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Giving weight to incretin-based pharmacotherapy for obesity-related sleep apnea: a revolution or a pipe dream?

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Abstract

Obesity is a chronic disease affecting over 670 million adults globally, with multiple complications including obstructive sleep apnea (OSA). Substantial weight loss in patients with obesity-related OSA can reduce or even eliminate OSA as well as reduce sleepiness and improve cardio-metabolic health. Evidence suggests that these improvements exceed those that occur with device-based OSA therapies like continuous positive airway pressure which continue to be the first-line of therapy. Resistance to weight management as a first-line strategy to combat OSA could arise from the complexities in delivering and maintaining adequate weight management, particularly in sleep clinic settings. Recently, incretin-based pharmacotherapies including glucagon-like peptide 1 (GLP-1) receptor agonists alone or combined with glucose-dependent insulinotropic polypeptide (GIP) receptor agonists have been developed to target glycemic control in type 2 diabetes. These medications also slow gastric emptying and reduce energy intake. In randomized, placebo-controlled trials of these medications in diabetic and non-diabetic populations with obesity, participants on active medication lost up to 20% of their body weight, with corresponding improvements in blood pressure, lipid levels, physical functioning, and fat mass loss. Their adverse effects are predominantly gastrointestinal-related, mild, and transient. There are trials currently underway within individuals with obesity-related OSA, with a focus on reduction in weight, OSA severity, and cardio-metabolic outcomes. These medications have the potential to substantially disrupt the management of OSA. Pending coming data, we will need to consider pharmacological weight loss as a first-line therapy and how that influences training and management guidelines.

Key words: OSA; obesity; OSA - pharmacotherapy; endocrinology; OSA - endocrine morbidity/interactions; weight management; incretins; weight loss

Introduction

Obesity is the major risk factor for the development of obstructive sleep apnea (OSA) [1]. Progressive weight gain results in worsening of sleep apnea, and weight loss results in reduction in sleep apnea severity. However, most patients with sleep apnea are treated with mechanical devices aimed at maintaining upper airway patency. These therapies include continuous positive airway pressure (CPAP), mandibular advancement splints or surgical approaches. In contrast, in most cases, the clinical sleep medicine field has been relatively indifferent to the potential of weight loss as a therapy for patients. This situation has been based on a prevailing view that weight loss is difficult to sustain and only partially successful in reversing OSA, often complicated by weight regain. Although bariatric surgery is recognized as having efficacy in sustained weight loss, it is generally reserved for more severe forms of obesity. Therefore, to some extent, there is a nihilistic view that weight loss through dietary, behavioral, or pharmacological means is difficult to implement in the clinical setting and is unlikely to yield sustained improvements in patients with OSA. Consequently, integration of obesity management is rarely practiced in the sleep clinic setting. However, there are still substantial limitations with existing mechanical therapies including poor uptake and high rates of attrition with CPAP, as well as, lower efficacy and/or access to alternatives such as dental devices and surgically implanted upper airway stimulation devices. On the other hand, recent advances in pharmacotherapy of obesity using therapies such as incretin hormones are now posing a challenge to the view that effective treatment of OSA through weight loss

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is unachievable. This Perspectives paper evaluates obesity treatment for OSA and then explores the potential for a "positive" disruption that incretins will bring to the existing management of OSA in patients with obesity. Whilst this disruption presents challenges in both sleep medicine training and therapeutic implementation, it also offers an important new opportunity for greater choice of treatment approaches for both clinicians and patients.

The global impact of obesity

Obesity, defined by a body mass index (BMI) ≥ 30 kg/m^2, is a chronic disease that affects more than 670 million adults globally [2]. It is associated with numerous complications including OSA, type 2 diabetes, cardiovascular disease (CVD), several cancers, osteoarthritis, and social stigmatization that degrades mental health [3–5]. Over the past four decades, the prevalence of obesity has nearly tripled in several highly developed nations, including the United States, where it exceeds 38% [6]. Obesity prevalence, however, is now rising rapidly in low and middle-income countries, many of which also grapple with the impact of undernutrition [2]. Moreover, complications of excess adiposity may occur in the overweight range (BMI 25–30kg/m^2) in some regions, e.g. South Asia and China. Global increases in obesity in youth underscore the urgent need to improve both the prevention and treatment of this disease [2].

Weight loss for obesity treatment

Expert guidelines typically recommend treatments for obesity based on an individual's BMI and risk of health complications. Diet and physical activity modification are appropriate for persons with a BMI of 25 kg/m^2 or more. Individuals with sleep apnea are at risk of weight gain such that many recommend diet and exercise education for all patients. Those with high BMI who are unable to reduce weight satisfactorily (e.g. 5%–10% loss) are eligible for adjunctive pharmacotherapy at a BMI of 30 kg/m^2 (or 27 kg/m^2 with a weight-related comorbidity). If not successful, bariatric surgery is an option at a BMI of 40 kg/m^2 (or 35 kg/m^2 with a comorbidity) [7].

Lifestyle programs that provide ≥14 sessions of diet, physical activity, and behavioral counseling over 6 months induce losses of 5%–8% of baseline weight and reduce, by 50% or more, the risk (over 3–4 years) of developing type 2 diabetes in persons with impaired glucose tolerance [8]. These losses are also associated with improvements in CVD risk factors including blood pressure and triglycerides [9]. Such programs, however, do not reliably yield losses > 10% of weight, which are associated with greater improvements in risk factors [9] and are needed to achieve clinically meaningful improvements in OSA and other conditions [10]. Importantly, most lifestyle-treated participants regain one-third of lost weight in the year following treatment, with further regain over time, resulting, in part, from an unfavorable metabolic adaptation [11].

Pharmacotherapies have existed for over 60 years and have been shown to induce modest weight loss (i.e. 6%–10% of baseline weight); however, expense and lingering concerns about possible adverse effects of anti-obesity medications (AOMs) have limited their use [12]. More recently, interest in AOMs has been ignited by a new understanding of the role of incretin hormones in the regulation of both glucose metabolism and energy intake [12]. This knowledge has led to the development of glucagon-like peptide receptor agonists which are now proving to be game-changers in obesity management (see discussion below).

Bariatric surgery approaches for weight loss have included sleeve gastrectomy and Roux-en-Y gastric bypass, as well as laparoscopic adjustable gastric banding. These procedures are indicated for patients with severe obesity (BMI ≥ 35kg.m^2) and usually at least one comorbidity. Regardless of the procedure, they all restrict food intake, improve appetite control, and result in weight loss of 20% to 30% of body weight in 1 year [13]. Several studies have shown long-term (20 years) weight-loss maintenance [13].

Importance of obesity in OSA pathogenesis

OSA pathogenesis involves a complex interplay of anatomical predisposition, pharyngeal dilator muscle function, arousal threshold, end-expiratory lung volume, and instability of ventilatory control [1]. Various endotypes (or mechanisms) have been recognized in OSA which are thought to contribute to disease expression and may be important therapeutically e.g. in personalizing therapy. Obesity is known to influence various OSA endotypes, although the exact underlying mechanisms of obesity-induced OSA are complex and incompletely understood [14]. Regardless, obesity is the major risk factor for OSA, although it is clearly interactive with maxillo-facial structure and respiratory endotypes. Importantly, obesity increases the collapsibility of the pharyngeal airway based on parapharyngeal fat deposition, with compelling data showing improved mechanics with weight loss in those experienced [15]. The deposition of fat with increasing body weight is likely systemic, but fat in the tongue and around the pharyngeal airway may be mechanistically important in OSA [16]. A second component relates to abdominal fat deposition which leads to reduced end-expiratory lung volume. Abdominal fat is thought to predispose individuals to pharyngeal collapse due to reduced caudal traction forces and diminished longitudinal tension on the upper airway [17]. A third component is related to gender differences in fat deposition which accumulates in the abdominal area in men versus the pelvic area in women. This variation in fat distribution might make obesity-induced reductions in end-expiratory lung volume particularly problematic in men with OSA. Of note, individuals with obesity without OSA have robust upper airway dilator muscle function as compared to individuals with obesity and OSA, suggesting an important component of pharyngeal dilator muscle control in obesity-related OSA.

Weight loss for OSA treatment

Given the clear causative role of obesity for OSA, it follows that several randomized controlled trials and observational studies have explored the efficacy of weight loss to alleviate OSA and improve health outcomes. Interventions have included dietary and/or lifestyle therapies [10, 18, 19], pharmacotherapy [20–22], and bariatric surgery [23–25]. Several meta-analyses [26–31] of studies demonstrate a consistent reduction in OSA severity determined from the AHI. Furthermore, regardless of the weight loss method, there is a clear dose–response relationship between the reductions in AHI and weight, albeit with marked intra- and inter-study heterogeneity [24, 31].

Dietary approaches to weight loss in OSA usually incorporate limiting high energy, high glycemic index foods, resulting in an overall reduction in usual caloric intake by at least 500 kcal/day. To maximize weight loss, intensive lifestyle programs, which combine these dietary regimens with a minimal amount of moderate to vigorous exercise each week have been used [10]. More

recently, very low-energy diet (VLED) programs that prescribe short-term meal replacement (with nutritionally balanced over-the-counter products like soups, shakes or bars) with exercise, have been used with greater effect [18, 19, 32]. A reduction in energy intake with the VLED (to < 800kcal/day) for between 4 and 12 weeks results in a target weight loss of ~10% (typically within 2 months). Meal replacements are then gradually replaced with a healthy diet, with the aim of sustaining weight loss long-term. A meta-analysis of four randomized trials in OSA, comparing intensive lifestyle programs to more conservative management or usual diet showed an overall weighted mean difference of −13.76 kg (or approximately 13.4% weight loss) [30]. However, a later meta-analysis that included both RCTs and observational (before/after) studies incorporating multiple dietary approaches, found more modest weight loss with a weighted mean difference in BMI = 3.1kg/m^2 (or approximately 6%) [26]. Overall, the studies indicate that VLED-based programs are superior. However, their long-term effectiveness may be no better than less expensive programs that incorporate more moderate energy restrictions. For example, maintenance of weight loss out to 10 years has recently been demonstrated in the SLEEP AHEAD study, which incorporated a moderate (1200–1800 kcal/day) energy-restricted diet with exercise in people with OSA and type 2 diabetes mellitus [33].

A small number of randomized and observational studies have also tested weight loss pharmacotherapies in conjunction with a calorie-deficit diet and exercise intervention in OSA. Pharmacotherapies have included appetite suppressants such as the serotonin and noradrenaline re-uptake inhibitor sibutramine (now discontinued) [22] and phentermine (combined with an anti-convulsant topiramate) [21], the lipase inhibitor orlistat [34], the earliest version of a GLP-1 receptor agonist liraglutide [20], and the wakefulness promoter armodafinil [35]. Compared to diet and exercise alone, the mean difference in weight loss with pharmacotherapy in these studies ranged from ~2.9 to 6.5 kg (approx. range 2.8% to 6.1%) [20, 21, 35]. In contrast, an uncontrolled observational study with sibutramine combined with diet and exercise resulted in 8.3 kg weight loss (~7.7%) [22].

Lastly, bariatric surgery approaches to weight loss in OSA have included sleeve gastrectomy and Roux-en-Y gastric bypass [36], as well as, laparoscopic adjustable gastric banding [24]. A recent meta-analysis of observational bariatric surgery studies reported a mean weight loss of 35.4 kg (or approximately 28%) [31]. Of note, some of this weight loss may include that achieved from mandatory short-term very low-calorie diets presurgery.

Overall, the (within group) weight reduction achieved with these different approaches in OSA was greater for bariatric surgery (28%) [31] than dietary/lifestyle (13.4%) [30] or pharmacological (up to 7.7%) [20–22, 35] approaches. As a result, the impact of surgical weight loss tends to reduce the AHI by a greater amount than dietary or pharmacological interventions, as evidenced by a meta-analysis, which showed an AHI reduction (mean weighted difference) for surgical versus intensive lifestyle interventions of −29.57 versus −11.39 events/hour, respectively [26]. However, it appears that the magnitude of reduction in AHI is moderated by the severity of OSA at baseline, irrespective of the weight loss method. For example, a recent meta-analysis of surgical studies showed smaller reductions in OSA occurring in studies with lower presurgery AHIs and larger reductions with higher presurgery AHIs [31]. Similarly, in a trial that used a VLED to achieve −18.7 kg (−16.5%) weight loss and −27 events/hour AHI reduction, those with severe OSA at baseline achieved a similar severity of OSA post-weight loss as those with moderate OSA [18].

Health outcome improvements after weight loss in OSA

Despite the marked differences in weight loss and OSA reduction achieved both between and within modalities, there appears to be a consistent improvement in sleepiness and cardio-metabolic health outcomes that either match or are superior to improvements seen with gold-standard CPAP therapy for OSA. Two meta-analyses showed that excessive daytime sleepiness determined from the Epworth Sleepiness Scale improved with bariatric surgery by −4.8 to −5.5 points [31, 37]. Similarly, several meta-analyses of lifestyle interventions showed a mean reduction in Epworth Sleepiness Scale of −2.6 to −3.4 points [27, 29, 37]. While there is a dose–response relationship between the amount of weight loss and reduced sleepiness, a recent meta-regression analysis of trials showed that the rate of improvement in sleepiness decreases with increasing weight loss [38]. Despite this, these weight loss changes are still greater than the −2.0 to −2.4 points reported for CPAP [29]. In addition to sleepiness, other important health outcomes also improve more with weight loss than with CPAP, even when weight loss is only modest. For example, in a randomized trial that compared CPAP alone, (dietary) weight loss alone, and CPAP combined with weight loss, weight loss of around 10% resulted in better insulin sensitivity and fasting triglyceride levels [39]. This same study also showed that in participants compliant with treatment, blood pressure improvements with weight loss far exceeded those with CPAP alone [39]. Crucially, even with more modest (~6%) weight loss and incomplete elimination of OSA, improvements in inflammation, insulin sensitivity, and fasting glucose appear to exceed those with CPAP [37]. Overall, the evidence suggests that improvements in all important health outcomes are greater with weight loss than with CPAP treatment and support a greater prioritization for weight loss as the primary treatment for obesity-related OSA.

New incretin-based pharmacotherapies for obesity

Glucagon-like peptide 1 (GLP-1) is released from L-cells of the small intestine and colon in response to nutrient intake [40]. It binds to GLP-1 receptors expressed in tissues in the pancreatic beta cells, gastric mucosa, and heart, as well as, in appetite-regulating centers, mainly in the hindbrain but also the hypothalamus. GLP-1 stimulates insulin secretion and inhibits glucagon release (in a glucose-dependent manner), slows gastric emptying, and reduces energy intake [40]. The half-life of native GLP-1 is approximately 2–3 minutes because of degradation by dipeptidyl peptidase 4 (DPP-4) [41]. Synthetic GLP-1 receptor agonists (GLP-1RA) are designed to resist this degradation [40]. To date, two GLP-1RA agents have been extensively investigated for weight loss.

Liraglutide is a once-daily subcutaneous injectable GLP-1RA originally approved for the management of type 2 diabetes at 1.2 and 1.8 mg/d doses. It was observed to reduce body weight by about 2%–3% without lifestyle counseling [42]. This information led to trials of a 3.0 mg/d dose which, when combined with monthly lifestyle counseling, induced a mean 1-year loss of 8.0% (8.4 kg vs. 2.8 kg for placebo) in persons with overweight/obesity but not type 2 diabetes [43]. Liraglutide was approved for chronic weight management in the United States in 2014 and in Europe in 2015.

Semaglutide 2.4 mg, a second-generation GLP-1RA, was approved for weight management in the United States in 2021

and in Europe in 2022, following earlier approval at 1.0 mg for type 2 diabetes. It has 94% homology with human GLP-1 and a half-life of approximately 180 hours, allowing weekly subcutaneous injection [40]. The medication is introduced gradually over 16 weeks (beginning with 0.25 mg) to limit gastrointestinal (GI) side effects [44]. Most of these GI adverse events were mild-to-moderate in severity, transient, and resolved without permanent discontinuation of the regimen. Semaglutide induces weight loss by reducing energy intake, with a 35% decrease observed in a laboratory-meal study [45]. Patients report increased satiation, as well as reduced hunger and food cravings [46], consistent with GLP-1 receptor agonism in brain regions associated with homeostatic and hedonic eating [47]. The safety and efficacy of semaglutide 2.4 mg was demonstrated in a series of trials known as Semaglutide Treatment Effect in People (STEP) with Obesity [48]. The principal findings of the first five trials were as follows.

(1) In STEP 1 in participants with overweight/obesity, but not type 2 diabetes, semaglutide reduced body weight by nearly 15% at 68 weeks, compared with 2.4% for placebo (both combined with monthly lifestyle counseling). Approximately 50% of semaglutide-treated participants lost 15% or more of body weight, and nearly one-third lost 20% [44, 49–51]. In contrast, in STEP 2, participants with overweight/obesity and type 2 diabetes who received semaglutide 2.4 mg lost about one-third less weight than those without diabetes [52].
(2) In STEP 5, participants prescribed semaglutide for 104 weeks achieved a 15% reduction in weight at 1 year, and this improvement was maintained at 2 years, showing the durability of weight loss with continued pharmacotherapy [51].
(3) Participants in STEP 3, who lost 16% of body weight with semaglutide, achieved significantly greater improvements in systolic and diastolic blood pressure, C-reactive protein, HbA1c, and triglycerides than those who lost 5.7% with intensive lifestyle modification, confirming the health benefits of larger weight losses [49].
(4) Following end-of-trial termination of semaglutide in STEP 1, participants regained approximately two-thirds of lost weight in the ensuing year.[53] STEP 4 yielded similar results,[50] underscoring the need for long-term therapy with AOMs, similar to the indefinite use of medications for other chronic diseases (e.g. diabetes, hypertension).[51]

In appropriately selected patients, free of a personal or family history of medullary thyroid disease, semaglutide was generally well tolerated; 7% of participants (vs. 3% on placebo) discontinued treatment because of adverse events, which were generally limited to the GI effects described previously[19]. The medication was associated with an increased risk of gallbladder-related disorders (2.6% vs. 1.2%), likely linked to rapid weight loss. Both liraglutide 1.8 mg and semaglutide 1.0 mg significantly reduced major adverse cardiovascular events in patients who, at baseline, had type 2 diabetes and CVD (or a high risk of it).[31,32] The ongoing SELECT trial (ClinicalTrials.gov NCT03574597) is now evaluating whether semaglutide 2.4 mg reduces major adverse cardiovascular events and other cardiovascular outcomes in patients with overweight or obesity and established CVD [53].

Combined incretin therapies

Success with semaglutide has accelerated efforts to develop agents that target multiple nutrient-stimulated hormone pathways involved in the regulation of energy intake [41, 54]. **Tirzepatide,** approved in the US and Europe for type 2 diabetes, combines (in a single molecule) glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonism [55]. In the SURMOUNT-1 trial in participants with overweight/obesity, but not type 2 diabetes, tirzepatide induced mean weight losses (at 72 weeks) of 19.5% and 20.9% of baseline weight at doses of 10 and 15 mg, respectively (compared with 3.1% for placebo). More than 60% of participants on both doses lost ≥15% of baseline weight, and more than half lost ≥20% of weight. Results of additional weight-management trials await completion [55].

Table 1. Key Phase III Trial Results of Semaglutide and Tirzepatide

Trial	Semaglutide 2.4 mg SC weekly					Tirzepatide 15 mg SC weekly
	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	SURMOUNT-1
Population	Obesity or overweight with ≥ 1 WRC No T2D	T2D with obesity or overweight	Obesity or overweight with ≥ 1 WRC No T2D	Obesity or overweight with ≥ 1 WRC No T2D	Obesity or overweight with ≥ 1 WRC No T2D	Obesity or overweight with ≥ 1 WRC No T2D
Comparison	Drug vs Placebo	Drug vs Placebo	Drug vs Placebo	Drug vs Placebo withdrawal	Drug vs Placebo	Drug vs Placebo
Background treatment	D&E	D&E	IBT	D&E	D&E	D&E
Baseline BMI (kg/m^2)	37.9	35.9	38.1	38.4	37.8	38.1
Endpoint (weeks)	68	68	68	68	104	72
Placebo subtracted weight loss (%)	12.4	6.2	10.3	12.4	12.6	17.8

SC =Subcutaneous. Obesity = BMI ≥ 30kg/m^2. Overweight = BMI ≥ 27kg/m^2. T2D = Type 2 Diabetes Mellitus. WRC = Weight-related comorbidities: hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease. D&E= Diet and Exercise program. IBT= Intensive Behavioral Therapy involving initial low-calorie diet (1000–1200kcal/day) then hypocaloric diet (1200–1800kcal/day) with prescribed physical and behavioral therapy. In STEP 4, all participants received semaglutide for 20 weeks followed by randomization to drug continuation or withdrawal to placebo. The placebo-subtracted weight loss is the group difference at 68 weeks, as measured from week 0 (not week 20).

Table 1 summarizes key phase III trial results of semaglutide and tirzepatide.

Similarly robust weight losses are expected by combining semaglutide with an amylin receptor agonist (cagrilinitide) [56]. Additional dual and triple (GIP/GLP-1/Glucagon) agonists are being explored, with the expectation of mean losses up to 24% of baseline weight [57], approaching those achieved with sleeve gastrectomy [13]. These new agents, provided they are available to persons who need them most—who are often socioeconomically disadvantaged—could revolutionize the management of obesity and its many complications, including OSA.

Future research and implications for sleep medicine

Obesity, particularly when associated with central adiposity, is strongly linked with OSA. The reality is that while current OSA treatment may improve sleepiness or other neuro-behavioral aspects of the disorder, studies that show improvement in cardio-metabolic outcomes including blood pressure are minimal. In contrast, treatment of obesity in OSA, even with modest loss of weight, can produce significant cardio-metabolic benefits [37, 39].

There is a growing pipeline of research on incretins for the management of obesity, which includes studies of longer-term use to modify cardiovascular risk and other complications of excess adiposity. In OSA, tirzepatide is being globally trialed (SURMOUNT-OSA, ClinicalTrials.gov NCT05412004) for its ability to reduce OSA severity, with results expected in 2024. Given the weight loss observed in incretin studies in obese patients, one could argue that, in time, such therapies will become mainstays of OSA treatment. Even patients with more severe forms of sleep-disordered breathing, such as obesity-hypoventilation syndrome, would benefit from these medications which may be pursued alone or combined with other treatments. Other specific groups, such as patients with the combination of severe mental illness, sleep apnea, and obesity exacerbated by anti-psychotic therapy may be best managed by incretins. Clearly, careful risk/benefit/cost-effectiveness data will be required to provide definitive recommendations.

We believe that, as a field, sleep medicine will need to add incretins into the armamentarium of OSA therapies. Already, there has been a growth in the specialization of obesity medicine, and questions remain on how this field will integrate with sleep medicine. Do we need to revise training and curricula for sleep medicine so that clinicians can confidently treat obesity? Perhaps interdisciplinary teams will be developed to manage the twin problems of obesity and sleep apnea with pharmacotherapy? Most medical practitioners in sleep medicine have dual training in pulmonary medicine, neurology, or psychiatry. Most obesity specialists come from a metabolic medicine or endocrinology background and there is an insufficient number available to address the global impact of disease for the foreseeable future. The pathway to a new construct in integrated care is unclear but will need to be implemented.

There are still many questions to be answered about incretin therapy as a treatment for OSA. Despite the major weight loss reported in recent studies, current evidence suggests that withdrawal from incretin treatment results in weight regain and the eventual reversal of cardio-metabolic improvements [58]. However, we do not know whether treatment needs to be maintained chronically versus intermittently. What happens with OSA? Whereas most participants in weight loss studies are female, OSA is more common in men. Do we have adequate data on the effects of incretins on different genders? How will CPAP users adapt if they have significant weight loss and resolution of OSA symptoms? The need for dynamic disease monitoring on and off CPAP treatment will be important as will a better understanding of the impact of severity of OSA and obesity on treatment response. There are also potential barriers with incretin therapy related to access, effectiveness, and management that will need to be overcome. Until recently, there was a world-wide shortage of semaglutide with access being restricted to patients with type 2 diabetes; however, in most countries this has been addressed. In addition, the high cost of formulations in some countries (especially the United States) [59] will likely still prevent many patients from accessing therapy. Wider affordability through subsidies by healthcare systems will depend on a better understanding of which target populations will derive the most benefit from treatment [60]. Proof of effectiveness will in turn, rely on a strong evidence base from randomized controlled trials including comparative effectiveness trials of weight loss versus mechanical therapy in OSA. Finally, sleep physicians will need to broaden their skills to include obesity management with incretin therapy as a treatment option for their patients. This must necessarily include an understanding of potential therapeutic side effects and patient barriers such as aversion to injectable formulations. This latter issue, although negligible will rapidly be addressed with oral (pill-based) formulations that are currently available or being developed [61].

Some commentators view obesity as gluttony that is only responsive to dietary limitation despite the wealth of information on its genetic and multi-factorial pathophysiology. Others have criticized the potential need for permanent use of incretins to maintain weight reduction despite similar use of anti-hypertensives, lipid-lowering drugs, acid suppression medication, and newer anti-coagulant therapy. Interestingly, incretins potentially have independent OSA-reducing effects on respiratory control [62], and a role in dementia prevention is possible [63]. Whether or not the incretin "revolution" will positively disrupt and modify management of OSA will be revealed by future research but clearly, it is a topic that warrants close attention from sleep clinicians and researchers. Ultimately, the focus must shift away from mechanical therapy for obesity-related OSA towards weight loss, the latter which is likely to produce multiple health outcome improvements that are superior, including all-cause mortality.

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