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USE OF GLP-1 ANALOGUES AND GASTROINTESTINAL EFFECTS IN PATIENTS OUTSIDE THE CLASSICAL PROFILE

Uso de Análogos de GLP-1 d Efeitos Gastrointestinais dm Pacientes fora do Perfil Clássico

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ABSTRACT

This study aimed to analyze, through a literature review, the gastrointestinal adverse effects associated with the use of glucagon-like peptide-1 (GLP-1) receptor agonists, with emphasis on semaglutide and tirzepatide, in patients outside the classical indication profile. This is a descriptive and analytical review conducted through searches in the PubMed/MEDLINE, SciELO, LILACS, and Google Scholar databases, using descriptors related to GLP-1, semaglutide, tirzepatide, gastrointestinal adverse events, and off-label use. Original studies, systematic reviews, and meta-analyses published in recent years and available in full text were included. The results showed that gastrointestinal symptoms represent the most frequent adverse events, particularly nausea, vomiting, diarrhea, constipation, abdominal pain, and early satiety, occurring predominantly during the first weeks of treatment and during dose escalation. A significant impact on tolerability, treatment adherence, and therapy discontinuation was observed, especially among individuals without continuous professional follow-up. It is concluded that although semaglutide and tirzepatide demonstrate high efficacy for weight loss, the occurrence of gastrointestinal effects requires appropriate clinical management, safe guidance, and monitoring, particularly in populations outside the classical indications.

Keywords*: GLP-1 receptor agonists; Semaglutide; Tirzepatide; Adverse effects; Weight loss.*

RESUMO

Este estudo teve como objetivo analisar, por meio de revisão de literatura, os efeitos adversos gastrointestinais associados ao uso de agonistas do receptor do peptídeo semelhante ao glucagon-1 (GLP-1), com ênfase em semaglutida e tirzepatida, em pacientes fora do perfil clássico de indicação. Trata-se de uma revisão descritiva e analítica, realizada a partir de buscas nas bases PubMed/MEDLINE, SciELO, LILACS e Google Scholar, utilizando descritores relacionados a GLP-1, semaglutida, tirzepatida, eventos adversos gastrointestinais e uso off-label. Foram incluídos estudos originais, revisões sistemáticas e meta-análises publicados nos últimos anos, disponíveis na íntegra. Os resultados evidenciaram que os sintomas gastrointestinais representam os eventos adversos mais frequentes, destacando-se náuseas, vômitos, diarreia, constipação, dor abdominal e plenitude precoce, com ocorrência predominante nas primeiras semanas e durante o escalonamento de dose. Observou-se impacto significativo na tolerabilidade, na adesão e na interrupção do tratamento, especialmente em indivíduos sem acompanhamento profissional contínuo. Conclui-se que, embora semaglutida e tirzepatida apresentem elevada eficácia para perda ponderal, a ocorrência de efeitos gastrointestinais exige manejo clínico adequado, orientação segura e acompanhamento, sobretudo em populações fora das indicações clássicas.

Palavras-chave: Agonistas do receptor GLP-1; Semaglutida; Tirzepatida; Efeitos adversos; Perda de peso.

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1. INTRODUCTION

The use of glucagon-like peptide-1 (GLP-1) receptor agonists, particularly semaglutide and tirzepatide, has expanded significantly in recent years, driven by their clinical benefits in glycemic control and their effectiveness in weight reduction (Moiz *et al*., 2025).

Although these medications were initially developed for the treatment of type 2 diabetes mellitus, a substantial increase in their use has been observed among patients outside the classical indication profile, including individuals primarily seeking weight loss, metabolic improvement, and aesthetic purposes. This trend highlights the need for further investigation regarding their safety across different clinical contexts (Rico-Fontalvo *et al*., 2024).

Among the most frequently reported adverse effects associated with GLP-1 receptor agonists are gastrointestinal symptoms, such as nausea, vomiting, diarrhea, constipation, abdominal pain, and early satiety. Although these events are generally described as mild to moderate, they may directly interfere with therapeutic adherence, contribute to treatment discontinuation, and negatively affect quality of life (Gorgojo-Martínez *et al*., 2022).

Furthermore, in individuals outside the classical indication profile, these effects may be underestimated, inadequately managed, or occur without continuous professional monitoring, increasing the risk of complications such as dehydration, hydroelectrolytic imbalances, and reduced dietary intake (Dias *et al*., 2025).

Given the growing non-traditional use of semaglutide and tirzepatide, it becomes necessary to characterize the frequency, intensity, and clinical relevance of gastrointestinal adverse effects in this specific population. Understanding these outcomes is essential to support safer clinical practices, provide appropriate patient guidance, improve tolerability strategies, and reduce treatment discontinuation rates, thereby contributing to the rational use of these medications (Fahin *et al*., 2025).

Thus, the main objective of this study is to evaluate the occurrence and clinical impact of gastrointestinal adverse effects associated with the use of semaglutide and tirzepatide in patients outside the classical indication profile, with emphasis on tolerability, treatment adherence, and the need for therapeutic discontinuation.

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2. METHODOLOGY

This is a literature review study with a descriptive and analytical approach, aimed at gathering and synthesizing scientific evidence on gastrointestinal adverse effects associated with the use of GLP-1 receptor agonists, particularly semaglutide and tirzepatide, in patients outside the classical indication profile. The research was conducted through a systematized search in scientific databases, with selection and critical analysis of articles published in recent years in order to ensure the timeliness and relevance of the information presented.

The bibliographic search was carried out in the PubMed/MEDLINE, SciELO, LILACS, and Google Scholar databases. For the search strategy, descriptors in Portuguese and English were used and combined using Boolean operators (AND and OR), including: “GLP-1,” “GLP-1 receptor agonists,” “semaglutide,” “tirzepatide,” “adverse effects,” “adverse events,” “gastrointestinal effects,” “nausea,” “vomiting,” “diarrhea,” “constipation,” “off-label use,” “weight loss,” and “adherence.” The searches were adapted according to the specific characteristics of each database, ensuring broader coverage of relevant studies.

Original articles, clinical trials, observational studies, systematic reviews, and meta-analyses addressing the use of semaglutide and/or tirzepatide and describing gastrointestinal adverse effects were included, particularly in contexts of use outside the classical indication, such as weight loss in individuals without type 2 diabetes mellitus. Studies published between 2021 and 2026 and available in full text in Portuguese, English, or Spanish were considered. Duplicate studies, isolated case reports, letters to the editor, conference abstracts without full text, studies without data related to gastrointestinal events, and publications lacking a clear methodology were excluded.

The selection of studies was carried out in three stages: title screening, abstract reading, and finally full-text analysis of the selected articles. After this screening process, the included articles were organized in a table for standardized data extraction. The variables analyzed included: type of study, population investigated, drug used (semaglutide or tirzepatide), dose and duration of use, indication context (diabetes or use for weight loss), main gastrointestinal adverse effects reported, symptom frequency, intensity, impact on treatment adherence, and treatment discontinuation rates.

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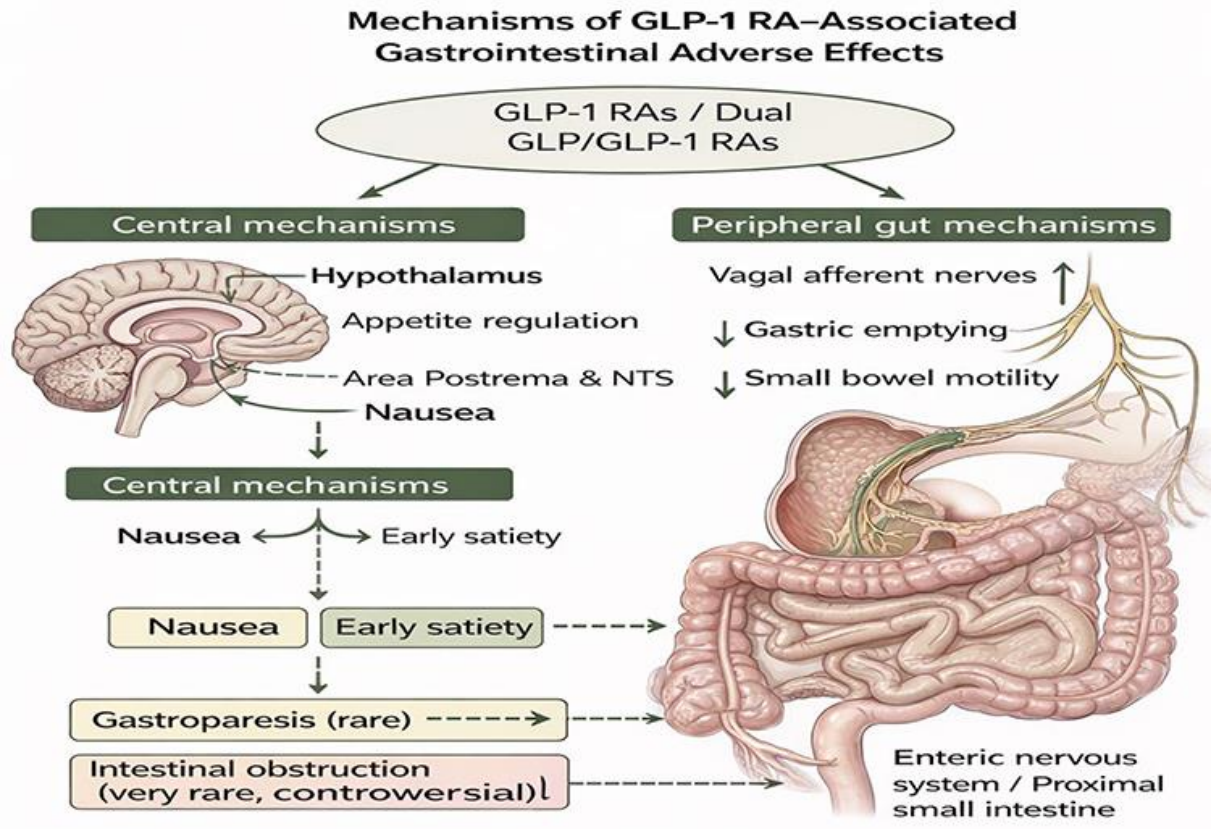
3. RESULTS AND DISCUSSION

The analyzed literature consistently demonstrates that glucagon-like peptide-1 (GLP-1) receptor agonists, particularly semaglutide and tirzepatide, are strongly associated with gastrointestinal adverse events, which represent the main clinical limitation to treatment tolerability and adherence (Isamaiel et al., 2025). Figure 1 presents a conceptual scheme developed based on previously published evidence and does not represent a single experimental model. Its purpose is to illustrate, in a didactic manner, the main central and peripheral mechanisms involved in the gastrointestinal effects related to the use of GLP-1 receptor agonists.

Figure 1. Mechanisms involved in gastrointestinal effects associated with GLP-1 receptor agonists. The diagram presents a conceptual synthesis of the central and peripheral physiological pathways involved in these effects. Central mechanisms include neural circuits located in the hypothalamus and brainstem, responsible for appetite modulation and the occurrence of nausea. Peripheral mechanisms include activation of vagal afferents, delayed gastric emptying, and reduced intestinal motility. The interaction of these processes may result in commonly reported clinical manifestations such as nausea, reduced appetite, early satiety, and constipation, as well as less frequent events such as gastroparesis and intestinal obstruction.



Source. Yilmaz; Bastemir (2026).

The reviewed studies indicate that nausea, vomiting, diarrhea, constipation, abdominal pain, and early satiety are among the most frequent symptoms, occurring mainly during the first weeks of use and during the dose-escalation period. These effects are described as dose-dependent and variable according to individual characteristics, including prior gastrointestinal sensitivity, dietary habits, and the presence of metabolic comorbidities (Gorgojo-Martínez et al., 2022; Gaw et al., 2024).

Data suggest that nausea is the most prevalent symptom among users of semaglutide and tirzepatide, often reported as the main source of discomfort and the primary reason for treatment dose reduction or discontinuation. In addition, tirzepatide, due to its dual action on GLP-1 and GIP receptors, has been associated with higher rates of gastrointestinal events in clinical trials, particularly at higher doses. However, the literature also suggests that despite the higher frequency of symptoms, tirzepatide demonstrates high efficacy in weight loss, which may influence patients to continue treatment even in the presence of gastrointestinal discomfort (Karrar et al., 2023; Mishra et al., 2023).

An important aspect identified is that in patients outside the classical indication profile, such as individuals without type 2 diabetes mellitus who use these drugs for weight loss, gastrointestinal effects may be underestimated or interpreted as an “expected” part of the weight loss process. This perception may favor inadequate practices, such as maintaining high doses despite intense symptoms, rapid dose escalation, and self-medication. Furthermore, in unsupervised contexts, there is an increased risk of dehydration, reduced protein intake, insufficient micronutrient consumption, and deterioration of nutritional status, particularly when recurrent vomiting or persistent diarrhea occurs (Witaszek et al., 2025).

The literature also highlights that treatment adherence is directly related to symptom intensity and the quality of clinical follow-up. Studies indicate that strategies such as gradual dose escalation, dietary guidance (smaller meals, reduction of fatty and ultra-processed foods), adequate hydration, and early symptomatic management reduce treatment discontinuation rates. Nevertheless, a significant proportion of patients discontinue use due to gastrointestinal intolerance, particularly when continuous professional support is lacking. This finding is particularly relevant in the current context, where the growing popularity of these medications has expanded their use without regular medical supervision (Mozaffarian et al., 2025).

Another point discussed in the studies is that the occurrence of gastrointestinal adverse effects should not be interpreted merely as a secondary event, but rather as a determinant factor for treatment

safety. Although most cases are self-limited, the literature reports associated complications such as significant dehydration, electrolyte disturbances, exacerbation of gastroesophageal reflux, and marked reduction in caloric intake, which may lead to weakness, dizziness, and deterioration in quality of life. Therefore, the evaluation of gastrointestinal tolerability should be considered an essential component of clinical monitoring, especially in individuals using these medications outside their original indications (Ghush; Hurtado, 2024).

Overall, the findings reinforce that the expansion in the use of semaglutide and tirzepatide requires greater attention to pharmacovigilance, particularly in non-classical populations. Despite their proven effectiveness in weight reduction, gastrointestinal effects represent the main barrier to treatment continuity and may lead to relevant clinical consequences when neglected. The literature indicates that the safe use of these medications depends on responsible prescription, appropriate patient guidance, continuous monitoring, and individualized dose escalation in order to minimize adverse events (Safwan et al., 2025).

Finally, although robust evidence exists regarding gastrointestinal events in controlled clinical trials, important gaps remain concerning their use in real-world settings, particularly among individuals outside the classical indication profile. In this context, observational studies and real-world data are needed to better understand the frequency, severity, and clinical impact of these effects in routine practice.

4. CONCLUSION

This study aimed to analyze, through a literature review, the gastrointestinal adverse effects associated with the use of GLP-1 receptor agonists, particularly semaglutide and tirzepatide, in patients outside the classical indication profile. Based on the reviewed findings, gastrointestinal symptoms emerge as the most frequent and clinically relevant adverse events, especially nausea, vomiting, diarrhea, constipation, abdominal pain, and early satiety, with a direct impact on tolerability, therapeutic adherence, and treatment continuity.

The results indicate that although most events are described as mild to moderate, their occurrence may significantly compromise quality of life and contribute to treatment discontinuation, particularly when adequate professional monitoring is lacking. Furthermore, in individuals using these medications for weight loss outside their original indications, adverse effects may be underestimated

or inadequately managed, increasing the risk of complications such as dehydration, significant reduction in food intake, and metabolic imbalances.

As a contribution to both society and the academic community, this study reinforces the need for the rational use of GLP-1 receptor agonists and highlights the importance of follow-up protocols focused on the prevention and early management of gastrointestinal adverse effects, particularly in non-classical populations. The synthesis presented may assist healthcare professionals in clinical decision-making, patient counseling, and the development of strategies that promote greater safety and adherence to treatment.

In light of these findings, future research should prioritize observational studies with real-world data and representative samples of individuals without type 2 diabetes mellitus, evaluating not only the frequency of gastrointestinal symptoms but also their severity, associated risk factors, nutritional impact, and the most effective strategies to improve tolerability and reduce treatment discontinuation.

REFERENCES

DIAS, D. D. *et al*. Nutritional approaches to enhance GLP-1 analogue therapy in obesity: a narrative review. **Obesities**, v. 5, n. 4, p. 88, 2025. DOI: 10.3390/obesities5040088.

FAHIM, S. A. *et al*. Comparative safety and side effects of semaglutide and tirzepatide: implications for clinical decision-making in obesity management. **Biomedicine & Pharmacotherapy**, v. 193, p. 118731, 2025. DOI: 10.1016/j.biopha.2025.118731.

GAW, C. E. *et al*. Glucagon-like peptide-1 receptor agonist cases reported to United States poison centers, 2017-2022. **Journal of Medical Toxicology**, v. 20, n. 2, p. 193-204, 2024. DOI: 10.1007/s13181-024-00999-x.

GHUSN, W.; HURTADO, M. D. Glucagon-like receptor-1 agonists for obesity: weight loss outcomes, tolerability, side effects, and risks. **Obesity Pillars**, v. 12, p. 100127, 2024. DOI: 10.1016/j.obpill.2024.100127.

GORGOJO-MARTÍNEZ, J. J. *et al*. Clinical recommendations to manage gastrointestinal adverse events in patients treated with GLP-1 receptor agonists: a multidisciplinary expert consensus. **Journal of Clinical Medicine**, v. 12, n. 1, p. 145, 2022. DOI: 10.3390/jcm12010145.

ISMAIEL, A. *et al*. Gastrointestinal adverse events associated with GLP-1 RA in non-diabetic patients with overweight or obesity: a systematic review and network meta-analysis. **International Journal of Obesity**, v. 49, n. 10, p. 1946-1957, 2025. DOI: 10.1038/s41366-025-01859-6.

KARRAR, H. R. *et al*. Tirzepatide-induced gastrointestinal manifestations: a systematic review and meta-analysis. **Cureus**, v. 15, n. 9, e46091, 2023. DOI: 10.7759/cureus.46091.

MISHRA, R. *et al*. Adverse events related to tirzepatide. **Journal of the Endocrine Society**, v. 7, n. 4, bvad016, 2023. DOI: 10.1210/jendso/bvad016.

MOIZ, A. *et al*. The expanding role of GLP-1 receptor agonists: a narrative review of current evidence and future directions. **EClinicalMedicine**, v. 86, p. 103363, 2025. DOI: 10.1016/j.eclinm.2025.103363.

MOZAFFARIAN, D. *et al*. Nutritional priorities to support GLP-1 therapy for obesity: a joint advisory from the American College of Lifestyle Medicine, the American Society for Nutrition, the Obesity Medicine Association, and the Obesity Society. **American Journal of Lifestyle Medicine**, 2025. DOI: 10.1177/15598276251344827.

RICO-FONTALVO, J. *et al*. Kidney effects of glucagon-like peptide 1 (GLP1): from molecular foundations to a pharmacophysiological perspective. **Brazilian Journal of Nephrology**, v. 46, n. 4, 2024. DOI: 10.1590/2175-8239-JBN-2024-0101en.

SAFWAN, M. *et al*. Gastrointestinal safety of semaglutide and tirzepatide vs. placebo in obese individuals without diabetes: a systematic review and meta-analysis. **Annals of Saudi Medicine**, v. 45, n. 2, p. 129-143, 2025. DOI: 10.5144/0256-4947.2025.129.

WITASZEK, T. *et al*. Gastrointestinal symptoms in obesity therapy: mechanisms, epidemiology, and management strategies. **Biomedicines**, v. 13, n. 10, p. 2362, 2025. DOI: 10.3390/biomedicines13102362.

YILMAZ, N.; BASTEMIR, M. Gastrointestinal Adverse Effects of GLP-1 and Dual GLP-1/GIP Receptor Agonists: A Comprehensive Update in Diabetic and Obese Populations. **Diabetes Metab Syndr Obes**. 2026;19:1-13 https://doi.org/10.2147/DMSO.S584175