Review

Advances in Injectable Pharmacotherapies for Obesity: Mechanisms, Efficacy, and Aesthetic Implications

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Advances in Injectable Pharmacotherapies for Obesity: Mechanisms, Efficacy, and Aesthetic Implications

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Abstract: Obesity remains a complex global health issue, necessitating multifaceted treatment approaches. Injectable pharmacotherapies have emerged as effective strategies to manage obesity by targeting metabolic pathways that regulate appetite, energy expenditure, and fat distribution. This review explores the mechanisms, clinical efficacy, and safety profiles of key injectable agents, including GLP-1 and GIP receptor agonists, pancreatic lipase inhibitors, and lipolytic compounds. Additionally, it highlights the aesthetic challenges following significant weight loss, such as skin laxity, and discusses the role of biostimulators and non-invasive technologies in mitigating these effects. Despite the therapeutic promise of injectable agents, their widespread application is hindered by adverse effects, high costs, and accessibility issues. This paper underscores the need for integrative treatment models that combine pharmacological interventions with aesthetic and behavioral therapies to optimize patient outcomes. Future research should focus on refining personalized protocols and expanding the accessibility of these treatments to diverse populations.

Keywords: overweight; injectable agents; weight loss; clinical pharmacology; metabolic modulation; aesthetic implication

1. Introduction

Overweight, encompassing both obesity and excess weight, is a complex, long-term condition that has become a highly prevalent public health issue, representing one of the most significant challenges to human health and well-being in the 21st century [1]. It is characterized by increased body fat storage, particularly intra-abdominal fat accumulation, and is associated with a higher risk of metabolic and cardiovascular diseases [2]. According to the World Health Organization (WHO), more than 1.9 billion adults are overweight, with over 650 million classified as obese, reflecting an alarming growth trend in recent decades [3]. In addition to direct health impacts, obesity poses a significant burden on healthcare systems and the global economy [4].

The pathophysiology of obesity is complex and multifactorial, involving a wide range of factors such as environmental, sociocultural, physiological, medical, behavioral, genetic, and epigenetic contributors that drive its onset and long-term persistence [5]. Key biological mechanisms include hypothalamic-pituitary axis dysregulation, insulin resistance, low-grade chronic inflammation, and hormonal alterations that modulate appetite and energy storage [6]. These complexities make therapeutic approaches challenging, necessitating strategies that go beyond traditional interventions like diet and physical exercise.

Given the limitations of conservative interventions, pharmacological treatments have emerged as effective alternatives, particularly for patients with grade II or higher obesity [7]. In recent years, the development of injectable agents has shown promising results, offering benefits such as improved

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adherence, sustained weight reduction, and better control of associated comorbidities. These agents target specific molecular pathways, including GLP-1, GIP, and beta-3 adrenergic receptors, and promote localized lipolysis through lipolytic compounds, thereby expanding the therapeutic arsenal [6]. However, their application extends beyond metabolic benefits, influencing aesthetic outcomes and patient quality of life [8,9]

This review delves into the pharmacological properties, clinical efficacy, and safety profiles of the leading injectable therapies for obesity, while addressing the aesthetic and psychosocial implications associated with rapid weight loss. By exploring the intersection between metabolic modulation and aesthetic interventions, this study aims to provide a comprehensive perspective on the evolving landscape of obesity treatment.

2. Materials and Methods

It is a narrative review of the literature. A search was conducted for studies published within the last 15 years in English, Portuguese, or Spanish on PubMed, focusing on intervention studies (clinical trials, or observational studies) available in full text, that address the use of injectable pharmacological agents for overweight management. They must also have discussed the subject meaning the use of pharmacological agents in overweight management.

The use of standard descriptors and Boolean operators for a systematic search (e.g., "name of the active ingredient" AND ("injectable" OR "injectable drugs") AND (obesity OR "localized fat" OR "metabolic accelerators" OR "weight loss")) produced scant results when applied time and study type filters. This seems to indicate a void of knowledge with their usage in this context, especially very rigorous studies like clinical trials.

To proceed, PubMed was searched with targeted keywords for each active ingredient, using time, language, availability of free full articles, and study type filters. Titles and abstracts were screened for relevance to the scope of the study. The selected studies which further Discussion below also served to build upon earlier works where data was presented in or before 2009 in the absence of more recently available studies. These provided information on the mechanism of action and clinical efficacy, as well as safety profiles, of injectable agents.

3. Physiology of Obesity

The pathophysiology of obesity highlights the dysregulation of the hypothalamic-pituitary axis, which is responsible for appetite control and energy balance [10]. Hormonal signaling alterations, such as leptin resistance and elevated ghrelin levels, lead to increased caloric intake and reduced energy expenditure [11].

Another critical factor is insulin resistance, which contributes to excessive fat storage, particularly visceral fat. This process is associated with increased hepatic lipogenesis and reduced lipolysis, exacerbating the chronic low-grade inflammatory state observed in obese individuals [12]. Pro-inflammatory cytokines, such as TNF-α and IL-6, released by dysfunctional adipose tissue, promote systemic inflammation and metabolic dysfunction [13].

Additionally, obesity is linked to gut microbiota dysbiosis, negatively affecting energy metabolism and hormonal homeostasis. Alterations in the gut-brain axis directly influence appetite regulation and lipid metabolism [14].

Overall, the main pathophysiological components of obesity include hormonal dysregulation—characterized by leptin resistance, increased ghrelin levels, and reduced GLP-1; insulin resistance, which affects lipogenesis and lipolysis; chronic inflammation driven by pro-inflammatory cytokines and adipose tissue dysfunction; and intestinal dysbiosis, disrupting the gut-brain axis and interfering with energy metabolism [15].

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4. Injectable Medications for Weight Loss

Injectable agents for weight loss have specific mechanisms of action, making them essential tools in obesity management. The main groups include GLP-1 receptor agonists, GIP receptor antagonists, pancreatic lipase inhibitors, lipolytic compounds used in mesotherapy, and beta-3 adrenergic agonists. These drugs target distinct metabolic and hormonal pathways, offering an integrated therapeutic approach for obese patients [16].

GLP-1 receptor agonists, such as liraglutide and semaglutide, mimic the action of the incretin hormone GLP-1, modulating appetite and glycemic metabolism. These drugs act on the central nervous system by activating anorexigenic neurons in the hypothalamic arcuate nucleus, promoting satiety and reducing appetite [17].

Additionally, they delay gastric emptying, prolonging postprandial satiety, and increase glucose-dependent insulin secretion while suppressing glucagon secretion, reducing hepatic gluconeogenesis. Liraglutide, administered subcutaneously in daily doses up to 3 mg, and semaglutide, administered weekly in doses up to 2.4 mg, have shown significant efficacy in weight reduction and metabolic control [6,18].

GIP receptor agonists enhance the action of gastric inhibitory peptide (GIP), an incretin that stimulates lipogenesis and energy storage. By inhibiting this pathway, these agents reduce visceral fat deposition and promote efficient energy utilization [19]. Tirzepatide, a dual GLP-1 and GIP agonist administered weekly in doses ranging from 5 mg to 15 mg, has demonstrated synergistic effects, enhancing weight loss and improving glycemic profiles [18].

Pancreatic lipase inhibitors, such as orlistat, act directly in the intestinal lumen by blocking pancreatic lipase activity and preventing the digestion of triglycerides into free fatty acids and monoglycerides. This mechanism reduces dietary fat absorption, increases lipid excretion in the feces, and promotes a negative energy balance. Orlistat, administered exclusively orally at doses of 120 mg three times a day, has been shown to be effective in weight reduction. It is usually used in combination with another injectable drug, although it is often associated with gastrointestinal side effects, such as steatorrhea [20].

Compounds used in mesotherapy, including phosphatidylcholine and sodium deoxycholate, promote localized lipolysis. Phosphatidylcholine destabilizes adipocyte cell membranes, facilitating the emulsification and release of triglycerides, while sodium deoxycholate acts as a detergent, solubilizing lipids and inducing adipocyte apoptosis [21]. These compounds are administered at concentrations of 2–5% for phosphatidylcholine and approximately 1% for deoxycholate in small volumes of 0.2–0.5 mL per injection site at intervals of 15 to 30 days. Despite their widespread use in aesthetic treatments, robust studies validating the long-term efficacy of mesotherapy are lacking [22].

Beta-3 adrenergic agonists stimulate beta-3 receptors, predominantly found in brown adipose tissue, promoting thermogenesis and increasing basal energy expenditure [23]. Mirabegron, initially developed for overactive bladder, exemplifies this class of medications and has shown potential, in doses of 50 mg to 200 mg per day, to activate brown adipose tissue and contribute to weight loss [24]. Studies suggest that the combination of beta-3 agonists, administered exclusively orally, with other injectable obesity therapies, such as GLP-1 agonists, may produce complementary and more effective results [25].

The distinct mechanisms of action of these drug groups demonstrate the complexity and efficacy of available therapeutic approaches for obesity management, underscoring their importance in clinical practice (Table 1).

Table 1. Overview of Drug Classes.

Drug Class	Medication Name	Brand Name	Dosage	Administration Interval	Manufacturer	Country of Origin
GLP-1 Receptor	Liraglutide	Saxenda®	0.6 mg to 3 mg per day, subcutaneous	Daily	Novo Nordisk	Denmark

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Agonists						
GLP-1 Receptor Agonists	Semaglutide	Ozempic®	0.25 mg to 2.4 mg per week, subcutaneous	Weekly	Novo Nordisk	Denmark
GLP-1 and GIP Receptor Agonists	Tirzepatide	Mounjaro®	5 mg to 15 mg per week, subcutaneous	Weekly	Eli Lilly	United States
Pancreatic Lipase Inhibitors	Orlistat*	Xenical®	120 mg three times per day, oral	Three times per day	Roche	Switzerland
Beta-3 Adrenergic Agonists	Mirabegron*	Betmiga®	50 mg to 200 mg per day, oral	Daily	Astellas Pharma	Japan

Source: Own elaboration. *Oral administration.

The adverse effects of injectable metabolic agents vary depending on their mechanisms of action, the dosages used, and the individual susceptibility of the patient. Among GLP-1 receptor agonists, liraglutide generally causes gastrointestinal symptoms such as nausea, vomiting, diarrhea, and constipation, as well as injection site reactions such as erythema and pruritus [26]. It has rarely been associated with pancreatitis, and preclinical studies have identified a potential risk of thyroid neoplasms. Semaglutide has a similar adverse effect profile, with nausea and vomiting being common, especially during the initiation or adjustment of treatment. In rarer cases, generalized weakness and hypoglycemia were observed, particularly when used with other hypoglycemic agents such as insulin [27].

Tirzepatide, a dual GLP-1 and GIP receptor agonist, is often associated with gastrointestinal disturbances, including nausea, diarrhea, and flatulence. It also carries a risk of pancreatitis in predisposed patients and hypoglycemia when combined with other antidiabetic medications [28]. Orlistat, a pancreatic lipase inhibitor, generally causes gastrointestinal side effects resulting from the inhibition of fat absorption. These effects include steatorrhea, flatulence, abdominal pain, and increased bowel frequency, especially in patients who do not adhere to low-fat diets [29].

Mirabegron, a beta-3 adrenergic agonist, can cause cardiovascular effects such as tachycardia and high blood pressure, as well as other side effects such as headache, dry mouth, and insomnia, due to its influence on the autonomic nervous system. Monitoring and individualizing treatment plans are essential for effective management of these adverse effects [30].

5. Injectable Metabolic Accelerators for Weight Loss

Injectable metabolic accelerators for weight loss can be classified based on their predominant mechanisms of action, such as thermogenesis stimulators, lipolysis modulators, appetite regulators, and metabolic optimizers. Each class plays a distinct role in the treatment of metabolic conditions such as obesity, metabolic syndrome, and body weight control [31].

Thermogenesis stimulators include compounds such as caffeine and taurine. Caffeine acts as an adenosine receptor antagonist, increasing the release of catecholamines and stimulating thermogenesis, leading to increased basal energy expenditure and the use of fat as an energy substrate. At high doses, caffeine inhibits the phosphodiesterase enzyme, leading to an increase in intracellular cyclic AMP (cAMP), prolonging the effects of catecholamines, and amplifying lipolysis. The recommended dose is 50 mg to 100 mg, administered intramuscularly weekly [32]. Taurine, on the other hand, modulates calcium ion transport and facilitates bile synthesis, promoting lipid metabolism and reducing visceral fat. Additionally, it has antioxidant properties that optimize mitochondrial function, with a dosage of 200 mg intramuscularly per week [33].

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Lipolysis modulators include L-carnitine, chromium picolinate, inositol, and choline. L-carnitine plays a crucial role in transporting fatty acids to the mitochondria, where they are oxidized and converted into energy, reducing fat deposits and increasing energy availability [34]. The usual dose is 200 mg to 600 mg intramuscularly, administered two to three times per week. Chromium picolinate improves insulin signaling, promoting glucose uptake by cells and reducing lipogenesis, with a dose of 100 mcg intramuscularly per week [35]. Inositol acts as a precursor to signaling molecules in lipid metabolism, aiding in the reduction of visceral fat and glucose metabolism, with a dosage of 100 mg to 200 mg weekly [36]. Choline, essential in the formation of acetylcholine and lipid metabolism, functions as a lipotropic agent, reducing liver fat at doses of 200 mg to 500 mg intramuscularly per week [37].

Appetite regulators include compounds such as N-acetyl, L-tyrosine, 5-HTP, L-theanine, and phenylalanine. N-acetyl is involved in the synthesis of neurotransmitters related to energy metabolism and appetite modulation, serving as an essential precursor in neuroendocrine regulation, with doses ranging from 20 mg to 50 mg intramuscularly per week [37]. L-tyrosine, a direct precursor to dopamine, norepinephrine, and epinephrine, enhances sympathetic activity and increases basal energy expenditure, with a similar dosage [38]. 5-HTP, a precursor to serotonin, reduces food cravings and regulates caloric intake, with doses of 4 mg to 20 mg intramuscularly per week [39]. L-theanine acts on GABA receptors, reducing anxiety and controlling emotional eating associated with highly caloric foods, with doses of 10 mg to 20 mg per week (40). Phenylalanine, a precursor to dopamine and norepinephrine, helps control appetite and modulate mood, contributing to reduced caloric intake at doses of 50 mg per week [38].

Metabolic optimizers include agents such as vitamin B12, L-arginine, ornithine, methionine, and HMB. Vitamin B12, essential for energy metabolism and neurological function, increases mitochondrial energy production and corrects metabolic deficiencies associated with obesity, administered at doses of 2500 mcg intramuscularly weekly [41]. L-arginine, a precursor to nitric oxide, enhances vasodilation and nutrient delivery to tissues, increasing fatty acid oxidation at doses of 200 mg to 600 mg [42] Ornithine participates in the urea cycle, promoting ammonia removal and assisting in muscle regeneration and fatigue reduction, with a dosage of 200 mg weekly [43]. Methionine acts as a methyl donor, supporting liver metabolism and reducing visceral fat at doses of 100 mg intramuscularly per week [44]. HMB, derived from leucine metabolism, reduces muscle protein breakdown and stimulates protein synthesis, helping preserve lean mass, with doses of 2 g to 3 g intramuscularly per week [45].

These injectable agents have distinct pharmacological profiles that, when grouped into classes, provide an integrated view of their therapeutic applications. Their specific properties allow for personalized protocols, optimizing results in the management of obesity and related metabolic conditions. It is essential that their use be supervised by qualified professionals, considering the individual needs of patients and potential adverse effects (Table 2).

Table 2. Pharmacological Details of Active Ingredients.

Active Ingredient	Classification	Dosage	Mechanism of Action
Caffeine	Thermogenesis Stimulant	50 mg to 100 mg/day	Adenosine antagonist; increases thermogenesis
Taurine	Thermogenesis Stimulant	200 mg/day	Promotes lipid metabolism and antioxidant function
L-Carnitine	Lipolysis Modulator	200 mg to 600 mg, 2-3 times/day	Transports fatty acids to the mitochondria
Chromium Picolinate	Lipolysis Modulator	100 mcg/day	Improves insulin signaling
Inositol	Lipolysis Modulator	100 mg to 200 mg/day	Supports lipid metabolism and reduces visceral fat
Choline	Lipolysis Modulator	200 mg to 500 mg/day	Involved in lipid metabolism and reduces liver fat

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N-Acetyl	Appetite Regulator	20 mg to 50 mg/day	Modulates neurotransmitters for appetite control
L-Tyrosine	Appetite Regulator	20 mg to 50 mg/day	Precursor of dopamine; increases energy expenditure
5-HTP	Appetite Regulator	4 mg to 20 mg/day	Precursor of serotonin; reduces food cravings
L-Theanine	Appetite Regulator	10 mg to 20 mg/day	Modulates GABA receptors; reduces food-related anxiety
Phenylalanine	Appetite Regulator	50 mg/day	Precursor of dopamine; controls appetite and mood
Vitamin B12	Metabolic Optimizer	2500 mcg/day	Improves energy metabolism and neurological function
L-Arginine	Metabolic Optimizer	200 mg to 600 mg/day	Precursor of nitric oxide; improves vasodilation
Ornithine	Metabolic Optimizer	200 mg/day	Involved in the urea cycle; reduces ammonia
Methionine	Metabolic Optimizer	100 mg/day	Methyl group donor; reduces visceral fat

Source: Own elaboration.

Injectable metabolic accelerators, while effective in managing metabolic conditions, may cause adverse effects in some patients, depending on the active compound, dosage, and individual sensitivity. Among thermogenesis stimulators, caffeine is associated with insomnia, tachycardia, tremors, anxiety, increased blood pressure, and gastrointestinal disturbances due to its action as an adenosine antagonist and stimulation of the sympathetic nervous system [32]. Taurine, generally well-tolerated, may cause nausea or abdominal discomfort at high doses [33].

Lipolysis modulators also present varying safety profiles. L-carnitine can cause a fish-like body odor, nausea, vomiting, muscle cramps, and diarrhea, especially at higher doses [34]. Chromium picolinate, rarely, can cause liver or kidney toxicity, along with symptoms such as rashes, headaches, and dizziness [35]. Inositol is generally well-tolerated but high doses may cause diarrhea, nausea, and fatigue [36]. Choline, essential for lipid metabolism, may result in strong body odor, nausea, excessive sweating, and, in some cases, hypotension [37].

Appetite regulators also present specific adverse effects. N-acetyl is associated with headaches, insomnia, irritability, and gastric discomfort [46]. L-tyrosine can cause anxiety, hypertension, insomnia, and palpitations, especially at higher doses [38]. 5-HTP, a serotonin precursor, may cause nausea, diarrhea, abdominal bloating, and, in rare cases, serotonin syndrome, especially when combined with antidepressants [39]. L-theanine has minimal adverse effects, rarely causing mild drowsiness or gastric discomfort [40]. Phenylalanine, a precursor to catecholamines, may cause hypertension, tachycardia, insomnia, anxiety, and irritability [38].

Metabolic optimizers also have specific adverse effects. Vitamin B12 may cause rashes, itching, diarrhea, and, in rare cases, severe allergic reactions [41]. L-arginine may cause gastrointestinal disturbances, including nausea, diarrhea, and abdominal cramps, as well as hypotension at high doses [42]. Ornithine is generally well-tolerated but may occasionally cause abdominal discomfort in some individuals [43]. Methionine, at high doses, may elevate homocysteine levels, increase cardiovascular risks, and may cause liver toxicity, nausea, and vomiting (Garlick, 2006).Finally, HMB (beta-hydroxy-beta-methylbutyrate) is considered safe but may cause mild gastrointestinal disturbances in some cases [45].

The adverse effects of metabolic accelerators depend on various factors and can be minimized with dose adjustments and regular patient monitoring. It is essential that the prescription and use of these agents are carried out under professional supervision, considering each patient's preexisting health conditions and medical history.

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6. Common Drug Interactions

Drug interactions involving pharmaceutical agents and metabolic accelerators are determined by their mechanisms of action, shared metabolic pathways, and physiological effects. These interactions may enhance or antagonize therapeutic outcomes and, in some cases, increase the risk of adverse effects (Table 3).

GLP-1 receptor agonists, such as liraglutide, semaglutide, and tirzepatide, have a significant risk of interacting with drugs that slow gastric emptying or alter intestinal transit. These agents slow gastric emptying, potentially altering the absorption of orally administered drugs and reducing the effectiveness of agents like orlistat, whose action depends on the presence of lipids in the gastrointestinal tract. Additionally, combining GLP-1 agonists with metabolic accelerators that stimulate the sympathetic nervous system, such as caffeine, can exacerbate nausea or gastrointestinal discomfort, commonly observed at the beginning of GLP-1 treatment [6].

Orlistat, a pancreatic lipase inhibitor, mainly interacts with fat-soluble compounds such as vitamins A, D, E, and K. When combined with metabolic accelerators that promote lipolysis, like L-carnitine and chromium picolinate, it may reduce the absorption of essential vitamins, impairing lipid metabolism over time. This interaction requires adequate vitamin supplementation to prevent nutritional deficiencies [20].

Beta-3 adrenergic agonists, like mirabegron, present a moderate risk of interaction with drugs that increase sympathetic activity, such as caffeine-based thermogenics. This combination may lead to undesirable cardiovascular effects, including tachycardia, elevated blood pressure, and palpitations. Mirabegron is also metabolized by cytochrome P450 (CYP2D6), which may alter the pharmacokinetics of drugs that share this metabolic pathway, increasing or reducing their effectiveness [25].

Lipid metabolism modulators, such as L-carnitine, choline, and inositol, generally have a low potential for direct interactions. However, their simultaneous use with metabolic accelerators may enhance the efficiency of energy metabolism. Elevated fatty acid oxidation, however, can increase ammonia levels in patients with impaired liver or kidney function, requiring careful monitoring. Co-administration with thermogenic agents, such as caffeine, should be evaluated cautiously, as it may exacerbate gastrointestinal effects like nausea and abdominal discomfort [34].

The concomitant use of appetite regulators, such as 5-HTP, L-tyrosine, and phenylalanine, with metabolic accelerators that stimulate the central nervous system can lead to sympathetic hyperactivity, causing insomnia, anxiety, and, in rare cases, serotonin syndrome. This interaction is particularly significant in patients already using antidepressants due to the risk of serotonin overload [39].

Finally, metabolic optimizers, such as vitamin B12 and HMB, have a low risk of significant interactions. However, high doses of L-arginine combined with metabolic accelerators may cause hypotension, especially in sensitive individuals or those taking antihypertensive medications. This combination requires monitoring, as it may impair tissue perfusion in critical areas [42].

Table 3. Drug Interactions and Clinical Recommendations.

Drug/Class	Potential Interactions	Clinical Recommendations
Liraglutide (GLP-1 Agonist)	Risk of reduced absorption of oral medications; potential nausea enhancement with thermogenics.	Monitor gastrointestinal symptoms and adjust oral medication doses.
Semaglutide (GLP-1 Agonist)	Risk of interaction with hypoglycemics; enhancement of gastrointestinal symptoms with caffeine.	Avoid combinations with potent hypoglycemics; start with low doses.
Tirzepatide (GLP-1 and GIP Agonist)	Risk of pancreatitis; interaction with hypoglycemics can cause hypoglycemia.	Monitor blood glucose and signs of pancreatitis; avoid aggressive combinations.

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Orlistat (Pancreatic Lipase Inhibitor)	Reduces absorption of fat-soluble vitamins; interactions with lipid modulators may exacerbate vitamin deficiencies.	Prescribe vitamin supplementation for long-term use.
Mirabegron (Beta-3 Agonist)	Interaction with thermogenics may cause tachycardia and increased blood pressure; interactions with CYP2D6.	Avoid combination with potent thermogenics in hypertensive patients.
L-Carnitine (Lipid Modulator)	Potential increase in ammonia with combined use; exacerbation of gastrointestinal disorders with thermogenics.	Monitor ammonia levels; adjust doses of synergistic agents.
Chromium Picolinate (Lipid Modulator)	Mild interactions; potential synergy with metabolic modulators.	Assess synergistic impacts; maintain adequate supplementation.
5-HTP (Appetite Regulator)	Risk of serotonin syndrome with antidepressants; interaction with thermogenics may cause insomnia.	Avoid patients taking antidepressants; monitor insomnia.
L-Arginine (Metabolic Optimizer)	Hypotension in combination with antihypertensives; interaction with thermogenics may exacerbate cardiovascular effects.	Monitor hypotension; carefully adjust in combined protocols.
HMB (Metabolic Optimizer)	Generally safe; minimal metabolic interactions with accelerators.	General monitoring; considered safe for therapeutic combinations.

Source: Own elaboration.

7. Safety and Toxicology

Metabolic agents used in therapeutic protocols generally have a well-established safety profile, with toxicity varying based on dosage, administration route, and the individual susceptibility of the patient. Among GLP-1 receptor agonists such as liraglutide, semaglutide, and tirzepatide, studies demonstrate overall safety when used at therapeutic doses with appropriate monitoring [48]. However, these compounds are contraindicated in individuals with a history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, due to preclinical findings suggesting risks associated with these specific conditions [6,18].

Orlistat, a pancreatic lipase inhibitor, is considered safe for long-term use due to its low systemic absorption. However, its effectiveness may require vitamin supplementation to prevent deficiencies of fat-soluble vitamins [20]. Similarly, mirabegron, a beta-3 adrenergic agonist, has a favorable safety profile but requires caution in patients with cardiovascular comorbidities or those on multiple medications, as it is metabolized by the cytochrome P450 system [25].

Lipid modulators, such as L-carnitine, inositol, choline, and chromium picolinate, exhibit high tolerability and safety when used at appropriate doses. Studies suggest that L-carnitine is particularly effective in optimizing energy metabolism, while chromium picolinate aids in glucose control, making both agents suitable for integrated protocols [34,35].

Appetite regulators, including 5-HTP, L-tyrosine, phenylalanine, and L-theanine, have a high safety profile when administered alone or in carefully adjusted combinations. These agents play crucial roles in controlling food intake and modulating neurotransmitters, making them widely used in weight loss strategies [38].

Metabolic optimizers, such as vitamin B12, L-arginine, ornithine, and HMB, also demonstrate high safety in studies, even with prolonged use. Vitamin B12 is essential for metabolic and neurological function, while HMB supports the preservation of lean mass, making it a valuable resource in protocols aimed at optimizing body composition [42,49–51].

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Available data indicates that these metabolic agents are safe for clinical use when administered according to individualized protocols and under professional supervision. Regular monitoring and personal adjustments are essential to maximize therapeutic effectiveness and minimize potential risks.

8. Injectable Weight Loss Agents and Aesthetic Dysfunctions: Strategies to Combat Skin Laxity with Biostimulators and Technologies

The use of injectable agents in obesity treatment has emerged as an effective tool for weight reduction and improvement of metabolic parameters. Key medications include GLP-1 and GIP receptor agonists, pancreatic lipase inhibitors, lipolysis modulators, and thermogenesis stimulators [52]. While these interventions promote fat loss and subsequent aesthetic enhancement, they often result in aesthetic dysfunctions such as excessive skin laxity, affecting both the face and body [5].

Rapid weight loss induced by agents like semaglutide and tirzepatide is associated with a significant reduction in subcutaneous adipose tissue volume, leading to tissue laxity. This phenomenon arises due to the loss of mechanical support provided by fat, highlighting the need for complementary interventions to address this aesthetic condition (6). Beyond physical impacts, post-weight loss skin laxity can generate significant psychosocial consequences, often overlooked by healthcare professionals. The focus on fat reduction tends to neglect the emotional discomfort and body dissatisfaction that accompany residual skin laxity. Patients report decreased self-esteem, insecurity regarding appearance, and difficulties maintaining motivation to continue treatment, underscoring the importance of comprehensive and multidisciplinary care [53].

The psychosocial effects of skin laxity are even more pronounced in the face, as changes in facial contour directly affect the patient's aesthetic perception and identity. Facial fat loss accentuates nasolabial folds, deepens tear troughs, and causes cheek ptosis, resulting in an aged appearance. Dissatisfaction with these effects can lead to anxiety and depression, negatively impacting quality of life and social interactions [54]. The neglect of this aspect by professionals focusing solely on body weight loss reinforces the need for approaches that integrate facial and body treatments. Addressing skin laxity through body harmonization involves not only fat reduction but also collagen stimulation to prevent and treat cutaneous laxity [55]. This integrated approach highlights the importance of treating obesity while implementing protocols that improve skin quality, promoting patient self-esteem and overall well-being.

Collagen biostimulators, such as poly-L-lactic acid (PLLA) and calcium hydroxyapatite (CaHA), play a crucial role in tissue restructuring for patients undergoing weight loss therapies. These agents promote a controlled inflammatory response that stimulates the synthesis of type I and III collagen, restoring skin firmness and elasticity [56]. Studies show that PLLA, when injected into deep dermal layers, induces neocollagenesis for up to 18 months post-procedure. PLLA acts through indirect biostimulation: its microparticles, upon injections, trigger a mild inflammatory response that leads to new collagen production over time, providing gradual and natural improvement in skin texture and firmness [57].

Widely used in facial rejuvenation, poly-L-lactic acid (PLLA) stimulates endogenous collagen production, resulting in significant improvements in skin firmness and elasticity. Its efficacy and safety have been demonstrated in recent studies [56]. Additionally, PLLA effectively restores facial volume lost due to aging, addressing static wrinkles, particularly in the mid and lower face. The gradual and natural volumization achieved with PLLA enhances facial contours and overall appearance. Complementing PLLA, calcium hydroxyapatite not only stimulates collagen production but also acts as an immediate dermal filler. Its microparticles provide structural support while promoting tissue regeneration and continuous collagen synthesis. This dual mechanism yields both immediate and progressive results, making it ideal for treating areas like the cheeks, jawline, and temples, which are prone to laxity following fat loss [58].

In addition to biostimulators, technologies such as fractional radiofrequency, high-intensity focused ultrasound (HIFU), and CO_2 laser are employed to induce collagen fiber contraction and stimulate neocollagenesis. Acting synergistically with biostimulators, these technologies enhance results and improve skin firmness [59]. Fractional radiofrequency heats the deep skin layers to

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temperatures between 40-45°C, causing partial denaturation of existing collagen fibers and initiating a repair process that leads to the synthesis of new fibers [60].

High-intensity focused ultrasound (HIFU) penetrates various skin depths (1.5 mm to 4.5 mm), creating thermal coagulation points in the superficial muscular aponeurotic system (SMAS). This non-surgical lifting effect is particularly effective for the neck, submental area, and jawline [61]. Fractional CO_2 laser, by removing superficial skin layers while stimulating deeper collagen production, addresses laxity associated with wrinkles and scars, contributing to comprehensive facial revitalization [62]. The combination of these therapies provides a robust solution for treating skin laxity, particularly in patients who have experienced significant weight loss.

9. Discussion

Overweight is a complex condition that requires multifaceted approaches to its successful management. It is strongly linked to some very serious metabolic, cardiovascular, and psychosocial comorbidities and complications and, arguably, represents one of the greatest contemporary global public health challenges, if not burdens, on healthcare systems. This has further opened newer frontiers whereby the use of injectable medications and metabolic stimulators in weight loss is gaining ground over the traditional ways of dietary, physical, and behavioral methods [40].

The most common medications used to treat obesity are GLP-1 receptor agonists, including liraglutide and semaglutide. They act as analogs to endogenous incretins, the modulation of food intake being one of their mechanisms through the enhancement of satiety and deceleration of gastric emptying [63]. They also have glucose-dependent insulinotropic effects, which is advantageous, especially for patients with type 2 diabetes. According to them, results of clinical studies for semaglutide show the achievement of more than 15% weight loss within 68 weeks, which is significantly better compared to non-pharmacological interventions [64]. The GLP-1 agonists are restricted by adverse reactions, such as nausea, vomiting, and diarrhea. Severe adversities can lead to pancreatitis and cholelithiasis, which need continuous medical monitoring and risk-benefit analysis with caution [26]. Moreover, their subcutaneous route of administration and high cost may limit their access, particularly in developing countries [51].

Another important therapeutic group is injectable metabolic stimulants- L-carnitine, inositol, choline, and taurine-targeting these processes along with fatty acid oxidation, lipolysis, and mitochondrial function [31]. For instance, L-carnitine is required for the transport of fatty acids to the β-oxidation inside the mitochondrial matrix. Inositol has been related to sensitization to insulin and mobilization of stored fats, whereas choline performs emulsification of lipids and a function in liver health. Indeed, along with its antioxidant properties, it has a role in controlling lipid metabolism as well as cardiovascular function [65]. Even though regarded as safe, the metabolic accelerators can evoke GI discomfort and reactions at the site of injection, particularly when very high doses are involved. The available data on the effectiveness of these compounds are very scanty, which principally justifies the necessity to further work on establishing standardized protocols and possible interactions with other pharmacological treatments.

The injectable agents work for weight loss, no doubt, but rectification of the aesthetic sequel afterward, such as increased skin sagging at areas of massive fat reduction, needs an integrated and personalized approach [66]. For example, facial laxity not only hurts the eye but also causes a mentally unhealthy patient, eliciting the need for concomitant treatments that encourage tissue reorganization and support psychologically. Aesthetic interferences proved effective in skin firmness and quality, handling post-weight loss flabbiness [67].

The combination of biostimulators and non-invasive technologies provides an effective approach to deep skin treatment, promoting collagen stimulation and the natural restoration of facial contours. Personalizing protocols according to individual characteristics enhances results, increases patient satisfaction, and improves treatment adherence [55].

On the other hand, injectable medications for weight loss have several advantages. The use of injectable medications for weight loss is associated with several major limitations. Indeed, clinical

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studies tend to be of small sample, short follow-up period, and heterogeneous results, which complicate the possibility of generalizing their findings [68]. Among them are side effects, high costs, and frequent dosing that compromise patient adherence. Yet another challenge would be that metabolic accelerators may interact with other medications. As observed for L-arginine, such an excellent when combined with antihypertensives causes hypotension. These interactions emphasize a team approach to managing obesity, including physicians, pharmacists, and nutritionists.

Safe only if administered in the prescribed dose and regular monitoring is adhered. Has an attractive safety profile, but contraindicated in patients with past history related to medullary thyroid carcinoma or multiple endocrine neoplasia type 2, as risks of tumors observed in the preclinical study [69]. On the other hand, compounds such as L-carnitine and choline have a low-to-moderate risk that involves toxicity if administered inappropriately. Although their prolonged use might lead to imbalances or liver overload, it allows room for personalized protocols and constant qualified professional supervision.

The future in the management of obesity with injectable medications lies in the development of more effective and safer treatments. Dual agonists, both of GLP-1 and GIP, are more effective than traditional agonists and there is a hope for better weight loss with good metabolic control [70]. Moreover, the revolution that could be brought about in therapeutic approaches by using biomarkers and artificial intelligence to personalize treatments may allow more specific and individualized interventions. New biological and metabolizable entities boosting fat burning and preservation of lean mass are also in the pipeline. Nanotechnology and controlled-release systems can enhance and reduce ineffectiveness by housing higher potency within the formulation.

These agents would seem to not only induce metabolic benefits but also elicit psychosocial improvements—a quite worthy component within an integrative, multidisciplinary approach. Nevertheless, issues of safety, efficacy, and above all adherence still beg for research and innovation efforts. The heavy lifting of maximizing the effects of these treatments on global health will demand evidence generation, professional education, and access initiatives.

10. Conclusions

Pharmacotherapy for weight loss not only restores glycemic control and reduces cardiometabolic risk factors—sometimes independently of weight reduction—but also mitigates the metabolic adaptation that limits further weight loss. This process occurs gradually and represents a unique yet underrecognized challenge in obesity therapy and, by extension, in medicine. While no single pharmacotherapy currently offers both complete efficacy and safety in promoting weight loss and improving metabolism, the combination of injectable therapies has emerged as a promising strategy. These therapies provide benefits for weight reduction and metabolic health, although long-term success will depend on ease of administration, affordability, and the minimization of side effects. Following significant weight loss, patients may experience undesirable aesthetic outcomes, such as skin laxity, which often require complementary treatments. Collagen biostimulators, microfocused ultrasound, and fractional radiofrequency have demonstrated efficacy in improving skin quality and restoring firmness. Injectable agents, such as GLP-1 and GIP receptor agonists, have shown effectiveness in managing weight and enhancing metabolic parameters. However, the future of obesity treatment lies in the development of personalized therapies that address weight loss, metabolic optimization, and aesthetic outcomes in a comprehensive manner. This integrated approach not only enhances clinical outcomes but also improves self-esteem, significantly contributing to the patient's overall well-being and quality of life.

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