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PERSPECTIVE ON THE Rx PIPELINE

Understanding changes in the medication market and their impact on cost and care.

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Perspective on the Rx Pipeline

Elixir continuously monitors the drug pipeline. As treatment options change, we evaluate and share our perspective on the clinical benefits, cost-effectiveness and overall impact to payers and patients. Our Perspective on the Rx Pipeline report provides ongoing actionable insights from our team of clinical experts and the steps we are taking to protect and improve plan performance.

INCLUDED IN THIS EDITION:

Weight Loss Medications

The Skinny About Weight Loss Medications

It's difficult to scroll through social media or watch the news without hearing about one of the latest weight loss drugs on the market. From their suspected use in Hollywood or the vlog updates from users that discuss their progress and experiences, weight loss medication options have made their way back to the top of the trend list.

But, they are not new. Way before supersized fries, Big Gulps and jazzercise, in 1959, one of the first FDA-approved weight loss medications hit the market with the drug phentermine, brand name Adipex. Phentermine is an appetite suppressant meant for short-term use and it is still on the market today. Over the last 65 years, many new drugs have been released specifically to help fight the growing concern of obesity. The weight loss medications continue to evolve along with their impact on treatment and plans.

A Common, Chronic and Costly Disease

Overweight and obesity are defined by the Centers for Disease Control and Prevention (CDC) as "weight that is higher than what is considered healthy for a given height".[1] About 3 of 4 adults over 20 years old in the United States are either overweight or obese.[2] In the United States, obesity affects 100.1 million (41.9%) adults and 14.7 million (19.7%) children and accounts for approximately $147 billion in annual health care costs.[3] Even with all the attention and visibility, the prevalence of obesity continues to increase, jumping from 30.5% of the U.S. population in 2000 to 41.9% in 2020.[4]

1 IN 3 adults struggle with obesity[5]

1 IN 5 children struggle with obesity

Obesity is associated with increased morbidity and mortality caused by comorbidities such as high blood pressure, high cholesterol, type 2 diabetes (T2DM), cardiovascular disease, sleep apnea, osteoarthritis, certain cancers, depression and anxiety. Cardiovascular disease is likely the largest driver of mortality in obese patients.[6] In a study that analyzed trends in the prevalence of obesity between 1980 and 2015, more than two thirds of deaths related to high Body Mass Index (BMI) were attributed to cardiovascular disease.[7]

Weighing in On an Obesity Diagnosis

The most common tool to evaluate weight in correlation with height is the BMI. The BMI categorizes the weight/height ratio by underweight, healthy weight, overweight and obesity and is regularly referenced in guidelines and used in clinical practice. However, the use of BMI as a weight assessment has been under controversy for many years due to its inaccuracy in predicting disease across racial and ethnic groups, sexes, genders and age. Recently, the American Medical Association (AMA) stated that other factors such as body composition, belly fat, waist circumference and genetics also play a role and should be considered and used in conjunction with BMI to diagnose obesity.[8]

Category	BMI kg/m^2
Underweight	<18
Healthy weight	18 and <25
Overweight	25 and <30
Obesity Class I	30 and <35
Obesity Class II	35 and <40
Obesity Class III	>40

Standards of Care for Weight Loss Management

The Endocrine Society and The American Gastroenterological Association (AGA) have both published guidelines on the pharmacological management of obesity, in 2015[9] and 2022[10] respectively.

The Endocrine Society's clinical practice guideline recommends the following treatment based on BMI (kg/m^2) level:

BMI	Recommended Treatment
≥ 25	Diet, exercise and behavioral modification
≥ 27 and at least one weight-related comorbidity (e.g., high blood pressure, T2DM)	Drug therapy
≥ 30	Drug therapy

When it comes to the drug therapy, both guidelines suggest a patient-tailored approach dependent on any existing health conditions such as high blood pressure or T2DM and they should be monitored for efficacy and safety monthly for the first three months, then every three months thereafter.

If the patient experiences weight loss ≥ 5% at three months, then the medication should be continued. If the weight loss is < 5% at three months, or tolerability is an issue, the medication should be discontinued, and an alternative should be considered.

FDA-Approved Drugs for Weight Management[11]

There are currently six FDA-approved medications for chronic weight management. These medications work in a variety of ways and come in a variety of forms and dosing schedules. Some medications suppress appetite, reduce cravings and control hunger while others decrease dietary fat absorption. Of the medications approved for chronic weight loss, the glucagon-like peptide-1 (GLP-1) receptor agonists (RA) have increased in popularity due to their increased weight loss as compared to other agents, dual type 2 diabetes mellitus (T2DM) indication, less frequent administration and potential cardiovascular benefit.

Brand Generic	Route	Mechanism of Action	Dosing Frequency
Contrave® bupropion, naltrexone	Oral	Norepinephrine-dopamine reuptake inhibitor (NDRI), opioid antagonist	Twice daily
Qsymia® phentermine, topiramate	Oral	Sympathomimetic anorectic, antiepileptic	Once daily
Saxenda® liraglutide	Subcutaneous	Glucagon-like peptide-1 (GLP-1) receptor agonist (RA)	Once daily
Wegovy® semaglutide	Subcutaneous	Glucagon-like peptide-1 (GLP-1) receptor agonist (RA)	Once weekly
Xenical orlistat	Oral	Lipase inhibitor that decreases dietary fat absorption	Three times daily
Zepbound tirzepatide	Subcutaneous	Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)	Once weekly

The Good the Bad and the Popularity of GLP-1s

Glucagon-like peptide-1 Receptor Agonists (GLP-1 RAs) bind to and activate the GLP-1 receptor, which causes regulation of appetite and caloric intake, slows gastric emptying, increases glucose-dependent insulin secretion and decreases inappropriate glucagon secretion.[12]

GLP-1 RAs are:

- Approved for chronic weight management under the brand names, Saxenda, Wegovy and as the GLP-1 RA and GIP agonist, Zepbound.
- Approved for T2DM with the brand names, Byetta, Mounjaro™, Ozempic®, Trulicity®, Rybelsus® and Victoza®.
- Available in both oral and subcutaneous formulations with dosing frequencies ranging from daily to weekly.

Common adverse effects

It is important to note that, while GLP-1 RA medications are considered safe, there are some common adverse effects that patients and prescribers should be aware of prior to initiating therapy.[13]

- Many contain a boxed warning regarding thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), and are contraindicated in those with a personal or family history of MTC cancer or multiple endocrine neoplasia syndrome type 2a or 2b.
- Gastrointestinal side effects such as nausea, vomiting, diarrhea and abdominal pain are common and are thought to play a role in weight loss efficacy.

As more people utilize these agents, more information will become available about the rarer adverse effects including concerns of stomach paralysis and increased risk of aspiration during anesthesia due to delayed gastric emptying.

Glucagon-like peptide-1 Receptor Agonists (GLP-1 RAs)

Regulates appetite and caloric intake

Slows gastric emptying

Increases glucose-dependent insulin secretion

Decreases inappropriate glucagon secretion.[13]

Increase in Demand

One of the biggest notes about GLP-1 RAs is their increased off-label use for weight loss for those with normal or near-normal BMIs without T2DM. This can probably be attributed to social media trends and celebrity influences that piqued interest in the use of pharmacological treatments to lose weight. The surge in demand has caused many of the GLP-1 RAs to be out of stock over the last months leaving some patients who meet the indication requirements of obesity and/orT2DM struggling to obtain the medication.[14]

The increased demand has also led some manufacturers to compound semaglutide (Ozempic, Wegovy) with unauthorized ingredients. This sparked the FDA to issue a statement in May of 2023 to warn against the use of compounded semaglutide.[15]

Cardiovascular Benefit from Weight Loss Medication

In August 2023, Novo Nordisk announced positive results from the SELECT trial that analyzed the use of semaglutide in reducing the risk of major adverse cardiovascular events (MACEs).[16] The trial evaluated 17,000 patients, 45 years of age or older and overweight or obese with established cardiovascular disease and no prior history of diabetes. The randomized, double-blind, parallel-group study evaluated if taking semaglutide 2.4 mg (Wegovy) weekly was superior to placebo when added to standard of care for the prevention of major adverse cardiovascular events (MACEs).[16]

The results found that adding the semaglutide demonstrated a 20% reduction in MACEs as compared to placebo. While the full results of the trial have not yet been shared or peer reviewed, Novo Nordisk plans to file for a label expansion with the FDA for Wegovy by the end of 2023. If approved, it may be the first glucagon-like peptide-1 (GLP-1) agonist indicated to reduce cardiovascular mortality in those who are overweight or obese without a diagnosis of diabetes.[16]

New GLP-1 RAs Keep Coming

While the demand is hot, the medication pipeline includes many derivations of GLP-1 RA to hopefully increase their weight loss potential. Some of these include additional mechanisms of action such as:

- More glucose-dependent insulinotropic polypeptide (GIP) agonists, like Zepbound. GIP agonists work in synergy with GLP-1 RAs and may increase insulin sensitivity and glucagon while decreasing food intake, nausea and body weight.[17]
- Increasing glucagon that may reduce body weight and contribute to appetite suppression, as well as promote energy expenditures, mobilize fat and increase heat production.[18]
- Amylin agonist, already available as Symlin,® which is currently approved to treat diabetes and results in weight loss for some patients.

These products do have potential side effects and it is likely that if a patient stops taking them, the weight will return.

GLP-1 RA WEIGHT MANAGEMENT DRUG PIPELINE[13]

	Pipeline Drug Name	Mechanism of Action	Stage	Clinical Pearl
2024	**NN9932** *Generic: Semaglutide*	GLP-1 agonist	Phase III	• Oral • Mean BW at 68 weeks: −15.1% • Less patients reached BW reduction of ≥10% than in the tirzepatide trial
2024	**CagriSema** *Generic: Cagrilintide; Semaglutide*	GLP-1 agonist, Amylin analog	Phase III	• Mean BW at 32 weeks: −15.6% • REDEFINE clinical trial ongoing
2026	**LY3502970** *Generic: Orforglipron*	GLP-1 agonist	Phase III	• Oral • Mean BW at 36 weeks: −13.5% (36 mg) and −14.7% (45 mg) • Ongoing clinical trials
2027	**LY3437943** *Generic: Retatrutide*	GLP-1 agonist, GIP agonist, Glucagon agonist	Phase III	• Once weekly • Mean BW at 48 weeks: −22.8% (8 mg), −24.2% (12 mg) • Over 90% of patients achieved BW reduction of ≥10% • Ongoing clinical trials
2027+	**CT-868**	GLP-1 modulator, GIP modulator	Phase II	• In clinical studies for type II and I diabetes as well
2027+	**ALT-801** *Generic: Pemvidutide[19]*	GLP-1 agonist, Glucagon agonist	Phase II	• Also being studied for non-alcoholic steatohepatitis (NASH) • Weekly dosing • MOMENTUM 48-week clinical trial (Phase II) is reviewing changes in lipids, blood pressure, and heart rate with results expected in 4Q 2023
2027+	**BI 456906** *Generic: Survodutide[20]*	GLP-1 agonist, Glucagon agonist	Phase II	• Also being studied for non-alcoholic steatohepatitis (NASH) • Pending start of three Phase III global studies

BW – bodyweight PDUFA – prescription drug user fee act

Non-GLP-1 RA Weight Management Drug Pipeline

Other novel weight loss medications are also in the pipeline, but in earlier phases of clinical studies. With GLP-1 RA producing significant results and having large patient uptake, other mechanisms of action appear to be less pressing in drug research but do exist.

Pipeline Drug Name	Mechanism of Action	Stage	Clinical Pearl
S-309309 (Shionogi)[21]	MGAT2 Inhibitor	Phase II	• Impacts lipid metabolism in small intestines
TNX-1900 (Tonix) *Generic: Oxytocin*	Calcitonin gene-related peptide (CGRP) inhibitor and oxytocin receptor	Phase II	• Nasal administration • Seeking obesity and other indications foremost such as chronic migraine treatment

The Acceptance of Care: Lifestyle or Disease?

The Center for Disease Control (CDC) considers obesity a complex disease. The American Medical Association officially recognized obesity as a disease in 2013. However, for commercial clients, weight loss coverage is often driven by benefit design and can be included or excluded if the indication is felt to be lifestyle in nature.

But the tides may be turning. In a recent survey of employer, union and health plan respondents 43% of plans currently cover FDA-approved medications for weight loss and another 28% were considering doing so in the next 1 to 2 years.[22]

The Centers for Medicare and Medicaid Services (CMS) also currently excludes weight loss and weight gain therapies from Medicare Part D. Current legislation, a bill titled “Treat and Reduce Obesity Act of 2023”[23], is being proposed by some members of the U.S. Senate. This bill would expand Medicare weight loss management coverage to those who are overweight and have one or more comorbidity. As additional results become available from trials such as SELECT and new indications potentially may be granted to reduce cardiovascular mortality, the coverage landscape may significantly change.

The Cost of Weight Loss Management is Heavy

GLP-1 RAs for weight loss carry a hefty price and no generic GLP-1 RAs for weight loss are available. The Institute for Clinical and Economic Review (ICER) reviewed weight loss management medications in: Treatments for Obesity Management in 2022. ICER noted that semaglutide and liraglutide were above the ICER Health-Benefit Price Benchmark. However, the landscape is evolving rapidly and assessment of long-term clinical benefits such as cardiovascular outcomes were not available for this ICER review.

Drug Name	Annual Net Price	ICER Health-Benefit Price Benchmark (HBPB)
Semaglutide	$13,618	$7,500 – $9,800
Liraglutide	$11,760	$3,800 – $4,800
Phentermine/Topiramate	$1,465	$3,600 – $4,800
Bupropion/Naltrexone	$2,094	$1,800- $2,400

Impact to Pharmacy Care Experience

The influx of pharmaceutical options for weight loss has had an impact on patients, providers and benefit plans. From increased requests and managing medication shortages, to controlling high costs, these drugs are tipping the scale in many directions.

GLP-1 RAs are helping patients experience positive weight loss, but their side effects may be limiting some from long-term use. And, while the use of these drugs may empower some providers and patients to make significant weight loss management changes in relatively short periods of time, the providers are also dealing with possible off-label use of the medications for weight loss for those patients who may not necessarily clinically qualify as overweight/obese.

As more drugs (possibly more effective drugs) are FDA approved, the interest in weight loss products and the challenges for plans and payers will continue.

Payer Action Plan

Payers should closely monitor the use of weight loss medications and GLP-1 RA for weight loss and diabetes. Utilization management tools such as a prior authorization process to prevent off label use of GLP-1 RAs is suggested. As more GLP-1 RAs gain FDA approval for weight loss, a preferred products list may also offer a valuable advantage.

Elixir's clinical team closely watches the pipeline and its National Pharmacy and Therapeutics (P&T) Committee reviews newly approved products for appropriate drug placement and utilization management. Decisions regarding lifestyle vs. non-lifestyle status of weight loss management medication for Commercial payers currently lie in their benefit design choice. Member satisfaction, payer and patient cost, and clinical endpoints such as improvement in cardiovascular health may be points to consider in choosing to cover weight loss medication. Utilization management will continue to be key as lifestyle modifications are considered essential to maintain a healthy weight. Medicare coverage of weight loss medications will continue to be dictated by Centers for Medicare and Medicaid Services guidance and Elixir will review legislation or updates as they occur to help provide guidance.

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