Therapeutics, Pharmacology and Clinical Toxicology

Editorial

Ther Pharmacol Clin Toxicol
Volume: 24, Issue: 1, January–March 2026

Received: 27 February 2026
Accepted: 5 March 2026

The GLP-1 revolution arrives at Europe's doorstep: are we ready? a call to action for romanian pharmacotherapy

Dragoș **Crețoiu** [1, 2] *

[1] Department of Medical Genetics, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[2] Polizu Clinical Hospital, Alessandrescu-Rusescu National Institute of Mother and Child Health, Bucharest, Romania

*** Correspondence to:** Dragoș Crețoiu, Department of Medical Genetics, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania. E-mail: dragos@cretoiu.ro

A pharmacotherapeutic tipping point

In the span of just ninety days—from December 2025 through March 2026—the pharmacological landscape of GLP-1 receptor agonists (GLP-1 RAs) has undergone a transformation that would have been difficult to predict even two years ago. The United States Food and Drug Administration (FDA) approved oral semaglutide 25 mg as the first oral GLP-1 RA for chronic weight management in December 2025, with commercial availability beginning in January 2026 [1]. Barely three months later, a higher-dose injectable formulation—semaglutide 7.2 mg—was approved under the Commissioner's National Priority Voucher program, with the pivotal STEP UP trial demonstrating mean weight loss of 18.7% at 72 weeks regardless of treatment adherence in adults with obesity without diabetes [2]. In parallel, the World Health Organization (WHO) issued conditional recommendations for the use of GLP-1 RAs in obesity treatment as part of comprehensive, lifelong care, and added these agents to its Essential Medicines List for type 2 diabetes [3]. The European Medicines Agency (EMA) accepted a Summary of Product Characteristics update for oral semaglutide (Rybelsus) incorporating cardiovascular outcome data from the SOUL trial, strengthening the evidence base for cardiovascular benefits in type 2 diabetes [4].

These are not incremental advances. They represent a *paradigmatic shiftin* how we conceptualize pharmacotherapy for metabolic disease—a shift that extends well beyond glycemic control into obesity, cardiovascular prevention, metabolic dysfunction-associated steatohepatitis (MASH), and potentially neurodegenerative disorders. The question confronting clinicians, regulators, and healthcare policymakers in Romania and across Central and Eastern Europe is not whether this revolution will reach us, but whether we will be ready when it does.

Beyond glycemic control: the expanding pharmacological footprint

The original development of GLP-1 receptor agonists was grounded in incretin physiology and the treatment of type 2 diabetes. What has emerged since is far more ambitious. In the United States, semaglutide now holds approved indications spanning type 2 diabetes, chronic weight management (in adults and adolescents), cardiovascular risk reduction, and—through accelerated approval—the treatment of MASH with moderate-to-advanced hepatic fibrosis [5]. Completed trials have demonstrated benefit in heart failure with preserved ejection fraction (HFpEF) and chronic kidney disease, while the EVOKE program investigating oral semaglutide in early Alzheimer's disease reported negative primary endpoint results in November 2025, with trials subsequently discontinued [6]. Meanwhile,

the competitive landscape is intensifying: tirzepatide, a dual GLP-1/GIP receptor agonist, has demonstrated superior weight loss in head-to-head trials with semaglutide [7], while next-generation agents such as retatrutide (a triple GLP-1/GIP/glucagon agonist), CagriSema (semaglutide plus cagrilintide), and oral non-peptide agonists like orforglipron are advancing through late-stage clinical development [8].

This expansion in indications is pharmacologically logical. GLP-1 receptors are expressed not only in the pancreas but across the cardiovascular system, liver, kidneys, and central nervous system. The pleiotropic effects of GLP-1 receptor agonism—anti-inflammatory, anti-atherogenic, appetite-modulating, and potentially neuroprotective—offer a mechanistic rationale for what the clinical data are now confirming. For a journal situated at the intersection of therapeutics, pharmacology, and clinical toxicology, this drug class demands close scrutiny.

Emerging safety signals: the toxicological dimension

The enthusiasm surrounding GLP-1 receptor agonists must be tempered by a sober assessment of their safety profile, particularly as doses escalate and indications broaden. The gastrointestinal adverse effect burden—nausea, vomiting, diarrhea, constipation—remains the principal limitation and the leading cause of treatment discontinuation. With the newly approved semaglutide 7.2 mg dose, gastrointestinal events were reported in 70.8% of participants in STEP UP [2].

More concerning is the emergence of dysesthesia—a neurological symptom characterized by altered skin sensation, burning, or pain—which was observed at notably higher rates with the 7.2 mg dose across both trials in the STEP UP program. In STEP UP (adults with obesity without diabetes), dysesthesia-related events were reported in 22.9% of participants receiving semaglutide 7.2 mg, compared to 6.0% with 2.4 mg and 0.5% with placebo; in STEP UP T2D, the corresponding rates were 18.9%, 4.9%, and 0% [2]. The FDA has stated it is conducting further investigations into this signal. While symptoms appear largely reversible upon dose reduction, the dose-dependent pattern raises important mechanistic questions about GLP-1 receptor engagement in the peripheral nervous system that remain unanswered.

Additionally, the EMA and the Heads of Medicines Agencies (HMA), through their Executive Steering Group on Shortages (MSSG), have raised alarm about the off-label use of GLP-1 receptor agonists for cosmetic weight loss in individuals without clinical obesity, noting that this practice worsens existing supply shortages and exposes patients to risks outside the approved therapeutic framework [9]. The proliferation of falsified or illegally marketed semaglutide products through online channels further compounds the toxicological risk, as these preparations may lack the quality assurance standards of approved formulations.

The European access paradox

There is a striking dissonance between the global recognition of GLP-1 receptor agonists as transformative therapeutics and the reality of their accessibility across European healthcare systems. The WHO has included GLP-1 therapies on its Essential Medicines List, yet most European countries that reimburse these agents do so primarily for diabetes indications. For obesity—a condition that the WHO itself now recognizes as a chronic disease warranting pharmacological intervention—reimbursement remains the exception rather than the rule [10].

The reasons vary: German statutory law explicitly excludes weight management medications from public insurance; cost-effectiveness thresholds in countries like Canada and the United Kingdom impose stringent barriers; and in many Central and Eastern European healthcare systems, obesity pharmacotherapy simply does not appear in the reimbursement catalogue [10, 11]. This situation raises significant ethical concerns. As a recent analysis in *The Lancetargued*, blanket refusals of coverage for a treatment of proven cardiovascular and metabolic benefit are difficult to justify when the alternative is the continued burden of untreated obesity on already strained healthcare systems [10].

The oral semaglutide formulation may partially address the accessibility issue by reducing the logistical barriers of injectable therapy, but it does not resolve the fundamental questions of cost, reimbursement, and prescribing infrastructure.

The situation across Central and Eastern Europe warrants particular scrutiny. Unlike Western European systems where the debate centers on cost-effectiveness thresholds and willingness-to-pay calculations, many CEE healthcare systems face a more fundamental barrier: obesity remains underrecognized as a reimbursable chronic disease in clinical practice, and the institutional infrastructure for multidisciplinary obesity management is either nascent or entirely absent. Poland, for instance, has begun piloting obesity treatment programs within its National Health Fund framework, yet reimbursement for GLP-1 receptor agonists in the obesity indication remains unavailable. Hungary has similarly restricted coverage to type 2 diabetes, despite national obesity prevalence exceeding 30% in

the adult population. Bulgaria and Croatia face analogous constraints, compounded by lower per-capita healthcare expenditure and limited capacity for health technology assessment. The result is a widening therapeutic gap within the European Union itself—a gap measured not merely in access to a single drug class, but in the systemic readiness to address a disease that the WHO has declared a global health emergency.

Romania's specific vulnerabilities

Romania illustrates, in sharp relief, the challenges facing lower-income EU member states as the GLP-1 revolution unfolds. Several compounding vulnerabilities must be acknowledged.

First, while Romanian professional societies—including the Romanian Federation of Diabetes, Nutrition and Metabolic Diseases and the Romanian Society of Endocrinology—have published obesity care recommendations that reference GLP-1 receptor agonists, no Ministry of Health therapeutic protocol or CNAS reimbursement protocol exists for semaglutide or liraglutide in the obesity indication. Ozempic is available and reimbursed by CNAS for type 2 diabetes under Sublist C, Section C2, code P5 (the National Diabetes Program), but the situation for obesity is starkly different. Wegovy (semaglutide 2.4 mg) has been authorized and is commercially available in Romanian pharmacies by prescription; however, it is entirely excluded from CNAS reimbursement. At a monthly out-of-pocket cost exceeding 1,000 Lei at the maintenance dose—representing roughly one-fifth of the average net monthly salary reported by the National Institute of Statistics—this effectively places the treatment beyond the reach of the vast majority of patients who would benefit from it. The disconnect between professional society recommendations and the absence of a formal reimbursement pathway means that prescribing occurs without standardized patient selection criteria, monitoring schedules, or follow-up expectations.

Second, while Romania maintains a functioning pharmacovigilance system through ANMDMR's Directorate of Pharmacovigilance and Risk Management, integrated with EU-level mechanisms via EudraVigilance, there is no publicly documented GLP-1-specific active surveillance program. The dysesthesia signal identified with higher-dose semaglutide, for instance, requires targeted monitoring and systematic reporting that goes beyond passive spontaneous notification—particularly as these agents enter therapeutic contexts (obesity, MASH) where the patient population and risk profile differ substantially from the type 2 diabetes setting in which long-term safety data were originally generated.

Third, the absence of reimbursement for obesity indications creates a two-tiered system in which access is determined by ability to pay rather than by clinical need. Given Romania's substantial and growing obesity burden—with adult prevalence rates that mirror the broader Central and Eastern European pattern—and the well-documented cardiovascular and metabolic consequences this entails, the health economic argument for systematic intervention deserves rigorous evaluation.

The pharmacoeconomic calculus, moreover, extends beyond the direct cost of the medication itself. Untreated obesity in Romania drives a substantial downstream burden: elevated rates of type 2 diabetes, hypertension, ischemic heart disease, and certain malignancies—conditions that collectively account for a disproportionate share of CNAS expenditure on hospitalizations and chronic disease management. International modeling studies have consistently demonstrated that early pharmacological intervention for obesity, when combined with lifestyle modification and sustained follow-up, yields net savings over a five- to ten-year horizon through reductions in cardiovascular events, diabetes-related complications, and bariatric surgical referrals. Romania lacks, to date, any published health-economic evaluation of GLP-1 receptor agonists calibrated to its own epidemiological profile, healthcare cost structure, and disease trajectory. Without such data, the reimbursement discussion remains anchored in sticker price rather than in value-based assessment—a framing that systematically disadvantages therapies with high acquisition costs but significant long-term return on investment.

Fourth, the unregulated online market for GLP-1 agonists, including compounded and potentially counterfeit formulations, poses a direct toxicological hazard to Romanian patients who seek these medications outside the formal healthcare system. This is not a hypothetical risk; the EMA/HMA MSSG has explicitly flagged the circulation of falsified GLP-1 products across the EU, including falsified Ozempic pens identified at wholesaler level [9].

A call to action

The convergence of clinical evidence, regulatory approvals, and WHO endorsement creates an imperative for the Romanian medical and pharmacological community to act—proactively, not reactively. The following actions are proposed.

Development of national clinical guidelines

The Romanian Society of Pharmacology, in collaboration with the relevant medical specialty

societies (endocrinology, cardiology, internal medicine, and obesity medicine), should initiate the development of evidence-based clinical guidelines for GLP-1 receptor agonist use across their approved and emerging indications, with particular attention to patient selection criteria, contraindications, and monitoring protocols in the Romanian clinical context.

Health technology assessment for reimbursement

A formal health economic evaluation of GLP-1 receptor agonists for obesity indications—incorporating Romanian-specific epidemiological data, cost structures, and projected healthcare savings from cardiovascular and metabolic risk reduction—should be commissioned to inform reimbursement policy decisions by CNAS.

Strengthened pharmacovigilance

ANMDMR should establish dedicated monitoring pathways for GLP-1 receptor agonist safety signals, including the dysesthesia signal at higher doses, gastrointestinal complications, and potential long-term effects in non-diabetic populations. Active pharmacovigilance, rather than passive reporting alone, is essential given the pace at which new formulations and indications are emerging.

Continuing medical education

Clinicians require up-to-date training on the expanding pharmacology of GLP-1 receptor agonists, the distinction between approved and off-label use, and the clinical management of adverse effects. This journal, through its CME-accredited program with the Romanian College of Physicians, is well-positioned to deliver such content to practicing physicians.

Engagement in the European policy dialogue

Romanian pharmacologists, health economists, and policymakers should participate actively in the evolving European-level discussions on equitable access to GLP-1 therapies. The forthcoming EMA review of oral semaglutide for obesity in the EU represents a critical decision point at which the Romanian perspective—reflecting the realities of a lower-income healthcare system—must be heard.

Conclusion

The GLP-1 receptor agonist class represents the most significant expansion of the pharmacotherapeutic arsenal for metabolic and cardiovascular disease in a generation. The pace of approval, the breadth of emerging indications, and the sheer volume of clinical evidence compel attention. At the same time, the toxicological unknowns of escalating doses, the ethical dimensions of access inequity, and the practical challenges of integrating these therapies into overburdened healthcare systems demand a response that is measured, evidence-informed, and urgently organized.

Romania cannot afford to be a passive observer of this pharmacological revolution. The cost of inaction—in preventable cardiovascular events, in unmonitored adverse effects, in a growing black market for unregulated products—will be borne by our patients. As a journal dedicated to the advancement of therapeutics, pharmacology, and clinical toxicology, we recognize our responsibility to facilitate the scientific dialogue and professional education that this moment requires.

The revolution has arrived. The question is whether we will lead, follow, or simply watch it pass.

Acknowledgments

Conflict of interest

The author declares no conflicts of interest.

References

1. Novo Nordisk. FDA approves Novo Nordisk's Wegovy® pill, the first and only oral GLP-1 for weight loss in adults. Press release. December 22, 2025.
2. Novo Nordisk. Wegovy HD (semaglutide 7.2 mg) approved in the US, providing 20.7% mean weight loss. Press release. March 19, 2026. See also: Wharton S, et al. Once-weekly semaglutide 7.2 mg in adults with obesity (STEP UP). Lancet Diabetes Endocrinol. 2025;13(11):949–963; and Lingvay I, et al. Once-weekly semaglutide 7.2 mg in adults with obesity and type 2 diabetes (STEP UP T2D). Lancet Diabetes Endocrinol. 2025;13(11):935–948.
3. World Health Organization. WHO issues global guideline on the use of GLP-1 medicines in treating obesity. December 1, 2025.
4. European Medicines Agency. Rybelsus (semaglutide): SmPC variation accepted September 18, 2025, incorporating SOUL cardiovascular outcome data. EMA procedural steps and SmPC update.
5. Novo Nordisk. Wegovy® prescribing information. Approved indications: chronic weight management, cardiovascular risk reduction, MASH with moderate-to-advanced fibrosis. US FDA, 2021–2025.
6. Novo Nordisk. Evoke phase 3 trials did not demonstrate a statistically significant reduction in Alzheimer's disease progression. Press release. November 24, 2025. Trials: NCT04777396 (EVOKE), NCT04777409 (EVOKE+).
7. Aronne LJ, Horn DB, le Roux CW, et al; SURMOUNT-5 Trial Investigators. Tirzepatide as compared with semaglutide for the treatment of obesity. N Engl J Med. 2025;393(1):26–36. doi:10.1056/NEJMoa2416394.
8. Abdelrahman RM, Musa TH, Arbab IA, et al. Harnessing GLP-1 receptor agonists for obesity treatment: prospects

and obstacles on the horizon. J Obes. 2025;2025:9919810. doi:10.1155/jobe/9919810.
9. European Medicines Agency. EU actions to tackle shortages of GLP-1 receptor agonists. MSSG recommendations. June 2024; updated 2025.
10. Dellgren JL, Persad G, Emanuel EJ. International coverage of GLP-1 receptor agonists: a review and ethical analysis of discordant approaches. Lancet. 2024;404(10455):902–906. doi:10.1016/S0140-6736(24)01356-4.
11. IQVIA. Outlook for obesity in 2026: from consolidation to acceleration. EMEA Market Report. January 2026.