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Incretin Drug Revolution: The Challenges of Hope

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ABSTRACT

Over 800 million people worldwide meet the criteria for obesity, highlighting the need for safe and effective treatments. Recent advances reshaped the paradigm of adipose as an organ that regulates hunger, satiety, insulin sensitivity, and inflammation. Clinical obesity is a chronic condition linked to excess visceral adipose in which the health risk has already manifested. This definition reflects our understanding of obesity, rather than relating it to body size, weight-based conditions, or elevated body mass index. Clinical guidelines recommend pharmacotherapy for children and adults meeting the criteria for obesity. Because few independent diverse trials compare obesity drugs, doctors must resort to trial-and-error to predict usefulness. And the lack of diversity may impact drug safety for at-risk populations. For example, Black and Hispanic adults are at the highest risk for obesity, but few participated in drug trials. The discovery of incretins led to incretin-based hormone drugs that bind glucagon-like peptide-1 or glucose-dependent insulinotropic polypeptide receptors. The media attention around these repurposed type 2 diabetes drugs brings hope for obesity treatment in clinical practice. Manufacturers market incretin drugs as a panacea for neurological, metabolic, and cardiovascular conditions. Filling a unique therapeutic gap between lifestyle modification and bariatric surgery, incretin drugs may help some people. Yet, with any medication, balancing benefits and risks optimizes health. Thus, long-term safety studies comparing incretin drugs in a diverse population are needed for the development of safe and effective treatments. Understanding the health benefits after bariatric surgery, drug therapy, and combination therapy may help guide future clinical practice.

A magical remedy to control human metabolism has evaded scientists for over 130 years. Since the nineteenth century, manufacturers have sold various weight-lowering tonics, banned from sale because of safety issues. As the philosopher Santayana said, "Those who cannot remember the past are condemned to repeat it." And predictably, without understanding the underlying cause for adipose dysfunction or correcting past clinical trial design flaws, manufacturers continue to develop risky treatments for obesity—a controversial word defined by the Centers for Disease Control and Prevention (CDC) as a body mass index (BMI) of 30 or more. Since the US Food and Drug Administration (FDA) began regulating drugs in 1938, manufacturers have failed to produce safe and effective medicines to regulate metabolism.[1] Amphetamines and sympathomimetic drugs led to abuse, cardiac damage, suicidality, cancer, and even death (Figure 1).[2] With over 800 million people worldwide meeting criteria for obesity, the need for safe treatments led to the discovery of incretins.

Incretin drugs include glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) and dual-acting therapies that bind GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors. Recent media campaigns focus attention on these repurposed therapies, bringing hope for clinical obesity treatment. These incretin drugs improve glycemic control and lower total body weight up to 20%,

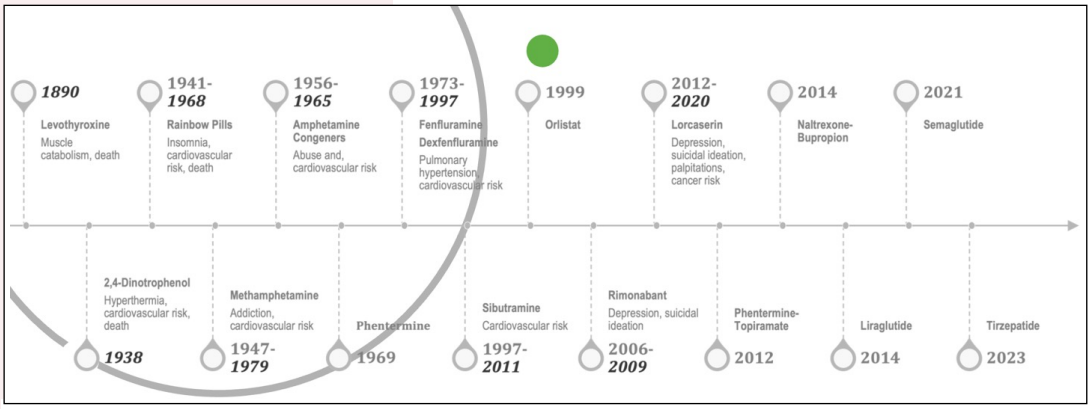

Figure 1. Timeline for FDA regulation of drugs treating clinical obesity.[2] Bold italicized dates signify the year of removal. FDA, US Food and Drug Administration.

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but questions remain.[3] As medical writers, sorting fact from misinformation preserves data integrity and conveys related health risks. Although one must acknowledge the role that incretin therapies play in balancing human metabolism, conclusions must be drawn with caution. Contrary to news reports, this article points out some critical issues regarding obesity clinical trials and raises concerns about the side effects and long-term safety of incretin drugs.

DEFINING DISEASE: CLINICAL TRIALS FOR OBESITY

The World Health Organization defines obesity as uncontrolled adipose accumulation that impairs health. About 42% of US adults meet criteria for obesity, and the child and adolescent rate has almost quadrupled since 1990.[4,5] Despite a century of continued investigation, our understanding of obesity as a chronic disease is not shared across scientific, public health, or political fields. Without common symptoms or diagnostic biomarkers, identifying the underlying cause for adipose dysfunction remains difficult. The controversy about obesity influences social stigma, clinical practice, public health policy, and more. Evidence demonstrating that individuals with elevated BMI can be metabolically healthy contributes to the confusion.[6]

Defining clinical obesity as a higher visceral mass associated with an existing metabolic dysfunction reflects our current understanding of the adipose organ.[7,8] This definition links visceral adipose mass to metabolic health rather than body size, weight-based conditions, or elevated BMI. Intra-abdominal distribution of visceral adipose causes chronic low-grade inflammation, hypertrophy, and fibrosis with increased health risks (Figure 2).[4]

In 2023, the American Medical Association (AMA) recognized that using BMI as the only defining characteristic for obesity can racially exclude and harm certain individuals.[9] Although imaging modalities more precisely calculate adipose distribution, the low cost and ease of application keeps BMI in use. Variations in body shape, bone mass, genetics, and waist circumference can alter the risk estimate.[8] For example, BMI fails to identify sarcopenic obesity, a loss of muscle mass in the presence of clinical obesity. To resolve this, the AMA recommends combining BMI with other indices.[9] However, obesity clinical trials and population studies continue to use BMI.

In the past 40 years, the obesity pandemic patterns have changed. Interestingly, recent urbanization has shifted the obesity prevalence to least-developed countries. The influx of unprocessed, high-calorie foods and other common drivers may contribute to the rising rates.[10] In children, developmental factors affecting weight can disrupt the balance of energy intake and expenditure. These broad environmental, preconception, and prenatal exposures are risk factors for obesity with consequences into adulthood.[5] In adults, complex interconnected risk factors influence weight:[10]

- Biological
- Social
- Food industry influences
- Physical safety
- Lived experiences

Evidence shows a higher risk of developing obesity for youth living in lower social strata or exposed to inequalities.[5] Similarly, racial and ethnic disparities exist in the prevalence

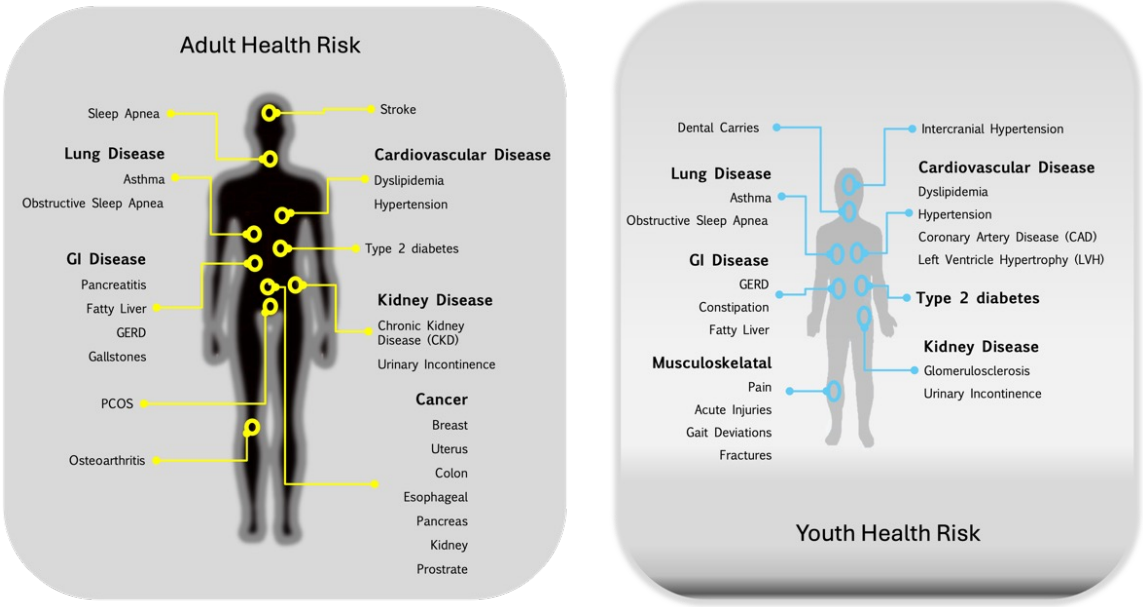

Figure 2. Health risks related to clinical obesity.[4,5] Adult is defined as age ≥20 years, and youth is defined as age 2-19 years. GERD, gastroesophageal reflux disease; GI, gastrointestinal; PCOS, polycystic ovarian syndrome.

for obesity in the United States (Figure 3). The increased prevalence of obesity in Black and Hispanic adults underscores the need for diversity in obesity clinical trials.

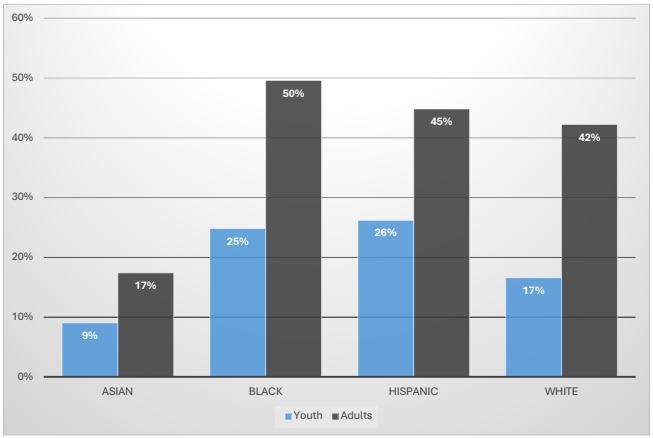

Figure 3. US racial and ethnic differences in the prevalence of adults with BMI ≥30 and youth greater than the ninety-fifth percentile.[11,12] Adults are defined as age ≥20 years, and youth are defined as age 2-19 years. BMI, body mass index.

Lack of Diversity in Clinical Trials for Obesity

Clinical trials for obesity should accurately reflect the characteristics of the disease population.[13] But a recent meta-analysis revealed that obesity clinical trial participants comprised of 74% White adults, mainly women (Table 1).[13] In the United States, the CDC reports the highest risk for obesity in Black (50%) and Hispanic (45%) adults, but only 18% Black and 19% Hispanic adults participated in the drug trials.[13] This lack of diversity during obesity drug testing creates a gap in understanding the risks and benefits of obesity therapies for diverse populations. Future studies aim to increase diversity by decentralizing clinical trial centers. But some of the difficulty surrounding diversity in testing is the need for clear guidance in clinical obesity care.

GUIDING CLINICAL CARE FOR OBESITY

Evidence suggests that lifestyle modification and physical activity remain cornerstones for optimizing health but only provide minimal reductions in weight. Using these data, all guidelines suggest pharmacotherapy for adults who are not pregnant and have a BMI ≥27 in the presence of a weight-related condition or a BMI of ≥30.[14] Similarly, the American Academy of Pediatrics recommends pharmacotherapy for children 8 years and older who meet criteria for obesity.[11]

The latest clinical guidelines for individuals with obesity tether lifestyle modification to all pharmacotherapy treatment, tailoring therapy to each individual.[14] Thus, for treatment optimization, clinicians need a wide range of effective and safe medications for obesity.[15] Because a large body of evidence suggests that weight reductions between 10% and 15% improves cardiometabolic health, guidelines aim for reductions of ≥10%.[4] Yet before 2021, most clinical trial participants reported obesity drug inefficacy rates ranging from 59% to 80% (Figure 5). As an alternative, bariatric surgery became a standard obesity option as part of a flexible care approach. For some patients, bariatric surgery remains a viable long-term solution, improving glucose and lipid levels.[4] However, postsurgical complications combined with facility and specialist requirements limit widespread use.

The success of individualized obesity care plans depends on identifying individuals for treatment and applying the correct therapy at the right time. Health care providers remember the past and remain vigilant when prescribing new obesity drugs. However, media attention drives the demand for incretin drugs, highlighting drug claims of lowered glycemic index, cardiovascular risk, and weight loss of 20% or more.[16] Although incretin therapies may fill the therapeutic gap between lifestyle modification and surgery, balancing health benefits with risks remains important when choosing drug treatment.

Approved Long-Term Pharmacotherapies for Clinical Obesity

In the United States, 6 long-term drugs treat clinical obesity, mainly targeting weight loss (Table 1). Like any treatment, balancing health benefits with risk helps optimize care. Yet without robust, independent clinical trials comparing treatments, doctors typically use trial-and-error when prescribing obesity drugs. Another common practice is off-label use of low-cost therapies. For example, phentermine and topiramate are 2 of the most used drugs in pediatrics. Although phentermine is approved for short-term weight loss in children, topiramate is not. But phentermine with topiramate (Phen/Top) is approved for long-term weight loss in patients 12 years and older. Topiramate, an antiepileptic drug, can affect cognition, sleep, and memory; because of carbonic anhydrase inhibition, the compound also increases risk of taste alteration, metabolic acidosis, and nephrolithiasis. Topiramate has teratogenic effects and can cause fetal harm. As an alternative, the FDA approved naloxone with bupropion (Nal/Bu) for use in adults. Nal/Bu may elevate blood pressure and increase risk of hepatotoxicity or suicidal ideation.

Comparing Long-Term Therapies for Weight Loss

One review of 28 random controlled trials included orlistat, Phen/Top, Nal/Bu, and liraglutide. Interestingly, the study showed that clinical trial participants reported the most success using Phen/Top (75% efficacy) compared with orlistat (44%), Nal/Bu (55%), or liraglutide (63%).[18] More recently, a systematic review and meta-analysis was

Table 1. FDA-Approved Drugs for Clinical Obesity Treatment[11,16,17]

Drug Name	Brand Name	Usage, y	Dosage	Clinical Trial Demographics
Orlistat	Alli (OTC); Xenical	≥12	Capsule: Alli, 60 mg; Xenical, 120 mg	XENDOS 55% women; mean age, 43 y; average BMI, 37; 71% White adults
Phentermine with topiramate	Qsymia	≥12	Phentermine/topiramate: 3.75 mg/23 mg; 7.5 mg/46 mg; 11.25 mg/69 mg; 15 mg/92 mg	EQUIP 83% women; mean age, 43 y; average BMI,42; 80% White adults CONQUER 70% women; mean age, 51 y; average BMI, 36; 85% White adults
Naltrexone with bupropion	Contrave (US); Mysimba (EU)	≥18	Naltrexone/bupropion: 8mg/90mg	COR-I 85% women; mean age, 44 y; average BMI 36; 82% White adults COR-II 85% women; mean age, 44 y; average BMI, 36; 83% White adults
Liraglutide	Saxenda	≥12	18 mg dial-a-dose pen delivering customizable doses: 30 at 0.6 mg; 15 at 1.2 mg; 10 at 1.8 mg; 7 at 2.4 mg; 6 at 3 mg	SCALE 78% women; mean age, 45 y; average BMI, 38; 85% White adults
Semaglutide	Wegovy	≥12	Single-use, color-coded pens: teal, 0.25 mg; pink, 0.5 mg; brown, 1mg; blue, 1.7mg; black, 2.4 mg	STEP 1 73% women; mean age, 46 y; average BMI, 38; 75% White adults
Tirzepatide	Zepbound	≥18	Single-use 0.5 mL pen or vial, comes in doses: 2.5 mg; 5 mg; 7.5 mg; 10 mg; 12.5 mg; 15 mg	SURMOUNT-1 67.5% women; mean age, 45 y; average BMI, 38; 70% White adults

BMI, body mass index; COR-I, Contrave Obesity Research I; COR-II, Contrave Obesity Research II; EU, European Union; FDA, US Food and Drug Administration; OTC, over the counter; SCALE, Satiety and Clinical Adiposity Liraglutide Evidence; STEP 1, Semaglutide Treatment Effect in People with Obesity; XENDOS, Xenical in the Prevention of Diabetes in Obese Subjects.

performed using 53 clinical trials for obesity drugs. The findings showed that tirzepatide effectively reduced waist circumference by 6.77 cm compared with semaglutide (3.74 cm) and liraglutide (2.30 cm).[19] In a subanalysis, semaglutide was the only incretin drug to effectively reduce low-density lipoprotein and total cholesterol yet showed the highest discontinuation rate because of gastrointestinal (GI) events. In fact, safety concerns for the incretin drugs are warranted at higher doses. Except for orlistat, a local-acting lipase inhibitor, all obesity therapies act by increasing norepinephrine to decrease appetite. Understanding neuroendocrine signals that regulate hunger helps elucidate related health risks for these drugs.

Pharmacotherapies: Balancing Appetite

Two opposing types of neurons in the hypothalamus balance energy intake to control appetite. The agouti-related peptide/neuropeptide Y (AgRP/NPY) neurons constantly co-release γ-aminobutyric acid (GABA) and NPY peptides to lower sympathetic activity, turning on appetite (Figure 4). Once food enters the stomach, the gut releases incretins and adipose releases leptin, slowing intestinal motility to prolong satiety.[20] The opposing pro-opiomelanocortin/cocaine-amphetamine-related transcript (POMC/CART) neurons receive these gut signals to enhance sympathetic release of norepinephrine, turning off appetite. Many pharmacotherapies for weight loss increase sympathetic activity and norepinephrine to turn off appetite.

GABA-modulating drugs like topiramate increase the brain's sympathetic activity to lower appetite. But sympathomimetic drugs like phentermine stimulate sympathetic release of norepinephrine to lower appetite.[16] Bupropion and naltrexone also stimulate sympathetic activity but directly activate POMC/CART neurons to diminish hunger. Interestingly, naltrexone acts as a long-acting opioid antagonist to change the brain's response to food by altering the dopamine-reward system.[16] Incretin drugs mimic the actions of GLP-1 and GIP that stimulate glucose-dependent increases in insulin, slow gastric emptying, and extend satiety to lower appetite. Although GLP-1 RAs suppress pancreatic-glucose-dependent release of glucagon, GIP receptor agonists stimulate it.[15] But the low permeability of incretin drugs likely prevent access through the blood-brain barrier. Supporting this, studies indicate that incretin drugs signal the hypothalamus via the dorsal vagal complex, which may explain the negative side effects like nausea and vomiting.[15]

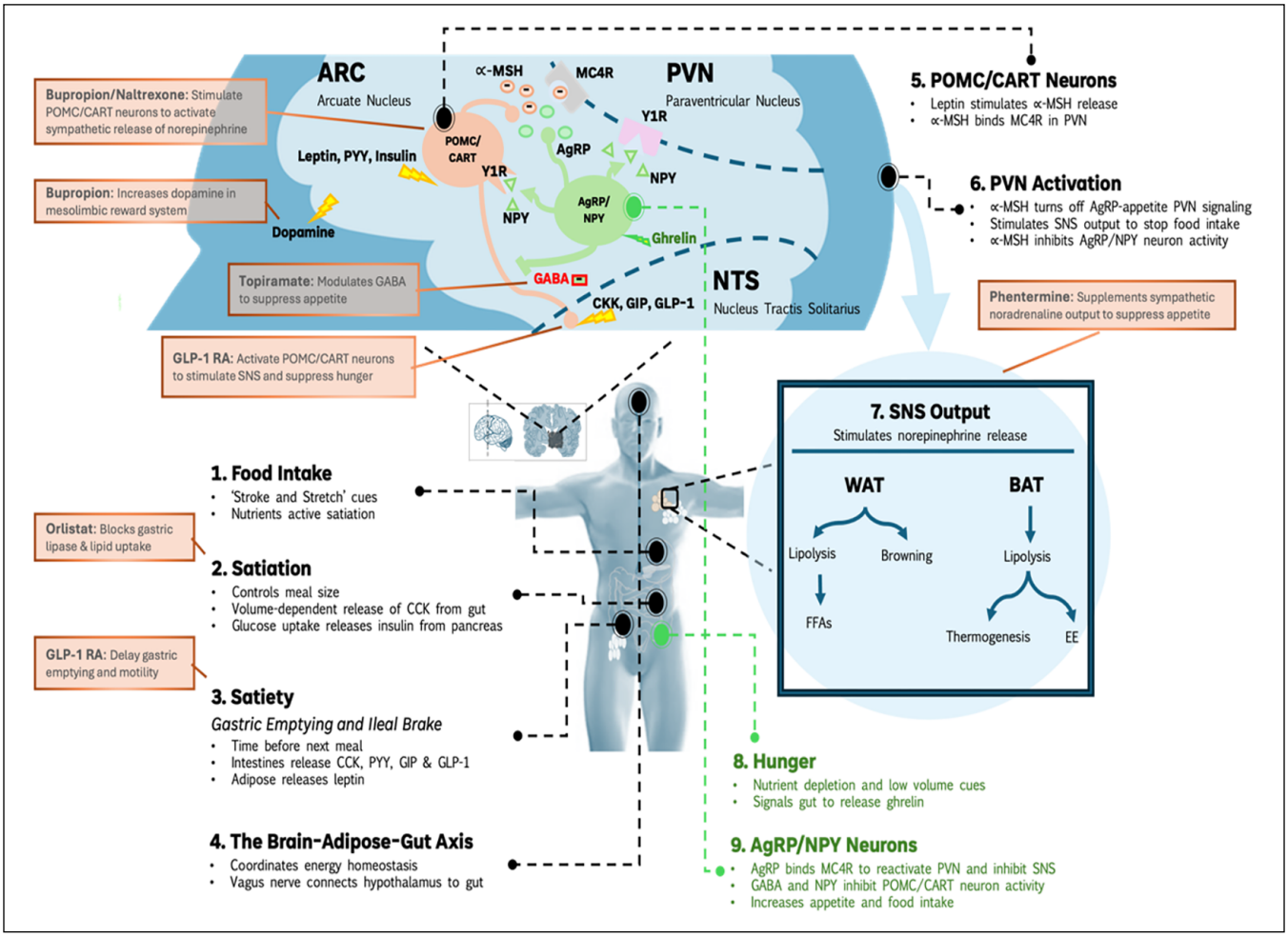

Figure 4. Pharmaceutical action to extend satiety for energy homeostasis.[20] *α-MSH, α-melanocortin stimulating hormone; AgRP/NPY, agouti-related peptide/neuropeptide Y; ARC, arcuate nucleus; BAT, brown adipose tissue; CCK, cholecystokinin; EE, energy expenditure; FFAs, free fatty acids; GABA, γ-aminobutyric acid; GLP-1 RA, glucagon-like peptide-1 receptor agonist drugs including tirzepatide; MC4R, melanocortin 4 receptor; POMC/CART, pro-opiomelanocortin/cocaine-amphetamine-related transcript; PYY, peptide YY; SNS, sympathetic nervous system; WAT, white adipose tissue; Y1R, NPY 1 receptor.*

The Incretin Drug Revolution

Incretin drugs are not new. Liraglutide debuted a decade ago, but the drug was not as effective compared with the more recent incretin drugs. The dose required to treat obesity is almost twice that for glucose management in type 2 diabetes. During the Satiety and Clinical Adiposity Liraglutide Evidence trials, liraglutide reduced total body weight by 6.1%.[21] Liraglutide did not receive much publicity with high discontinuation rates, GI side effects, and cancer risk. To improve safety and effectiveness, the manufacturer of liraglutide set out to find a compound with a longer half-life.

Researchers discovered semaglutide, extending the half-life to 168 hours. During the Semaglutide Treatment Effect in People with Obesity trials, this compound improved cardiometabolic health and reduced weight by 12.6% (Figure 5).[21] But similar to other incretin therapies, almost 40% of trial participants reported nausea, 70% experienced GI disorders, and almost 10% discontinued the drug.[15]

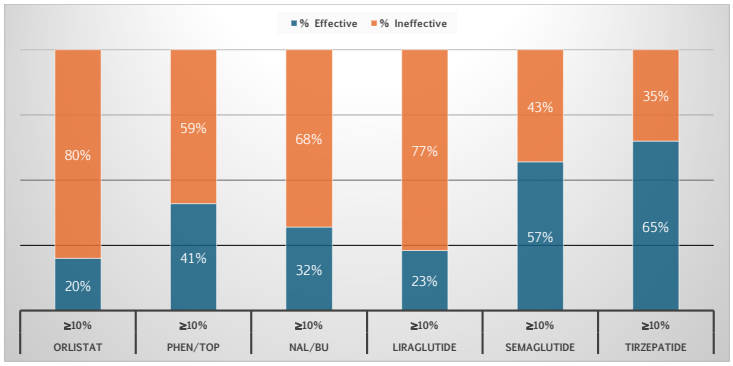

Figure 5. Percent of individuals experiencing ≥10% weight reduction from drug treatment during clinical trial testing.[17,21] *Nal/Bu, naltrexone with bupropion.*

The newest incretin drug, tirzepatide, binds GLP-1 and GIP receptors in the gut.[16] This dual-acting drug has been the most

successful incretin therapy thus far, with 62% of participants having ≥15% weight reduction, and more than half having ≥20% weight reduction (Figure 6). However, about a quarter of participants discontinue treatment because of GI symptoms.[22] It has been shown that incretin therapies remain ineffective for about 20% of individuals.[23] Some patients require dose adjustments, therapy changes, or surgery to reach weight goals. Although there are several known benefits for incretin therapies, several challenges remain.

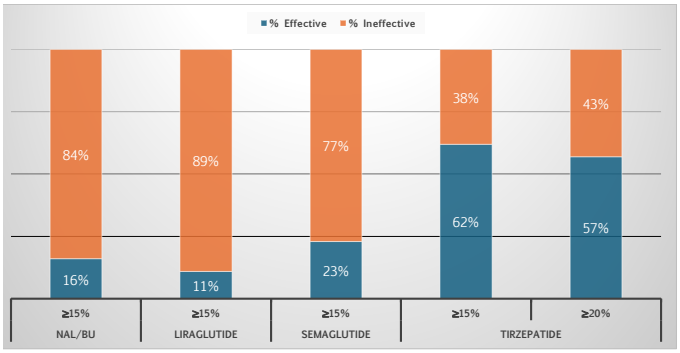

Figure 6. Percent of individuals experiencing ≥15% or ≥20% weight reduction from drug treatment during clinical trial testing.[17,21] *Nal/Bu, naltrexone with bupropion.*

Challenges of Incretin Therapy: Shifting Satiety

The incretin drug revolution brings hope for treating obesity and many weight-related conditions. However, sympathetic-extension of satiety may increase long-term risks for chronic disease, including risk for renal disorders and thyroid cancer.[16] The brain's default hunger state may support long-term health, fueling cellular activity through fatty acid metabolism. In contrast, incretin drugs shift the metabolic state to satiety, forcing the brain and other tissues to rely on glucose.[24] Although the consequences of this shift are unclear, sympathomimetic and incretin drugs increase risk for hypertension, glaucoma, and heart rate (Table 2).[25,26]

Incretin drugs may also come with increased risk for anxiety. One study linked chronic activation of AgRP/NPY neurons with increased anxiety and colitis.[27] Supporting this, some individuals taking incretin drugs report increased anhedonia and suicidality.[15] Other challenges of incretin drugs are linked to gastric emptying and include ileus, gastroparesis, and decreased drug absorption.[28,29]

Another complicating issue includes the plateau effect. Over time, increased incretin drug dosing may no longer decrease net body mass. This effect has been reported by individuals taking semaglutide and highlights lifestyle modifications as an important part of overall treatment.[15] Using incretin therapies requires a life-long commitment because health gains disappear with discontinuation. Some studies report up to two-thirds of the original weight returns after discontinuation.[29]

Table 2. Comparison of Mean Heart Rate Increases for Obesity Drugs[25,26]

Drug	Beats Per Minute
Phen/Top	0.6-1.6
Semaglutide	1-2
Liraglutide	3-8
Tirzepatide	3-6
Nal/Bu	0.9-1.2

Nal/Bu, naltrexone with bupropion; Phen/Top, phentermine with topiramate.

LOOKING AHEAD

In summary, incretin therapies bring a dynamic phase in drug development for treating obesity. These drugs lower glycemic index, reduce cardiovascular risk, and may benefit liver and neurodegenerative conditions. However, the health risks of prolonged satiety states to cardiac, renal, and other tissues remain unclear. Incretin drugs have been linked to increased risk for thyroid cancer, suicidality, and elevated heart rate. These medication side effects must be balanced with health benefits and cost, which factor heavily into optimizing individualized clinical obesity treatment plans. Given the limited number of high-quality randomized trials comparing obesity drugs, doctors must resort to trial-and-error to predict usefulness. In addition, long-term safety studies in diverse populations are needed to better understand incretin drug effects on growth and development. By 2030, more than 8.5 billion people are estimated to meet criteria for obesity worldwide.[10] Now more than ever, learning from past mistakes can help improve the quality of clinical obesity care. It is crucial to determine the risks and long-term health benefits of bariatric surgery, drug therapy, and combination treatments to help guide future clinical practice.

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