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Mini-Review

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New Horizons. A New Paradigm for Treating to Target with Second-Generation Obesity Medications

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Abbreviations: AACE, American Association of Clinical Endocrinology; ABCD, adiposity-based chronic disease; BMI, body mass index; CNS, central nervous system; CVD, cardiovascular disease; ER, extended release; FDA, US Food and Drug Administration; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; LDL-c, low density lipoprotein cholesterol; PYY, peptide YY; RCT, randomized clinical trial; SELECT, semaglutide effects on heart disease and stroke in patients with overweight or obesity trial; STEP, semaglutide treatment effect in people with obesity program; T2D, type 2 diabetes mellitus.

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Abstract

In treating obesity as a chronic disease, the essential goal of weight loss therapy is not the quantity of weight loss as an end unto itself but rather the prevention and treatment of complications to enhance health and mitigate morbidity and mortality. This perspective on obesity care is consistent with the complications-centric American Association of Clinical Endocrinology (AACE) obesity guidelines and the diagnostic term of adiposity-based chronic disease (ABCD). Many complications require 10% to 20% weight loss to achieve therapeutic goals; however, existing obesity medications fail to produce ≥10% weight loss in the majority of patients. In June, 2021, semaglutide 2.4 mg/week was approved for chronic weight management. Phase 3 clinical trials demonstrated that this medication produced > 10% placebo-subtracted weight loss, more than half of patents lost ≥15%, and over one third lost ≥20% of baseline weight. This essentially doubles effectiveness over existing obesity medications, provides sufficient weight loss to ameliorate a broad range of complications, and qualifies as the first member of a second-generation class of obesity medications. The advent of second-generation medications fully enables a treat-to-target approach for management of ABCD as a chronic disease. Specifically, with this degree of efficacy, second-generation medications permit active management of body weight as a biomarker to targets associated with effective treatment and prevention of specific complications. ABCD can now be managed similar to other chronic diseases such as type 2 diabetes, hypertension, and atherosclerosis, which are treated to biomarker targets that can be modified based on the clinical status of individual patients

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[ie, hemoglobin A1c (HbA1c), blood pressure, and low-density lipoprotein cholesterol (LDL-c)] to prevent the respective complications of these diseases.

Key Words: obesity, anti-obesity medications, obesity complications, chronic disease

Introduction: A New Horizon for Obesity Medicine

The advent of a new paradigm in obesity care has transpired due to recent developments in obesity medicine combined with a better understanding of obesity as a chronic disease. At the core of this transformation is the introduction of a medication, with additional drugs under development, having a degree of efficacy and safety that substantially surpasses antecedent therapies. Despite the huge burden of patient suffering and social costs exacted by obesity, the disease is underdiagnosed and there is widespread lack of access to evidence-based therapy (1). In this sense, healthcare systems have failed our patients and our societies. Hopefully, as will be discussed, new therapeutic tools will change the way clinicians approach the disease and enable a new paradigm of care that will more effectively benefit larger numbers of patients.

Three new concepts will be developed. The first pertains to the designation of second-generation medications for the treatment of obesity. In general, a second-generation medication should entail a considerable advance in efficacy and/or safety compared to previous medications for a disease which, in effect, facilitates a significant change in treatment and ability of clinicians to improve patients' health. In addition, the therapeutic effect should be sustained when applied to chronic diseases given their long-term natural history. A definition specific for the pharmacotherapy of obesity will be proposed based on the degree of efficacy required to substantially improve patient outcomes to a degree than can be transformative for obesity care. This will be discussed in the context of a recently approved medication that meets the defined criteria for a second-generation obesity medication together with others in development with this same potential.

The availability of second-generation medications is integrally linked with the second and third concepts that constitute a new paradigm for obesity care. The second concept is the use of % weight loss as a biomarker that can actively be managed within a range associated with optimal outcomes in patients with obesity. In this way, obesity is managed similar to other chronic diseases in which therapeutic efficacy is based on the control of a biomarker [eg, HbA1c in diabetes, blood pressure in hypertension, LDL-c in cardiovascular disease (CVD)] within a range known to be associated with the prevention and treatment of complications. The use of % weight loss as a biomarker is coupled with the third concept which is a treat-to-target approach for patients with obesity. Obesity is a chronic disease of energy balance driven by dysregulated interactions involving satiety factors and the central nervous system (CNS) resulting in increased caloric intake and an excess in adipose tissue mass (2-4). The increase in adiposity causes chronic complications that confer increased morbidity and mortality. As a chronic disease, treatment improves the health of patients by preventing and treating obesity complications (5,6). As will be discussed, different complications require different amounts of weight loss for prevention and treatment (5). Second-generation medications for the first time allow clinicians to manage % weight loss (ie, the biomarker) into a target range that has been shown to ameliorate specific complications. Depending on the complication profile present in different patients, the target for % weight loss can be individualized. This is in contrast with preexisting medications that often lack the degree of efficacy to optimally address many complications and where the primary focus is on the kilograms of weight loss per se; in other words, treating the biomarker to the extent possible as the end point of therapy without regard to the attendant clinical outcomes of the chronic disease.

Obesity, Complications, and Adiposity-based Chronic Disease

It has become clear that obesity is a chronic disease (6) that involves more than an increase in body mass. The diagnosis of obesity based on body mass index (BMI; weight in kg/height in m^2) uses an indirect measure of adiposity that provides no information regarding the impact of excess weight on health (7). As with other chronic diseases, it is the complications of obesity that impair health and confer morbidity and mortality (5,8). The mass of adipose tissue gives rise to biomechanical complications such as obstructive sleep apnea and osteoarthritis while abnormalities in the distribution and function of adipose tissue contribute to cardiometabolic disease complications. Cardiometabolic disease begins with insulin resistance, which is initially subclinical but eventually produces clinical manifestations that include metabolic syndrome, prediabetes, elevated blood pressures, dyslipidemia, and hepatic steatosis. These manifestations indicate risk for progression to the end-stage manifestations of cardiometabolic disease, namely type 2 diabetes (T2D), nonalcoholic steatohepatitis, and CVD. The development of obesity exacerbates insulin resistance

and impels progression of cardiometabolic disease toward these ultimate outcomes (9). In this context, ABCD has been suggested as a more precise clinical and diagnostic term for obesity by the AACE (10) and the European Association for the Study of Obesity (11). ABCD indicates what we are treating—namely, abnormalities in the mass, distribution, and function of adipose tissue—and why we are treating it, a chronic disease that gives rise to complications that require prevention and treatment. Accordingly, the complications-centric AACE clinical guidelines for obesity emphasize the prevention and treatment of complications as the end point of therapy rather than the amount of weight lost per se (5).

While weight loss is highly effective for treating and preventing ABCD complications, the dose-response for weight loss to achieve clinical benefit varies as a function of the various complications (4,5). In patients with ABCD and prediabetes or metabolic syndrome, 10% weight loss is maximally effective for preventing progression to overt diabetes (5,12); in patients with T2D, the more weight loss the better where weight loss of >5% to 15% or more provides progressive improvements in HbA1c, blood pressure, and lipids (13); for obstructive sleep apnea, ≥10% weight loss is needed for predictable improvements in the apnea/hypopnea index; and in nonalcoholic fatty liver disease (14,15), 5% to 10% weight loss will reduce steatosis but >10% weight loss is required in nonalcoholic steatohepatitis to improve inflammation and fibrosis (5,16,17). Prevention of CVD events and mortality may require >10% weight loss based on case-control studies and meta-analyses of the bariatric surgery literature (18-20) and on results from the Look AHEAD study in patients with T2D that assessed outcomes as a function of degree of weight loss (21). Overall, in considering the degree of weight loss required to ameliorate these common complications in ABCD, interventions are needed that reliably produce 10% to 20% weight loss.

The Evolution and Rationale for Obesity Pharmacotherapy

In the late 1950s and 1960s, sympathomimetic amines (eg, phentermine, benzphetamine, diethylpropion) were approved for short-term weight reduction encompassing a treatment period of a few weeks. Due to a lack of understanding regarding obesity pathophysiology, it was considered that once weight was lost in the short-term there was no need for ongoing treatment. As a consequence, we are lacking long-term safety data on these drugs to this day. Orlistat was approved in 1999 for chronic weight management, which acts intraluminally to impair intestinal fat digestion and absorption. It has since become clear that the excess in adipose tissue mass is the result of abnormalities in satiety hormones interacting with CNS feeding centers (2-4). Specifically, the interaction of orexigenic hormones such as ghrelin and anorexigenic hormones such as leptin, cholecystokinin, peptide YY (PYY), and amylin with hypothalamic satiety centers is dysregulated resulting in a level of caloric intake that generates and sustains excess adiposity. There are also maladaptive responses following weight loss that are important aspects of obesity pathophysiology. Weight loss resulting from a hypocaloric diet triggers increments in the orexigenic hormone and ghrelin and a decrease in anorexigenic hormones including glucagon-like peptide 1 (GLP-1), amylin, cholecystokinin, and PYY. This results in greater hunger and increased caloric intake. In addition, there is a reduction in energy expenditure that contributes to positive energy balance. These maladaptive responses work against the patient, promote weight regain back to the previous high level of adiposity, and explain why weight loss is often not sustained with lifestyle interventions. In this sense, obesity protects obesity as a function of disease pathophysiology.

Medications were needed for chronic administration that could blunt appetite by counteracting abnormalities in the satiety hormone-CNS axis. Three such medicines approved by the FDA, fenfluramine, sibutramine, and lorcaserin have been discontinued due to safety concerns. However, from 2012 to 2014, 3 centrally acting medicines were approved for chronic weight management that continue to be available to clinicians, phentermine/topiramate extended release (ER; a sympathomimetic amine combined with a gabaminergic drug used for epilepsy), naltrexone ER/bupropion ER (an opioid receptor antagonist combined with a dopamine/norepinephrine reuptake inhibitor used for depression), and liraglutide 3 mg/day (a GLP-1 receptor agonist) (5). All met the FDA criteria for efficacy in phase 3 randomized clinical trials (RCTs); mean placebo-subtracted weight loss was ≥ 5% or the proportion of patients who lost ≥5% body weight was ≥35% and double that observed in the placebo group. In June, 2021, the FDA approved another GLP-1 receptor agonist, semaglutide 2.4 mg subcutaneously once a week, for chronic weight management. This medication essentially doubled the weight loss observed in phase 3 RCTs compared with corresponding data for preexisting obesity medications (22-24). A case will be made that the availability of a medication with this degree of efficacy constitutes a "new horizon" in the care of patients with obesity.

A Second-generation Obesity Medication

A second-generation medication should generally entail a considerable advance in efficacy and/or safety and facilitate a significant change in treatment. While real-world

experience is critical in qualifying a medication as second generation, these qualities can more immediately and rigorously be ascertained based on RCTs. As previously discussed, an obesity medication that safely achieves 10% to 20% weight loss in the majority of patients would constitute a powerful therapeutic option given the relationship between weight loss and clinical benefits pertaining to ABCD complications.

Prior to approval of semaglutide 2.4 mg, all medications available to clinicians (orlistat, phentermine/topiramate ER, naltrexone ER/bupropion ER, and liraglutide 3 mg) resulted in <10% mean placebo-subtracted weight loss at 1 year, as shown in Table 1. With respect to categorical weight loss, the percentage of subjects losing ≥10% of baseline weight was far less than 50% and many fewer lost ≥15%. Clearly, these medications were not ideal and could not optimally be used to effectively manage complications in many patients. In essence, clinicians and patients had to be satisfied with the weight loss and health benefits achieved with these medications since they did not enable a robust ability to actively manage patients toward treatment goals. With this in mind, the qualities delineated in Box 1 would characterize a medication with the capacity to transfigure obesity care and would provide clinicians with the tools to substantially and predictably enhance health in the majority of patients.

Box 1. Definition of a Second-generation Obesity Medication

- Ability to safely produce an average of >10% placebo-subtracted weight loss in randomized clinical trials (ie, over that attributable to lifestyle interventions) in the majority of patients or
- Ability to safely produce a ≥15% weight loss in over half the patients as an adjunct to lifestyle.

Semaglutide 2.4 meets these qualifications as the first example of a second-generation medication for general treatment of obesity based on (i) its superior efficacy compared to previously approved medications for chronic weight management and (ii) the health benefits associated with this degree of weight loss regarding the treatment of ABCD complications. Key phase 3 RCTs assessing efficacy and safety of semaglutide 2.4 mg (the STEP trials) were published in leading journals in 2021 (22-24). Across STEP trials, mean placebo-subtracted weight loss was

Table 1. Efficacy of obesity medications in randomized clinical trials

Drug	% Weight loss		% with ≥ 10%		% with ≥ 15%		% with ≥ 20%	
	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo
Orlistat (ref 25)								
XENDOS 1 year	10.6	6.2	41	20.8				
XENDOS 4 year	5.8	3.0	26.2	15.6				
Phentermine/topiramate ER[a] (26-28)								
EQUIP	10.9	1.6	47.2	7.4	32.3	3.4		
CONQUER	9.8	1.2	37.0	7.0				
SEQUEL 2 yr	9.3	1.8	50.3	11.5	24.2	6.6	9.2	2.2
Naltrexone ER/bupropion ER (29-31)								
COR-I	6.1	1.3	25.0	7.0	12	2		
COR-II	6.4	1.2	28.3	5.7	13.5	2.4		
COR-BMOD	9.3	5.1	41.5	20.2	29.1	10.9		
Liraglutide 3 mg (32-34)								
SCALE Maintenance	6.7	0.1	26.1	6.3	11.0	3.1		
SCALE Ob & PreDM 1 year	9.2	3.5	33.1	10.6	14.4	3.5		
SCALE Ob & PreDM 3 year	7.1	2.7	24.8	9.9	11.0	3.1		
Semaglutide 2.4 mg (22-24,35,36)								
STEP 1	14.8	2.4	69.1	12.0	50.5	4.9	32.0	1.7
STEP 3	16.0	5.7	75.3	27.0	55.8	13.2	35.7	3.7
STEP 4	17.4	5.0	79.0	20.4	63.7	9.2	39.6	4.8
STEP 5 2 year	15.2	2.6	61.6	13.3	52.1	7.0	36.1	2.8
STEP 8	15.8	1.9	70.9	15.4	55.6	6.4	38.5	2.6

All data represents primary analyses for each study [eg, intention to treat (ITT), ITT/last observation carried forward (LOCF), LOCF with imputation, treatment policy estimand].

Abbreviations: % with ≥, % = % of subjects achieving ≥ 10%, ≥ 15%, and ≥ 20% weight loss from baseline; Ob, obesity; PreDM, prediabetes.

[a]Dose is phentermine 7.5 mg/topiramate 46 mg except 15 mg/92 mg in EQUIP.

consistently >10%, averaging 12.3%, and consistently more than half of patients lost ≥15% of baseline weight and over a third lost ≥20% (Table 1). The safety profile of semaglutide 2.4 mg was not different from other GLP-1 receptor agonists in that the main adverse events were gastrointestinal, in particular, nausea experienced early during dose escalation, which was usually mild to moderate and improved over time. A second potential example of a second-generation medication is setmelanotide approved by the FDA in November 2020. However, this melanocortin receptor agonist is currently only approved for use in three rare genetic conditions involving mutations in the pro-opiomelanocortin, proprotein subtilisin/kexin type 1, and leptin receptor genes (37,38) and does not appear to be highly effective in non-monogenic obesity (39).

The Capacity to Treat ABCD to Target and the Use of % Weight Loss as a Biomarker

A medication with the efficacy of semaglutide 2.4 mg allows for a treat-to-target approach that is routinely employed in the management of other chronic diseases. In T2D, hypertension, and atherosclerosis, treatment is directed at a biomarker, not because the biomarker itself is of primary importance, but because the complications of the disease can effectively be mitigated if the biomarker is managed within a target range. Examples are shown in Figure 1. In diabetes, for example, clinicians treat the biomarker HbA1c to a target of ≤7.0% (40) or ≤6.5% (41) because evidence indicates this will minimize vascular complications such as retinopathy, neuropathy, chronic kidney disease, and CVD risk. The disease of hypertension involves control of blood pressure levels. However, the reduction in mmHg is not an end unto itself; rather, the goal is to prevent complications such as congestive heart failure, stroke, and chronic kidney disease. Finally, to prevent and treat CVD, LDL-c serves as a biomarker that is managed to a level based on patient risk estimates (42). In each instance, treatment to target for each biomarker (HbA1c, blood pressure, and LDL-c) is individualized based on an individual patient's overall risk, other comorbid conditions, and status regarding the natural history of the disease.

Similarly, in ABCD, the efficacy afforded by second-generation obesity medications allows clinicians to use % weight loss as a biomarker to indicate whether treatment is sufficient to prevent and treat specific complications. Thus, the amount of weight loss is not of isolated importance or a goal unto itself but is used to determine whether the intensity of therapy is sufficient to ameliorate complications present in individual patients. Percentage weight loss is a more appropriate biomarker than body weight or BMI since any given value provides similar benefits with respect to complications over a wide range of BMI even though patients with a high baseline BMI will lose more kilograms of weight than those with a lower baseline BMI (5). Figure 2 illustrates the variable range of weight loss necessary for treating specific cardiometabolic and biomechanical complications. The shaded area represents the 10% to 20% weight loss that is observed in the clear majority of patients using semaglutide 2.4 mg, which was not achievable with preexisting first-generation obesity medications. Thus, second-generation medications will allow clinicians to reach targets of weight loss that will predictably treat or prevent a broad spectrum of complications in ABCD. As with other chronic diseases, the management of the biomarker (% weight loss) is individualized based on what is needed to treat specific complications present in each patient (5). Semaglutide 2.4 mg also begins to close the gap in weight loss achieved with medications vs bariatric surgery procedures, and indeed the ≥20% weight loss observed in over a third of patients with semaglutide 2.4 mg overlaps with that following adjustable gastric band, gastric sleeve,

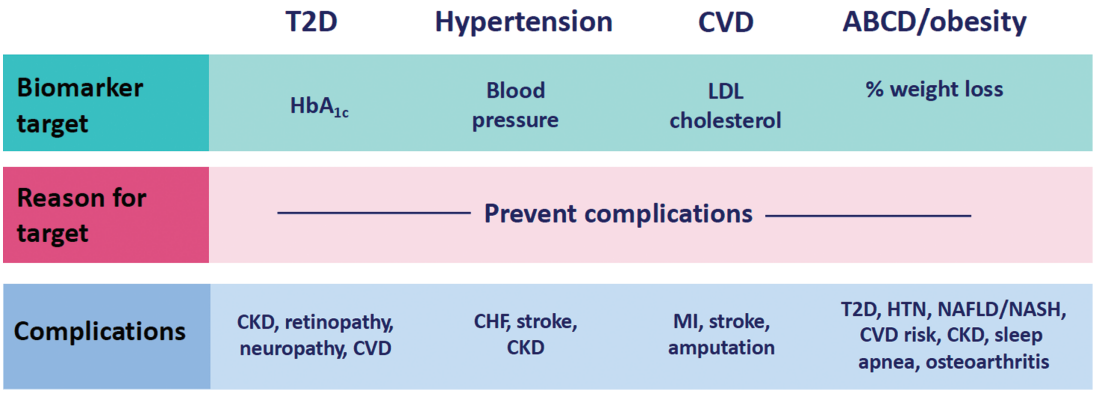

Figure 1. Treating chronic diseases to target. Abbreviations: ABCD: adiposity-based chronic disease; CHF: congestive heart failure; CKD: chronic kidney disease; CVD: cardiovascular disease; HTN: hypertension; LDL: low-density lipoprotein; MI: myocardial infarction; NAFLD: non-alcoholic fatty liver disease: NASH, non-alcoholic steatohepatitis.

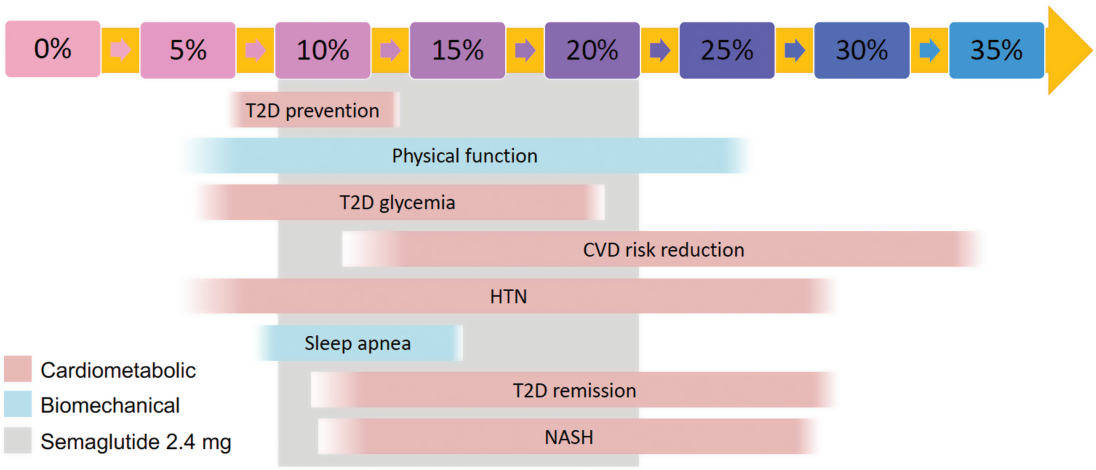

Figure 2. Treating ABCD/obesity to target for prevention and treatment of complications. Abbreviations: ABCD: adiposity-based chronic disease; CVD: cardiovascular disease; HTN: hypertension; NASH, nonalcoholic steatohepatitis;T2D, type 2 diabetes.

and gastric bypass procedures. This raises the question as to whether semaglutide will also reduce CVD events and mortality as has been observed following bariatric surgery (18-20). In fact, lower doses of subcutaneous liraglutide (43) and semaglutide (44) produced lesser degrees of weight loss yet were shown to be cardioprotective in patients with T2D. The ongoing SELECT trial is a cardiovascular outcome trial powered for superiority in patients with obesity but without diabetes and will hopefully address this question in ABCD (45).

This paradigm of care is fully consistent with risk stratification and staging of obesity. Several approaches have been proposed for the general staging of patients with obesity such as the Edmonton protocol (46) and the AACE obesity guidelines (5), and cardiometabolic disease staging (47,48) helps clinicians stratify patients over a broad range of risk for progression to T2D and CVD. The AACE guidelines simply stratify patients as stage 0 in the absence of complications, stage 1 if there are 1 or more complications that are mild-moderate in severity, and stage 2 if there is at least 1 severe complication (5). The target for weight varies based on the presence of specific complications as well as the severity of those complications so that more aggressive therapies can be used to achieve therapeutic targets in patients with higher risk or more severe complication profiles. ABCD/obesity is a highly prevalent disease and aggressive therapy is not safe or feasible in all patients. Treatment decisions based on disease staging and individualized treatment-to-target would predictably enhance the benefit-risk ratio and cost effectiveness of interventions. The presence of second-generation medications adds to the value and purpose of disease staging by enabling active management based on severity and individualized targets for weight loss. Finally, there have been proposals to reform the inadequate International Classification of Diseases 10 coding system for obesity (49-50). The proposed coding approaches are medically actionable and encode degrees of disease severity based on the presence and severity of complications (49), as exists in International Classification of Diseases 10 codes for other chronic diseases. Again, second-generation medications like semaglutide 2.4 mg permit more effective management of ABCD within the context of these new proposed classification approaches.

Additional Second-generation Medications

While semaglutide 2.4 mg is the first second-generation medication for general treatment of obesity, it is not likely to be the last. Other medications are under development that appear to have these qualities in early phase trials. For example, tirzepatide, a dual gastric inhibitory polypeptide (GIP) and GLP-1 receptor agonist, produces weight loss approaching ~12% in patients with T2D (51,52), which exceeds the ~10% weight loss achieved by semaglutide 2.4 mg in patients with T2D in the STEP 2 trial (53). Patients with T2D characteristically lose less weight in response to any intervention compared with nondiabetic individuals and, to date, all published data for tirzepatide involves patients with T2D. Predictably, tirzepatide would produce more weight loss in patients without diabetes and has the potential to meet the criteria for a second-generation drug for the general treatment of obesity once data become available in non-diabetic patients. Other promising medications under development include additional multiagonist GLP-1/glucagon/GIP peptides, long-acting amylin analogs (54,55), activin II receptor agonists that reduce body fat while increasing

muscle mass (56), and the combinations of GLP-1 receptor agonists with other satiety hormones such as amylin (55), PYY, and oxyntomodulin. Therefore, the future of obesity pharmacotherapy is bright, and we should anticipate the availability of additional second-generation medications. This will enhance the ability of clinicians to individualize treatment and more effectively treat-to-target. With any weight loss intervention, there is variability in the response and patients may not achieve target levels for reductions in body weight. Therefore, it is advantageous to have multiple second-generation medications, in addition to first generation drugs, in the armamentarium to enhance the ability of clinicians to identify effective treatment regimens in individual patients. Multiple available medications also allows for use of drug combinations. The regulation of body weight is complex and represents the combined action of multiple pathways. Drug combinations that target multiple pathways produce greater weight loss than when these drugs are used as single agents (57,58). Eventually, the combination of medications with different mechanisms of action will be possible as is common practice for other chronic diseases such as T2D and hypertension.

In summary, the advent of second-generation medications fully enables the treatment of ABCD as a chronic disease. The marked increment in efficacy over first-generation drugs permits active management of the % weight loss as a biomarker to targets associated with effective treatment and prevention of specific complications.

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