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Advances In Weight Loss Drug Development And The Impact On Provider Services

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Excess body weight afflicts more than two-thirds of Americans. Until recently, pharmacological interventions have been incremental at best. In 2021, the FDA approved Wegovy (semaglutide) for chronic weight management, delivering the first results even remotely comparable to bariatric surgery. Herein, we detail the growing weight loss drug pipeline, strategies manufacturers are utilizing to expand access, as well as the impact that greater pharmacological options have on provider services. Obesity specialists may be in a unique position, being more knowledgeable with navigating insurance coverage, at the intersection of manufacturer hub services. Virtual care companies providing access to weight loss drugs are also coming into their own as the pipeline and market expands. Finally, the associated impact of significant weight loss on appearance may drive further involvement of ancillary services in the broader medspa and aesthetic services market.

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I. Excess Body Weight Afflicts The Majority Of Americans

Excess body weight afflicts more than two-thirds of Americans, with more than 33%[1] of adults and 20%[2] of adolescents further characterized with obesity. The estimated healthcare burden of obesity has been estimated at > $190B[3] per year in related illnesses. This includes the incidence of type 2 diabetes (T2D) and cardiovascular diseases, as well as increased mortality for cancers of the esophagus, colon and rectum, liver, gallbladder, pancreas and kidney. Furthermore, it complicates the management of multiple diseases, enhancing the prospect for unfavorable outcomes; the COVID-19 pandemic is an example of this.

Factors routinely cited as accounting for the steep increase in obesity in the US and worldwide are increased access to energy-dense foods coupled with reduced physical activity. Sleep disorders and deprivation, chronic stress and the use of certain prescription medications are further contributors to weight gain. Beyond behavioral factors, genetic and epigenetic factors related to the environment each appreciably contribute to obesity, with an estimated heritability of ~40–70%.[4,5] Growing recognition of obesity as a chronic disease with impacts across the aforementioned comorbidities, provide a framework for increased payor coverage, provider specialization and investor interest in program development.

II. Behavioral And Pharmacological Approaches Have Compared Poorly Against Surgery Until Recently

Bariatric surgery represents the most effective approach to weight loss and a benchmark for which to compare behavioral and pharmacological interventions. Until recently, the latter has been incremental at best, limiting providers' options from an efficacy standpoint.

In 2021, the FDA approved Wegovy (semaglutide 2.4 mg, weekly subq) for chronic weight management in adults with obesity or overweight with at least one weight-related condition (e.g., high blood pressure, cholesterol, or T2D), for use in addition to a reduced-calorie diet and increased physical activity. This followed the lower dose Ozempic (semaglutide 0.5-2 mg, weekly subq) approval for use in adults with T2D in late 2017.

This now constitutes the second glucagon-like peptide 1 receptor (GLP1R) agonist registered for body weight management, although the most efficacious. Saxenda

[1] https://www.niddk.nih.gov/health-information/health-statistics/overweight-obesity [Accessed June 2023].

[2] Skinner A.C., Ravanbakht S.N., Skelton J.A., Perrin E.M., Armstrong S.C. Prevalence of obesity and severe obesity in US children 1996-2016. Pediatrics. 141(3):e20173459 (2018).

[3] Cawley, J. & Meyerhoefer, C. The medical care costs of obesity: an instrumental variables approach. J. Health Econ. 31, 219–230 (2012).

[4] Maes, H. H., Neale, M. C. & Eaves, L. J. Genetic and environmental factors in relative body weight and human adiposity. Behav. Genet. 27, 325–351 (1997).

[5] Bray, M. S. et al. NIH working group report — using genomic information to guide weight management: from universal to precision treatment. Obesity 24, 14–22 (2016).

(liraglutide 3 mg, daily subq) was approved by the FDA in 2014 for treatment of adult obesity and in 2020 for obesity in adolescents aged 12–17 years. This followed the lower dose Victoza (liraglutide 0.6-2mg mg, daily subq) approval by the FDA in 2010 as an adjunct to diet and exercise to improve glycemic control in adults with T2D.

An oral weight-loss equivalent of these drugs would be transformative to the market. Pfizer is currently developing a twice-daily GLP1 agonist pill. Eli Lilly is also working on an oral version of the T2D subcutaneous injection Mounjaro, and Structure Therapeutics is developing a similar oral drug.

III. Several Therapeutic Targets In The Pipeline Deserve Attention

Pharmacological interventions until recently have been incremental at best and fraught with adverse event issues at worst. There have been significant anti-obesity medication failures that have occurred both prior to and after regulatory approval. Most of these pertain to adverse cardiovascular effects (sibutramine, fenfluramine, dexfenfluramine, rainbow pills), increased suicidal risk (rimonabant) or enhanced likelihood of drug dependence and abuse (methamphetamine).

TABLE 1: Therapeutic Targets For Weight Lowering

Glucagon-like peptide 1 Receptor (GLP1R)- GLP1-related drug candidates (Table 2A-F): Outside of semiglutide and liraglutide, several other peptide and small-molecule GLP1R agonists are currently in clinical development, including formulations designed for oral administration. GLP1R agonist (GLPR-NPA) is currently in phase II clinical trials at Eli Lilly for oral administration.

Glucose-dependent Insulinotropic Polypeptide (GIP)-related drug candidates (Table 2B-D): Engagement of GIPR agonism for the treatment of obesity and T2D is regarded with notable skepticism, as the insulinotropic effect of GIP is diminished in patients with T2D.

Growth/Differentiation Factor 15 (GDF15) (Table 2L): Macrophage inhibitory cytokine 1 (MIC1; also known as GDF15) has gained attention as a target for obesity treatment. Animal models suggest decreases in body weight in diet-induced obese mice and non-human primates, suggesting a homeostatic role in energy homeostasis.

Peptide Tyrosine Tyrosine (PYY) (Table 2H): Released from intestinal cells in response to a meal, it has demonstrated the ability to decrease food intake in rodents and humans and has stimulated the development of analogues for the treatment of obesity.

Ghrelin (Table 2K): Envisioned strategies to harness ghrelin biology for potential treatment of obesity include suppression of active circulating hormone and antagonism of signaling at its receptor, the growth hormone secretagogue receptor (GHSR).

Amylin (Table 2I-J): Amylin (also known as IAPP) is a peptide that is co-secreted with insulin and reduces food intake through central control of satiety pathways. Amylin has also been shown to affect hedonic control of eating, including a reduction in feeding reward neurocircuits.

Leptin, Leptin Sensitizers and Melanocortin-4 (MC4) Agonists (Table 2G): Whereas leptin appears not to hold promise as a stand-alone therapy for the treatment of common obesity, its combination with pramlintide (Amylin Pharmaceuticals) induces greater body weight loss in individuals of excess weight relative to treatment with either drug alone.

TABLE 2: Therapeutic Targets For Weight Lowering And Associated Comorbidities In Clinical Development

Agent	Company	Phase	Indication
A. GLP1/glucagon dual agonists			
Cotadutide (MEDI0382)	AstraZeneca	2	T2D, NASH
BI 456906	Boehringer Ingelheim	2	Obesity, T2D
Efinopegdutide (LAPSGLP/GCG)	Hanmi Pharmaceutical	2	NASH
OXM	Eli Lilly	1	T2D
B. GIP/GLP1 dual agonists			
Tirzepatide	Eli Lilly	3	Obesity, T2D
GIP/GLP peptide I	Eli Lilly	1	T2D
GIP/GLP peptide II	Eli Lilly	1	T2D
C. GIP/GLP1/glucagon tri-agonists			
HM15211 (LAPSTriple Agonist)	Hanmi Pharmaceutical	2	NASH
GGG tri-agonist	Eli Lilly	1	T2D
D. GIPR agonists			
GIPR agonist long acting	Eli Lilly	1	T2D
E. GLP1R agonists			
Efpeglenatide (LAPSExd4 Analog)	Hanmi Pharmaceutical	3	T2D
Rybelsus	Novo Nordisk	3	Obesity
Danuglipron (PF-06882961)	Pfizer	2	Obesity, T2D
GLPR-NPA	Eli Lilly	1	T2D
PF-07081532	Pfizer	1	T2D
F. Glucagon analogue			
HM15136 (LAPSGlucagon Analog)	Hanmi Pharmaceutical	1	Obesity
G. Leptin sensitizers			
Withaferin A	Academic, non-commercial	1	Obesity, T2D
H. Y2R agonists			
PYY analogue	Eli Lilly	1	T2D
NN9748 (NN9747)	Novo Nordisk	1	Obesity, T2D
NNC0165-1875+semaglutide	Novo Nordisk	2	Obesity, T2D
I. Amylin/calcitonin dual agonists			
KBP-089	Nordic Biosciences	1	T2D
J. Amylin analogues			
Cagrilintide	Novo Nordisk	2	Obesity, T2D
K. Drugs targeting the ghrelin pathway			
CYT009-GhrQb	Cytos Biotechnology	1	Obesity
L. Other appetite suppressants			
GDF15 (LA-GFD15)	Novo Nordisk	1	Obesity
LY-3463251 (GDF15 Agonist)	Lilly	1	T2D, Obesity
JNJ-9090/CIN-109 (GDF15 Agonist)	Jansenn/CinFina Pharma	1	Obesity

Candidates with obesity indication in light blue; Phase of clinical trial in green shading- later stages are darker .

Despite numerous disappointments, several prominent therapeutic targets are worth continued attention outside of incretins and GLP1 (e.g., Wegovy, Saxenda) which were predominately focused on diabetes and evolved as an obesity drug through concurrent empirical observations of body weight lowering. These targets include leptin, ghrelin, and growth differentiation factor 15 (GDF15) which were initiated and advanced with obesity constituting the primary therapeutic purpose **(TABLES 1 & 2)**.

IV. The Heterogeneity Of Weight Loss Benefits Obesity Practices, Even If Pipeline Advancement Is Challenged

Obesity is a heterogeneous condition constituted by often multiple genetic, neurobehavioral, endocrine, metabolic and potentially epigenetic processes. It remains to be determined whether single mechanisms in drug action will actually prove successful in treatment of most patients with obesity, or whether far more diverse customization will be required. In a related manner, drug candidates that fail in monotherapy may prove successful in combination therapies.

Efficacy studies struggle with the question of how much additional weight reduction is advisable in a finite period, and the duration necessary for documenting it with confidence. There is also the question of what is most needed to accelerate the realization of the next leap forward in safely normalizing body weight.

In these regards, proper dosage, monitoring and adjunctive therapy—pharmacological and behavioral—open the door for greater physician involvement. This may increasingly be the case as future treatments are aligned with diagnostic biomarker testing to target dysregulation with pharmacological intervention.

V. While Medicare FFS Does Not Cover Rx Weight Loss, There Is Growing Interest

Medicare coverage of obesity services does not include drugs that are prescribed for weight loss, although obesity screening, behavioral counseling, and bariatric surgery are covered. Furthermore, the 2003 law that established the Medicare Part D prescription drug benefit explicitly prohibits Part D plans from covering drugs used for weight loss.

With evidence that GLP1s lead to significant weight loss with potential benefit to associated comorbidities, manufacturers and other stakeholders are seeking a change in law to allow coverage under Medicare. A bipartisan group of lawmakers proposed legislation in the prior (117th) Congress, the Treat and Reduce Obesity Act (H.R. 1577/S. 596), that would authorize Part D coverage of medications when used for the treatment of obesity or weight loss management in overweight individuals with related comorbidities. Thus far, a similar bill has not been introduced in the current Congress. The challenge remains cost, and framing impact in the lens of offset from reduced comorbidities. At $13,600/year and high prevalence of obesity in the US, calculations of budget impact exceed 25% of current Medicare Part D spend.

VI. Commercial Payor Policies Benefit Candidates With Dual Obesity And T2D Labels

Though most private insurers do not cover GLP1 drugs approved for weight loss, they often cover the same drugs at lower doses to treat T2D. Thus physicians have begun exploiting a loophole to prescribe semaglutide drugs (Wegovy, Ozempic) to obese patients through their comorbidities, namely diabetes or high blood sugar levels.

VII. Select Medicaid States Cover Prescription Weight Loss

In contrast to Medicare and commercial plans, 10 states have broad coverage for weight loss drugs in their Medicaid policy. Medicaid programs that cover a large number of obesity drugs include CA, KS, MN, WI, MI, PA, VA, DE, RI and NH. Other states offering more limited coverage include NM, LA, TN, GA, SC and NJ. Of note, CT will begin covering obesity drugs through Medicaid in July 2023.

VIII. Reimbursement Challenges Provide Advantages To Candidates With Dual Obesity Data And T2D Label

The $8.8B U.S. medical weight loss market grew nearly 17% in the past year, putting aside the challenges of the pandemic.[6] Whereas conventional wisdom would assume the rise of self-administered weight loss drugs would lead to decreased physician involvement, the market may in fact be entering a new era of medical approaches that combine behavioral and pharmacological interventions requiring providers skilled in not only weight management, but payor policies and manufacturer programs.

The alignment of T2D with obesity may allow for greater potential for reimbursement, as commercial payors and Medicare reimburse the former and not the latter. Indeed, a number of manufacturers are engaging in this strategy with their pipeline drugs, seeing a means into obesity treatment through T2D prescribing.

Given this avenue, obesity specialists may be in a unique position, being more knowledgeable with navigating insurance coverage in this area. Among more lenient plans, some insurers may only cover certain brands. Some health plans may require evidence that weight loss strategies such as exercise or diet changes have not worked previously, while other plans may require a coinciding behavioral weight-loss program if coverage is provided.

If patients are able to secure coverage for weight loss drugs, their out-of-pocket costs could still be significant. Thus a provider knowledgeable in manufacturer hub services for weight loss and T2D may more efficiently guide patients to assistance programs to help pay those costs. In addition, these providers may be more in tune with payor requirements for continued coverage. For example, health plans may require weight loss milestones to continue coverage, while others may terminate coverage if the patient successfully loses enough weight.

[6] Market Data LLC. "The U.S. Medical Weight Loss Market", (2023).

IX. Future Considerations

Beyond traditional obesity treatment services, novel weight loss drugs have catalyzed increased demand through other channels. The associated impact of significant weight loss on appearance may coincide with further involvement of medspa practices and the broader aesthetic services market.

In addition, employers are seeing increased demand for obesity care benefits which has catalyzed an uptick in virtual care companies providing access to weight loss drugs such as Noom, Ro, and WeightWatchers through their purchase of telehealth company Sequence, Everly Health and other well-known consumer-facing platforms. Teladoc Health recently announced it was expanding its telehealth services to include prescribing obesity drugs.

In evaluating the impact of drug, procedural and behavioral advances in weight loss, strategy considerations must be paired with attention to state and federal regulatory, commercial payor, drug pipeline and landscape, market size, growth and competitive dynamics. Marwood's consulting services span federal and state regulatory and legislative considerations, payor/benefit manager dynamics across Medicare, Medicaid and commercial plan perspectives, as well as strategic and operational considerations including pipeline analysis, market sizing, growth outlook, referral source views, competitive landscape, performance improvement and practice compliance.

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