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Epidemiology of Drugs for the Treatment of Obesity

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ABSTRACT

In the present review we analyze how the drugs currently used in the treatment of obesity present a complex risk-benefit profile. It seems to be clear that it is closely dependent on the characteristics of the individual patient (metabolic or psychiatric comorbidities, use of other drugs, etc.) in determining both efficacy and adherence to treatment. In addition, the patient's psychological aspect may compromise the entire treatment.

Pharmacovigilance is a key element in promoting a more conscious, individualized, and sustainable clinical use and not only in ensuring the safe use of medicines.

Keywords
Pharmacovigilance, Obesity, Metabolic Diseases.

Introduction
Metabolic diseases are a group of disorders in which alterations in the biological processes regulating the metabolism of carbohydrates, lipids, and proteins, may manifest in different forms such as diabetes, dyslipidemias, metabolic syndrome, and obesity, with a significant impact on long-term health [1].

According to the 2022 WHO Europe report, nearly 60% of adults and almost 30% of pediatric subjects (29% of males and 27% of females) are overweight or obese, making obesity recognized as a chronic and relapsing disease with pandemic spread. The prevalence of obesity among adults in the European region is higher than in any other WHO region, except the Americas, and is therefore among the leading causes of death and disability in the European region, causing more than 1.2 million deaths per year, corresponding to over 13% of total mortality [2].

Adipocytes initially undergo hypertrophy and subsequently hyperplasia
Adipose tissue, particularly in the visceral area, is now considered an active endocrine organ, capable of secreting adipokines (leptin, adiponectin, resistin) and pro-inflammatory cytokines (TNF-α, IL-6).

Hypertrophy reduces capillary perfusion of the tissue, creating local hypoxia and stimulating factors such as HIF-1α, which promote fibrosis and oxidative stress. Adipocyte expansion promotes the recruitment of macrophages and immune cells, causing a state of chronic low-grade inflammation [3].

Role of bioactive molecules:
- Leptin: under physiological conditions regulates satiety and energy expenditure; in obesity, plasma concentration increases, but signal efficacy is reduced due to receptor insensitivity (leptin resistance).
- Adiponectin: under physiological conditions promotes insulin sensitivity and exerts anti-inflammatory and anti-atherogenic effects. In obesity, however, its plasma concentration decreases, consequently reducing metabolic protection.
- Resistin and visfatin: adipokines involved in mechanisms linking obesity with insulin resistance and atherosclerosis.
- Pro-inflammatory cytokines (TNF-α, IL-6, MCP-1): increase adipose expansion; stimulate serine phosphorylation of IRS-1

(insulin receptor substrate-1), inhibiting the insulin signaling cascade and thus contributing to the development of insulin resistance [3].

In chronic low-grade inflammation, pro-inflammatory cytokines (TNF-α, IL-6, MCP-1) are released, which in turn alter adipocyte function; by stimulating uncontrolled lipolysis with excessive release of free fatty acids, they interfere with the insulin signaling pathway by inhibiting IRS-1 phosphorylation and reducing PI3K-AKt pathway activity. All this results in an inadequate response of peripheral tissues (muscle, liver) to insulin action, leading to the development of insulin resistance.

This mechanism represents one of the main pathogenetic links connecting obesity to type 2 diabetes mellitus. Hyperlipolysis causes an excess of free fatty acids (FFA), increasing plasma concentrations of VLDL and triglycerides; pro-inflammatory cytokines also contribute to endothelial dysfunction and atherogenesis, underlying further obesity-related complications such as dyslipidemias and atherosclerosis.

In addition to promoting the onset of insulin resistance, type 2 diabetes mellitus, and atherosclerosis, obesity is also responsible for numerous other complications affecting various organs and systems; among the main ones are non-alcoholic fatty liver disease, obstructive sleep apnea syndrome, various neoplasms (particularly involving the colon, breast, and endometrium), degenerative osteoarticular diseases, and several endocrine and reproductive dysfunctions [3].
Treatment strategies include lifestyle interventions, pharmacological therapies, and bariatric/metabolic surgery.

Pharmacological therapy is indicated in patients with BMI ≥ 30 kg/m² or ≥ 27 kg/m² in the presence of obesity-related comorbidities (type 2 diabetes, hypertension, dyslipidemias). The history of pharmacological therapy for obesity is characterized by numerous failures, as several molecules approved by regulatory agencies were subsequently withdrawn after marketing due to the onset of unexpected serious adverse effects or because of an unfavorable risk/benefit ratio emerging from studies aimed at evaluating long-term safety. Some examples of drugs withdrawn from the market are:

- Fenfluramine in 1997 due to the risk of developing pulmonary hypertension and heart valve abnormalities.
- Rimonabant in 2009, a cannabinoid antagonist, because of an unfavorable risk/benefit ratio, with an increased risk of psychiatric disorders and suicidal ideation.
- Sibutramine in 2010 due to increased cardiac risks.
- Lorcaserin in 2020 at the request of the FDA, because of an increased risk of developing malignant tumors [4].

Among the drugs approved by the EMA (and AIFA) for the long-term treatment of obesity and currently marketed in Europe are:

- Orlistat
- Liraglutide
- Naltrexone/bupropion combination
- Semaglutide
- Tirzepatide
- Setmelanotide

These drugs are classified as:

- Intestinal lipase inhibitors (orlistat)
- GLP-1 receptor agonists (liraglutide and semaglutide)
- Dual GLP-1/GIP agonists (tirzepatide)
- Central combinations (naltrexone/bupropion)
- MC4R receptor agonists (setmelanotide)

Orlistat

It is a selective inhibitor of pancreatic lipases, reducing the absorption of dietary fats by the digestive tract by approximately 30% at full dose and 25% at half dose, with a consequent increase in fecal excretion. Systemic absorption of Orlistat is minimal, <1%. It was approved by the EMA in July 1998 and marketed in two dosages: 120 mg and 60 mg, to be taken during the three main meals (breakfast, lunch, and dinner). The 60 mg dosage was approved by the EMA in 2007 as an over-the-counter medication. Orlistat is considered less effective than other drugs, with a weight loss of about 3–5% compared with placebo. The main adverse effects are gastrointestinal (steatorrhea, fecal urgency, oily flatulence), limiting therapeutic adherence. It is no longer used as a first-line drug but remains an alternative for patients who cannot or do not wish to take incretin-based drugs [4].

Liraglutide

It is an analogue of human glucagon-like peptide-1 (GLP-1), marketed since 2009 as an antidiabetic drug at a dose of 1.8 mg/day and since 2015 as a weight-loss drug, in addition to lifestyle modifications, at a dose of 3.0 mg/day. This drug has an amino acid sequence 97% identical to endogenous GLP-1 and, unlike other drugs of the same class, it crosses the blood-brain barrier.

The receptors on which liraglutide acts are present both peripherally and centrally:
At the peripheral level, in the pancreas and digestive tract, where receptor activation causes increased insulin secretion in diabetic patients, reducing blood glucose levels without inducing hypoglycemia. It also slows gastric emptying and stimulates β-cell regeneration by reducing apoptosis.

At the central level, in the arcuate nucleus on neurons expressing the POMC (pro-opiomelanocortin) polypeptide and the CART neuropeptide (cocaine- and amphetamine-regulated transcript), which have an anorexigenic role and synergize with POMC via α-MSH. Activation of these receptors increases satiety and reduces appetite. Central GLP-1 receptors are also located in the mesolimbic area, the ventral tegmental area, and the nucleus accumbens: in this way, liraglutide also influences the mesolimbic reward circuit.

The half-life of liraglutide is approximately 13 hours, compared to the few minutes of native GLP-1, and this allows for a single daily administration, namely 3 mg/day [4]. A weight loss of 8–10% of

body weight has been observed. Among the most common adverse effects are nausea and vomiting, while the risk of pancreatitis is rarer. Currently, liraglutide is used less and less, as it is often replaced by drugs with better efficacy such as semaglutide and tirzepatide [5].

Naltrexone/bupropion combination

The individual active ingredients have been marketed for over 30 years with therapeutic indications different from weight control: bupropion is an antidepressant capable of inhibiting dopamine and norepinephrine reuptake, while naltrexone is a μ-opioid receptor antagonist used in alcohol and opioid withdrawal treatment. Regarding the use of the combination for weight loss, it is hypothesized that the effect occurs at the level of the arcuate nucleus and the mesolimbic dopaminergic system. The co-administration of naltrexone and bupropion enhances the activation of POMC neurons compared to the individual drugs administered separately, promoting satiety and appetite control. This combination was approved by the EMA in March 2015 for the treatment of obesity and overweight with comorbidities in addition to lifestyle modifications. The approved daily dose for body weight control is 32 mg of naltrexone and 360 mg of bupropion, to be taken in two administrations at breakfast and dinner [4].

Semaglutide

Like liraglutide, it is a GLP-1 receptor analogue that, in addition to slowing gastric emptying, is able to reduce hunger and increase the feeling of satiety. In a phase 2 study in which semaglutide was compared with liraglutide, weight loss at the end of the 52 weeks of treatment with semaglutide was almost double that observed with liraglutide. It was approved in Europe in 2019 as an antidiabetic drug at a dose of 0.5–1.0 mg/week, while in 2022 the EMA authorized its use for the treatment of overweight complicated by comorbidities and obesity, at a dose of 2.4 mg/week administered subcutaneously, having a half-life of approximately 170 hours that allows weekly administration [4].

Tirzepatide

It is a long-acting synthetic peptide and the first dual agonist of both GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 receptors. Activation of the GLP-1 receptor slows gastric emptying, producing a greater sense of satiety, and acts on hypothalamic POMC/CART neurons reducing appetite. Furthermore, it stimulates pancreatic β-cells by increasing glucose-dependent insulin secretion and reduces glucagon secretion, improving glycemic control. Through agonism of the GIP receptor, it enhances glucose-induced insulin secretion, modulates lipid metabolism, and increases insulin sensitivity in adipose and muscle tissue.

The synergistic action on both receptors amplifies weight loss and improvement of glucose metabolism compared to GLP-1 agonists alone. In the SURMOUNT studies (phase 3), an average weight loss of up to 21% of body weight over 72 weeks was demonstrated, and more than 50% of patients achieved a ≥15% reduction in body weight [6]. A recent retrospective study published in Mayo Clinic Proceedings and reported by the Italian Society of Obesity (SIO) analyzed the efficacy of tirzepatide in adult patients with type 1 diabetes mellitus (T1D) and overweight or obesity. The study included 51 subjects with BMI ≥27 kg/m² treated with tirzepatide for a minimum period of 3 months, with a median follow-up of 8 months. The results showed a significant reduction in body weight: the average weight loss recorded was 8.5%, reaching 12.2% in patients followed for 12 months.

In addition to its impact on weight, tirzepatide resulted in improved glycemic control, with an average reduction in glycated hemoglobin of 0.9%. A significant decrease in daily insulin requirement was also observed, equal to 31.6%, indicating improved insulin sensitivity. The adverse effects reported were mainly gastrointestinal, such as nausea (13.7% of patients), without a significant increase in hypoglycemic episodes; in rare cases it may cause pancreatitis [7]. According to European regulations and EMA data, tirzepatide is available in prefilled single-use pens in different dosages for subcutaneous administration:

- 2.5 mg
- 5 mg
- 7.5 mg
- 10 mg
- 12.5 mg
- 15 mg

Tirzepatide is administered subcutaneously regardless of meals, and the dose is gradually increased every 4 weeks by 2.5 mg until the maximum authorized dose of 15 mg once weekly is reached. The gradual increase aims to improve gastrointestinal tolerability and reduce adverse effects during the initial treatment cycles.

In conclusion, this study suggests that tirzepatide may represent a good and promising therapeutic option also in subjects with type 1 diabetes mellitus associated with obesity, promoting significant body weight reduction, improved glycemic control, and decreased insulin resistance, with a favorable safety profile [7].

Setmelanotide

It is a selective melanocortin-4 receptor (MC4R) agonist and represents a targeted therapy in monogenic forms of obesity linked to defects in the pro-opiomelanocortin (POMC) pathway, proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR).

Under physiological conditions, leptin stimulates POMC neurons in the hypothalamus; these release α-MSH, which binds to the MC4R receptor, determining satiety and increased energy expenditure. When mutations occur in POMC, PCSK1, or LEPR, this signaling pathway is interrupted, so MC4R neurons do not receive stimulation, resulting in uncontrolled hyperphagia and severe early-onset obesity.

As a direct MC4R agonist, setmelanotide bypasses the upstream defect and activates MC4R receptors in the hypothalamus, reducing appetite (anorexigenic action), increasing energy expenditure,

and leading to significant weight loss in patients with responsive mutations. Clinically, a weight loss ≥10% of body weight has been demonstrated in more than 80% of treated patients, accompanied by a marked reduction in hyperphagia measured with validated scales [8]. Its efficacy is specific, as it is observed only in patients with these types of mutations, while it is absent in all other forms of obesity. Among the most common adverse effects are local injection site reactions, nausea, vomiting, and diarrhea; among the more specific adverse effects are skin and scar hyperpigmentation (due to activation of cutaneous melanocortin receptors). Among the rarer adverse effects are depression, suicidal ideation, and hypertension. Setmelanotide is administered subcutaneously once daily at doses ranging from 1 mg to 3 mg/day, adjusted according to tolerability and clinical response [8,9].

Pharmacovigilance and Safety Measures of Anti-Obesity Drugs

Pharmacovigilance plays a fundamental role in the management of anti-obesity drugs, since these therapies, although effective in promoting body weight reduction and improving metabolic parameters, may be associated with significant adverse events that require constant monitoring. In the European Union, the EMA, through the PRAC (Pharmacovigilance Risk Assessment Committee), supervises the benefit/risk profile of these medicinal products, adopting risk minimization and management measures in accordance with GVP principles.

GVP Module V provides guidelines for the preparation of Risk Management Plans (RMPs), mandatory tools for marketing authorization holders [10,11]. The RMP aims to identify relevant risks (both identified and potential), fill any information gaps, and plan the pharmacovigilance activities necessary to ensure that the benefit/risk profile remains favorable over time [10]. It also defines the risk minimization measures to be applied when necessary and establishes procedures for periodic updates based on new scientific evidence [11].

GVP Module XVI explores Risk Minimisation Measures (RMMs), namely strategies to reduce the probability and severity of adverse events. These measures may be "routine", such as the standard information contained in the summary of product characteristics (SmPC) and package leaflet, or "additional", including educational programs for healthcare professionals and patients, alert cards, or controlled monitoring registries. With the most recent revision (Rev. 3, 2024), the EMA emphasized the use of innovative digital tools, the direct involvement of patients and clinicians in the design of RMMs, and the use of real-world data to evaluate their effectiveness [12].

For the most recent anti-obesity drugs, pharmacovigilance measures have focused on specific risks and monitoring programs. GLP-1 receptor agonists and dual drugs, such as liraglutide, semaglutide, and tirzepatide, are subject to intensive monitoring to promptly detect gastrointestinal, cardiovascular, pancreatic adverse events, hypoglycemia, and other possible treatment-associated complications:

Semaglutide – Adverse events and pharmacovigilance

Gastrointestinal events (nausea, vomiting, diarrhea), often dose-dependent, are very common, and technical datasheets recommend gradual titration to reduce the incidence of such reactions [13].
Pancreatitis and biliary complications: reports of acute pancreatitis and cholelithiasis have led to strengthened monitoring, with mandatory clinical surveillance and prompt reporting of persistent abdominal symptoms [13].

Ophthalmological risks: from 2023 to 2025, the EMA adopted targeted interventions for semaglutide. Non-arteritic anterior ischemic optic neuropathy (NAION) was included in the SmPC and package leaflet and, although a very rare event, is actively monitored through spontaneous reporting systems, with the recommendation to immediately discontinue therapy in the presence of compatible visual symptoms [14].
Pregnancy registry: a European registry has been established to collect data on maternal and fetal outcomes in women exposed to the drug, in order to fill important safety gaps.

A group of international academic researchers conducted a phase 3, randomized, double-blind, placebo-controlled clinical study, supported and sponsored by Novo Nordisk, the company that developed the drug Wegovy®. The study lasted 68 weeks and enrolled 1,961 adults (1,306 treated with semaglutide and 655 with placebo) with BMI ≥30 kg/m², or ≥27 kg/m² with at least one weight-related comorbidity, excluding patients with type 2 diabetes mellitus. Participants were randomized to receive semaglutide 2.4 mg subcutaneously once weekly or placebo. All subjects followed a standardized lifestyle intervention program: hypocaloric diet and increased physical activity. The dose was gradually titrated starting from 0.25 mg weekly, with progressive increases every 4 weeks until reaching the target dose of 2.4 mg, to reduce gastrointestinal events. The primary endpoints were: percentage change in body weight from baseline to week 68 and percentage of subjects achieving ≥5% weight loss at week 68. Secondary endpoints included: percentage of subjects with ≥10% and ≥15% weight loss, changes in cardiometabolic parameters (blood pressure, lipid profile, blood glucose, HbA1c, waist circumference). The participants' mean baseline body weight was 105.3 kg and mean BMI was 37.9 kg/m²; at week 68, the average reduction in body weight was:
- 14.9% with semaglutide 2.4 mg
- 2.4% with placebo

The percentages of weight loss were:
- ≥5% body weight loss: 86.4% with semaglutide vs 31.5% with placebo
- ≥10%: 69.1% vs 12.0%
- ≥15%: 50.5% vs 4.9%

Significant improvements were observed in cardiometabolic parameters: systolic and diastolic blood pressure, fasting glucose and HbA1c, lipid profile, waist circumference.

The most frequent adverse events were gastrointestinal (nausea,

diarrhea, constipation, vomiting). Treatment discontinuation due to adverse effects occurred in 7% of participants treated with semaglutide vs 3.1% in the placebo group.

The conclusion of this study was that semaglutide 2.4 mg weekly, associated with lifestyle interventions, produces substantial and clinically significant weight reductions in adults with obesity or overweight, with associated cardiometabolic benefits [15].

Tirzepatide

It showed greater efficacy in trials in terms of weight reduction compared to other treatments, but with a safety profile characterized by dose-dependent gastrointestinal events, pancreatitis, and biliary disorders [16,17]. The EMA required a detailed RMP, including these risks as identified and with specific clinical recommendations: discontinue treatment in the presence of pancreatitis and monitor patients for biliary symptoms or dehydration [17]. Gradual titration remains an integral part of risk minimization measures. The widespread use in Europe has made the collection of real-world data through PSURs and post-marketing analyses a priority.

At the same time, surveillance on possible suicidal ideation and thyroid cancer risk confirmed the absence of a causal relationship, but the collection of real-world data remains active [17,18].

An international group of researchers conducted a phase 3, multicenter, randomized, double-blind, placebo-controlled clinical study carried out in several countries. This study was funded and sponsored by Eli Lilly and Company, the company that developed the drug (Mounjaro®). Adults (≥18 years) with body mass index (BMI) ≥30 kg/m² or ≥27 kg/m² in the presence of at least one weight-related comorbidity (e.g., hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease) were enrolled. Patients with type 2 diabetes mellitus were excluded to avoid interference with metabolic endpoints. All participants received standardized support for lifestyle modification, including dietary counseling and physical activity recommendations. Subjects were assigned in a 1:1:1:1 ratio to receive subcutaneous tirzepatide once weekly at doses of 5 mg, 10 mg, 15 mg, or placebo. Assignment was performed through centralized randomization and stratified according to the presence of prediabetes at baseline. Administration was double-blind. All patients assigned to tirzepatide started with 2.5 mg weekly, with the dose increased by 2.5 mg every 4 weeks until the target dose (5, 10, or 15 mg) was reached. This gradual titration phase was designed to improve tolerability, particularly to reduce gastrointestinal adverse events. The double-blind treatment period lasted 72 weeks, followed by a 4-week follow-up after treatment discontinuation. During the study, regular visits were conducted to monitor body weight, metabolic parameters, and clinical safety. The primary endpoints were:

- Percentage change in body weight from baseline to week 72
- Proportion of participants with ≥5% weight reduction at week 72

Secondary endpoints included the proportion of subjects with ≥10%, ≥15%, and ≥20% body weight loss, as well as changes in cardiometabolic risk factors (blood pressure, lipid profile, blood glucose, HbA1c).

Participants treated with tirzepatide showed substantial and dose-dependent reductions in body weight compared to baseline: approximately 15.0% with the 5 mg dose, 19.5% with the 10 mg dose, and 20.9% with the 15 mg dose, while the placebo group showed a reduction of approximately 3.1%. The percentage of subjects achieving at least 5% weight loss was very high in the tirzepatide groups: 85% with 5 mg, 89% with 10 mg, and 91% with 15 mg, compared to 35% in the placebo group. Even for higher thresholds of weight loss, tirzepatide showed excellent results: among patients who lost ≥20% of initial body weight, the 10 mg and 15 mg groups reached percentages around 50–60%, while the placebo group had much lower percentages, close to 3–5%. Significant improvements were observed in cardiovascular and metabolic parameters: reduction in blood pressure, improvement in lipid profile, and fasting glucose.

Regarding safety, the most common adverse events were gastrointestinal (nausea, vomiting, diarrhea, constipation), occurring especially during the dose titration phase, generally with mild or moderate intensity. Treatment discontinuations due to adverse events were relatively few: approximately 4.3% (5 mg), 7.1% (10 mg), 6.2% (15 mg) versus 2.6% in the placebo group [16].

Liraglutide

It shares the typical adverse effects of the GLP-1 class, namely gastrointestinal events, risk of pancreatitis, and biliary complications. In the context of pharmacovigilance, a distinctive element concerns the early discontinuation of therapy: treatment must be stopped after 12 weeks at a dose of 3.0 mg/day if weight loss does not reach at least 5% of baseline. This criterion represents a concrete risk minimization measure that limits long-term exposure without clinical benefit, thereby reducing the potential impact of adverse events [19].

Orlistat

For established drugs such as orlistat, pharmacovigilance focuses on gastrointestinal events and malabsorption of fat-soluble vitamins, recommending vitamin supplementation when necessary [20]. Pharmacovigilance has also documented rare cases of hepatotoxicity [21], which are subject to ongoing evaluation by the EMA and monitoring through PSURs [22]. The main measures consist of recommendations for vitamin supplementation and monitoring for clinical signs of liver damage. In some clinical contexts, discontinuation is indicated if a weight reduction >5% is not achieved within 12 weeks, a measure that helps optimize the risk/benefit ratio [20].

Naltrexone/bupropion

The naltrexone/bupropion combination required specific interventions in 2025 due to potential neuropsychiatric events (seizures, suicidal ideation) and cardiovascular risks. The drug remained on the market, but with strengthened risk minimization measures: introduction of a patient information card to prevent

interactions with opioids, a checklist for prescribers aimed at identifying contraindications (psychiatric disorders, history of seizures), and discontinuation of treatment if weight loss after 16 weeks is less than 5%. Annual reassessment of therapy is also recommended, with particular attention to cardiovascular outcomes. These tools complement routine RMMs and aim to strengthen safety of use in at-risk populations [23].

Setmelanotide

Intended for rare forms of monogenic obesity, it requires particular attention to events of skin hyperpigmentation and mood alterations. The EMA has imposed a mandatory post-authorization safety study (PASS) and enhanced monitoring in the RMP, with particular attention to the pediatric population. Psychiatric and dermatological monitoring is recommended during treatment in order to prevent clinically relevant consequences in the context of chronic therapy [24].

Conclusions

Interpretation of results and risk-benefit evaluation

The analysis conducted highlighted how the drugs currently used in the treatment of obesity present a complex risk-benefit profile. It also confirms that the most recent GLP-1 receptor agonists and new multi-agonist combinations are effective, capable of inducing significant weight reduction. The risk-benefit balance proves to be closely dependent on the characteristics of the individual patient (metabolic or psychiatric comorbidities, use of other drugs, etc.) in determining both efficacy and adherence to treatment. In particular, the patient's psychological aspect should not be overlooked, as it may compromise the entire treatment.

In this context, pharmacovigilance emerges as a key element not only in ensuring the safe use of medicines, but also in promoting more conscious, individualized, and sustainable clinical use. The integration of data from spontaneous reports, observational studies, and real-world registries enables a more complete understanding of the risk profile, especially in complex patients who are often excluded from registration clinical trials.

Future perspectives in obesity pharmacotherapy are oriented toward the development of molecules with multiple mechanisms of action, capable of acting simultaneously on different metabolic and neuroendocrine targets, but also toward more sophisticated monitoring strategies [25]. The evolution of pharmacovigilance, in this scenario, will need to be proactive, based on predictive models and the integrated use of big data, artificial intelligence, and digital reporting systems [26]. At the same time, the interconnection between clinical data, disease registries, and patient-reported information may promote more timely and accurate monitoring of risk signals. This will make it possible to identify patterns of adverse events early and intervene with targeted prevention and management measures. The regulatory dimension will also need to evolve, ensuring greater transparency, interoperability of information systems, and collaboration among authorities, healthcare professionals, and the pharmaceutical industry.

In 2025, an article entitled "Emerging pharmacotherapies for obesity: A systematic review-Pharmacol Review" was published, listing new molecules under development such as oforglipron, ecnoglutide, combinations with GLP-1/amylin, etc. Weight-loss percentages in trials are reported (between 7–24%), but the need for long-term follow-up for safety and efficacy is emphasized [27]. Another recent 2024 study entitled "Pharmacotherapy for obesity: moving towards efficacy improvement – diabetology and metabolic syndrome" explains how pharmacological interventions are seeking to surpass the 5–10% weight-loss threshold, which was previously the norm, in order to achieve more ambitious results. However, it specifies that interventions alone are not sufficient, and that good nutritional education, physical exercise, and behavioral support are necessary [28]. Also in 2025, another important study entitled "Unintended Consequences of Obesity Pharmacotherapy: A Nutritional Approach to Ensuring Better Patient Outcomes" serves as a reminder because it explains the importance of pharmacological therapy within a multidisciplinary context that also considers the patient's nutritional and psychological status, and highlights nutrition-related adverse effects: loss of lean mass, deficiencies, dehydration [29]. Furthermore, in 2024, an important pharmacovigilance study highlighted the fact that not all patients respond in the same way, and that risk changes depending on the drug, dose, and individual conditions. It is a real-world study based on FAERS reports measuring digestive adverse reactions associated with various anti-obesity drugs, with stratified analyses [30].

In general, it can be stated that recent studies suggest that genetic variants and individual factors (e.g., optic vascular anatomy, history of pancreatic disease, predisposition to cholelithiasis) may modulate the risk of adverse events. Future pharmacovigilance should include strategies to identify at-risk subgroups (e.g., biobanks linked to adverse event reports) and, when appropriate, recommend preventive screening or genetic testing in selected populations. For example, projects such as the United Kingdom's Yellow Card Biobank are exploring precisely this approach [31], alongside the use of apps for direct reporting, wearables for monitoring vital parameters, and digital follow-up platforms that allow real-time collection of safety data and improve surveillance sensitivity, especially for events that occur early (e.g., dehydration, GI symptoms, visual alterations, mood changes) [32]. Active patient participation is also crucial for evaluating the effectiveness of risk minimization and for the timely discontinuation of the drug in the event of clinically significant signals.

Regulatory authorities are already adopting concrete measures: label updates, mandatory pregnancy registries, PASS studies, and recommendations for discontinuation in the event of serious adverse events. In the foreseeable future, we will see greater use of digital RMMs, conditional stop-rule criteria (e.g., discontinuation if weight loss is not achieved), and periodic reports based on RWD that may lead to timely revisions of the RMP [10].

All these measures are necessary to exploit the clinical benefits without underestimating rare but potentially serious risks, and to ensure that rapid therapeutic changes are accompanied by safety and appropriate prescribing.

Despite the introduction of new GLP-1 receptor agonists and dual drugs having marked a turning point in the treatment of obesity, it is essential to impose continuous vigilance regarding possible adverse events in order to maintain a favorable benefit/risk ratio. Pharmacovigilance, therefore, should not be considered merely a post-marketing control tool, but a dynamic pillar of the therapeutic process, capable of generating useful knowledge for treatment personalization.

At the same time, it is essential to recognize that therapeutic safety concerns not only the clinical aspect, but also the human one. In conclusion, we can affirm that modern, participatory, and patient-oriented pharmacovigilance not only contributes to improving the safety of anti-obesity drugs, but also represents a pillar for building a more personalized, ethical, and sustainable medicine.

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