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Research Article

Algorithmic Approach to Pharmacotherapy in Obesity Management and Diabetes, Considering Comorbidities and Medication Suitability: Introducing the G-SLIM™ Algorithm

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Abstract

Obesity, defined by excessive and abnormal fat accumulation, remains a rapidly escalating global health crisis. It is a major contributor to numerous comorbidities, increased morbidity and mortality, and poses significant clinical and public health challenges. Furthermore, obesity and type 2 diabetes are closely interconnected through a complex interplay of metabolic, hormonal, and inflammatory pathways. Effectively addressing obesity is essential for both the prevention and management of type 2 diabetes. Given their strong association, weight control emerges as a critical strategy in reducing the global burden of diabetes. Managing obesity is complex due to its multifactorial nature, as well as a combination of significant biases toward the disease and lack of education. There are many approaches to dealing with obesity, such as lifestyle, pharmacotherapy, and surgery. This paper focuses on pharmacotherapy by introducing the G-SLIM™ algorithm and its potential role in providing a structured approach to pharmacotherapy for obesity management. It draws parallels to established treatment algorithms for other chronic conditions like diabetes, hyperlipidemia, and hypertension by introducing stepwise and layering medication selections. It explores the prevalence and challenges of obesity management and the economic impact of current pharmacological options. When a single medication is ineffective—due to inadequate weight loss, adverse effects, medical contraindications, or limited accessibility- this article outlines strategies for selecting an alternative therapy. An example of an effective medication is a GLP-1 receptor agonist, with additional therapies introduced based on the patient's response and individual needs. It presents a stepwise, layered approach to medication initiation, targeting the various pathophysiological mechanisms involved in obesity. Additionally, certain medications may address both diabetes and weight management, which should be considered during treatment planning. In conclusion, the G-SLIM™ algorithm employs a structured, stepwise approach to pharmacotherapy for obesity and diabetes, emphasizing the strategic layering of medications to address multiple pathophysiological targets. This method mirrors evidence-based treatment paradigms used in other chronic diseases such as diabetes, hyperlipidemia, and hypertension, reinforcing the importance of combination therapy in achieving long-term management and improved clinical outcomes.

Keywords: Obesity, Type 2 diabetes, Pharmacotherapy, GLP-1 receptor agonists, Insulin resistance, Chronic inflammation, G-SLIM™ algorithm, Stepwise treatment approach, Weight management

1. Introduction

Globally, obesity has become a chronic illness. The World Health Organization (WHO) reported in 2021 that Obesity has reached epidemic proportions globally, with at least 2.8 million people dying each year as a result of being overweight or obese [1]. Projections suggest that by 2030, 29 U.S. states will have over 50% of their adult population classified as obese [2]. Obesity is associated with numerous health complications affecting multiple organ systems. It significantly increases the risk of type 2 diabetes, which can lead to microvascular and macrovascular complications, including neuropathy, nephropathy, retinopathy, atherosclerosis, hypertension, and stroke [3,4]. Excess adiposity also affects the liver: simple steatosis can progress to metabolic dysfunction-associated steatohepatitis (MASH), resulting in inflammation, fibrosis, and impaired liver function [5,6]. Respiratory function is similarly compromised in obesity, with individuals experiencing asthma, obstructive sleep apnea, dyspnea, and reduced lung capacity due to altered lung mechanics and increased airway resistance [7–9]. Obesity also stresses weight-bearing joints, particularly the lower back, hips, and knees, increasing the risk of osteoarthritis and chronic pain, which further limits mobility [10,11]. Furthermore, obesity can lead to psychological problems such as anxiety, depression, low self-esteem, and social stigmatization [12,13]. Elevated BMI can impair fertility in both men and women by disrupting hormonal balance and reproductive function [14,15]. Women are more likely than men to experience conditions such as polycystic ovary syndrome (PCOS), a common endocrine disorder that can impair fertility and increase the risk of pregnancy complications [16,17]. Additionally, the psychological burden of weight-related challenges may contribute to chronic stress and maladaptive coping behaviors, further complicating efforts to achieve and sustain a healthy lifestyle [13–15]. Furthermore, obesity increases the risk of several malignancies, including breast, colon, endometrial, kidney, and liver cancers, mediated by endocrine disruptions, chronic low-grade inflammation, and alterations in adipokine signaling [18–22].

The economic impact of obesity is substantial, driven by increased healthcare costs, reduced workforce productivity, and greater strain on public resources. Consequently, obesity hinders economic growth and development. Obesity is projected to reduce the global gross domestic product (GDP) by an estimated 2-3% and rise to over 3% annually by 2060, driven by increasing healthcare expenditures, reduced workforce productivity, and other economic burdens [23,24]. The effects of obesity raise medical care costs substantially for every category of expenditure (outpatient, inpatient, and prescription drugs), and for both public health insurance programs and private health insurers. According to the Joint Economic Committee, they projected that the share of U.S. adults who are obese will rise from between 44.9 percent and 47.5 percent in 2024 to between 51.4 percent and 56.6 percent by 2034. These projections are based on a linear regression over the prior 10 years and 31 years of obesity rate data. They estimate that obesity will result in $8.2 to $9.1 trillion in excess medical expenditures over the next decade [25]. The Centers for Medicare & Medicaid Services estimated national health spending grew 8.2% in 2024 and expects a 7.1% increase in 2025, the agency reported. CMS projects national health spending will average 5.8% per year through 2033, led by a 7.8% increase annually in Medicare spending [26]. These figures highlight the critical need for effective prevention strategies, particularly as public health and biosafety concerns continue to escalate. Investing in obesity prevention and treatment is among the most cost-effective public health strategies, offering substantial returns across health and economic sectors. OECD analysis shows that every dollar spent on preventing obesity generates up to a six-fold economic return [27].

Effective obesity management requires a comprehensive, multidisciplinary approach that includes lifestyle interventions focused on nutrition and physical activity, behavioral modification, pharmacotherapy, and, when appropriate, surgical intervention. Treating obesity is inherently complex and demands a multimodal strategy. While healthy eating and regular exercise are foundational to weight management, addressing the root causes of obesity—particularly the underlying hormonal and pathophysiological disturbances—is essential for long-term success [28-30]. Pharmacotherapy plays a critical role in this effort by directly targeting these biological mechanisms, offering a more effective and sustainable solution for many individuals. It serves as an effective adjunct to lifestyle interventions, particularly for individuals with BMI ≥30 kg/m^2 or ≥27 kg/m^2 with comorbidities. Approved medications—including orlistat, phentermine/topiramate, naltrexone/bupropion, and liraglutide—primarily act by reducing appetite or enhancing satiety, while orlistat decreases fat absorption. Average additional weight loss ranges from 3–10%, improving cardiometabolic outcomes. Drug selection should be personalized based on comorbidities, contraindications, and patient preferences, with ongoing monitoring for efficacy and safety. Emerging agents, such as semaglutide and tirzepatide, offer promise for more substantial and sustained weight reduction [31-34].

This paper will focus primarily on the pharmacological aspects of obesity and diabetes management within this broader, multidisciplinary framework, and will introduce the conceptual G-SLIM™ algorithm. The G-SLIM™ framework offers a conceptual, structured, pathway-specific approach to obesity pharmacotherapy, enabling clinicians to sequentially or simultaneously target key neurohormonal and metabolic mechanisms.

2. Methods

Review based on literature searches, which included the spread of obesity globally, etiology of obesity, link between diabetes and obesity, and inflammation, obesity management, and focusing on pharmacotherapy for obesity management, and introducing the G-SLIM™ algorithm as a conceptual approach for pharmacotherapy. The novelty of the G-SLIM™ algorithm is not to propose a new pharmacologic hierarchy,

but rather to provide a practical, clinician-facing decision support tool that operationalizes existing best practices in individualized obesity management. Furthermore, a brief review of the impact of obesity on economic growth is presented

2.1. Etiology of Obesity

A complex interplay of genetic factors strongly influences the rising global prevalence of obesity. Research has shown that genetics can significantly affect key physiological processes such as appetite regulation, energy metabolism, and fat storage. These inherited predispositions may make some individuals more vulnerable to weight gain in today's obesogenic environment—characterized by high-calorie food availability, sedentary lifestyles, and chronic stress. Understanding the genetic underpinnings of obesity underscores the need for personalized treatment approaches that move beyond one-size-fits-all strategies. Polygenic (common) and monogenic (rare, severe) forms of obesity are often viewed separately, research shows they share common genetic and biological roots—especially involving brain regulation of body weight. Large-scale genome-wide association studies (GWAS) and sequencing advances have accelerated gene discovery, while cross-disciplinary, post-GWAS efforts integrating omics data are now translating these genetic findings into biological understanding and potential treatments [35].

Environmental and social influences play a pivotal role in driving the obesity epidemic. Contemporary lifestyles, marked by the widespread consumption of calorie-dense, highly processed foods and increasingly sedentary routines, create a sustained energy imbalance. This combination of excessive caloric intake and insufficient physical activity significantly accelerates the rise in obesity rates. Additionally, emotional eating—a coping mechanism often triggered by stress, boredom, depression, or anxiety—can lead to overeating and weight gain. Unhealthy eating habits developed during childhood may also persist into adulthood, further increasing the risk of obesity over time. Socioeconomic status, education, and access to healthy foods strongly influence obesity risk [36].

Medications are another important contributor to weight gain. Several drug classes—including antidepressants, antipsychotics, and corticosteroids—can alter metabolism, increase appetite, or promote fluid retention [37]. Additionally, certain antihypertensives, such as beta-blockers, as well as common antihistamines like diphenhydramine (Benadryl), have also been associated with weight gain, underscoring the importance of evaluating pharmacologic side effects in weight management strategies [38].

Sleep plays a critical role in metabolic regulation, and its disruption can significantly contribute to weight gain. Inadequate or poor-quality sleep-including conditions such as sleep apnea—can disrupt the normal balance of hunger-regulating hormones, such as leptin and ghrelin, leading to increased appetite, cravings for high-calorie foods, and reduced satiety. These hormonal imbalances, combined with the fatigue and stress associated with sleep deprivation, help explain the strong link between sleep disorders and obesity [39].

Hormonal imbalances are key contributors to weight gain and impaired metabolism. Conditions such as polycystic ovary syndrome (PCOS) in females and hypothyroidism can slow metabolic processes and disrupt energy regulation. Additionally, metabolic hormone dysfunctions—such as insulin resistance and leptin resistance—further exacerbate weight gain by impairing glucose utilization, promoting fat storage, and diminishing satiety signals. These hormonal disruptions create a physiologic environment that makes weight loss particularly challenging without targeted intervention [40].

Individuals with a lower resting metabolic rate burn fewer calories at rest and during physical activity, which can make weight management more difficult. This variation in metabolic rate—often influenced by genetics, age, body composition, and hormonal factors—plays a significant role in individual differences in susceptibility to weight gain [41].

Socioeconomic disparities significantly influence obesity risk. Individuals with lower income often face limited access to nutritious foods, safe environments for physical activity, and healthcare resources. In many cases, highly processed and fast foods—typically cheaper and more accessible—become the default, contributing to higher obesity rates in underserved communities [42].

Cultural and social influences play a meaningful role in shaping attitudes toward food, body image, and health. In some cultures, a larger body size may be viewed as a sign of health, prosperity, or beauty, reflecting values that differ from mainstream Western ideals [43].

Age is a significant factor in weight regulation, as metabolic rate naturally declines over time and physical activity levels often decrease with age. These changes contribute to a higher risk of weight gain and increased difficulty in maintaining a healthy weight [41].

Emerging research indicates that the composition and diversity of the gut microbiome—the trillions of bacteria residing in the digestive tract—may significantly influence body weight regulation. These microorganisms can affect how the body digests and absorbs nutrients, modulate energy extraction from food, and even influence fat storage and inflammation. Imbalances in the gut microbiota (known as dysbiosis) have been associated with increased risk of obesity and metabolic disorders, suggesting a potential role for the microbiome in weight management [44].

2.2. The Link Between Diabetes, Obesity and Inflammation

The pathophysiological relationship between obesity and type 2 diabetes is intricate, with obesity recognized as one

of the most significant and well-established risk factors for the onset and progression of the disease; moreover, the risk increases with advancing age, even among individuals without additional predisposing factors. The accumulation of an excessive amount of body fat. Fat stored around internal organs, which further exacerbates metabolic dysfunction, causes insulin resistance and β-cell dysfunction, which causes type 2 diabetes, and the risk of type 2 diabetes increases linearly with an increase in body mass index. A series of studies conducted in mouse models and in humans has demonstrated alterations in adipose tissue biology that link obesity with insulin resistance and β-cell dysfunction. These alterations include adipose tissue fibrosis (increased rates of fibrogenesis and expression of genes involved in extracellular matrix formation), inflammation (increased proinflammatory macrophage and T cell content and the production of PAI-1), and the production of exosomes that can induce insulin resistance. On the other hand, diabetes is associated with obesity, which is primarily attributed to the development of insulin resistance, whereby glucose is increasingly converted to fat. The accumulated visceral fat impairs insulin signaling, limiting the ability of muscle and fat cells to absorb glucose from the bloodstream. Consequently, the pancreas compensates by releasing additional insulin in an attempt to regulate blood glucose levels. Chronic hyperinsulinemia induces reduced tissue responsiveness to insulin signaling, prompting compensatory β-cell hyperplasia in the pancreas. However, persistent insulin demand eventually leads to β-cell dysfunction and inadequate insulin secretion, culminating in hyperglycemia and the development of type 2 diabetes [45].

Additionally, chronic low-grade systemic inflammation represents a key mechanism linking obesity to metabolic dysfunction. Excess adiposity promotes sustained immune activation and the release of pro-inflammatory cytokines such as TNF-α, IL-6, and C-reactive protein, thereby impairing insulin signaling and contributing to the pathogenesis of type 2 diabetes [46]. Pro-inflammatory cytokines not only promote insulin resistance but also exert cytotoxic effects on pancreatic β-cells, thereby accelerating the deterioration of glucose homeostasis [47,48]. Visceral fat accumulation is particularly deleterious, as it recruits adipose tissue–resident immune cells that secrete inflammatory mediators into the systemic circulation, exacerbating insulin resistance across multiple tissues. This establishes a self-perpetuating cycle in which excess adiposity drives metabolic dysfunction through impaired insulin signaling. In the absence of infection, the maintenance of normoglycemia requires compensatory hyperinsulinemia, which paradoxically fosters further fat deposition, particularly in the abdominal region [49]. Concurrently, obesity-induced inflammation contributes to metabolic stress and oxidative damage by elevating intracellular reactive oxygen species, disrupting cellular function. The synergistic interplay of obesity, chronic inflammation, and insulin resistance not only underpins the pathogenesis of type 2 diabetes but also heightens susceptibility to a spectrum of metabolic comorbidities, including cardiovascular disease, hypertension, non-alcoholic fatty liver disease, and diabetes-related complications such as retinopathy, neuropathy, and nephropathy [50].

2.3. Obesity Management

Effectively managing obesity requires a multidisciplinary approach that encompasses change of lifestyle (through nutritional changes, increased physical activity, and behavioral interventions), pharmacotherapy, and, when appropriate, surgical options [28–30]. Despite growing awareness of the many contributing factors, obesity remains difficult to manage due to its complex, multifactorial nature and the need for personalized treatment strategies [28–30]. The presence of comorbidities—such as type 2 diabetes, cardiovascular disease, and mental health conditions—adds another layer of complexity, requiring an integrated approach that simultaneously supports weight loss and the management of coexisting health issues.

The cornerstone of medical management for obesity remains lifestyle changes, including a reduced-calorie diet and increased physical activity, combined with behavioral strategies such as cognitive-behavioral therapy, goal-setting, self-monitoring, and stress management to support long-term adherence. However, sustaining long-term adherence to dietary restrictions and physical activity can be challenging. Several well-established programs support the tracking of key lifestyle components—namely diet, exercise, sleep, and meditation—such as the My Viva Plan (MVP), which holistically integrates nutrition, physical activity, and mindfulness programs [51]. The therapeutic approach could parallel pharmacologic interventions for other chronic diseases with behavioral components, such as diabetes or hypertension, where medications complement lifestyle interventions to optimize outcomes. Importantly, if a patient's response to a specific anti-obesity medication (AOM) is suboptimal, clinicians may adjust treatment by selecting an alternative or combination therapy, as individual responses to medications vary substantially. The following steps were suggested for obesity management: dietary modification, physical activity, and behavioral therapy should be integrated as foundational components for all individuals with a BMI ≥ 25 kg/m^2. Pharmacotherapy and bariatric surgery are recommended as adjuncts when lifestyle interventions alone are insufficient. Specifically, anti-obesity pharmacotherapy is indicated for patients with a BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 with obesity-related comorbidities such as hypertension, dyslipidemia, type 2 diabetes, or obstructive sleep apnea. The selection of anti-obesity medications should consider comorbid conditions and contraindications [52]. In this paper, we highlight the role of pharmacotherapy as an important adjunct for addressing management in both metabolic dysregulation and weight reduction in patients with obesity and diabetes.

2.4. Pharmacotherapies for Obesity Management

Obesity pharmacotherapies have emerged as an important strategy to disrupt the interrelated cycle of obesity, type 2 diabetes, and chronic inflammation.

Among pharmacologic options for obesity management, GLP-1 receptor agonists (such as semaglutide and liraglutide) and dual GIP/GLP-1 agents (such as tirzepatide) are particularly beneficial for individuals with obesity and comorbid type 2 diabetes, elevated cardiovascular risk, fatty liver disease (metabolic-associated steatotic liver disease, MASLD), or chronic kidney disease (CKD), as they improve glycemic control, promote weight reduction, reduce hepatic steatosis, and have demonstrated both cardiovascular and renal protective effects [53,54]. However, these agents are contraindicated in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN-2). Orlistat may be advantageous in patients with obesity and dyslipidemia, as it lowers LDL cholesterol through inhibition of dietary fat absorption [55]. Naltrexone/bupropion is often considered for individuals with obesity and coexisting depression, emotional eating, or addictive behaviors, as it modulates reward pathways and reduces cravings. However, it should be avoided in those with uncontrolled hypertension or seizure disorders [56,57]. Sympathomimetic agents, including phentermine, phendimetrazine, and diethylpropion, may be used as short-term adjuncts in individuals with obesity and low cardiovascular risk, particularly when fatigue or low energy are prominent features; however, they should be used with caution in patients with cardiovascular disease or hypertension due to their stimulant effects. While these agents are approved for short-term use, they are often prescribed off-label for longer durations under close medical supervision [58]. Off-label options such as metformin may be appropriate for patients with obesity and insulin resistance, prediabetes, or polycystic ovary syndrome (PCOS) due to its insulin-sensitizing properties. However, kidney function should be closely monitored because of the risk of lactic acidosis, particularly in those with impaired renal function [59,60]. Topiramate may be preferred in individuals with obesity and comorbid migraine or seizure disorders, but should be used with caution in patients with a history of nephrolithiasis (kidney stones) due to its potential to increase the risk of stone formation [61]. Naltrexone alone may provide modest benefit in obesity with alcohol or opioid use disorder, consistent with its approved role in substance dependence [62]. Ultimately, pharmacologic selection should be individualized, balancing efficacy, comorbid conditions, contraindications, and patient-specific factors [63].

Several classes of medications are currently FDA-approved for obesity or weight management, while others are used off-label when supported by clinical evidence [64].

2.5. Approved Pharmacotherapies and Mechanism of Action

- **Glucagon-like peptide-1 (GLP-1) receptor agonists:** Semaglutide (Wegovy; Ozempic for diabetes) mimics endogenous GLP-1, reducing appetite, delaying gastric emptying, enhancing satiety, and improving glycemic control, leading to clinically meaningful and sustained weight loss.
- **Dual GLP-1/GIP receptor agonist:** Tirzepatide (Mounjaro/Zepbound) activates both GLP-1 and GIP receptors, offering synergistic effects on satiety, insulin secretion, and glycemic control, with superior weight loss efficacy compared to GLP-1 monotherapy.
- **Phentermine–Topiramate extended release (Qsymia):** Combines a sympathomimetic appetite suppressant (phentermine) with an antiepileptic (topiramate) that enhances satiety, producing significant weight loss. Monitoring is required due to potential cardiovascular and neuropsychiatric side effects.
- **Naltrexone–Bupropion extended release (Contrave)**: Targets both the hypothalamic melanocortin system (regulating appetite) and the mesolimbic dopamine reward pathway (reducing cravings), resulting in weight reduction and improved adherence in some patients.
- **Orlistat (Xenical/Alli):** A gastrointestinal lipase inhibitor that decreases intestinal fat absorption, leading to modest weight loss. Its use is limited by gastrointestinal side effects but provides a non-systemic option useful in patients with contraindications to centrally acting drugs.
- **Sympathomimetics:** Phentermine, diethylpropion, and phendimetrazine act centrally as norepinephrine- and dopamine-releasing agents, reducing appetite via hypothalamic appetite regulation pathways. Although FDA-approved for short-term use (up to 12 weeks), they are sometimes prescribed off-label for long-term weight management under careful monitoring.

2.6. Off-Label Medications for Weight Management with Mechanism of Action

Several agents not FDA-approved for obesity are used in select populations based on evidence of modest weight benefit or overlapping indications [65].

- **Metformin** — improves insulin sensitivity, widely used in insulin resistance or prediabetes.
- **Bupropion alone** — dopaminergic/noradrenergic activity reduces appetite.
- **Naltrexone alone** — opioid receptor antagonist with appetite-modulating properties.
- **Topiramate** — an antiepileptic with appetite-suppressing and satiety-enhancing effects.
- **SGLT2 inhibitors** — e.g., empagliflozin (Jardiance), dapagliflozin (Farxiga), canagliflozin (Invokana), which promote caloric loss via glycosuria, resulting in modest weight reduction and additional cardiovascular and renal protective benefits.

Table 1 summarizes the principal agents currently commonly used to manage obesity and type 2 diabetes, their use in these conditions, and their adverse reactions. Among these, glucagon-like peptide-1 (GLP-1) receptor agonists, such as semaglutide, are becoming a first line of treatment, as recommended by WHO and the European Association for the Study of Obesity (EASO) [66,67]. Semaglutide, a pure GLP-1 receptor agonist, promotes substantial weight loss, improves insulin sensitivity, reduces appetite, delays gastric emptying, and enhances glycemic control. Tirzepatide, in contrast, is a dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist that provides additional metabolic benefits by synergistically targeting two incretin

pathways. Notably, beyond their metabolic effects, GLP-1 receptor agonists have been shown to act directly on immune cells, including T cells, where they modulate cytokine production and attenuate inflammation, suggesting a dual role in both metabolic and immune regulation [68-70]. Other therapeutic agents, such as metformin and sodium–glucose cotransporter-2 (SGLT2) inhibitors, contribute to weight reduction, improved insulin sensitivity, and decreased inflammatory signaling [71]. Collectively, these medications reduce visceral adiposity, lower circulating inflammatory markers, alleviate β-cell stress, and mitigate the long-term complications of diabetes.

Medication/ Class	Mechanism of Action	Use in Type 2 Diabetes	Use in Obesity	Common Adverse Reactions	References
GLP-1 Receptor Agonists Examples: Semaglutide (Wegovy, Ozempic), Liraglutide (Saxenda, Victoza), Dulaglutide (Trulicity)	Mimic endogenous GLP-1, enhancing glucose-dependent insulin secretion, suppressing glucagon, delaying gastric emptying, and reducing appetite.	Improve postprandial and fasting glycemic control; reduce HbA1c; lower cardiovascular risk in high-risk patients.	Promote clinically meaningful weight loss by reducing appetite and caloric intake.	Gastrointestinal: nausea, vomiting, diarrhea, constipation. Rare: pancreatitis, gallbladder disease.	[68-70]
Metformin	Improves hepatic and peripheral insulin sensitivity; decreases hepatic gluconeogenesis.	First-line therapy for type 2 diabetes; effective and low cost.	Not formally approved for obesity, but may support modest weight loss, especially in insulin-resistant individuals.	Gastrointestinal intolerance (nausea, diarrhea). Rare: lactic acidosis (in predisposed patients).	[72,73]
SGLT2 Inhibitors Examples: Canagliflozin, Empagliflozin, Dapagliflozin	Block renal glucose reabsorption, promoting glycosuria and mild osmotic diuresis.	Lower blood glucose and HbA1c; reduce cardiovascular and renal risk in appropriate patients.	Causes modest weight reduction via urinary caloric loss.	Genitourinary infections, dehydration, and hypotension. Rare: diabetic ketoacidosis.	[74-76]
Dual GLP-1/GIP Receptor Agonist Tirzepatide (Mounjaro, Zepbound)	Activates both GLP-1 and GIP receptors, enhancing insulin secretion, reducing glucagon, slowing gastric emptying, and suppressing appetite.	Produces robust improvements in glycemic control; superior HbA1c reduction compared to GLP-1 agonists alone.	Induces substantial weight loss, with efficacy exceeding that of GLP-1 agonists.	Gastrointestinal symptoms (nausea, vomiting, diarrhea). Possible risk of pancreatitis.	[77-79]

Table 1: Common Medications Used in The Management of Type 2 Diabetes and Obesity, Mechanism of Action, Use in Type 2 Diabetes and Obesity and Adverse Effects

In individuals with concurrent obesity and type 2 diabetes, pharmacologic interventions can effectively target both glycemic control and weight reduction. Selection of therapy is guided by the severity of hyperglycemia, degree of adiposity, and presence of comorbid conditions. In some cases, combination regimens may be employed under careful clinical supervision to optimize outcomes while minimizing drug–drug interactions and adverse effects. Individualized treatment planning in collaboration with healthcare providers remains essential to ensure both safety and efficacy.

When combined with lifestyle interventions, these pharmacotherapies—both approved and off-label—can significantly reduce body weight, improve insulin sensitivity, and mitigate cardiometabolic risk. As mentioned

above, selection of the most appropriate agent requires individualized consideration of efficacy, safety, comorbidities, contraindications, patient preferences, and cost.

Emerging therapies, including oral formulations of GLP-1 receptor agonists, as well as next-generation dual and triple incretin agonists (e.g., GLP-1/GIP or GLP-1/GIP/glucagon combinations), show strong potential to expand long-term treatment options for obesity [78]. While most currently approved agents have favorable safety profiles, tailoring therapy to account for patient comorbidities remains essential to minimize adverse effects and optimize outcomes.

2.7. The Role of an Algorithmic Approach in Obesity Pharmacotherapy Management

Chronic disease management routinely employs stepwise algorithms that strategically combine medications to target complementary biological pathways. In type 2 diabetes, treatment typically begins with metformin, with additional agents added to address distinct mechanisms such as insulin secretion, insulin resistance, or renal glucose reabsorption [81]. In hyperlipidemia, statins form the foundation, with adjunctive therapies like ezetimibe incorporated to modulate alternative lipid pathways [82]. Similarly, hypertension management often starts with an ACE inhibitor or ARB, followed by the addition of a diuretic or calcium-channel blocker to act on separate physiologic systems [81]. Obesity pharmacotherapy can be approached in the same systematic, stepwise algorithmic manner, using sequential or combination therapies to modulate diverse pathways implicated in disease pathophysiology, including dopaminergic signaling, insulin and leptin resistance, and mesolimbic reward circuitry. This framework not only mirrors established models in other chronic diseases but also provides a rational, mechanistically driven strategy for optimizing long-term outcomes in obesity [82].

2.8. Introducing the G-SLIM™ Algorithm: A Conceptual Structured Approach for Obesity Pharmacotherapy Management

We proposed the conceptual G-SLIM™ algorithm to address the complexity of obesity pharmacotherapy management and ensure a directive approach. This algorithm provides a framework for healthcare providers to tailor obesity medication treatment based on individual patient characteristics, optimizing both efficacy and cost-effectiveness.

The G-SLIM™ algorithm does not propose a new pharmacologic hierarchy but instead functions as a practical, clinician-facing decision support tool that operationalizes existing best practices in obesity management. It is fully aligned with current guidance from organizations such as the American Association of Clinical Endocrinology and the American Diabetes Association, which emphasize a complication-centric, individualized approach and avoid rigid stepwise sequencing of anti-obesity medications. Consistent with these frameworks, G-SLIM™ reflects contemporary practice by prioritizing high-efficacy incretin-based therapies where appropriate and incorporating key principles such as reassessment at 3–6 months, continuation thresholds (e.g., ≥5% weight loss), and treatment adjustment through dose escalation, switching, or combination therapy based on patient response.

Importantly, the G-SLIM™ algorithm has not undergone formal clinical validation and is not intended as a predictive or evidence-generating tool. Rather, it serves as a conceptual framework that translates guideline-level recommendations into an accessible, point-of-care format. It is designed to complement—not replace—clinical judgment, supporting clinicians in systematically considering patient-specific factors, therapeutic options, and treatment response without prescribing rigid pathways or superseding individualized decision-making.

The algorithm's simplified structure, including its categorization of therapies, is intended to guide clinical thinking rather than reflect a formal evidence hierarchy derived from trials. Similarly, Figure 1 provides a high-level visual overview of the decision-making process, while detailed clinical nuances and stepwise considerations are described in the manuscript text. This approach balances usability with clinical complexity, offering clarity without oversimplification.

G-SLIM™ is therefore best understood as a cognitive aid for clinicians involved in obesity management who prescribe pharmacotherapy. It is not a clinical guideline or formal review, but a structured tool to support individualized, evidence-aligned treatment decisions.

Before proceeding through each step of the G-SLIM™ algorithm, it is crucial to assess the patient's condition, including the cause of obesity, any contraindications to the treatments under consideration, and to evaluate the affordability of the medications. Additionally, the patient's comorbid conditions and preferences, such as a preference for oral medications over injections, should be considered to ensure that the chosen treatment plan is both effective and acceptable to the patient.

As mentioned above, like other chronic disease management algorithms, the G-SLIM™ algorithm emphasizes the stepwise introduction and layering of the selected medications on top of each other. This means that healthcare providers should consider the additive effects of combining therapies to enhance overall effectiveness rather than discontinuing one medication before starting another. This stepwise layering can help achieve more comprehensive management of obesity, addressing multiple pathways involved in energy balance and weight regulation. When monotherapy is insufficient, clinicians should evaluate potential contraindications, drug affordability, and comorbid conditions before escalating therapy. In such cases, adding another agent targeting a different pathway in obesity pathophysiology may enhance efficacy, but requires careful monitoring to minimize adverse effects and interactions.

The G-SLIM™ mnemonic provides a conceptual framework for obesity pharmacotherapy, organized into five mechanistic categories: 'G' for GLP-1 and GIP agonists, 'S' for sympathomimetic agents, 'L' for therapies targeting leptin resistance, 'I' for agents addressing insulin resistance, and 'M' for interventions modulating the mesolimbic reward system. This structured approach supports rational drug selection by aligning pharmacologic agents with underlying pathophysiologic pathways, while requiring clinicians to account for contraindications, comorbidities, affordability, and potential adverse effects in individualized treatment planning (Figure 1). Each element of the G-SLIM™ framework prompts clinicians to consider potential pharmacologic options within that mechanistic category. Therapeutic layering involves the sequential addition of agents, enabling simultaneous modulation of multiple physiological pathways to address the complex pathophysiology of obesity. Categories may be bypassed if contraindicated or inappropriate; however, the overarching strategy emphasizes combination therapy to optimize outcomes. In patients who reach a weight-loss plateau or require further reduction after initiation of a single agent, clinicians should evaluate the next category and consider adding a complementary medication. At each step, careful consideration must be given to contraindications, affordability, comorbid conditions, and patient preferences to ensure safety and adherence. Importantly, the algorithm should be re-evaluated at every clinical encounter, as evolving medical status, financial considerations, or treatment tolerability may necessitate modification. This iterative approach ensures that obesity pharmacotherapy remains individualized, adaptive, and aligned with the patient's long-term therapeutic goals.

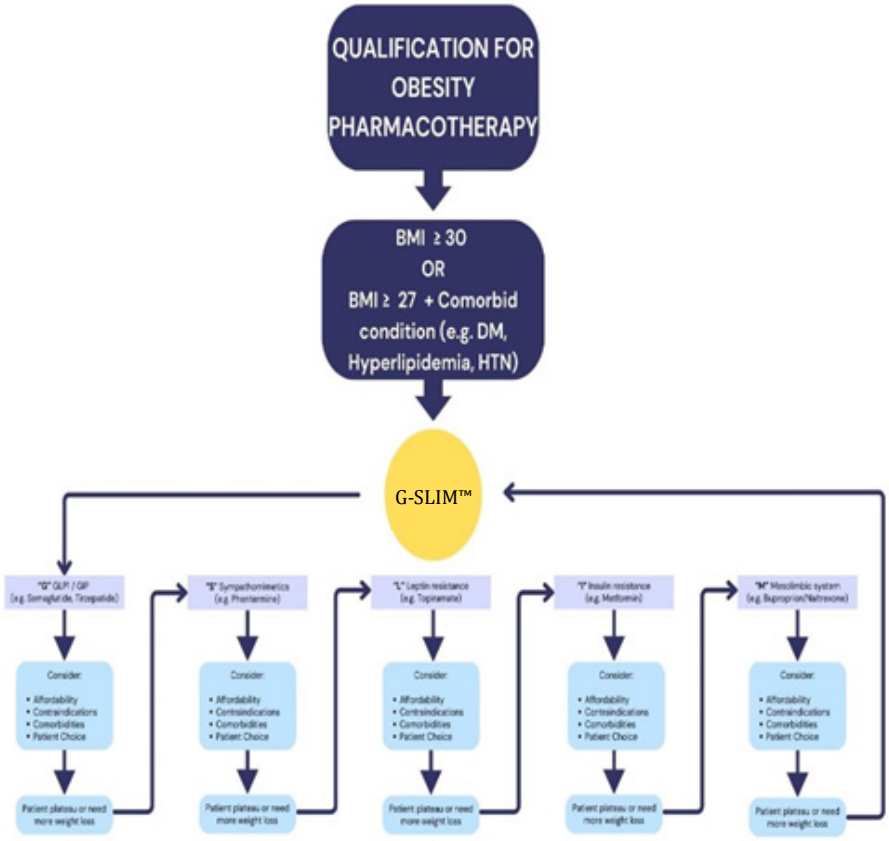

Figure 1: Illustrates the stepwise G-SLIM™ mnemonic and the layering of obesity pharmacotherapy classes in a flowchart format

The following outlines a stepwise framework for pharmacologic selection and therapeutic layering within the G-SLIM™ algorithm, providing a structured approach to obesity management.

1. G (GLP-1/GIP Agonists): This class includes GLP-1 and dual GLP-1/GIP receptor agonists, which enhance insulin secretion, suppress glucagon, promote satiety, reduce food intake, and support significant weight reduction. Given their robust efficacy in inducing weight loss (typically 15–20%), proven benefits in glycemic management, and established cardiovascular risk reduction (e.g., with semaglutide), these agents should be prioritized as first-line pharmacotherapy. If contraindications exist, the patient reaches a weight-loss plateau, additional reduction is required, or affordability is a barrier, the clinician should consider advancing to or layering with the next therapeutic category.

2. S (Sympathomimetics): Sympathomimetic agents act centrally to suppress appetite and increase energy expenditure via stimulation of the central nervous system. This class is among the most affordable options and, despite

FDA approval limited to short-term use, has seen widespread long-term application in clinical practice. Evidence from multiple studies supports the safety and effectiveness of extended phentermine use in carefully selected, low-risk individuals. If weight loss plateaus or additional reduction is required, or contraindications exist, clinicians should consider progressing to or layering with the next therapeutic class.

3. L (Leptin Resistance): Leptin resistance is a common feature of obesity, impairing appetite regulation and energy balance. Therapeutic strategies in this category aim to enhance leptin sensitivity or mimic leptin's physiological effects. Topiramate, particularly when combined with the sympathomimetic phentermine, exemplifies this approach and has demonstrated efficacy in promoting weight loss. As a generic medication, topiramate is widely accessible and cost-effective. In cases of treatment plateau or insufficient weight reduction, or when contraindications exist, clinicians should consider advancing to or layering with the next pharmacologic category

4. I (Insulin Resistance): Insulin resistance is a hallmark of obesity and contributes to impaired glucose metabolism and excess fat accumulation. Pharmacologic strategies targeting this pathway aim to improve insulin sensitivity, thereby enhancing glucose utilization and reducing adiposity. Metformin exemplifies this class, offering well-documented efficacy, wide availability as a generic, and excellent affordability. In instances of treatment plateau or inadequate weight reduction, or when contraindications exist, therapy may be advanced or layered with the next pharmacologic category

5. M (Mesolimbic System): The mesolimbic system, a key neural circuit governing reward and motivation but also implicated in addictive behaviors, contributes significantly to cravings and compulsive eating in obesity. Pharmacotherapies that modulate dopaminergic signaling within this pathway can help attenuate maladaptive reward responses to food. The fixed-dose combination of naltrexone (8 mg) and bupropion (90 mg), marketed as Contrave, represents an accessible and cost-effective option within this category.

In summary, the G-SLIM™ framework offers a conceptual, structured, pathway-specific approach to obesity pharmacotherapy, enabling clinicians to sequentially or simultaneously target key neurohormonal and metabolic mechanisms. This framework directly or indirectly offers treatment to patients with diabetes. If comprehensive pharmacologic strategies fail to achieve sufficient weight reduction, patients should be evaluated for bariatric or metabolic surgery. Established options include Roux-en-Y gastric bypass, sleeve gastrectomy, and biliopancreatic diversion with duodenal switch, as well as less invasive procedures such as intragastric balloon placement and endoscopic sleeve gastroplasty. Importantly, surgical interventions are not limited to a final option after pharmacotherapy failure; rather, they may serve as the initial, intermediate, or adjunctive modality depending on patient characteristics, comorbidities, and treatment goals, underscoring the need for an integrated, multimodal approach to obesity management.

Despite its utility, important gaps remain. Future research is warranted to refine and validate a more comprehensive, evidence-based algorithm for obesity pharmacotherapy. Such efforts should incorporate multidimensional considerations, including medication efficacy, safety profiles, long-term outcomes, cardiovascular benefits, patient comorbidities, and cost or affordability. Advancing research in these areas will be essential to enhance the precision and clinical applicability of algorithm-driven approaches in obesity care.
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3. Conclusions

The management of obesity requires a comprehensive, multidisciplinary strategy that integrates nutrition, physical activity, behavioral interventions, pharmacotherapy, and surgical options, while also addressing the economic and access barriers that often limit care. Obesity and type 2 diabetes are closely interconnected through a complex interplay of metabolic, hormonal, and inflammatory pathways. Effectively addressing obesity is essential for both the prevention and management of type 2 diabetes, which can prevent microvascular and macrovascular complications, including neuropathy, nephropathy, retinopathy, atherosclerosis, hypertension, and stroke. As with other chronic diseases, such as diabetes, hyperlipidemia, and hypertension, an algorithmic framework can be used for obesity. As a structured therapeutic roadmap. The G-SLIM™ algorithm is designed as both a guide and a conceptual framework, keeping the major pathophysiologic pathways of obesity in focus and helping clinicians systematically consider targeted therapies. By incorporating contraindications, comorbid conditions, affordability, and patient-specific factors, it facilitates individualized care while offering cost-effective alternatives when higher-priced agents are not accessible. Equally important, patients must be closely and regularly monitored to ensure efficacy, promptly identify adverse effects, and adjust therapy as needed. In doing so, the G-SLIM™ roadmap provides clinicians with a structured yet flexible approach to obesity pharmacotherapy, supporting safe, effective, and personalized treatment. Furthermore, G-SLIM™ provides therapeutic benefits both directly and indirectly to individuals with diabetes and its associated comorbidities. Expanding equitable access to these therapies, alongside continued research and policy initiatives, will be essential to reducing the global burden of obesity and improving long-term health outcomes. Future research is warranted to refine and validate a more comprehensive, evidence-based algorithm for obesity pharmacotherapy. Advancing research in these areas will be essential to enhance the precision and clinical applicability of algorithm-driven approaches in obesity care.

Ethics statement

No human subject was involved in this research; only

citations from literature

Conflict of Interest

Dr Zaid Jabbar is an obesity consultant, MD. Dr Riyadh Rehani and Matthew Jabbar have no conflict of interest.

Author Contributions

ZWJ created the G-SLIM™ algorithm and contributed to writing the paper. MZJ worked on creating the design for the G-SLIM™ figure, RNR contributed to writing the paper, literature review, and references, formatting the paper to the journal style, and acted as the corresponding author.

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