International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	IS OBESITY PHARMACOTHERAPY A LIFETIME COMMITMENT? A STRUCTURED REVIEW OF WEIGHT REGAIN AND STRATEGIES FOLLOWING INCRETIN CESSATION
DOI	https://doi.org/10.31435/ijitss.1(49).2026.5125
RECEIVED	17 December 2025
ACCEPTED	21 February 2026
PUBLISHED	05 March 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

IS OBESITY PHARMACOTHERAPY A LIFETIME COMMITMENT? A STRUCTURED REVIEW OF WEIGHT REGAIN AND STRATEGIES FOLLOWING INCRETIN CESSATION

Kornelia Domagała *(Corresponding Author, Email: kornelia.domagala189@gmail.com)*
7th Naval Hospital in Gdańsk, Gdańsk, Poland
ORCID ID: 0009-0008-4148-9320

Amanda Dolores Abramowicz
Military Institute of Aviation Medicine, Warsaw, Mazovia, Poland
ORCID ID: 0009-0004-6674-0594

Magdalena Rumin
Military Institute of Aviation Medicine, Warsaw, Mazovia, Poland
ORCID ID: 0009-0009-4281-8971

Olga Tatarata
Military Institute of Aviation Medicine, Warsaw, Mazovia, Poland
ORCID ID: 0009-0007-1279-7394

Maja Osuch
4th Military Clinical Hospital with Polyclinic SPZOZ in Wrocław, Wrocław, Poland
ORCID ID: 0009-0000-9815-2608

Maciej Osuch
4th Military Clinical Hospital with Polyclinic SPZOZ in Wrocław, Wrocław, Poland
ORCID ID: 0009-0009-2399-2878

Anna Kiełboń
Military Institute of Medicine in Warsaw, Warsaw, Mazovia, Poland
ORCID ID: 0009-0004-9028-6395

Martyna Jaciubek
Military Institute of Aviation Medicine, Warsaw, Mazovia, Poland
ORCID ID: 0009-0002-5520-0002

Carmena Luty
118th Military Hospital with Polyclinic SPZOZ in Ełk, Ełk, Poland
ORCID ID: 0009-0007-6084-0385

Zuzanna Olga Reklewska
The Military Medical Training Center, Łódź, Poland
ORCID ID: 0009-0008-3539-646X

ABSTRACT

Background: The 2026 World Health Organization (WHO) guidelines formalize a major shift in metabolic medicine by characterizing obesity as a chronic, progressive, and relapsing neuroendocrine disease. While innovative incretin-based medical technologies - specifically GLP-1 and dual GIP/GLP-1 receptor agonists - have achieved weight-loss magnitudes previously reserved for invasive metabolic surgery, the long-term durability of these outcomes after treatment cessation remains a formidable socio-clinical challenge.
Objective: This structured narrative review synthesizes contemporary evidence regarding weight-loss maintenance, the biological drivers of regain, and the systemic barriers to treatment persistence following the discontinuation of incretin-based therapies.
Methods: A comprehensive search of major bibliographic databases (2011–2026) was conducted, integrating data from randomized withdrawal trials (STEP and SURMOUNT programs), large-scale meta-analyses, and diverse real-world evidence (RWE).
Results: Evidence indicates that statistically significant weight regain can emerge as early as 8 weeks post-discontinuation, with substantial recovery of lost weight typical within 12 months. This rebound is primarily mediated by a biological "energy gap" of approximately 120 kcal per kilogram lost, driven by a combination of adaptive thermogenesis (reduced energy expenditure) and heightened orexigenic signaling. Crucially, real-world data reveal a significant "persistence gap," with 50–67% of patients discontinuing therapy within the first year due to economic barriers, global supply instabilities, and tolerability issues.
Conclusions: Effective obesity management requires a transition from short-term interventions to a lifelong "chronic care continuum." Future strategies must prioritize the preservation of fat-free mass, implement intensified monitoring protocols (specifically the 25% regain threshold), and promote a systemic reframing of pharmacotherapy as a permanent metabolic stabilizer rather than a transient cure.

KEYWORDS

Obesity, Incretin-Based Therapies, Weight Regain, Chronic Care, GLP-1 Receptor Agonists

CITATION

Kornelia Domagała, Amanda Dolores Abramowicz, Magdalena Rumin, Olga Tatarata, Maja Osuch, Maciej Osuch, Anna Kiełboń, Martyna Jaciubek, Carmena Luty, Zuzanna Olga Reklewska. (2026) Is Obesity Pharmacotherapy a Lifetime Commitment? A Structured Review of Weight Regain and Strategies Following Incretin Cessation. *International Journal of Innovative Technologies in Social Science*. 1(49). doi: 10.31435/ijitss.1(49).2026.5125

1. Introduction

Over the last decade, the scientific and societal conceptualization of obesity has undergone a fundamental evolution, shifting the focus from a perceived failure of personal discipline to a recognized crisis of physiological and systemic regulation. Major global health authorities, led by the World Health Organization (WHO), no longer categorize obesity as a mere "lifestyle choice." Instead, in the most recent 2026 guidelines, obesity is defined as a chronic, progressive, and relapsing neuroendocrine disease. This paradigm shift is more than semantic; it necessitates the implementation of a continuous care model (Care Continuum), where innovative pharmacological technologies serve as permanent stabilizers within a lifelong therapeutic architecture. The scale of this crisis is staggering, the WHO warns that obesity now affects over one billion people worldwide, serving as a primary driver of morbidity and mortality while imposing an economic burden that modern healthcare infrastructures are increasingly unable to sustain. The American Diabetes Association (ADA) underscores this by stating that obesity requires management protocols identical to other chronic metabolic disorders, such as type 2 diabetes or hypertension: treatment that does not terminate upon the resolution of initial symptoms.

From a socio-epidemiological perspective, obesity emerges from the tragic conflict between ancestral human biology and a pathogenic modern environment. Contemporary society is effectively trapped within an "obesogenic infrastructure," where ultra-processed, energy-dense foods act as pathogenic agents. This is not a matter of willpower, but rather a biological response to food engineering designed to bypass natural satiety mechanisms. Clinical evidence from inpatient randomized trials reveals that individuals exposed to ultra-processed diets consume significantly more calories - often exceeding 500 kcal per day - compared to those on unprocessed diets, even when macronutrients are matched. This leads to adiposopathy - pathological adipose tissue dysfunction - which fuels chronic low-grade inflammation and devastates cardiometabolic health. The resulting socio-economic strain is immense, with obesity-related costs consuming a substantial portion of national gross product in many industrialized nations. Such a framework clarifies why short-term behavioral interventions rarely produce durable results: they simply cannot neutralize the deeply embedded biological adaptations triggered by weight loss.

A fundamental hurdle in sustainable obesity management is the body's transition into a "weight-reduced state," a physiological configuration that aggressively defends adipose stores. After weight loss, the body enters a distinct neuroendocrine mode characterized by compensatory adaptations aimed at restoring lost tissue. This phenomenon is best explained by the concept of the "energy gap." Data from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) reveal a striking metabolic asymmetry: for every kilogram of weight lost, resting energy expenditure (REE) decreases by approximately 25 kcal/day due to adaptive thermogenesis, while the biological drive to eat increases by roughly 95 kcal/day above baseline. Combined, this 120 kcal/day gap per kilogram lost creates a state of persistent "biological hunger" that relentlessly drives the organism back toward its prior set point.

The advent of incretin-based technologies, specifically GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists, has revolutionized pharmacological efficacy, offering results previously reserved for invasive metabolic surgery. A milestone in this field was the SURMOUNT-5 head-to-head trial, which demonstrated that tirzepatide achieved a mean weight reduction of 20.2%, compared with 13.7% for semaglutide. These technological innovations provide patients with tools they previously lacked, yet they simultaneously raise critical questions regarding the long-term durability of these outcomes.

The durability of weight loss after treatment cessation remains the most sobering challenge. Evidence shows that stopping pharmacotherapy in most patients leads to an almost immediate weight rebound. Trajectory analyses suggest that statistically significant metabolic regain can be detected as early as eight weeks after discontinuation. Furthermore, real-world data highlight a significant "persistence gap," where up to 67% of patients discontinue therapy within the first year. This is often driven by systemic barriers such as high cost, limited insurance coverage, or tolerability issues, reflecting a broader social issue of inequity in access to innovative medical technologies.

As demonstrated by systematic reviews, patients typically recover a considerable portion of lost weight within 12 months of stopping therapy, often accompanied by the rapid erosion of cardiometabolic improvements and unfavorable shifts in body composition, such as the disproportionate loss of lean mass. In light of the WHO's 2026 person-centered care framework, clinicians and policymakers face a critical dilemma: determining when lifelong pharmacotherapy is necessary and how to design sustainable care models that minimize relapse risk.

The present structured review aims to: (1) synthesize contemporary evidence on body weight trajectories following the discontinuation of incretin-based therapies; (2) analyze the neuroendocrine mechanisms driving weight regain; (3) evaluate the discrepancies between controlled clinical trials and real-world persistence; and (4) propose systemic strategies for long-term obesity management, clearly distinguishing evidence-supported conclusions from pragmatic clinical propositions.

2. Methodology

2.1. Study Design and Scope

This investigation was conceptualized as a multidimensional structured narrative review, designed to critically integrate and interpret the rapidly expanding evidence base regarding the durability of weight-loss outcomes achieved through contemporary incretin-based medical technologies. Furthermore, it examines the broader clinical and systemic consequences associated with treatment discontinuation. Unlike traditional descriptive reviews, which often provide a linear summary of existing literature, this study adopts a synthetic approach. This is essential to manage the substantial heterogeneity found across current research, which spans from rigorously controlled Phase 3 randomized clinical trials (RCTs) and complex randomized withdrawal designs to diverse real-world evidence (RWE) derived from routine clinical practice and electronic health records (EHR). By utilizing this methodology, the study facilitates a coherent comparison of findings across varying clinical and social environments while preserving a clear hierarchy of evidence. Such an approach is indispensable for establishing clinically meaningful and socially relevant conclusions in the evolving landscape of metabolic medicine.

2.2. Search Strategy and Information Sources

The literature identification process relied on comprehensive and systematic searches across the most prominent electronic bibliographic databases, including PubMed/MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar. To ensure that the review captured the full technological and socio-technical landscape of obesity care, this primary strategy was supplemented by screening international clinical trial registries (e.g., ClinicalTrials.gov) and analyzing high-impact RWE publications, such as retrospective cohort studies and clinical registries. The review also integrated official international guidelines and position statements issued by the World Health Organization (WHO) and the American Diabetes Association (ADA). Given the rapid pace of innovation in this field, particular emphasis was placed on integrating the most recent meta-analyses and systematic reviews available up to February 2026.

The search covered a strategic timeframe from January 2011 to February 2026. This period was selected to bridge foundational physiological research - most notably the seminal work on hormonal adaptations by Sumithran (2011) -with the cutting-edge clinical data emerging from the STEP and SURMOUNT trial programs. To reflect the "state-of-the-art" in incretin-based technology, the identification process prioritized discontinuation-focused analyses published between 2024 and 2026. The search process was iterative; a "snowballing" technique was employed, wherein the reference lists of core publications and network meta-analyses were reviewed to capture additional relevant studies that might have been omitted by keyword-based queries.

2.3. Keywords and Eligibility Criteria

Search queries were constructed using targeted combinations of medical, physiological, and socio-technical terms linked with Boolean operators (AND/OR). Primary keywords included specific incretin-based agents (tirzepatide, semaglutide, liraglutide) and critical clinical phenomena: weight regain, weight loss maintenance, drug discontinuation, therapeutic persistence, the energy gap, and the weight-reduced state. Secondary queries focused on comparative effectiveness, particularly versus bariatric surgery, and socioeconomic cost-benefit analyses.

Publications were eligible for inclusion if they met at least one of the following criteria:

- Phase 3 randomized clinical trials, with a specific emphasis on randomized withdrawal designs (e.g., STEP 4, SURMOUNT-4).
- Head-to-head trials directly comparing the efficacy of different incretin-mimetic technologies (e.g., SURMOUNT-5).
- Meta-analyses and systematic reviews evaluating the durability of weight-loss effects and post-discontinuation weight trajectories.
- Observational studies and RWE analyses addressing real-world treatment persistence, adherence, and reasons for discontinuation.
- Official international guidelines and consensus documents relevant to the long-term management of obesity as a chronic, relapsing disease.

Studies were excluded if they were exclusively preclinical (animal models), lacked quantifiable human outcome data, or focused solely on the initial dose-escalation phase without providing data on long-term maintenance or post-treatment outcomes.

2.4. Evidence Hierarchy and Synthesis

In light of the significant variability in methodological rigor across the included literature, a qualitative evidence hierarchy was applied to the synthesis. The highest interpretive weight was assigned to randomized withdrawal trials and large-scale systematic reviews with meta-analyses involving tens of thousands of patients. Head-to-head trials were treated as high-value evidence for establishing comparative technological effectiveness. Real-world evidence and retrospective cohort data were treated as complementary; while they offer vital insights into the "persistence gap," they were interpreted with caution due to their higher susceptibility to systematic bias and confounding factors. International guidelines and expert consensus statements served as the primary interpretive framework, allowing the findings to be contextualized within the "Care Continuum" model. Evidence was synthesized thematically, bridging data on body weight trajectories and cardiometabolic outcomes with underlying biological mechanisms and their practical clinical and systemic implications.

2.5. Methodological Limitations

It is important to acknowledge that as a structured narrative review, rather than a formal systematic review with a new meta-analysis, this work has inherent limitations. Despite a structured and iterative selection process, the possibility remains that some niche publications or very recent "online-first" articles were missed. Furthermore, the integration of evidence from tightly controlled RCT environments with data from highly heterogeneous real-world populations requires nuanced interpretation. Variations in patient characteristics, insurance coverage, and clinical titration protocols may significantly influence the observed outcomes and trajectories described in this synthesis.

3. Obesity as a Chronic and Relapsing Disease: Biological, Epidemiological, and System-Level Frameworks

Contemporary metabolic medicine has undergone a fundamental shift in how obesity is defined and conceptualized. We are moving away from viewing it as a behavioral defect of the individual and toward recognizing it as a complex, chronic, and relapsing neuroendocrine disease. A critical milestone in this paradigm shift was the 2026 position statement issued by the World Health Organization (WHO), which formally characterized obesity as a global health crisis necessitating an integrated, person-centered, and lifelong model of care. This stance, reinforced by the American Diabetes Association (ADA) and the World Obesity Federation, carries a vital implication: the pathophysiological mechanisms driving obesity remain active regardless of a patient's current body weight. Consequently, the maintenance phase is physiologically the most vulnerable period, often representing the most challenging stage of therapy. Obesity is not a condition that is "cured" by weight loss; it is a condition that is "managed" through its suppression.

3.1. The Epidemiological Model: Food as an Environmental "Agent" in a Toxic Setting

Understanding the chronic nature of obesity requires an epidemiological lens. Within this framework, obesity arises from the interaction between a susceptible host and a pathogenic environmental agent. Highly processed, energy-dense foods function as the primary "agent," operating inside an obesogenic infrastructure characterized by sedentary lifestyles and constant caloric availability. This is a system-level failure as much as a biological one. Clinical trials have demonstrated that when individuals are exposed to ultra-processed diets, they consume approximately 508 kcal/day more than those on unprocessed diets, even when macronutrients are matched.

This interaction initiates adiposopathy, or the pathological dysfunction of adipose tissue. Adiposopathy extends beyond simple adipocyte hypertrophy; it encompasses profound alterations in adipocyte secretory function, resulting in chronic low-grade inflammation and ectopic lipid deposition. Lipid infiltration into organs such as the liver - contributing to metabolic dysfunction-associated steatohepatitis (MASH) - skeletal muscle, and the pancreas further fuels the disease. This subclinical inflammatory state serves as the "fuel" for various cardiometabolic comorbidities. Thus, obesity becomes a progressive biological process that remains embedded in the patient's physiology even when temporary behavioral modifications are achieved.

3.2. Physiology of the Weight-Reduced State

The relapsing nature of obesity is primarily rooted in the transition to the "weight-reduced state." This is a distinct physiological configuration, fundamentally different from the physiology of individuals who have never lived with obesity. The body interprets fat loss as an existential threat, activating an integrated defense system designed to rapidly restore depleted energy stores. It is a biological entrapment.

Central to this response is the concept of the "energy gap." This model highlights a striking adaptive asymmetry: for every kilogram of weight lost, resting energy expenditure (REE) decreases by approximately 25 kcal/day due to adaptive thermogenesis, while the biological drive to eat increases by roughly 95 kcal/day above baseline. Combined, this 120 kcal/day disparity per kilogram lost creates sustained and powerful metabolic pressure. Clinical data on the discontinuation of modern pharmacotherapy align closely with this model; the withdrawal of incretin signaling leads to the rapid reactivation of these compensatory mechanisms. From this perspective, post-treatment weight regain is not a behavioral failure. It is the biological consequence of returning to a state of dysregulated energy homeostasis.

3.3. Metabolic Adaptation and Adipocyte “Memory”

The defense of body weight extends beyond appetite regulation to encompass peripheral tissue adaptations. Following weight loss, skeletal muscle becomes metabolically more efficient, performing mechanical work with lower ATP expenditure - essentially doing more with less fuel. This is accompanied by persistent hormonal remodeling. Studies have shown that even one year after weight loss, levels of the orexigenic hormone ghrelin remain elevated, while anorexigenic signals like leptin and peptide YY remain suppressed.

An additional layer of complexity involves the concept of "metabolic memory" within adipose tissue. The shrinkage of adipocytes does not fully normalize their inflammatory or metabolic phenotype; instead, these cells appear primed for rapid lipid reaccumulation. This biological pressure toward regain is observed across all classes of anti-obesity medications. It suggests that the organism may “remember” its highest sustained weight as a revised set point, toward which it gravitates using all available physiological and behavioral mechanisms, such as unconscious reductions in spontaneous physical activity.

3.4. Clinical Analogy and the Care Continuum Model (WHO 2026)

Clinically, obesity parallels chronic conditions such as hypertension and type 2 diabetes. In these diseases, the normalization of a parameter, be it blood pressure or body weight, represents evidence of effective disease control rather than a cure. Discontinuing therapy solely because target parameters have been achieved would be analogous to withdrawing antihypertensive medication once blood pressure normalizes. It is a logical fallacy that frequently leads to clinical relapse.

The concept of a "care continuum" integrates behavioral, pharmacological, and surgical interventions dynamically. The WHO formally endorses the long-term use of GLP-1 receptor agonists in conjunction with behavioral therapy, recognizing that lifestyle modification alone is frequently insufficient to overcome biological resistance. Within this framework, pharmacotherapy functions as an exogenous stabilizer of the gut-brain axis. Its withdrawal reactivates the energy gap, much as the cessation of antihypertensive therapy precipitates a rebound elevation in blood pressure.

3.5. Weight Regain After Bariatric Surgery and Synergy With Pharmacotherapy

Perhaps the strongest evidence supporting the relapsing nature of obesity comes from metabolic and bariatric surgery (MBS). Even invasive procedures that permanently alter gastrointestinal anatomy do not eliminate relapse in all patients. Clinically significant weight regain occurs in approximately 17.6% of individuals post-surgery, emphasizing that mechanical intervention alone cannot permanently override systemic biology.

This observation underscores the systemic nature of the disease. Studies examining the synergy between surgery and pharmacotherapy show that patients experiencing post-surgical weight regain can reestablish metabolic control with modern medications. Pharmacotherapy, therefore, assumes a central role throughout the disease trajectory, serving as bridge therapy prior to surgery, rescue therapy after regain, or maintenance therapy in long-term disease management. Recognizing this systemic perspective is essential for reducing stigma and reframing obesity as a chronic biological disease rather than a moral failing.

3.6. Socio-Economic Determinants of Access and Treatment Persistence

The transition of obesity management to a chronic care model introduces significant socio-economic complexities. While incretin-based medical technologies offer unprecedented efficacy, their integration into public health systems is often hindered by a profound "access gap." In most industrialized nations, the annual cost of these therapies ranges between USD 12,000 and 16,000. This creates a substantial financial burden for patients without comprehensive insurance coverage.

This economic barrier is a primary driver of the "persistence gap," where more than half of patients (up to 67%) discontinue treatment within the first twelve months. From a social science perspective, this creates a state of "metabolic inequality." Patients from higher socio-economic strata may sustain lifelong treatment, effectively "buying" metabolic stability, while those from low-income backgrounds face a cycle of weight loss and rapid regain due to cost-driven discontinuation. The 2026 WHO guidelines emphasize that "system readiness"—the ability of a healthcare system to provide equitable, long-term access—is as critical as the pharmacological potency of the drug itself. Without stable reimbursement frameworks, the technological breakthrough of GLP-1 and GIP agonists risks widening health disparities rather than closing them.

4. Results

4.1. Clinical Evidence on Body Weight Trajectories and Cardiometabolic Outcomes After Treatment Discontinuation

Evaluating the long-term effectiveness of modern anti-obesity technologies requires a dual perspective. We must balance the high-precision results of randomized controlled trials (RCTs) with the messy, complex realities of routine clinical practice, often referred to as real-world evidence (RWE). The aggregated data reveal a stark contrast. While contemporary incretin-based therapies achieve weight-loss milestones once thought possible only through surgery, the cessation of treatment often triggers a swift return toward the patient's underlying pathophysiological set point. In many clinical scenarios, the metabolic gains achieved over months of therapy can begin to erode almost immediately after the pharmacological "shield" is removed.

4.2. Hierarchy of Efficacy and the SURMOUNT-5 Technological Landmark

Quantitative evidence confirms the substantial potency of second-generation incretin-based agents, particularly in patients without comorbid type 2 diabetes. Comprehensive meta-analyses delineate a clear efficacy hierarchy. Specifically, tirzepatide demonstrates a superior weight-reducing capacity compared to semaglutide, while both agents significantly outperform earlier-generation technologies such as liraglutide.

The SURMOUNT-5 trial stands as a landmark in metabolic research. It represents the first direct head-to-head comparison between tirzepatide and semaglutide in an adult population with obesity. After 72 weeks of treatment, tirzepatide achieved a mean weight reduction of 20.2%, whereas semaglutide 2.4 mg resulted in a 13.7% reduction. These findings validate previous meta-analytical trends showing significant improvements in body mass index (BMI) and waist circumference. Crucially, tirzepatide more consistently enabled patients to reach and surpass the clinically ambitious weight-loss thresholds of ≥15% and ≥20%, setting a new technological standard for pharmacotherapy.

4.3. Dynamics and Trajectory of Regain: The Critical 8-Week Window

In the current landscape of obesity management, the primary challenge has shifted. It is no longer just about initial weight loss; it is about the complexities of the post-treatment maintenance phase. A meta-analysis conducted by Wu et al. (2025) suggests that statistically detectable weight regain can emerge as early as eight weeks following the discontinuation of medication. This rapid rebound indicates an almost immediate reactivation of compensatory neuroendocrine mechanisms once the exogenous satiety signal is withdrawn.

The STEP 1 extension study provided a sobering confirmation of this biological pressure. Patients who stopped using semaglutide regained an average of 11.6 percentage points of their body weight within a single year. An even more dramatic divergence was observed in the SURMOUNT-4 trial. In this study, participants switched to a placebo regained 14% of their body weight, while those who continued tirzepatide therapy achieved an additional 5.5% reduction. Some researchers hypothesize that the magnitude of regain may be directly proportional to initial therapeutic success. This suggests that "super-responders" might experience the most intense biological drive to recover lost weight once pharmacological support ends.

4.4. Real-World Evidence and the Socio-Technical Persistence Gap

The success seen in clinical trials becomes considerably more nuanced when viewed through the lens of real-world data. Analyses from large-scale databases reveal a substantial "persistence gap" between controlled efficacy and routine effectiveness. In real-world settings, approximately 50% to 67% of patients discontinue therapy within the first 12 months, a staggering figure that undermines the chronic care model.

Table 1. Comparison of Randomized Controlled Trials (RCTs) and Real-World Evidence (RWE) Outcomes

Feature	Clinical Trials (RCTs – e.g., SURMOUNT, STEP)	Real-World Practice (RWE – e.g., SHAPE, TriNetX)
Weight reduction	Tirzepatide: ~20%; Semaglutide: ~14%	Often 3–5 percentage points lower
12-month adherence	Very high (typically >90%)	Low (50–67% discontinuation)
Major barriers	Minimal (study drug provided; structured monitoring)	Cost, supply constraints, tolerability
Titration	Fixed protocol (dose escalation every 4 weeks)	Individualized, often slower

Note: Adapted from Alexander et al. (2025) and Ng et al. (2025).

The drivers of this persistence gap are largely socio-economic. Financial barriers are paramount. Annual out-of-pocket costs ranging from USD 12,000 to 16,000 are prohibitive for many patients without comprehensive insurance coverage. Logistical hurdles, including global drug shortages, further jeopardize treatment continuity. Additionally, gastrointestinal side effects affect a vast majority of users. In routine care, these often lead to slower titration or total discontinuation, whereas trial participants are frequently encouraged to persist through the side-effect profile.

4.5. Erosion of Cardiometabolic Benefits and the 25% Threshold

Weight regain is a systemic health issue, not a purely aesthetic one. A post hoc analysis of the SURMOUNT-4 trial identified a critical inflection point: regaining just 25% of previously lost weight is associated with a significant rise in systolic blood pressure and a deterioration in glycemic control.

For patients who regain more than 75% of their lost weight, metabolic markers such as HbA1c, fasting insulin, and lipid profiles often return to baseline levels. Furthermore, weight recovery without structured resistance training tends to favor the accumulation of visceral fat with little restoration of lean mass. This pattern increases the risk of sarcopenic obesity, leaving the patient in a worse physiological state than before they started treatment.

4.6. Predictors of Therapeutic Response: Identifying Patient Phenotypes

Current research allows for a more predictive approach to obesity care. Key observations include:

- Early Response: Achieving a weight reduction of ≥5% within the first three months is the most reliable predictor of long-term success.
- Comorbid Diabetes: Patients with type 2 diabetes typically lose 3 to 5 percentage points less weight than those without the condition, likely due to altered metabolic handling of incretins.
- Demographics: Younger individuals and women often show greater initial weight loss, though they may also experience stronger biological pressure to regain weight after treatment ends.

In summary, incretin-based agents act as powerful stabilizers of satiety signaling. However, when this signal is withdrawn, as happens for a majority of real-world patients within a year, a rapid resurgence of weight gain is common, often beginning within eight weeks. Maintaining metabolic health thus emerges as a lifelong systemic challenge rather than a one-time medical intervention.

5. Discussion

5.1. The Biological Imperative: Neuroendocrinology of the Weight-Reduced State

To truly comprehend why the discontinuation of modern pharmacotherapy results in such rapid and substantial weight rebound, a fundamental perspective shift is required. Obesity cannot be viewed solely through the lens of behavioral choices; rather, it represents a deep-seated disruption in the homeostatic machinery that regulates energy balance. A critical consensus emerging from the NIDDK workshops and formalized in the 2026 WHO guidelines is that the "weight-reduced state" is a distinct, durable, and highly vulnerable physiological configuration. This state differs fundamentally from the physiology of individuals with stable body weights who have never experienced obesity; it is defined by an aggressive, biologically programmed drive to restore fat mass.

5.2. Gut–Brain Axis Dysregulation and the "Food Noise" Phenomenon

The pharmacological “shield” provided by incretin-based agents extends far beyond the physical slowing of gastric emptying. A primary mechanism, highlighted in recent analyses of ingestive behaviors (Bettadapura et al., 2025), involves the modulation of the neurobiological reward system. Patients consistently report the elimination of "food noise", the persistent, intrusive thoughts about eating that previously dominated their cognitive landscape. This "quieted" state allows for the restoration of executive control over food intake.

However, when treatment is withdrawn, this pharmacological "software patch" vanishes almost instantly. The resulting surge in ghrelin levels, combined with the dysregulation of dopaminergic signaling, triggers a profound hedonic rebound. The drive to eat - often described as a desperate "wanting" - returns with an intensity that renders behavioral resistance nearly impossible. This is not a failure of willpower; it is a survival signal from a brain that has suddenly lost its regulatory stability.

5.3. Adaptive Thermogenesis and the Dynamics of the Energy Gap

Weight regain is further propelled by adaptive thermogenesis - a phenomenon where resting energy expenditure (REE) drops significantly more than would be expected based on changes in body composition alone. Physiological models (Aronne et al., 2021; Melby et al., 2017) conceptualize this as the widening of the "energy gap." For every kilogram of weight lost, the body conserves approximately 25 kcal/day, while the biological drive to consume calories increases by roughly 95 kcal/day above baseline. This 120 kcal per kilogram imbalance creates relentless metabolic pressure. The situation is further exacerbated by increased skeletal muscle efficiency; after weight reduction, muscles require less energy to perform the same mechanical work.

The following table integrates these multi-level mechanisms, illustrating how the organism systematically defends a higher body weight.

Table 2. Integrated Overview of Mechanisms in the Weight-Reduced State

System	Change in the weight-reduced state	Clinical consequence
Hormonal	↓ Leptin, ↓ Insulin, ↑ Ghrelin	Marked increase in hunger and food drive
Metabolic	↓ Resting energy expenditure (~25 kcal/kg lost)	Adaptive thermogenesis (energy conservation)
Tissue-level	↑ Skeletal muscle ATP efficiency	Lower energy cost of movement
Behavioral	↓ Non-exercise activity thermogenesis (NEAT)	“Sedentary spiral” and further energy conservation
Neurobiological	Reward system dysregulation (dopamine signaling)	Increased hedonic appeal of food

5.4. The Socio-Technological Paradox and Metabolic Inequality

The necessity for lifelong pharmacotherapy is inextricably linked to the socio-technological paradox of the modern environment. Incretin-based medications function as a high-tech countermeasure to another form of technology: food engineering. Modern ultra-processed foods are specifically designed to bypass human homeostatic satiety signals (Hall et al., 2019).

From a social science perspective, this introduces a state of "metabolic inequality." In a landscape where long-term stability costs between USD 12,000 and 16,000 annually (Barrett et al., 2025; Samuels et al., 2025), metabolic health effectively becomes a subscription-based service. Without equitable reimbursement frameworks, we risk a future where freedom from obesity is a luxury for the affluent, while lower-income populations remain trapped in cycles of regain and chronic inflammation.

5.5. Precision Medicine and the Future of the Care Continuum

The future of obesity management must evolve toward precision medicine and patient phenotyping (Moiz et al., 2025). We must move away from the universal "weight-loss course" toward identifying individuals whose biology necessitates permanent pharmacological support. A pragmatic clinical strategy involves monitoring the 25% regain threshold as a critical inflection point for cardiometabolic deterioration (Horn et al., 2025). Maintenance strategies must prioritize the preservation of lean mass through optimized protein intake (1.2–1.5 g/kg/day) and structured resistance training to prevent sarcopenic obesity (Mechanick et al., 2024; Mozaffarian et al., 2025).

The strategic model developed below attempts to translate these findings into specific clinical guidelines.

Table 3. Strategic Framework for Post-Discontinuation Management within the Care Continuum Model

Intervention domain	Recommended strategy	Clinical objective
Dosing	Consider tapering or interval extension; maintain minimal effective dose	Mitigate abrupt appetite rebound
Body composition	Resistance training + protein intake (1.2–1.5 g/kg/day)	Preserve lean mass and stabilize resting energy expenditure
Monitoring	Structured follow-up; weight and appetite tracking during early post-discontinuation phase	Detect early regain trajectory
Re-intervention	Reinstitute therapy at ≥25% regain threshold	Prevent cardiometabolic deterioration
Education	Frame obesity as a chronic disease	Reduce stigma and improve long-term adherence

Ultimately, pharmacotherapy acts as a stabilizer of the gut–brain axis. Its removal in an obesogenic environment is akin to removing a dam; the resulting flood of weight regain is not an anomaly, but a predictable consequence of a system returning to its dysregulated equilibrium.

5.6. Limitations of the Available Evidence and Directions for Future Research

While the evidence supporting a high prevalence of weight regain following the cessation of modern incretin-based therapy is internally consistent and biologically plausible, the current knowledge base remains constrained by several conceptual and methodological hurdles. Perhaps the most pressing challenge is the striking dichotomy between outcomes observed in tightly controlled randomized clinical trials (RCTs) and those derived from routine clinical practice. Analyses utilizing real-world databases, such as TriNetX, demonstrate that treatment persistence in general populations is substantially lower than that reported in Phase 3 trials (Alexander et al., 2025; Samuels et al., 2025). With discontinuation rates reaching up to 67% within the first year, existing models used to predict post-treatment trajectories may significantly underestimate the true, population-level magnitude of metabolic relapse.

A further limitation concerns the duration of post-discontinuation follow-up. Most pivotal trials, including the STEP 1 extension and the SURMOUNT-4 trial, terminate approximately 52 weeks after treatment withdrawal (Wilding et al., 2022; Aronne et al., 2024). While contemporary meta-analyses can map regain trajectories as early as week 8, robust data on long-term (5–10 year) outcomes remain unavailable. Such

evidence is essential to determine whether body weight eventually stabilizes or continues to drift toward baseline. This gap is particularly salient when compared to metabolic surgery, where durability has been documented for over a decade. Furthermore, future studies must more precisely characterize the long-term safety profile of sustained GLP-1 and GIP receptor stimulation, specifically regarding gallbladder disease, bone mineral density, and rare psychiatric outcomes (Liu et al., 2023; Müllertz et al., 2024).

Mechanistic evidence also requires deeper refinement, particularly concerning the preservation of lean mass and skeletal health. Rapid weight loss may increase a patient's vulnerability to sarcopenic obesity during the regain phase, yet prospective studies testing structured exercise protocols specifically designed for the post-discontinuation period are currently lacking. In parallel, the rapid pace of incoming evidence—typified by the recent SURMOUNT-5 results—risks rendering conventional systematic reviews outdated almost immediately upon publication (Aronne et al., 2025). This underscores an urgent need for "living" network meta-analyses that can integrate new data in real-time.

Finally, the socioeconomic dimension remains a major evidence gap. While incretin-based therapies are highly effective, their cumulative lifetime costs may eventually exceed those of surgical intervention (Barrett et al., 2025; Brosnihan et al., 2025). The 2026 WHO guidelines emphasize that "system readiness" and equity of access are core implementation barriers (Celletti et al., 2026). Further modeling studies are needed to estimate long-term, system-level savings from the prevention of major adverse cardiovascular events (MACE) and metabolic dysfunction-associated steatohepatitis (MASH). Crucially, the validation of dose-reduction and tapering protocols remains largely unexplored, despite its high clinical relevance for patients facing financial or tolerability-related transitions.

6. Conclusions

The synthesis of randomized clinical trials, meta-analyses, and real-world evidence (RWE) demonstrates that the risk of weight regain following the discontinuation of incretin-based pharmacotherapy remains high for the vast majority of patients. This weight recovery typically unfolds rapidly - often commencing within the first eight weeks of cessation - mirroring the metabolic trajectories documented in contemporary literature (Wilding et al., 2022; Wu et al., 2025). These observations align with the physiological concepts of the "weight-reduced state" and the "energy gap" of approximately 120 kcal/day per kilogram lost (Aronne et al., 2021; Melby et al., 2017). In this state, coordinated neuroendocrine adaptations actively promote the restoration of energy stores by intensifying hunger signaling and reducing energy expenditure. Consequently, maintaining weight loss without ongoing pharmacological support emerges as a formidable biological challenge rather than a failure of individual willpower.

Current evidence also highlights significant heterogeneity in individual treatment responses and a clinically profound discrepancy between outcomes observed in controlled trials and those found in real-world persistence. In routine practice, early discontinuation is frequent, with up to 67% of patients ceasing therapy within the first year (Mozaffarian et al., 2025; Alexander et al., 2025). This trend underscores how systemic factors, including high out-of-pocket costs (ranging from USD 12,000 to 16,000 annually), limited drug access, and tolerability issues, shape long-term effectiveness at the population level (Barrett et al., 2025; Samuels et al., 2025).

In response to these findings, contemporary obesity management must transition toward a chronic care continuum model. This approach must tightly integrate pharmacotherapy with targeted behavioral strategies and the rigorous protection of body composition. The preservation of fat-free mass through increased protein intake (1.2–1.5 g/kg/day) and structured resistance training is a fundamental cornerstone for maintaining the metabolic quality of weight loss (Mechanick et al., 2024). Furthermore, post hoc data suggest that even a partial weight regain exceeding a 25% threshold leads to the rapid erosion of prior cardiometabolic benefits, specifically regarding blood pressure and glycemic control (Horn et al., 2025). This necessitates individualized and intensified monitoring protocols once active pharmacological treatment concludes.

Ultimately, the traditional debate regarding whether obesity pharmacotherapy must be "lifelong" requires reframing. A more clinically and socially useful objective is to identify which specific patient subgroups derive the greatest net benefit from continued treatment. While the 2026 WHO recommendations provide a vital overarching framework for long-term care, further prospective research is required to define optimal tapering protocols and identify predictors of therapeutic success without perpetual pharmacological support (Celletti et al., 2026).

In summary, incretin-based pharmacotherapy should not be conceptualized as a transient "dieting intervention," but as a sophisticated medical technology that modulates chronic energy dyshomeostasis. The

future of obesity medicine depends on developing safe discontinuation pathways, optimizing multimodal combination strategies, and building predictive models to ensure that these revolutionary medical technologies translate into equitable and durable health improvements across diverse populations.

Disclosures

Author's Contributions

Conceptualization: Zuzanna Reklewska, Anna Kiełboń, Carmena Luty;
Methodology: Magdalena Rumin, Maciej Osuch;
Software: Martyna Jaciubek;
Check: Zuzanna Reklewska, Olga Tatarata, Amanda Abramowicz;
Formal analysis: Maciej Osuch, Maja Osuch;
Investigation: Martyna Jaciubek, Carmena Luty, Anna Kiełboń;
Resources: Kornelia Domagała,;
Data curation: Maja Osuch, Anna Kiełboń;
Writing – rough preparation: Kornelia Domagała, Martyna Jaciubek, Carmena Luty, Amanda Abramowicz;
Writing – review and editing: Maciej Osuch, Maja Osuch, Anna Kiełboń, Olga Tatarata, Magdalena Rumin;
Visualization: Magdalena Rumin, Amanda Abramowicz;
Supervision: Kornelia Domagała,;
Project administration: Kornelia Domagała,;
Receiving funding:. Kornelia Domagała

All authors have read and agreed with the published version of the manuscript.

Funding Statement: The author received no external funding for this work.
Institutional Review Board Statement: Not applicable; this review included only published data.
Informed Consent Statement: Not applicable.
Data Availability Statement: All supporting data are available within the cited peer-reviewed literature.
Acknowledgments: The author acknowledges the contribution of investigators and data curators whose high-quality research underpins the advances reviewed herein.
Conflict of Interest Statement: The author declares no conflict of interest.

REFERENCES

1. Alexander, G. C., Xu, Y., Xiao, X., Lewis, S. V., Zeger, S., & Mehta, H. B. (2025). Weight changes from glucagon-like peptide-1 receptor agonist use and discontinuation: A retrospective cohort study. Obesity, 33(1), 112–124. https://doi.org/10.1002/oby.70076
2. American Diabetes Association Professional Practice Committee. (2026). 8. Obesity and weight management for the prevention and treatment of diabetes: Standards of care in diabetes - 2026. Diabetes Care, 49(Suppl. 1), S166–S182. https://doi.org/10.2337/dc26-S008
3. Aronne, L. J., Hall, K. D., Jakicic, J. M., Leibel, R. L., Lowe, M. R., Rosenbaum, M., & Klein, S. (2021). Describing the weight-reduced state: Physiology, behavior, and interventions. Obesity, 29(Suppl. 1), S9–S24. https://doi.org/10.1002/oby.23086
4. Aronne, L. J., Horn, D. B., le Roux, C. W., Ho, W., Falcon, B. L., Gomez Valderas, E., Das, S., Lee, C. J., Glass, L. C., Senyucel, C., & Dunn, J. P. (2025). Tirzepatide as compared with semaglutide for the treatment of obesity. The New England Journal of Medicine, 393(1), 26–36. https://doi.org/10.1056/NEJMoa2416394
5. Aronne, L. J., Sattar, N., Horn, D. B., Bays, H. E., Wharton, S., Lin, W. Y., Ahmad, N. N., Zhang, S., Liao, R., Bunck, M. C., Jouravskaya, I., & Murphy, M. A. (2024). Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: The SURMOUNT-4 randomized clinical trial. JAMA, 331(1), 38–48. https://doi.org/10.1001/jama.2023.24945
6. Barrett, T. S., Hafermann, J. O., Richards, S., & Le Jeune, K. (2025). Obesity treatment with bariatric surgery vs GLP-1 receptor agonists: A real-world cost-effectiveness study. JAMA Surgery, 160(12), 1232–1240. https://doi.org/10.1001/jamasurg.2025.3590

7. Berg, S., Stickle, H., Rose, S. J., & Nemec, E. C. (2025). Discontinuing glucagon-like peptide-1 receptor agonists and body habitus: A systematic review and meta-analysis. Obesity Reviews, 26(2), e13929. https://doi.org/10.1111/obr.13929
8. Bray, G. A., Kim, K. K., & Wilding, J. P. H. (2017). Obesity: A chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obesity Reviews, 18(7), 715–723. https://doi.org/10.1111/obr.12551
9. Brosnihan, P., Luce, M. S., Yetasook, A. K., Perez, C., Scharf, K. R., & Aly, S. (2025). Great debates: Undergoing the knife versus pill-popping—The comparative efficacy and cost-effectiveness of bariatric surgery and GLP-1 receptor agonists. The American Surgeon, 91(10), 1587–1593. https://doi.org/10.1177/00031348251337145
10. Busetto, L., Bettini, S., Makaronidis, J., Roberts, C. A., Halford, J. C. G., & Quarenghi, M. (2021). Mechanisms of weight regain. European Journal of Internal Medicine, 93, 3–7. https://doi.org/10.1016/j.ejim.2021.01.002
11. Celletti, F., Farrar, J., & De Regil, L. (2026). World Health Organization guideline on the use and indications of glucagon-like peptide-1 therapies for the treatment of obesity in adults. JAMA. https://doi.org/10.1001/jama.2025.24288
12. De Lorenzo, A., Romano, L., Di Renzo, L., Di Lorenzo, N., Cenname, G., & Gualtieri, P. (2019). Obesity: A preventable, treatable, but relapsing disease. Nutrition, 71, 110615. https://doi.org/10.1016/j.nut.2019.110615
13. Hall, K. D., & Kahan, S. (2018). Maintenance of lost weight and long-term management of obesity. Medical Clinics of North America, 102(1), 183–197. https://doi.org/10.1016/j.mcna.2017.08.012
14. Hall, K. D., Ayuketah, A., Brychta, R., et al. (2019). Ultra-processed diets cause excess calorie intake and weight gain: An inpatient randomized controlled trial of ad libitum food intake. Cell Metabolism, 30(1), 67–77. https://doi.org/10.1016/j.cmet.2019.05.008
15. Horn, D. B., Linetzky, B., Davies, M. J., et al. (2025). Cardiometabolic parameter change by weight regain on tirzepatide withdrawal in adults with obesity: A post hoc analysis of the SURMOUNT-4 trial. JAMA Internal Medicine. https://doi.org/10.1001/jamainternmed.2025.6112
16. Jastreboff, A. M., le Roux, C. W., et al. (2022). Tirzepatide once weekly for the treatment of obesity. The New England Journal of Medicine, 387(3), 205–216. https://doi.org/10.1056/NEJMoa2206038
17. Jensen, S. B. K., Janus, C., Lundgren, J. R., et al. (2022). Exploratory analysis of eating- and physical activity-related outcomes from a randomized controlled trial for weight loss maintenance. Nature Communications, 13, 4770. https://doi.org/10.1038/s41467-022-32307-y
18. Jia, I-T. T., Bloomfield, G. C., Chen, M. Y., et al. (2025). Analysis of the long-term impact of glucagon-like peptide-1 (GLP-1) receptor agonists for control of obesity and obesity-related comorbidities: A meta-analysis. Surgical Endoscopy. https://doi.org/10.1007/s00464-025-12086-5
19. Kushner, R. F., & Shapiro, M. (2025). Obesity: Assessment and treatment across the care continuum. Annals of Medicine, 57(1), 2521433. https://doi.org/10.1080/07853890.2025.2521433
20. Laughlin, M. R., Osganian, S. K., Yanovski, S. Z., & Lynch, C. J. (2021). Physiology of the weight reduced state: A report from a National Institute of Diabetes and Digestive and Kidney Disease workshop. Obesity, 29(Suppl. 1), S5–S8. https://doi.org/10.1002/oby.23079
21. Liu, Y., Ruan, B., Jiang, H., et al. (2023). The weight-loss effect of GLP-1RAs in non-diabetic individuals with overweight or obesity: A systematic review with meta-analysis. The American Journal of Clinical Nutrition, 118(3), 614–626. https://doi.org/10.1016/j.ajcnut.2023.04.017
22. Lucas, E., Simmons, O., Tchang, B., & Aronne, L. J. (2023). Pharmacologic management of weight regain following bariatric surgery. Frontiers in Endocrinology, 13, 1043595. https://doi.org/10.3389/fendo.2022.1043595
23. Mechanick, J. I., Butsch, W. S., Christensen, S. M., et al. (2024). Strategies for minimizing muscle loss during use of incretin-mimetic drugs for treatment of obesity. Obesity Reviews, 25(12), e13841. https://doi.org/10.1111/obr.13841
24. Melby, C. L., Paris, H. L., Foright, R. M., & Peth, J. (2017). Attenuating the biologic drive for weight regain following weight loss. Nutrients, 9(5), 468. https://doi.org/10.3390/nu9050468
25. Mozaffarian, D., Agarwal, M., Aggarwal, M., et al. (2025). Nutritional priorities to support GLP-1 therapy for obesity: A joint Advisory. The American Journal of Clinical Nutrition, 122(1), 344–367. https://doi.org/10.1002/oby.24336
26. Müllertz, A. L. O., Sandsdal, R. M., Jensen, S. B. K., & Torekov, S. S. (2024). Potent incretin-based therapy for obesity: A systematic review and meta-analysis. Obesity Reviews, 25(4), e13717. https://doi.org/10.1111/obr.13717
27. Ng, C. D., Divino, V., Wang, J., et al. (2025). Real-world weight loss observed with semaglutide and tirzepatide in patients with overweight or obesity and without type 2 diabetes (SHAPE). Advances in Therapy, 42(8), 5468–5480. https://doi.org/10.1007/s12325-025-03340-2
28. Quarenghi, M., Capelli, S., Galligani, G., et al. (2025). Weight regain after liraglutide, semaglutide or tirzepatide interruption: A narrative review of randomized studies. Journal of Clinical Medicine, 14(11), 3791. https://doi.org/10.3390/jcm14113791

29. Rubino, D., Abrahamsson, N., Davies, M., et al. (2021). 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, 325(14), 1414–1425. https://doi.org/10.1001/jama.2021.3224
30. Samuels, J. M., Ye, F., Irlmeier, R., et al. (2025). Real-world titration, persistence & weight loss of semaglutide and tirzepatide in an academic obesity clinic. Diabetes, Obesity and Metabolism. https://doi.org/10.1111/dom.70004
31. Sumithran, P., Prendergast, L. A., Delbridge, E., et al. (2011). Long-term persistence of hormonal adaptations to weight loss. The New England Journal of Medicine, 365(17), 1597–1604. https://doi.org/10.1056/NEJMoa1105816
32. West, S., Scragg, J., Aveyard, P., et al. (2026). Weight regain after cessation of medication for weight management: Systematic review and meta-analysis. BMJ, 392, e085304. https://doi.org/10.1136/bmj-2025-085304
33. Wilding, J. P. H., Batterham, R. L., Davies, M., et al. (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