerations may be particularly difficult to assign to a single wedge in the design. In particular, the role of social media may simultaneously enhance engagement through peer narratives and visibility while also propagating misinformation, stigma, or unrealistic expectations regarding outcomes [143]. Nevertheless, while social media itself may have broad implications pertaining to GLP-1RA adherence, we did not identify existing literature specifically examining social media influences on adherence, discontinuation, or persistence. Nevertheless, we did identify other areas unrepresented by Peh and colleagues with relevance to GLP-1RAs, including co-administered medications, reinitiation/switching medications, biometric measures of disease severity, geographic classifications, nicotine or tobacco use, specialty of the prescriber, and psychiatric illness. The breadth of impacts from specific factors across dimensions suggests that the WHO framework, although robust, benefits from ongoing updates to remain aligned with current therapeutic and societal contexts.

In our framework, all 5 dimensions have equal area, as in the original WHO model, to emphasize that all 5 dimensions of factors underpinning discontinuation and adherence have great relevance. We include the inscribed circle of Peh and colleagues to emphasize the interconnectedness of the 5 dimensions [9]. Specific factors bulleted in Figure 2 are significant across multiple quantitative studies and/or well represented in qualitative studies.

6.2 | Clinical Implications

There are several practical implications for clinicians caring for people with diabetes or obesity who are candidates for GLP-1RAs:

1. **Normalize chronicity and set realistic expectations**. Frame GLP-1RA therapy as part of long-term management of chronic conditions rather than a short-term intervention. Clear discussions about the likelihood of rebound effects after discontinuing treatment may mitigate surprise and disappointment if discontinuation occurs.
2. **Proactively manage intolerability**. GI adverse effects are among the most frequently cited reasons for discontinuation. Proactive strategies including gradual dose escalation, anticipatory guidance, symptom-management plans, shared decision-making around dose adjustments, and temporary pauses may all improve patients' sense of control and, in turn, persistence on the medication.
3. **Discuss cost, coverage, and access**. Because insurance changes, prior authorization requirements, and out-of-pocket costs are common drivers of treatment interruptions, prescribers should routinely discuss coverage

continuity, formulary changes, and contingency plans for interruptions in access.

4. **Address stigma, identity, and psychological context**. Routine counselling should recognize the emotional and social dimensions of using a GLP-1RA, especially for WM. Validating patient concerns, exploring internalized weight bias, and situating GLP-1RAs within a broader framework of self-care rather than moral judgment may help sustain engagement.
5. **Tailor the approach to diabetes vs. obesity indications**. Patterns and drivers of discontinuation differ between individuals treated primarily for glycemic control versus for WM. In diabetes care, GLP-1RAs are often 1 component of a complex regimen with established cardiometabolic indications. In obesity care, they may be experienced as the central, high-stakes intervention. Clinical conversations and monitoring strategies should reflect these unique contexts.

TABLE 2 | Real-world studies exploring factors related to adherence to, discontinuation of, or persistence on GLP-1RAs, organized according to the WHO Five Dimensions of Adherence.

General Factor	Specific Factor	References
Dimension 1: Medication-related factors		
Medication Effects	Risks, safety, or side-effects	Quantitative: [13, 14, 28, 46, 48, 50, 53, 63, 70, 76, 82, 91–102] Qualitative: [31, 79, 83, 86–88, 103–108]
	Effectiveness or efficacy	Quantitative: [13, 14, 46–48, 63, 70, 76, 82, 92, 95, 109–111] Qualitative: [31, 88, 90, 103, 106]
	Early response	Quantitative: [28, 48, 53, 62, 63, 76, 92, 102] Qualitative: [31, 86, 88, 105, 106, 108]
Medication Regimen	Medication from a different drug class for the ***same*** indication (specified medication/s or a count)	Quantitative: [4, 7, 24, 28, 40, 54–56, 65, 82, 94, 95, 97, 101–118] Qualitative: [77, 86, 119]
	Reinitiating GLP-1RAs or switching GLP-1RAs	Quantitative: [4, 13, 28, 36, 47, 54, 55, 67, 70, 80, 81, 97, 120–125] Qualitative: [31, 86, 87]
	Specific GLP-1RA agent (but not switching)	Quantitative: [2, 22, 23, 25–28, 36, 96, 126–129] Qualitative: [88, 119]
	Dosage	Quantitative: [12, 21, 26, 92, 98, 101, 120, 122, 130–132] Qualitative: [83]
	Frequency	Quantitative: [21, 95, 96, 132, 133] Qualitative: [88, 90]
	Medication from a different drug class for a ***different*** indication (specified medication/s or a count)	Quantitative: [7, 40, 94, 98, 114, 115, 134]
	Regimen familiarity	Quantitative: [2, 22, 63, 99, 102, 112, 114, 118] Qualitative: [31]
	Interference with routine	Qualitative: [31, 78, 88, 90, 104, 108]
Other Medication Properties	Out-of-pocket cost	Quantitative: [10–14, 22, 53, 65, 68, 76, 92–94, 97, 100, 109] Qualitative: [31, 87, 88, 90, 105, 108, 135]
	Formulation	Quantitative: [29, 49, 53, 56, 82] Qualitative: [90]
Patient-Specific Medication Issues	Acceptability	Quantitative: [94] Qualitative: [31, 87]
	Needle phobia	Qualitative: [31, 88]

(Continues)

TABLE 2 | (Continued)

General Factor	Specific Factor	References
Dimension 2: Condition-related Factors		
Disease Control	Biometric measures of disease severity	Quantitative: [2, 24, 27, 40, 56, 63, 65, 94, 95, 98, 99, 101, 102, 114, 115, 117, 118, 124, 128, 129, 133, 136] Qualitative: [88]
	Incident comorbidities and acute care	Quantitative: [7, 95, 115, 134, 137, 138]
	Physical function	Quantitative: [65, 114] Qualitative: [31]
Other Disease Characteristics	Indication for the medication	Quantitative: [27, 68, 70, 139]
Patient-Specific Disease Factors	Baseline comorbidities	Quantitative: [7, 12, 22, 24, 25, 27, 40, 63–65, 67, 70, 94, 98, 99, 102, 115, 116, 118, 124, 129, 133, 134, 139, 140]
	Time since diagnosis	Quantitative: [40, 98, 124, 133, 140] Qualitative: [86, 88]
Dimension 3: Socioeconomic Factors		
Economic Factors	Income	Quantitative: [12, 40, 64, 65, 70, 99, 128, 133, 140] Qualitative: [88]
	Insurance	Quantitative: [10, 13, 22, 24, 27, 64, 65, 68, 94, 97, 110] Qualitative: [31, 108]
	Education	Quantitative: [12, 40, 65, 133, 140] Qualitative: [88]
	Indices of social determinants of health	Quantitative: [2, 20, 24, 27, 68]
	Occupation	Quantitative: [74]
Lifestyle Factors	Nicotine or tobacco use	Quantitative: [40, 65, 114]
	Alcohol use	Quantitative: [65]
Social/ Environmental Factors	Geographic classifications	Quantitative: [10, 22, 40, 64, 65, 68, 128]
	Pregnancy	Quantitative: [46, 107, 109]
	Stigma	Qualitative: [86, 87]
	Social support	Qualitative: [31, 108]
Dimension 4: Healthcare System/HCP-related Factors		
HCP Characteristics	Communication	Qualitative: [63, 88, 90, 105, 119]
	Interaction with HCP/healthcare system	Quantitative: [54, 81, 95] Qualitative: [88, 105]
	Specialty of the prescriber	Quantitative: [98, 115, 141]
	Prescription practice	Qualitative: [77, 103]
	HCP's knowledge	Qualitative: [78, 79]
	Relationship	Qualitative: [88, 90]
	Trust in provider	Qualitative: [88, 90]
	Shared decision-making	Qualitative: [90]

(Continues)

TABLE 2 | (Continued)

General Factor	Specific Factor	References
Healthcare System Characteristics	Information support	Qualitative: [31, 83, 88]
	Drug supply	Quantitative: [28, 97, 110]
	Policies/regulation processes	Qualitative: [31]
Dimension 5: Patient-related Factors		
Behavioural Factors	For example, Integration into lifestyle, self-regulatory fatigue, planning	Not definitively addressed in relation to discontinuation, adherence, and/or persistence
	Emotions	Qualitative: [25, 27, 31, 86, 90, 103, 106]
Cognitive and Psychological Factors	Commitment	Quantitative: [63, 102]
	Expectation of treatment	Qualitative: [31, 78, 86]
	Forgetfulness	Quantitative: [92] Qualitative: [90]
	Intentional non-adherence	Quantitative: [93] Qualitative: [31, 87]
	Knowledge	Quantitative: [100] Qualitative: [78]
	Motivations/goals	Qualitative: [31, 86, 104]
	Perceptions	Qualitative: [31]
	Psychiatric illness	Quantitative: [25, 27, 40]
	Risk estimation	Qualitative: [31, 103]
Non-modifiable characteristics	Demographics (i.e., one or more among age, sex, race/ethnicity)	Quantitative: [12, 20, 22, 24, 27, 40, 46, 52, 56, 63–65, 67, 70, 91, 94, 98, 99, 115, 116, 118, 124, 128, 129, 132–134, 139, 140, 142] Qualitative: [31, 86, 88]
	Treatment responsibility	Quantitative: [63] Qualitative: [104]
Priorities	Competing needs	Quantitative: [94] Qualitative: [87]
	Quality of life	Qualitative: [83, 106]

Note: Measures were at baseline unless specified as "incident." Quantitative studies needed to have included the specific factor as a reason for discontinuation, adherence, or persistence; or the study needed to present a comparison of adherence, discontinuation, and/or persistence measure with the specific factor.
Abbreviations: HCP, Healthcare personnel; T2DM,Type 2 diabetes mellitus; WM, Weight management.

Interventions following these clinical implications may yield limited long-term benefit without parallel health-systems support for persistence and continuity of care. Policies restricting obesity-treatment coverage or requiring repeated reauthorization may disproportionately destabilize treatment among individuals with fewer financial resources, potentially widening disparities in long-term cardiometabolic outcomes. Given the rapidly evolving evidence base and heterogeneity of adherence measures, these recommendations represent provisional, expert opinion and require prospective interventional validation.

6.3 | Interventions to Improve Adherence

Effective adherence interventions are typically multilevel, targeting multiple barriers simultaneously [8]. Despite recognition of this complexity, adherence interventions specific to obesity pharmacotherapy remain underexplored, and strategies in T2DM have been studied within a limited range of approaches.

RCTs in T2DM populations demonstrate that technology-enabled interventions can produce modest but meaningful improvements in adherence. Real-time medication monitoring combined with SMS reminders enhances regimen precision and is well accepted by patients [144], with further evidence suggesting that reminders triggered only after missed doses may sustain improved adherence as long as 2 years [145]. Nurse-led consultation interventions have demonstrated an increase in objectively measured adherence without compromising treatment satisfaction [146]. Evidence for GLP-1RAs remains limited to digital tools primarily supporting trial engagement rather than real-world adherence [147].

Across the 5 dimensions of adherence, several key intervention targets are understudied for GLP-1RAs. Medication-specific

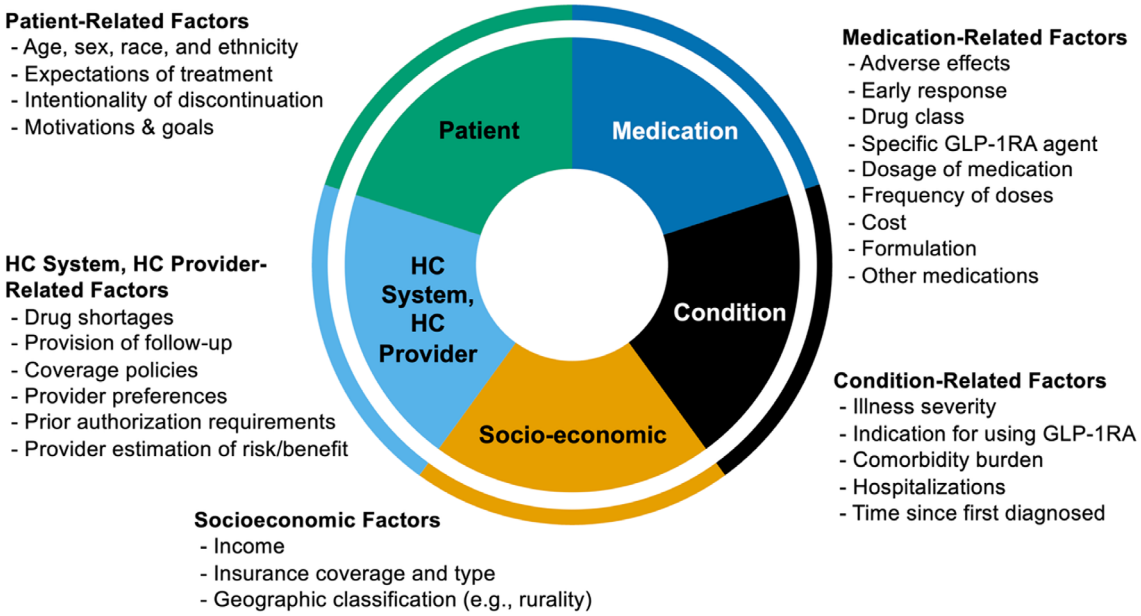

FIGURE 2 | Adapted conceptual framework for factors relevant to adherence and/or discontinuation of GLP-1RAs.

modifications such as electronic dose-event monitoring [148] and simplification of dose titration [149] remain opportunities within incretin pharmaceutical design. Given that T2DM and obesity frequently present with comorbidities, integrated-care-model designs are an established intervention approach lacking translation to the GLP-1RA domain [8]. Socioeconomic strategies include interventions reducing out-of-pocket costs and leveraging case management [150]. While clinicians play a central role in patient education [149] and face-to-face behavioural strategies [151], their efforts are constrained by limited tools and systemic barriers [8]. Interventions focusing on factors within the patient dimension are common across adherence interventions for chronic disease management; but these strategies, including patient education [149] and motivational interviewing [152], are also understudied in GLP-1RAs.

6.4 | Limitations of the Evidence and of This Review

Several limitations of the current evidence base merit emphasis. Most quantitative data on GLP-1RA persistence and discontinuation derive from administrative claims, subject to misclassification; lack detailed clinical and psychosocial information; and often apply heterogeneous definitions of adherence, persistence, and discontinuation. Follow-up durations are typically limited to 1 to 3 years, even as these therapies are envisioned as long term. Survey studies may be affected by selection bias and rely on retrospective self-report of reasons for stopping treatment. Qualitative studies, while rich in contextual detail, are often small and not designed to generate population-level estimates.

Interpretation of treatment engagement outcomes is hindered by substantial heterogeneity in the inclusion or operationalization of adherence, discontinuation, and persistence. Many studies used the terms interchangeably or failed to define parameters constituting the measure, despite a vast literature on adherence and persistence with customary definitions [153]. While an 80% cutoff for proportion of days covered in the measurement of adherence is broadly accepted across studies, a great variety exists in what number of days without a prescription constitutes a discontinuation event (see Table S1). Such heterogeneity limits comparisons between studies. Authors' use of sensitivity analysis regarding time thresholds has occasionally buffered non-uniformity. Translation of real-world clinic data into analysable data also proves challenging, for instance, in the assumption of stockpiling when prescriptions are filled early (versus assuming the prescription had been lost and needed early refill) [120]. Study dates are occasionally a point of comparison, perhaps reflecting the novelty and popularity of emerging formulations in distinct "epochs." [4, 7, 24, 40, 67, 70, 115, 133].

Qualitative research on this topic has been subject to several important methodological limitations. Selection bias is a recurring concern, particularly in studies using purposive sampling [77, 83], recruitment from a single site or healthcare system [90, 105, 108, 135], and the challenge of including individuals with unfavourable experiences [107]. In addition, studies often employ single-timepoint designs, limiting the ability to capture changes in attitudes or behaviours [104]. Studies have also pointed to the absence of comparison groups as a missed opportunity for contextualization [106, 108]. Recall bias has also been identified as a concern [88, 106]. Future qualitative studies on GLP-1RA discontinuation might ideally integrate repeat measures both during use and after discontinuation and leverage broader recruitment pools that include comparison groups with data-collection events as near as possible to discontinuation events [86].

Our narrative review modality prioritizes conceptual integration over methodological scoring. We did not conduct a formal systematic review or risk-of-bias assessment and may have missed relevant studies, particularly those published in languages other than English or in non-indexed sources. Nevertheless, our aim was exploratory, seeking to situate findings within an existing framework. Heterogeneity across study designs, populations, and health systems limits the ability to make direct comparisons or

summarize pooled-effect estimates. Heterogeneity in qualitative methodologies, reporting standards, and analytic frameworks across studies limited the feasibility of applying formal approaches to qualitative synthesis. A narrative approach allows a flexible, concept-driven integration of emerging evidence. Finally, the rapidly evolving incretin landscape means that evidence on newer agents and formulations will likely expand substantially soon.

7 | Future Directions

Future research should focus first on standardization of terminology and outcome measures related to GLP-1RA discontinuation, including clear, operational definitions of reinitiation and treatment switching. Without harmonization, discontinuation constructs risk becoming fragmented and noncomparable across studies, limiting interpretability and synthesis. In parallel, research efforts should align discontinuation and persistence outcomes with predefined adherence frameworks, enabling more coherent hypothesis testing and cross-study comparison. Given that these therapies are expected to be used long term, extended longitudinal observations are necessary to better characterize real-world treatment trajectories. Survey-based studies may be enhanced with prospective repeated-measures designs that capture evolving attitudes toward treatment.

The literature examining the mental health consequences of GLP-1RA discontinuation remains sparse, despite growing concern raised in recent commentaries (e.g., Wadden, et al., 2025 [154]; Endo and Kami, 2025 [85]; Carminati et al., 2025 [84]). This gap underscores an urgent need for systematic, theory-driven investigation of discontinuation processes and outcomes.

Finally, directed exploration of modifiable system-level and provider-level factors is warranted, particularly those anticipated to enhance healthcare system support, equip clinicians with adherence-promoting tools, and sustain patient persistence. Such work will be essential for confirming the relevance of established, generalized adherence constructs in the GLP-1RA context and for informing the development of targeted, scalable interventions.

8 | Conclusions

Discontinuation of GLP-1RAs is common in T2DM and WM care and often reflects a dynamic trajectory rather than a 1-time event. Improving adherence and persistence will require integrated strategies that address tolerability, expectations, and the understudied role of the healthcare system, while distinguishing temporary treatment gaps and within-class optimization from permanent cessation. Future research should standardize persistence and discontinuation definitions and pair clinical data with patient-centered qualitative work to clarify mechanisms and guide equitable interventions targeting patients at greatest risk of discontinuation.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Characteristics and main findings of real-world studies evaluating GLP-1RAs across clinical indications.