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PHARMACOLOGICAL AND SURGICAL TREATMENT OF OBESITY: INTEGRATING THE ROLES OF INFLAMMATION AND GUT DYSBIOSIS- REVIEW

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ABSTRACT

Obesity is a metabolic disease characterized by chronic systemic inflammation and dysbiosis of gut microbiota. This review explores relationships between obesity, inflammatory pathways, and gut microbiome composition within a clinical perspective, concentrating on pharmacological and surgical options. Current therapeutic strategies consist of GLP-1 receptor agonists, orlistat, naltrexone-bupropion combination therapy, and bariatric surgery. Significantly, therapeutic advantages go far beyond weight decrease to consist of improved microbial diversity, decreased inflammation (reflected as a decrease in inflammatory markers such as CRP, IL-6, and TNF-α), and metabolic outcomes. The present review demonstrates that successful obesity therapy requires both the normalisation of gut microbial function and the elimination of systemic inflammation, underscoring the significance of microbiota-related modalities for total obesity treatment.

KEYWORDS
Obesity, Treatment, Inflammation, Microbiota, Bariatric Surgery

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1 Multifactorial pathogenesis of obesity

Obesity is associated with alterations in gut microbiota that promote chronic low-grade inflammation (Cheng et al., 2022). Individuals with obesity typically exhibit a higher Firmicutes to Bacteroidetes ratio, reduced microbial diversity (Zheng, 2025), and lower levels of beneficial bacteria such as Akkermansia, Bacteroides, Bifidobacterium, and Lactobacillus (Scheithauer et al., 2020). In contrast, pro-inflammatory bacteria, including Enterobacteriaceae and other Proteobacteria that produce lipopolysaccharides (LPS), become more prevalent and contribute to inflammation (Du et al., 2021). The translocation of LPS across a compromised gut barrier initiates systemic inflammation through toll-like receptor-4 signalling (Mishra et al., 2023), resulting in elevated levels of inflammatory markers such as CRP, IL-6, and IL-1 (Louis et al., 2016), and promoting insulin resistance and metabolic disturbances. Inflammation induced by obesity further impairs adipose tissue function, increases pro-inflammatory leptin, and decreases anti-inflammatory adiponectin (Turpin et al., 2023), thereby perpetuating a cycle of dysbiosis, inflammation, and metabolic dysfunction (Randeni et al., 2024).

2.1 GLP-1 agonists

Glucagon-like peptide-1 (GLP-1) is one of the endogenous incretin hormones, which is derived from the proglucagon molecule. GLP-1 secretion by intestinal L-cells occurs immediately after a meal. Greater quantities of the peptide are secreted in response to carbohydrate-rich meals, which serves to prevent the occurrence of hypoglycemia. The secretion rate is also dependent on the gastric emptying rate. A large portion of the secreted GLP-1 is rapidly metabolized by the enzyme dipeptidyl peptidase-4 (DPP-4) (Holst, 2007). The remaining portion constitutes the pool of active hormone, which enters the bloodstream and binds to dedicated GLP-1 receptors, belonging to the G protein-coupled receptor family. Their presence has been confirmed, a.o., in pancreatic β-cells, adipose tissue, the duodenum, the heart, kidneys, and lungs (Drucker, 2018). The main physiological effects of GLP-1 include: enhancement of glucose-dependent insulin secretion, inhibition of glucagon secretion, delayed gastric emptying, and promotion of satiety (Drucker, 2018; Holst, 2007).

Modern medicine is increasingly utilizing GLP-1 receptor agonists in the pharmacotherapy of obesity. Semaglutide, liraglutide, and tirzepatide hold registered indications for this purpose (Jastreboff et al., 2022; Wilding et al., 2021). However, it should be noted that their therapeutic profile is significantly broader. GLP-1 agonists stimulate endogenous insulin secretion in a glucose-dependent manner, thereby regulating glycemia in patients diagnosed with type 2 diabetes (Nachawi et al., 2022). The clinically confirmed cardioprotective effects of this drug class make them recommended for patients with cardiovascular disease to reduce cardiovascular risk (Lincoff et al., 2023). The high comorbidity of obesity, type 2 diabetes, and cardiovascular disease in the population makes this drug class a key tool in a holistic therapeutic model (Lincoff et al., 2023; Nachawi et al., 2022). Agents belonging to the GLP-1 receptor agonist group, their registered indications, and the trade names of preparations containing them are summarized in Table 1.

Table 1. Agents belonging to the GLP-1 receptor agonist group, their registered indications, and the trade names of preparations containing them.

Active substance name	Trade names	Main registered indications
Semaglutide	Ozempic, Rybelsus, Wegovy	Type 2 diabetes (monotherapy or combination therapy) (Andersen et al., 2021). Reduction of cardiovascular risk in patients with type 2 diabetes and cardiovascular disease (Andersen et al., 2021). Treatment of obesity or overweight with comorbidities (Ghusn et al., 2022).
Liraglutide	Victoza, Saxenda	Type 2 diabetes in adults and children aged 10 years and older (Verma et al., 2018). Reduction of cardiovascular risk in patients with type 2 diabetes and established cardiovascular disease (Verma et al., 2018). Treatment of obesity or overweight with comorbidities (Pi-Sunyer et al., 2015).
Dulaglutide	Trulicity	Type 2 diabetes (monotherapy or combination therapy) (Scott, 2020). Reduction of cardiovascular risk in patients with type 2 diabetes with established cardiovascular disease or multiple risk factors (Gerstein et al., 2019).
Tirzepatide (dual agonist – GLP-1 and GIP receptors)	Mounjaro, Zepbound	Type 2 diabetes (Frías et al., 2021). Treatment of obesity or overweight with comorbidities (Frías et al., 2021; Jastreboff et al., 2022).
Exenatide	Byetta, Bydureon	Type 2 diabetes (Bode, 2012).
Lixisenatide	Adlyxin (USA), Lyxumia (Europe)	Type 2 diabetes (Rosenstock et al., 2013).

Table 2. Summary of key clinical trials evaluating GLP-1 receptor agonists for obesity treatment.

Trial/analysis	Intervention (Medication)	Duration	Key results and conclusions
STEP 1	Semaglutide (2.4 mg s.c. once weekly) vs placebo	68 weeks	Mean body weight reduction of **-14.9%** (vs -2.4% placebo) in patients with overweight/obesity without diabetes (Wilding et al., 2021).
STEP 5	Semaglutide vs placebo	104 weeks	Long-term body weight reduction of **-15.2%** (vs -2.6% placebo). Improvement in metabolic markers. Demonstrated that obesity requires chronic therapy (Garvey et al., 2022).

SELECT	Semaglutide (2.4 mg s.c. once weekly)	40 weeks (intervention)	**20%** reduction in MACE (Major Adverse Cardiovascular Events) risk in patients with overweight/obesity and established cardiovascular disease (Lincoff et al., 2023).
SURMOUNT-1	Tirzepatide (5 mg, 10 mg, 15 mg) vs placebo	72 weeks	Dose-dependent body weight reduction: **-15%** (5 mg), **-19.5%** (10 mg), **-20.9%** (15 mg) (vs -3.1% placebo) in patients without diabetes (Jastreboff et al., 2022).
SURMOUNT-3	Tirzepatide (post 12-week lifestyle intervention) vs placebo	72 weeks (pharmacotherapy)	Following a 12-week non-pharmacological intervention, pharmacotherapy induced a further mean body weight reduction of **-18.4%** (vs +2.5% placebo), indicating a synergistic effect (Wadden et al., 2023).
Meta-analysis (7 randomized controlled trials)	Liraglutide (3 mg)	N/A (meta-analysis)	Mean body weight reduction of **-4.81%** in adults with overweight or obesity (Lin et al., 2022).

2.1.1 Effect of GLP-1 agonists on chronic inflammation

GLP-1 agonists exhibit multiple anti-inflammatory effects. Specifically, these drugs suppress key inflammatory pathways by reducing pro-inflammatory cytokines, including TNF-ff, IL6, and IL-1 (CK & DJ, 2025), and act through both weight-dependent and weight-independent mechanisms. In patients with heart failure with preserved ejection fraction, semaglutide significantly reduced C-Reactive Protein (CRP) levels (Bonfioli et al., 2024), indicating a direct anti-inflammatory effect that is not solely attributable to weight loss.

2.1.2 Effect of GLP-1 agonists on microbial composition

GLP-1 agonists have been shown to substantially alter gut microbiota (K et al., 2024). These agents induce beneficial bacterial community growth (Bacteroides, Lactobacillus, and Bifidobacterium) while inhibiting the survival of harmful species (e.g., Enterobacteriaceae). Such microbial adjustment enhances gut barrier integrity and reduces systemic inflammation that are key components of metabolic dysfunction (K et al., 2024). Various GLP-1 agonists have different influences on the gut microbiota (KK et al., 2025). Liraglutide increases the abundance of beneficial genera associated with metabolic functions, whereas semaglutide promotes the growth of Akkermansia muciniphila despite a reduction in overall microbial diversity. Additionally, GLP-1 agonists increase the production of short-chain fatty acids, such as butyrate, propionate, and acetate, which serve as energy sources for colonocytes and play a role in appetite regulation (K et al., 2024).

2.2 Orlistat

Pancreatic lipase is the main enzyme facilitating the digestion of lipids in the human gastrointestinal system. Blocking this enzyme results in decreased fat absorption and consequently reduces caloric consumption (De La Garza et al., 2011; Elmaleh-Sachs et al., 2023). Orlistat, a synthetic inhibitor derived from lipstatin produced by Streptomyces, is the only pancreatic lipase inhibitor approved by both the FDA and EMA (Bialecka-Florjanczyk et al., 2018). Orlistat acts only in the gastrointestinal tract and is not systemically absorbed (De La Garza et al., 2011). Recent reports have shown its metabolic effects, in addition to weight reduction (Feng et al., 2023; Kwon et al., 2022). Feng et al. demonstrated hepatic steatosis reduction based on a 24-week orlistat treatment program with a 9.1% decrement of liver fat in MAFLD patients relative to controls (Feng et al., 2023),. Additionally, Kwon et al. found that, while low-intensity short-term doses of orlistat together with phentermine decreased pro-atherogenic oxysterols, the effects persisted after treatment cessation and evidence cardiovascular benefit independent of weight loss (Kwon et al., 2022). On the other hand, the effect of orlistat is lower than the recent incretin analogues (Kim et al., 2023; Valladares-Restrepo et al., 2023). For instance, one study demonstrated that one year of orlistat treatment led to a mean weight loss of –1.6 kg which was not statistically significant compared to a mean over the same period with liraglutide of –7.8 kg (Valladares-Restrepo et al., 2023).

2.2.1 Effect of orlistat on gut diversity

Orlistat appears to influence microbiotal diversity by increasing the abundance of Verrucomicrobia and Akkermansia. The therapeutic effects of orlistat were significantly weakened when researchers treated mice with antibiotics to deplete their gut bacteria. It shows that the beneficial effects of orlistat are not solely due to the drug's direct action on lipid absorption. Rather, it works synergistically with the gut microbiota. Furthermore, transplantation of microbiota from orlistat-treated mice to untreated mice alleviates lipid metabolic disorders effectively (C et al., 2025).

2.3 Naltrexone + bupropion

Naltrexone is a medication that blocks particularly the μ-opioid receptor that was initially approved for treating dependence on alcohol and opioids. Research has also indicated that naltrexone can impact eating behavior in animal studies(Panigrahi K, et al., 2019).Both the hypothalamic melanocortin system and the mesolimbic reward system are known to contain opioid neurons; thus, naltrexone may influence food consumption and body weight by modulating these two pathways. Although various types of opioid receptors exist, genetic and pharmacological data from preclinical research suggest that the μ-opioid receptor is crucial in regulating eating behavior (Billes et al., 2014).

Bupropion is an atypical antidepressant that is authorized for managing depression, seasonal affective disorder, and assisting with smoking cessation. It works by inhibiting the reabsorption of the catecholamines dopamine and norepinephrine while also acting as a weak blocker at nicotinic acetylcholine receptors. By preventing the reuptake of dopamine and norepinephrine, bupropion raises their extracellular levels in the brain, potentially affecting the activity of neurons that release these neurotransmitters. Given that the hypothalamic melanocortin system's activity is influenced by both dopamine and norepinephrine, and considering that diminished dopaminergic signaling in the hypothalamus has been associated with obesity, this system presents a possible site for bupropion’s effects (Billes et al., 2014).

2.3.1 Mechanism of action

Bupropion stimulates pro-opiomelanocortin (POMC) neurons, leading to an increase in the production and release of α-melanocyte-stimulating hormone (α-MSH) and β-endorphin. Naltrexone inhibits μ-opioid receptors (MOP-R), thereby preventing the autoinhibition of these POMC neurons by β-endorphin. Consequently, the combined use of naltrexone and bupropion results in a synergistic enhancement of POMC activity, surpassing the effects of either drug alone, which aids in appetite suppression and subsequent weight loss in individuals (Panigrahi K, et al., 2019, Billes et al., 2014).

Table 3.

Study Type	Trial Name(s)	Sample Size	Study Design	Primary Outcomes: Weight Loss	Safety Profile
Phase III COR Trials	COR-I, COR-II, COR-BMOD, COR-DM (le Roux et al., 2022)	~4,536 participants	Double-blind, placebo-controlled, 56-week	11–22 lbs (5–9 kg) average weight loss vs. placebo; 3.01% mean body weight reduction (95% CI: 2.47–3.54%) over 56 weeks	Generally well-tolerated
Binge Eating Disorder (BED) - Maintenance	Grilo et al. (2023)	66 patients with BED + obesity	Double-blind, placebo-controlled, 16-week maintenance	68.8% remission rate for NB (n=22/32) vs. 50.0% for placebo (n=17/34)	Minimal adverse events reported
BED - Combined Treatment	Grilo et al. (2022)	136 patients with BED + obesity (81.6% women)	2×2 factorial design, 16-week	NB alone: 31.3% remission; NB + Behavioral Weight Loss (BWL): 57.1% remission	Well-tolerated

BED - Single Agent	Grilo et al. (2023)	Smaller pilot trial	Randomized, double-blind, placebo-controlled	31.3% binge-eating remission with NB vs. 17.7% placebo	Minimal adverse events
Meta-Analysis: BED	Moawad et al. (2024)	Multiple RCTs	Systematic review and meta-analysis	Weight reduction: MD -8.52 kg vs. baseline; BMI reduction: MD -4.95 kg/m²	Generally safe
Meta-Analysis: BED Specificity	Roudbaraki et al. (2025)	444 BED participants	Fixed-effects meta-analysis (4 RCTs)	Significant weight loss: MD -3.57 kg ($p<0.001$); BMI: MD -1.24 kg/m² ($p<0.001$)	Moderate to low certainty of evidence
Liver Health	Bajaj et al. (2020)	2,073 subjects (NB n=1,310; placebo n=763)	Post hoc analysis, 56-week	Weight loss with NB: 8.7 kg vs. 3.2 kg placebo ($p<0.0001$)	Well-tolerated

Table 3 summarizes the main clinical evidence for the efficacy of the naltrexone/bupropion (NB32) combination in weight management. NB – Naltrexone/Bupropion, CI- Confidence Interval

2.3.2 Alterations in the microbiome and inflammatory responses during bupropion administration

Bupropion has shown therapeutic potential in patients with inflammatory bowel disease, as evidenced by improvements in both the Crohn's Disease Activity Index and Mayo scores (F et al., 2025). In a rat model of depression, bupropion administration restored beneficial bacterial populations such as Romboutsia and Muribaculum, while reducing potentially harmful bacteria including Staphylococcus, Streptococcus, and Bacteroides. Additionally, bupropion improved short-chain fatty acid profiles, specifically acetic and butyric acid, and reduced pro-inflammatory CD4+ T lymphocytes as well as IL-1 and CXCL2 levels. These microbiota changes were correlated with improvements in tryptophan metabolites and immune indicators, supporting a microbiota-mediated antidepressant mechanism (J et al., 2025).

Table 4.

Drug	Mechanism	Key anti-inflammatory effect	Effect on microbiota	Adverse effects
GLP-1 receptor agonists	Satiety/glucose control	Direct TNF-ff, IL-6, IL-17 suppression	↑ Akkermansia, Bacteroides, Lactobacillus	nausea, vomiting, and diarrhea, cholelithiasis, cholecystitis
Orlistat	Liphase inhibition	Indirect via microbiota rebalancing	↑ Verrucomicrobia, ↑ Akkermansia	bloating, diarrhea, and steatorrhea, deficiency of fat-soluble vitamins (A, D, E, and K)
Bupropion+naltrexone	synergistic enhancement of POMC activity	Depression-mediated inflammation reduction	↑ Beneficial bacteria, ↓ pathobionts	nausea, vomiting and constipation, dizziness, headache and tremor, increased BP

Table 4 presents the mechanisms of action, anti-inflammatory properties, effects on the microbiota, and adverse events associated with key anti-obesity drugs, such as GLP-1 receptor agonists, orlistat, and the bupropion–naltrexone combination.

GLP-1- glucagon like peptide 1;BP- blood pressure;IL- interleukin; POMC- pro-opiomelanocortin

3 Bariatric Surgery for the Treatment of Chronic Obesity

Bariatric surgery is the most effective intervention for obesity, demonstrating superior outcomes compared to dietary, exercise, or pharmacological approaches (Yoon & Arau, 2021). A meta-analysis reported that individuals with a body mass index (BMI) of 40 kg/m² or greater experienced 20–30 kg of sustained weight loss for up to 10 years, along with improvements in certain comorbidities. For those with BMIs between 35 and 39 kg/m², surgical intervention appears more effective, although the supporting evidence is less definitive (Maggard et al., 2005). The most frequently performed procedures include Sleeve Gastrectomy (SG), Roux-en-Y Gastric Bypass (RYGB), One-Anastomosis Gastric Bypass (OAGB or Mini-GB), Biliopancreatic Diversion with Duodenal Switch (BPD-DS), Adjustable Gastric Banding (AGB), and various endoscopic techniques. Currently, RYGB and SG are the predominant surgical methods employed (Kheirvari et al., 2020).

Table 5.

Procedure	Treatment Outcomes	Complications / Limitations	Need for Supplementation	Source
Roux-en-Y Gastric Bypass (RYGB)	Substantial and durable weight loss (~60–70% excess weight loss, EWL)	Vitamin and mineral deficiencies (B12, iron, calcium, vitamin D), marginal ulcers, internal hernias, dumping syndrome; requires lifelong supplementation.	High (B12, Iron, Calcium, Vitamin D)	(Luesma et al., 2022) (Maggard et al., 2005) (Abumrad & Albaugh, 2018)
Sleeve Gastrectomy (SG)	Weight loss of ~55–65% EWL within 1–3 years; improvement in glucose and lipid metabolism	GERD worsening, vitamin/micronutrient deficiencies, potential partial weight regain.	Moderate (B12, Iron, Vitamin D)	(Kheirvari et al., 2020), (Luesma et al., 2022), (Abumrad & Albaugh, 2018)
Biliopancreatic Diversion with Duodenal Switch (BPD-DS)	Greatest weight loss (70–80% EWL); strongest metabolic improvement—frequent remission of diabetes and dyslipidemia	High risk of protein, fat-soluble vitamin (A, D, E, K), and mineral deficiencies; steatorrhea; higher surgical complexity and morbidity.	Very high (Extensive lifelong supplementation)	(Abumrad & Albaugh, 2018), (Maggard et al., 2005)
One-Anastomosis / Mini-Gastric Bypass (OAGB / MGB)	Weight loss comparable to RYGB	Bile reflux, vitamin deficiencies, marginal ulcers or gastritis at the anastomosis site.	High (Fat-soluble vitamins, B12, Iron)	(Luesma et al., 2022), (Abumrad & Albaugh, 2018)
Adjustable Gastric Banding (AGB)	Moderate weight loss (~40–50% EWL)	Band slippage, erosion, infection, dysphagia, frequent reoperations or band removal.	Low (if diet adequate)	(Maggard et al., 2005), (Abumrad & Albaugh, 2018)
Endoscopic Techniques (Balloon, Endoscopic Sleeve, etc.)	Temporary weight loss (10–20% of initial weight)	Nausea, vomiting, rare perforation; transient effect after device removal.	Low or none (temporary treatment)	(Abumrad & Albaugh, 2018)

Table 5 summarises techniques and treatment results in bariatric surgery. EWL- Excess Weight Loss

Table 6.

Microbial/inflammatory factor	Direction of change	Source
Alpha diversity	Increased	(Koutoukidis et al., 2022)
Firmicutes/Bacteroidetes ratio	Decreased	(Soroceanu et al., 2025)
Akkermansia	Increased	(Hamamah et al., 2024)
Bacteroides	Increased	(Furet et al., 2010)
Enterobacteriaceae/Proteobacteria	Often increased early	(Paganelli et al., 2019)
Bifidobacterium, Lactobacillus	Decreased (notably after Sleeve Gastrectomy)	(Furet et al., 2010)
Richness (overall)	Partial restoration toward controls	(Koffert et al., 2020)
Lipopolysaccharide (LPS)/endotoxemia	Decreased	(Potrykus et al., 2022)
CRP	Decreased (sustained)	(Min et al., 2020)
IL-6, IL-1	Decreasd	(AbadJimnez et al., 2022)
Leptin	Decreased	(Min et al., 2020)
Adiponectin	Increased/normalized	(Gihring et al., 2023)

Table 6 shows the principal microbial and inflammatory responses to surgical obesity treatment. It shows consistent increases in alpha diversity and helpful taxa such as Akkermansia and Bacteroides, and decreases in pro-inflammatory markers including CRP, IL-6, and leptin. These findings taken together provide support for a partial return of gut microbial equilibrium and systemic inflammatory homeostasis upon treatment. IL-interleukin, LPS-Lipopolysaccharide; CRP- C-reactive protein

Summary

Obesity is a metabolic disease linked to gut dysbiosis and inflammatory mediators affecting metabolism and ultimately metabolic dysfunction. Patients tend to have a higher Firmicutes/Bacteroidetes ratio and elevated inflammatory markers (CRP, IL-6, TNF-α). Therapeutic options include GLP-1 receptor agonists (eg, semaglutide, liraglutide, tirzepatide), orlistat, naltrexone–bupropion, and bariatric surgery. GLP-1 agonists cause notable weight loss (~15–21%) by decreasing appetite, improving glucose metabolism, and restoring favorable gut flora. Orlistat presents with some weight loss, beneficial effect on gut microbiota, and metabolic parameter improvements. Naltrexone–bupropion reduces appetite with some degree of success and affects microbiota. Bariatric surgery including sleeve gastrectomy and Roux-en-Y gastric bypass is the most effective surgical approach for achieving sustained weight loss (50–70% excess weight loss) and for the improvement of comorbidities but it may result in micronutrient deficiencies and surgical complications. Surgery also promotes microbial diversity and decreases systemic inflammation. Complex management targeting the obesity–inflammation–microbiota axis and continued therapeutic innovation is essential for successful obesity management.

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AI: AI was utilized for assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process. In preparing this work, the author(s) used,,Grammarly'' for the purpose of checking and improving grammatical correctness. After using this tool, the author(s) have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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