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Effects of obesity therapies on sleep disorders

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Summary

Obesity is a significant risk factor for obstructive sleep apnea syndrome (OSAS), and has also been linked to reductions in sleep quality and quantity. Weight loss has been shown to be an effective treatment for improving OSAS; however, there is a high degree of variability in improvements of OSAS in response to weight loss. There are three modalities of obesity therapies: 1) lifestyle modification, which includes changes in dietary intake and physical activity, along with behavioral interventions; 2) pharmacologic agents; and 3) bariatric surgery. Individuals have a highly variable response to the various obesity interventions, and maintenance of weight loss can be especially challenging. These factors influence the effect of weight loss on sleep disorders. There is still a need for large, well-controlled studies examining short- and long-term efficacy of weight loss modalities and their impact on long-term treatment of OSAS and other sleep parameters, particularly in youth. Nonetheless, given our current knowledge, weight reduction should always be encouraged for people coping with obesity, OSAS, and/or sleep disruptions and resources identified to assist patients in choosing a weight loss approach that will benefit them the most.

Keywords: obesity interventions, weight loss, sleep, obstructive sleep apnea syndrome

1.1 Introduction

Over the past decade, the relationship between obesity and sleep has become more salient. Obesity has been identified as an important risk factor for the obstructive sleep apnea syndrome (OSAS) [1-6]; therefore, this syndrome will be the main focus of this review. OSAS is a common disorder with prevalence estimates of 15-25% in adult men and 5-10% in adult women [6-11], and between 2-15% in children [2, 12, 13]. It is associated with intermittent hypoxemia, hypercapnia, arousals and sleep fragmentation. Symptoms include snoring, snorting, pauses in breathing, mouth breathing and daytime sleepiness. Children may also exhibit hyperactivity or daytime behavioral problems [14-16]. In adults, there is an association with increased morbidity and mortality, stroke, hypertension, atrial fibrillation, injuries, and cognitive impairment and Alzheimer's disease [17-21]. Short- and long-term effects of untreated OSAS in pediatric patients include significant morbidity such growth failure [22], systemic [23-25] and pulmonary hypertension [26, 27], endothelial dysfunction [28, 29], and cognitive and behavioral deficits [16, 30-34]. Children who have both obesity and OSAS have increased cardiometabolic risk compared to children who are obese without OSAS. They also present with sleepiness, attention and executive dysfunction, mood concerns, and decreased quality of life [35-41]. There are little data regarding the long-term consequences of having both pediatric obesity and OSAS.

One common risk factor for OSAS in adults is excess adiposity [4-6, 10, 11, 42]. An estimated 1% increase in BMI is associated with a 3% increase in the apnea hypopnea index (AHI) [4]. In children 2-5 years of age, the most common cause of OSAS is adenotonsillar hypertrophy. However, as the prevalence of obesity in youth has dramatically increased, it is now recognized as a significant contributor to OSAS, particularly in adolescence [1-3]. Further,

there is a bidirectional relationship such that OSAS may promote further weight gain or may hinder weight loss efforts [42-48].

There are currently three interventions for weight loss: lifestyle modification altering diet and/or physical activity along with behavior change procedures, pharmacologic and surgical modalities. Often pharmacologic and surgical therapies are paired with lifestyle modification strategies. However, these are more limited in the pediatric population, reserved for the most severely obese and most often delayed until adolescence. We will discuss the three main modalities of weight loss as they relate to sleep with a primary focus on OSAS. Their impact on sleep duration, sleep architecture, and insomnia will also be discussed.

2.0 Lifestyle Modification Interventions (LMI) for Weight Loss

2.1 Obstructive Sleep Apnea Syndrome

LMI for weight loss focus on modifications to dietary intake, changes in sedentary and/or physical activities/exercise along with behavioral procedures (such as keeping food and activity logs, goal setting, stimulus control, and managing emotional eating and food cravings). LMI result in reduction in measures of adiposity of 4%-10% [49-52]; however, there is a high rate of relapse over time [51, 53-57]. Early, non-randomized studies suggested a relationship between weight loss and improvements in OSAS [58-63], but were conducted with small sample sizes andprimarily utilized very low-calorie diets (VLCD), with a high degree of variability between studies. More recently, several larger randomized controlled trials (RCTs) evaluating LMI on OSAS in adults have been conducted [64-67] (Table 1). Average weight losses from diet or diet plus LMI range from 3-18% with improvements in AHI ranging from 3-62% [68, 69].

The LookAHEAD Study is the most comprehensive RCT comparing diet plus an intensive lifestyle intervention (ILI) to diabetes education and support (DSE) in patients with

obesity, type 2 diabetes. A 10% reduction in initial weight was associated with a 20% improvement in AHI at 1 year [64]. An 11 kg weight reduction yielded a change in AHI by -5.4 ± 1.5 events/hr in the ILI group compared to a -0.6 ± 0.7 kg weight reduction and increase of +4.2 ± 1.4 events/hr in the DSE group at 1 year. Further, three times the number of participants in the ILI group had total remission of their OSAS at 1 year compared to those in a DSE [64]. At year 2, weight reductions from baseline were -7.4 ± 0.7 kg (ILI) *vs*. -0.8 ± 0.7 kg (DSE) with corresponding changes in AHI of -3.8 ± 1.5 events/hr ($p<0.001$) *vs*. 4.2 ± 1.4 events/hr ($p<0.001$; between groups, $p<0.001$), respectively. By year 4, changes in weight were diminished in ILI at -5.2 ± 0.7 kg *vs*. -0.8 ± 0.7 kg in DSE. However, AHI changes remained at -4.0 ± 1.6 events/hr ($p=0.015$) (ILI) *vs*. 3.7 ± 1.6 events/hr (DSE) ($p=0.02$; between groups $p=0.001$) [70]. Further, greater weight losses were associated with AHI reduction at year 4 [45, 70]. For both groups, every kilogram of weight loss had a 0.43 improvement in AHI. Greater changes in AHI occurred in individuals with higher baseline [70]. Remission of OSAS at year 4 was five times more common in ILI participants than DSE, and more than twice as many ILI participants compared to DSE participants improved their OSAS category.

Studies examining LMI and pediatric OSAS are limited. Two prospective studies examined behavioral weight loss on OSAS, both of which utilized a multidisciplinary inpatient intervention consisting of dietary restriction, physical activity, and psychosocial support [71, 72]. Of the children participating in the weight loss intervention, 61% (N=37/61) and 24% (N=9/38), respectively, were diagnosed with OSAS. Following intensive intervention, weight losses reduced AHI/respiratory disturbance index (RDI), but residual OSAS persisted in 33-38% of youth [71, 72]. There is an important need for more research examining the effects of LMI for weight loss in youth with OSAS and other sleep disorders.

These studies, as well as those presented in Table 1, indicate that weight losses from LMI have a positive effect on OSAS in the short- and long-term despite weight regain over time. However, in many cases, the effects are not curative. The amount of weight loss required to eliminate OSAS is not exact and there is variability in weight loss response to LMI, as well as in OSAS response to weight loss. Individual variability may be attributed to baseline weight and/or AHI, comorbidities, and other physiologic mechanisms.

2.2 Insomnia, Sleep Duration, and Sleep Quality

Three recent RCTs compared LMI for weight loss to a control condition regarding sleep quality and duration, and symptoms of insomnia [43, 73, 74]. In Sleep AHEAD (described above) [43], there were no differences in changes in sleep duration [total sleep time (TST)], continuity [wake after sleep onset (WASO)], and architecture of stage 1, 2, slow wave and rapid eye movement (REM) sleep between ILI and DSE groups, nor did they differ from baseline to year 1, 2, and 4. For all participants, changes in weight were not related to any sleep stages or TST at years 1, 2, and 4. A significant positive association was found for WASO with weight change. Overall reductions in AHI and not weight, over the 4 years was associated with increased REM and stage 2 sleep, and decreases in stage 1.

In a RCT examining weight loss intervention on sleep in obese [73], participants were prescribed the same diet (1200-1800 kcal/day depending on baseline weight) and physical activity goals (gradually increasing physical activity to 180 min/week) and randomized to differing amounts of behavioral support: 1) Usual Care (UC), 2) Brief Lifestyle Counseling (BLC), or 3) Enhanced Brief Lifestyle Counseling (EBLC). Weight losses at month 6 were 2.0 ± 0.5 kg, 3.5 ± 0.5 kg, 6.6±0.5 kg, respectively, with all groups statistically differing from each other. Although sleep duration increased in all groups at month 6, as assessed by the Pittsburgh

Sleep Quality Index (PSQI) [75], no statistically significant differences were observed (12.6 ± 8.4 mins, 6.6 ± 8.4 mins, and 6.6 ± 8.4 mins, respectively). At month 24, weight losses were 1.7 ± 0.7 in UC, 2.9 ± 0.7 in BLC, and 4.6 ± 0.7 ELBC from baseline. Sleep decreased from baseline to month 24 by 9.0 ± 9.0 mins in UC but increased 6.6 ± 9.0 mins and 13.8 ± 9.0 mins in BLC and EBLC ($p>0.05$). However, those who lost ≥ 5% *vs*. those who lost <5% of initial weight increased sleep by 21.6 ± 7.2 mins *vs*. 1.2 ± 6.0 mins ($p=0.0003$). Further, PSQI scores decreased (improved sleep) from baseline to months 6-24 in all groups, but there was no effect of treatment group. This study suggests that losing ≥ 5% of initial weight may be associated with improvements in sleep duration and quality.

Tan and colleagues conducted a 6 month RCT of an individualized diet that optimized nutrient composition with face-to-face and on-line counseling sessions (N=28) versus continued habitual lifestyle (N=21) among overweight and obese men (N=49) with chronic insomnia symptoms [74]. Sleep was assessed with a piezoelectric bed sensor, sleep diary, Epworth Sleepiness Scale (ESS), and the Basic Nordic Sleep questionnaire. At month 6, weight (-1.1 kg *vs*. +1.3 kg), waist (-0.7 cm *vs*. +1.7 cm), and fat mass (-0.7 kg *vs*. +0.9 kg) all significantly, albeit modestly, decreased compared to controls (ps<0.05). The intervention group also had shorter objective sleep onset latency (SOL) determined by the bed sensor after intervention compared to controls ($p<0.001$). No other objective or subjective measures differed between groups. Within the intervention group, TST ($p=0.004$), SOL ($p<0.001$) and sleep efficiency ($p=0.004$) improved, and participants reported less nocturnal awakenings ($p=0.035$) and nocturia ($p=0.001$). No significant relationships were found between weight change and objective sleep measures, although weight changes were modest.

2.3 Exercise and Sleep

Exercise is often key in LMI. While physical activity does not contribute to acute weight loss, it is a contributor to weight loss maintenance [57, 76] and improvements in sleep quantity and quality, OSAS and insomnia. A focus on physical activity and sleep is beyond the scope of this review and the reader is referred to several reviews on the topic [77-81].

3.0 Pharmacologic Agents for Weight Loss

The addition of weight loss medication to LMI can significantly improve weight loss. Sibutramine paired with LMI had shown similar results of weight loss on OSAS as described above [82, 83]; however, it has been withdrawn from the market due to cardiovascular adverse effects. Orlistat is a pancreatic lipase inhibitor that reduces intestinal absorption of fat and is approved by the U.S. Food and Drug Administration (FDA) for adults and adolescents for weight loss. The efficacy of orlistat on weight is modest, ranging from losses of 2.5-3.5 kg in adults [84, 85] and BMI changes of -0.5 to –4.2 kg/m^2 in adolescents [86, 87] .However, studies utilizing orlistat failed to assess sleep or sleep-disordered breathing. Similarly, the combination of naltrexone and bupropion extended release (NB) has been approved for weight loss, but no trials reporting sleep parameters have been conducted. In a pooled analysis of three phase 3, 56-week, randomized placebo-controlled studies utilizing NB, the percentage reduction of initial weight was 7.2-7.5% [88]. In trials examining use of NB for weight loss in obese and overweight patients, incidence of insomnia occurred in 9.2% on drug compared to 5.9% on placebo [89].

Lorcaserin is a selective serotonin (5HT2c) agonist developed for obesity treatment without the adverse effects on the heart observed with fenfluramine [84, 90]. Lorcaserin prescribed as 10 mg twice daily resulted in significantly greater weight losses in two RCTs (BLOOM: N=3182; BLOSSOM: N=4004) [91, 92] and is FDA-approved. Lorcaserin-treated participants obtained a 3.2% greater reduction in initial body weight than those on placebo at 1

year. None of the RCTs include assessment of sleep or sleep disorders nor are there studies describing the relation between lorcaserin and its effects on sleep or sleep disorders.

Different classes of medications for control of blood glucose levels [93-95] vary on their effects on weight, including some that contribute to weight gain (e.g., insulin secretagogues), some are weight neutral [e.g., dipeptidyl peptidase-4 (DDP-4) inhibitors and alpha-glucosidase inhibitors] and some facilitate weight loss [e.g., glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium-glucose co-transporter 2 (SGLT2) inhibitors] [94]. Their potential use in the treatment of obesity and the relation to sleep is limited. Metformin has been studied as it relates to sleep-disordered breathing; however, given its primary indication is not weight loss, it will not be reviewed here. Medications with indications for weight loss and in which sleep has been evaluated will be reviewed.

The combination of phentermine (Phen)/topiramate (TPM) extended release (ER) is FDA-approved as an adjunct to lifestyle modification for treatment of obesity/overweight . In a phase 2 RCT examining Phen/TPM ER plus LMI on moderate to severe OSAS, significant weight losses and reductions in AHI were seen at weeks 8 and 28 compared to placebo plus LMI [96]. Weight changes of -6.0 kg (0.63) in Phen/TPM ER were significantly greater than losses of -2.3 kg (0.63) in placebo at week 8 (p=0.0002), which corresponded to reductions of AHI of -26.4 events/hour (3.44) in Phen/TPM ER compared to -10.1 events/hour in placebo (p=0.0009). Improvements increased at week 28 with weight losses of -11.0 kg (1.2) in those treated with Phen/TPM ER versus -4.5 kg (1.21) in placebo (p=0.0006), as well as AHI reductions of -31.5 ±4.25events/hour versus -16.6 ± 4.15 events/hour (p=0.0008), respectively (Table 1).

Liraglutide is a glucagon-like peptide-1 (GLP-1) analog that has recently received FDA approval for weight management. There is also preliminary evidence from that suggest a link

between GLP-1 receptor signals and circadian systems and disordered sleep [95]. A 32-week RCT of 3.0 mg of liraglutide plus diet and physical activity counseling (N=180) versus placebo plus the same counseling (N=179) was conducted in non-diabetic patients with obesity and moderate to severe OSAS [97]. Mean change in body weight from baseline was -6.0 ± 0.5 kg in liraglutide versus -1.9 ± 0.4 kg in placebo ($p<0.0001$). Likewise, BMI and waist circumference were statistically different between groups, favoring liraglutide over placebo ($ps<0.0001$). Mean change in AHI was -12.2 ± 1.8 events/hour in liraglutide versus -6.1 ± 2.0 events/hour in placebo ($p=0.015$) (Table 1); however, treatment assignment, independent of weight loss, did not significantly affect the change from baseline to week 32 ($p=0.82$), indicating that the treatment effect was driven by weight loss. Similar to LMI alone, there was a statistically significant association between degree of weight loss and improvements of AHI: that losing ≥15% of initial weight had the greatest reductions in OSAS. Lowest oxyhemoglobin saturation (SpO_2) (%), percent of time with SpO_2 <90%, TST (mins), WASO (%), and ESS total score were not statistically different between groups [97].

Liraglutide has also been examined in a retrospective observational study of routine clinical practice as it relates to excessive daytime sleepiness (EDS) in obese participants with type 2 diabetes (N=158) [98]. There was a mean reduction of body weight, BMI, and waist circumference from baseline to 3 months post initiation of liraglutide of 4.4 kg, 1.7 kg/m^2, 3.2 cm, respectively. ESS score significantly decreased by -1.5 ± 3.0 ($p<0.0001$), and the change in ESS was associated with reduction in body weight ($r=0.269$, $p<0.05$); however this change may not be clinically relevant as the sample did not indicate sleepiness at baseline (baseline ESS was 5.9 ± 4.5).

It appears that approved pharmacologic agents for weight loss may benefit OSAS; however, very few studies have examined sleep parameters as an outcome. Further, there are no pediatric trials. Given the benefits of adding pharmacologic agents to LMI in inducing greater weight losses than LMI alone, and that greater weight losses have been shown to improve OSAS, there is a great need for large RCTs examining the effects of adding medications for weight loss on sleep parameters.

4.0 Weight loss surgery

The most frequent weight loss surgical methods include gastric bypass and the gastric sleeve. Both significantly improve induction and maintenance of weight loss and offer the greatest losses, with bypass yielding the largest losses and more is often indicated for specific cases (e.g., type 2 diabetes). The gastric sleeve has become a preferred surgery over the last few years [99]. Weight loss often results in improvement or cure of OSAS and improvement of EDS [100-102]. However, there is great variability in treatment response and the amount of weight loss required to eliminate OSAS is not clear. Laparoscopic gastric band surgery was approved by the FDA in 2001. However, this technique has fallen out of favor due to its rate of reoperation. A recent comprehensive study that analyzed the reoperation rate of 25042 Medicare beneficiaries, who underwent gastric band placement between 2006 and 2013, showed that 18.5% underwent reoperations. Importantly, the average rate of procedures per patient was 3.8 [103]. Biliopancreatic diversion is another effective surgical method utilized for the extremely obese. Nonetheless, it accounts for less than 2% of weight-loss surgeries worldwide possibly due to associated malnutrition [104]. The current article will mostly focus on gastric bypass and gastric sleeve.

Peromaa-Haavisto *et al* published a one-year follow up of 187 middle-aged adults who underwent Laparoscopic Roux-en-Y Gastric Bypass (LRYGB) [102]. The prevalence of OSAS decreased from 71% to 44%. However, moderate or severe OSAS still persisted in 20% of the patients after the surgery. Importantly, all patients lost weight (mean 32 kg) and weight loss did not correlate with OSAS improvement. Similar findings were reported by del Genio *et al*. who followed 36 patients with OSAS who underwent gastric sleeve surgery for 5 years [101]. The AHI improved in 80.6% (29/36) of patients after surgery from 32.8 ± 1.7 events/hour to 5.8 ± 1.2 events/hour (p= 0.001). Surprisingly, AHI improvements did not correlate with weight loss (BMI from 51.3 ± 11.6 kg/m^2 pre-operatively to 32.1 ± 6.6 kg/m^2,5 years after surgery, p <0.001) or with neck circumference (46.6 ± 3.7 cm pre-operatively to 42.1 ± 2.4 cm, 5 years after surgery, p <0.001) . They also reported reduction in ESS from 16.7 ± 2.4 to 7.1 ± 1.3 (p= 0.001). Another study followed 289 obese patients with OSAS who underwent Roux-en-Y Gastric Bypass (RYGB), 101 of whom underwent a post-operative polysomnogram 11 months (median) after bariatric surgery [100]. The BMI decreased from 56 ± 1 kg/m^2 to 38 ± 1 kg/m^2 (p<0.001) and the RDI from 51 ± 4 to 15 ±2 events/hour (p<0.001). ESS decreased from 10 ± 1 to 4 ±1, p <0.0001. This study showed a modest but significant correlation between the BMI and RDI (r= 0.27, p<0.001).

A study in China followed 44 obese adults with OSAS and type II diabetes treated with LRYGB [105]. They found that the change in AHI was correlated significantly with preoperative weight (r=0.298, p<0.05), preoperative waist circumference (r=0.307, p<0.05), and preoperative insulin resistance (IR) index (r=−0.301, p<0.05). Interestingly, the pre-operative BMI was 31.1 ± 3.4 kg/m^2, much smaller than western reports. ESS also decreased from 6.8 ± 4.7 to 3 ± 2.7 (p<0.001). Based on the aforementioned studies and other research presented in Table 2, we

conclude that weight loss surgery significantly improves OSAS; however, it is not possible to pre-operatively predict the level of improvement. This is possibly due to the interaction of anatomic factors and upper airway (UA) neuromotor function as both are instrumental to maintain airway patency during sleep [106, 107]. Weight loss surgery may reduce UA fat deposition but not necessarily change UA neuromotor function.

In addition to improvements in EDS, weight-loss surgery has been reported to improve subjective sleep quality, sleep duration and modifies sleep architecture. Toor *et al* studied 45 obese adults before and after weight loss surgery and compared them with 45 non-obese controls [108]. Participants completed the PSQI [75]. Obese participants reported poor sleep quality at baseline, including difficulty breathing, coughing or loud snoring, feeling too hot, and experiencing pain during the night. They also had decreased sleep duration, 6 hours *vs*. 7.2 hours in controls. Importantly, sleep quality as reported by the PSQI and BMI correlated independently with sleep duration. Participants were retested 3-12 months after surgery and obese participants showed significant improvement in both sleep quality and sleep duration. Specifically, the PSQI decreased from 8.8 preoperatively to 4.6 post-operatively ($p<0.001$) and sleep duration increased from 6 to 6.7 hours ($p<0.001$). These changes did not correlate with changes in BMI. A retrospective review of 19 obese adolescents before and after weight loss surgery, 14 of whom had OSAS, showed improvement in sleep efficiency (80.2% *vs*. 73.1%, p=0.01), reduced time in stage 1 sleep (7.2% *vs*. 3.7%, p=0.04), and reduced arousal index (7.6± 0.6/h *vs*. 11.3±1.2, p=0.01)[109]. This study did not include EDS measures. However, it is possible that the improvement in sleep architecture may have resulted in reduced daytime sleepiness.

Conclusions

Obesity is associated with OSAS and disruptions in sleep duration and quality. The reader is referred to two articles in this issue, "Epidemiology of sleep in relation to obesity, insulin resistance, and metabolic syndrome" and "Sleep influences on obesity, insulin resistance, and metabolic syndrome" for closer examination. Initial lifestyle, pharmacological and surgical therapy studies suggest that weight loss is associated with improvements in OSAS, sleep duration, and sleep quality, although with a high degree of variability in improvements observed. More research is needed to assess long-term effects of weight loss, as well as mechanisms of action, by different weight loss modalities on OSAS, insomnia, sleep duration, and sleep quality. Currently, long-term studies are promising with greater response for OSAS with those who maintain weight loss, especially in the pediatric population, who may experience significant long-term health benefits. Given our current knowledge, weight reduction should always be encouraged for people living with obesity, OSAS, and/or sleep disruptions and resources identified to assist patients in choosing a weight loss approach that will benefit them the most.

Table 1. Weight loss and obstructive sleep apnea in subjects undergoing behavioral lifestyle modification and/or medication and polysomnography

Authors (year)	Participant Characteristics	Weight Loss Intervention	Weight Outcomes	Sleep Outcomes
Tuomilehto et al, 2009 [65]	81 men and women AHI=5-15 events/hr (Mild) BMI=28-40 kg/m^2	RCT: Very low calorie diet (VLCD) (N=40) and visits with nutritionists at 2, 4, 6, 8, 10 wks. With general recommendation to increase physical activity and exercise Control group (N=41) single session of counseling with a physician and study nurse	Intervention *vs*. Control from baseline to 12 months Weight: -10.7% *vs*. -2.4% BMI: -3.5 *vs*. -0.8	Intervention *vs*. Control from baseline to 12 months AHI: -4 *vs*..0.3 When all participants combined, a weight reduction of 5 kg from initial body weight was associated with reduction of AHI of 2 units.
Tuomilehto et al., 2010 [110]	N=71 (see above)	2 year follow up of RCT above: N=35 in Intervention group N=36 in Control group	Intervention *vs*. Control 2 year follow up from baseline BMI: -2.4 ± 2.1 *vs*. -1.0 ±2.6 Weight: -7.3 ± 6.5 *vs*. -2.9 ± 7.5	Intervention *vs*. Control 2 year follow up from baseline AHI: -4.6 ± 4.9 *vs*. -0.5 ± 9.3 A weight reduction of 5 kg from initial was associated with reduction in AHI of 2.1 units. >15 kg weight loss associated with reduction of 6 units in AHI.

Johansson et al., 2009 [66]	63 obese men BMI=30-40 kg/m^2 AHI ≥ 15 treated with continuous positive airway pressure (CPAP)	RCT: Liquid VLCD for 7 weeks, followed by 2 weeks of gradual introduction of food until week 9 (N=60) Control Group: Usual diet for 9 weeks (N=33)	Intervention *vs*. Control from baseline to week 9 Weight: -18.7 ± 4.1 *vs*. +1.1 ± 1.9 BMI: -5.7 ± 1.1 *vs*. +0.3 ± 0.6 73% of intervention patients were non-obese BMI at week 9 *vs*. 0 in control	Intervention *vs*. Control from baseline to week 9 AHI: -25 ± 17 *vs*. -2 ± 5 In intervention group, a dose-response relationship existed between weight loss change in AHI (r=0.4, p=0.04).
Johansson et al., 2011 [111]	N=63	Observational: Control participants from above RCT crossed over to intervention and completed same intervention as above and all participants underwent weight loss maintenance phase (weeks 9-52): Maintenance Intervention: Three, one hour group therapy meetings every month led by a nurse and dietitian plus each patient was seen by a nurse for anthropometry measurements and a dietitian for individual dietary advice.	Intervention *vs*. Control from baseline to 1 year Weight: −12.1 ± 9.0 BMI: −3.7 ± 2.7 Percent Body Fat: −3.9 ± 3.7%	Intervention *vs*. Control from baseline to 1 year AHI: −17 ± 16 Epworth Sleepiness Scale: −2 ± 3
Foster et al., 2009 [64]	264 overweight and obese men and women	RCT: Diet + Intensive Lifestyle Intervention including prescription to increase physical activity to 175 min/week of	ILI *vs*. DSE baseline to 12 months: Weight:	ILI *vs*. DSE baseline to 12 months: AHI:

	Diagnosed with type 2 diabetes	moderate intensity exercise (ILI) (N=139) Diabetes Support Education (DSE) (N=125)	-10.8 ± 0.7 *vs*. -0.6 ± 0.7 BMI: -3.8 ± 0.3 *vs*. -0.2 ± 0.3	-5.4 ± 1.5 *vs*. +4.2 ± 1.4 Participants with 10 kg or more of weight loss had the greatest reductions in AHI.
Kuna et al., 2013 [70]		RCT from above: 2- and 4-year outcomes	ILI *vs*. DSE baseline to 2 years Weight: -7.4 ± 0.7 *vs*. -0.8 ± 0.7 ILI *vs*. DSE at 4 years Weight: -5.2 ± 0.7 *vs*. -0.8 ± 0.7	ILI *vs*. DSE baseline to 2 years AHI: -3.8 ± 1.5 *vs*. 4.2 ± 1.4 ILI *vs*. DSE at 4 years AHI: -4.0 ± 1.6 *vs*. 3.7 ± 1.6
Shechter et al., 2017 [45]		RCT from above	Years 1, 2, and 4 See above	ILI *vs*. DSE from baseline to year 1 REM-AHI: -10.6 ± 3.7 *vs*. 5.4 ± 3.7 NREM-AHI: -5.1 ± 2.6 *vs*. 3.0 ± 2.6

				Adjusted for weight change: REM-AHI: -8.0 ± 3.7 *vs*. 4.0 ± 3.6 NREM-AHI: -2.5 ± 2.6 *vs*. 0.8 ± 2.5 ILI *vs*. DSE from baseline to year 2 REM-AHI: -7.1 ± 1.3 *vs*. 1.3 ± 3.6 NREM-AHI: -3.7 ± 2.6 *vs*. 4.0 ± 2.6 Adjusted for weight change: REM-AHI: -5.8 ± 3.6 *vs*. 0.2 ± 3.6 NREM-AHI: -2.5 ± 2.6 *vs*. 2.1 ± 2.6 ILI *vs*. DSE from baseline to year 4 REM-AHI: --12.0 ± 3.8 *vs*. -3.9 ± 3.8

				NREM-AHI: -3.3 ± 2. *vs*. 3.0 ± 2.8 Adjusted for weight change: REM-AHI: -11.0 ± 3.7 *vs*. -5.6 ± 3.8 NREM-AHI: -3.2 ± 2.6 *vs*. 1.0 ± 2.7
Kajaste et al., 2004 [67]	31 obese men with a diagnosis of OSA	Initial 6 week VLCD After 6 weeks, individualized CBT + dietary counseling two to four times a month during the first 6 months, once a month during the next 6 months, and every second month during the second year. However, patients were allowed to regulate the process themselves.	From baseline, weight change at: 6 months: -19.1±10.2 12 months: -18.3±13.2 24 months: -12.6±14.7	From baseline, change in ODI_4 at: 6 months: 23 ± 18 12 months: 25 ± 23 24 months: 32 ± 26 Correlations between changes in weight and in ODI_4 were 0.59 ($P<0.01$) at 6 months, 0.68 at 12 months ($P<0.01$) and 0.75 ($P<0.01$) at 24 months
Barnes et al., 2009 [112]	12 obese men and women with mild to moderate OSA	VLCD using meal replacements followed by introduction to low calorie diet plus supervised resistance and aerobic exercise program over 16 weeks	From baseline to week 16: Weight: - 12.9% ± 7.7%	From baseline to week 16: AHI: -24.6 ± 12 to -18.3 ± 11.9 (25% reduction) A significant correlation between weight loss and

				change in AHI (R = 0.66, p = 0.04). Sleep efficiency improved significantly from 74.7 ±10.7%. to 84.1 ± 8.6%
Nerfeldt et al., 2010 [113]	24 men and 9 women BMI=33-50 kg/m^2 AHI=6-93 19 on CPAP and 4 used mandibular retaining devices	8 weeks LCD using meal replacement (800 kcal) with gradual advancement to eat balanced low calorie diet with group support. Group meetings once/month for 3 months, at 6 months, once/month until 2 year follow up.	From baseline to month 24: Weight: 122 ± 19 to 110 ± 15 BMI: 40 ± 5 to 35 ± 3	From baseline to month 24: AHI: 43 ± 24 to 28 ± 19 ODI_4: 42 ± 23 to 23 ± 15 Arousal Index: 24 ± 15 to 11 ± 11 ESS: 9 ± 4 to 5 ± 3
Kemppainen et al., 2008 [114]	52 men and women BMI=28- 40 kg/m^2 Mild OSA	RCT: Intervention (N=26): a VLCD with a supervised lifestyle program Control Group (N=26): Routine lifestyle counseling	Intervention *vs*. control from baseline to month 3 BMI: -5.4 *vs*. 0.49	Intervention *vs*. control from baseline to month 3 AHI: -3.2 ± 9.2 *vs*. -1.3 ± 5.5 Significant correlation between reduction of AHI and change in BMI (r=0.393, P=0.04)
Winslow et al., 2012 [96]	45 men and women with moderate to severe OSA	Phase 2, randomized, double-blind, placebo-controlled study of phentermine/topiramate extended release (Phen/TPM ER) + lifestyle	Phen/TPM ER *vs*. Placebo at week 8 Weight:	Phen/TPM ER *vs*. Placebo at week 8 AHI:

	BMI=30-40 kg/m^2	modification (N=22) *vs*. placebo + lifestyle modification (N=23)	-6.0 ± 0.63 *vs*. -2.3 ± 0.63 Phen/Top *vs*. Placebo at week 28 Weight: -11.0 ± 1.24 *vs*. -4.5 ± 1.21	-26.4 ± 3.44 *vs*. -10.1 ± 3.44 Phen/Top *vs*. Placebo at week 28 AHI: -31.5 ± 4.25 *vs*. -16.6 ±4.15 PSQI: a significant difference between treatment and placebo in the mean change in PSQI at Week 28 ESS: No significant differences were reported between treatment groups in the ESS evaluation at Week 8 or 28.
Blackman et al., 2016 [97]	359 men and women with moderate to severe OSA BMI ≥ 30 kg/m^2 AHI ≥ 15	RCT, double-blind placebo-controlled study of 3.0 mg of liraglutide + diet and physical activity lifestyle modification counseling every 4 weeks (N=180) *vs*. placebo + diet and physical activity lifestyle modification counseling every 4 weeks (N=179)	Liraglutide *vs*. Placebo at week 32 Weight: -6.0 ± 0.5 *vs*. -1.9 ± 0.4 (P<0.0001) BMI: -2.2 ± 0.2 *vs*. -0.6 ± 0.1	Liraglutide *vs*. Placebo at week 32 AHI: -12.2 ± 1.8* *vs*. -6.1 ± 2.0* (P=0.015) ODI_4: -9.5 ± 1.7* to -5.2 ± 1.9* (P=0.06) ESS: -2.5 ± 0.3* *vs*. -2.3 ± 0.3* (P=0.15)

				FOSQ: 1.3 ± 0.2* *vs*. 1.1 ± 0.1* (P=0.16)

Data presented as Mean Change ± SD (when available) or *SE.

Abbreviations: BMI: body mass index; AHI: apnea hypopnea index; ODI_4: Oxygen Desaturation Index of 4 Percent; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; Phen/TPM ER: phentermine/topiramate extended release combination medication; FOSQ: Functional Outcomes of Sleep Questionnaire

Units of AHI is events/hr, BMI is kg/m^2, and weight is kg unless otherwise indicated.

Table 2. Weight loss and obstructive sleep apnea in subjects undergoing weight-loss surgery and polygraphy or polysomnography.

Authors, year	Participants N	Type of surgery	Weight outcomes		Sleep outcomes	
			Pre-op BMI (kg/m^2)	Post-op BMI (kg/m^2)	Pre-op AHI (N/hour)	Post-op AHI (N/hour)
Peromaa-Haavisto, 2017 [102]	132	LRYGB	43.9±6.4	33.0±5.1	27.6±24.6	9.9±11.2
del Genio, 2016 [101]	36	Gastric sleeve	51.3±11.6	32.1±6.6	32.8±1.7	5.8±1.2
Zou J, 2015 [105]	44	LRYGB	31.1±3.4	24.4±2.6	22.4±17.8	7.1±9.4
Fredheim JM, 2013 [115]	44	RYGB	47.5±5.6	33.5^	29.3±24.1	7.7^
Rao A, 2009 [116]	350*	Laparoscopically adjustable gastric banding	45.2 [33-60]	30 [23-40]	38.1[16.6-137.7]	13.2[0.6-91.7]
Varela JE, 2007 [117]	56	LRYGB	49.9±9	Not reported. 73% mean excess weight loss	35±10 29 participants required CPAP	Not reported. No participant required CPAP
Haines KL, 2007 [100]	101	Roux-en-Y Gastric Bypass	56±1	38±1	51±4	15±2

Poitou C, 2006 [118]	35	LRYGB or laparoscopically adjustable gastric banding	51.3±1.4	39.9±1.3	24.5±2.7	9.7±1.3

Data presented as Mean ± SD or median [range] Laparoscopic Roux-en-Y Gastric Bypass (LRYGB), Roux-en-Y Gastric Bypass (RYGB)

*A sub-set of 75 participants underwent post-operative polysomnography and only data of this subset are presented.

^SD not provided

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REFERENCES

1. Alonso-Alvarez, M.L., et al., *Obstructive sleep apnea in obese community-dwelling children: the NANOS study.* Sleep, 2014. **37**(5): p. 943-9.
2. Marcus, C.L., et al., *Diagnosis and management of childhood obstructive sleep apnea syndrome.* Pediatrics, 2012. **130**(3): p. E714-E755.
3. Marcus, C.L., et al., *Evaluation of pulmonary function and polysomnography in obese children and adolescents.* Pediatr Pulmonol, 1996. **21**(3): p. 176-83.
4. Peppard, P.E., et al., *Longitudinal study of moderate weight change and sleep-disordered breathing.* JAMA, 2000. **284**(23): p. 3015-21.
5. Young, T., P.E. Peppard, and S. Taheri, *Excess weight and sleep-disordered breathing.* J Appl Physiol (1985), 2005. **99**(4): p. 1592-9.
6. Young, T., J. Skatrud, and P.E. Peppard, *Risk factors for obstructive sleep apnea in adults.* JAMA, 2004. **291**(16): p. 2013-6.
7. Bixler, E.O., et al., *Effects of age on sleep apnea in men: I. Prevalence and severity.* Am J Respir Crit Care Med, 1998. **157**(1): p. 144-8.
8. Bixler, E.O., et al., *Prevalence of sleep-disordered breathing in women: effects of gender.* Am J Respir Crit Care Med, 2001. **163**(3 Pt 1): p. 608-13.
9. Young, T., et al., *The occurrence of sleep-disordered breathing among middle-aged adults.* N Engl J Med, 1993. **328**(17): p. 1230-5.
10. Punjabi, N.M., *The epidemiology of adult obstructive sleep apnea.* Proc Am Thorac Soc, 2008. **5**(2): p. 136-43.
11. Peppard, P.E., et al., *Increased prevalence of sleep-disordered breathing in adults.* Am J Epidemiol, 2013. **177**(9): p. 1006-14.
12. Hakim, F., L. Kheirandish-Gozal, and D. Gozal, *Obesity and Altered Sleep: A Pathway to Metabolic Derangements in Children?* Semin Pediatr Neurol, 2015. **22**(2): p. 77-85.
13. Rosen, C.L., et al., *Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity.* J Pediatr, 2003. **142**(4): p. 383-9.
14. O'Brien, L.M., et al., *Sleep and neurobehavioral characteristics of 5- to 7-year-old children with parentally reported symptoms of attention-deficit/hyperactivity disorder.* Pediatrics, 2003. **111**(3): p. 554-63.
15. Carvalho Bos, S., et al., *Sleep and behavioral/emotional problems in children: a population-based study.* Sleep Med, 2009. **10**(1): p. 66-74.
16. Marcus, C.L., et al., *A randomized trial of adenotonsillectomy for childhood sleep apnea.* The New England journal of medicine, 2013. **368**(25): p. 2366-76.
17. Moran, M., et al., *Sleep disturbance in mild to moderate Alzheimer's disease.* Sleep Med, 2005. **6**(4): p. 347-52.
18. Tworoger, S.S., et al., *The association of self-reported sleep duration, difficulty sleeping, and snoring with cognitive function in older women.* Alzheimer Dis Assoc Disord, 2006. **20**(1): p. 41-8.
19. King, S. and N. Cuellar, *Obstructive Sleep Apnea as an Independent Stroke Risk Factor: A Review of the Evidence, Stroke Prevention Guidelines, and Implications for Neuroscience Nursing Practice.* J Neurosci Nurs, 2016. **48**(3): p. 133-42.
20. Ifergane, G., et al., *Obstructive Sleep Apnea in Acute Stroke: A Role for Systemic Inflammation.* Stroke, 2016. **47**(5): p. 1207-12.
21. Koo, B.B., et al., *Observational Study of Obstructive Sleep Apnea in Wake-Up Stroke: The SLEEP TIGHT Study.* Cerebrovasc Dis, 2016. **41**(5-6): p. 233-41.

22. Marcus, C.L., et al., *Determinants of growth in children with the obstructive sleep apnea syndrome.* Journal of Pediatrics, 1994. **125**(4): p. 556-62.
23. Marcus, C.L., M.G. Greene, and J.L. Carroll, *Blood pressure in children with obstructive sleep apnea.* American Journal of Respiratory & Critical Care Medicine, 1998. **157**(4 Pt 1): p. 1098-103.
24. Amin, R.S., et al., *Left ventricular hypertrophy and abnormal ventricular geometry in children and adolescents with obstructive sleep apnea.* Am.J.Respir.Crit Care Med., 2002. **165**(10): p. 1395-1399.
25. Amin, R.S., et al., *Twenty-four-hour ambulatory blood pressure in children with sleep-disordered breathing.* American Journal of Respiratory & Critical Care Medicine, 2004. **169**(8): p. 950-6.
26. Miman, M.C., T. Kirazli, and R. Ozyurek, *Doppler echocardiography in adenotonsillar hypertrophy.* International Journal of Pediatric Otorhinolaryngology, 2000. **54**(1): p. 21-6.
27. Tal, A., et al., *Ventricular dysfunction in children with obstructive sleep apnea: radionuclide assessment.* Pediatric Pulmonology, 1988. **4**(3): p. 139-43.
28. Gozal, D., et al., *Neurocognitive and endothelial dysfunction in children with obstructive sleep apnea.* Pediatrics, 2010. **126**(5): p. e1161-7.
29. Kheirandish-Gozal, L., et al., *Endothelial progenitor cells and vascular dysfunction in children with obstructive sleep apnea.* American Journal of Respiratory & Critical Care Medicine, 2010. **182**(1): p. 92-7.
30. Montgomery-Downs, H.E., V.M. Crabtree, and D. Gozal, *Cognition, sleep and respiration in at-risk children treated for obstructive sleep apnoea.* European Respiratory Journal, 2005. **25**(2): p. 336-42.
31. Chervin, R.D., et al., *Sleep-disordered breathing, behavior, and cognition in children before and after adenotonsillectomy.* Pediatrics, 2006. **117**(4): p. e769-78.
32. Marcus, C.L., et al., *Effects of Positive Airway Pressure Therapy on Neurobehavioral Outcomes in Children with Obstructive Sleep Apnea.* American Journal of Respiratory & Critical Care Medicine, 2012.
33. O'Brien, L.M., et al., *Neurobehavioral correlates of sleep-disordered breathing in children.* Journal of Sleep Research, 2004. **13**(2): p. 165-72.
34. Gozal, D., *Sleep-disordered breathing and school performance in children.* Pediatrics, 1998. **102**(3 Pt 1): p. 616-20.
35. Xanthopoulos, M.S., et al., *Neurobehavioral functioning in adolescents with and without obesity and obstructive sleep apnea.* Sleep, 2015. **38**(3): p. 401-10.
36. Perfect, M.M., et al., *Risk of behavioral and adaptive functioning difficulties in youth with previous and current sleep disordered breathing.* Sleep, 2013. **36**(4): p. 517-525.
37. Beebe, D.W., et al., *Neuropsychological effects of pediatric obstructive sleep apnea.* J Int Neuropsychol Soc, 2004. **10**(7): p. 962-75.
38. Beebe, D.W., *Neurobehavioral morbidity associated with disordered breathing during sleep in children: a comprehensive review.* Sleep, 2006. **29**(9): p. 1115-34.
39. Blunden, S.L. and D.W. Beebe, *The contribution of intermittent hypoxia, sleep debt and sleep disruption to daytime performance deficits in children: consideration of respiratory and non-respiratory sleep disorders.* Sleep Med Rev, 2006. **10**(2): p. 109-18.
40. Beebe, D.W., et al., *The association between sleep disordered breathing, academic grades, and cognitive and behavioral functioning among overweight subjects during middle to late childhood.* Sleep, 2010. **33**(11): p. 1447-1456.

41. McNally, K.A., et al., *Iowa Gambling Task performance in overweight children and adolescents at risk for obstructive sleep apnea.* J Int Neuropsych Soc, 2012. **18**(3): p. 481-489.
42. Newman, A.B., et al., *Progression and regression of sleep-disordered breathing with changes in weight: the Sleep Heart Health Study.* Arch Intern Med, 2005. **165**(20): p. 2408-13.
43. Shechter, A., et al., *Sleep architecture following a weight loss intervention in overweight and obese patients with obstructive sleep apnea and type 2 diabetes: relationship to apnea-hypopnea index.* J Clin Sleep Med, 2014. **10**(11): p. 1205-11.
44. Shechter, A., *Obstructive sleep apnea and energy balance regulation: A systematic review.* Sleep Med Rev, 2016.
45. Shechter, A., et al., *Effects of a lifestyle intervention on REM sleep-related OSA severity in obese individuals with type 2 diabetes.* Journal of Sleep Research, 2017.
46. Romero-Corral, A., et al., *Interactions between obesity and obstructive sleep apnea: implications for treatment.* Chest, 2010. **137**(3): p. 711-9.
47. de la Eva, R.C., et al., *Metabolic correlates with obstructive sleep apnea in obese subjects.* J Pediatr, 2002. **140**(6): p. 654-9.
48. Punjabi, N.M., et al., *Sleep-disordered breathing and insulin resistance in middle-aged and overweight men.* Am J Respir Crit Care Med, 2002. **165**(5): p. 677-82.
49. Wadden, T.A. and M.L. Butryn, *Behavioral treatment of obesity.* Endocrinol Metab Clin North Am, 2003. **32**(4): p. 981-1003, x.
50. Butryn, M.L., V. Webb, and T.A. Wadden, *Behavioral treatment of obesity.* Psychiatr Clin North Am, 2011. **34**(4): p. 841-59.
51. Wadden, T.A., et al., *Behavioral treatment of obesity in patients encountered in primary care settings: a systematic review.* JAMA, 2014. **312**(17): p. 1779-91.
52. Pi-Sunyer, X., et al., *Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial.* Diabetes Care, 2007. **30**(6): p. 1374-83.
53. Wadden, T.A., M.L. Butryn, and C. Wilson, *Lifestyle modification for the management of obesity.* Gastroenterology, 2007. **132**(6): p. 2226-38.
54. Butryn, M.L., et al., *Maintenance of weight loss in adolescents: current status and future directions.* J Obes, 2010. **2010**: p. 789280.
55. Look, A.R.G., *Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study.* Obesity (Silver Spring), 2014. **22**(1): p. 5-13.
56. Wadden, T.A., et al., *One-year weight losses in the Look AHEAD study: factors associated with success.* Obesity, 2009. **17**(4): p. 713-22.
57. Wadden, T.A., et al., *Four-year weight losses in the Look AHEAD study: factors associated with long-term success.* Obesity (Silver Spring), 2011. **19**(10): p. 1987-98.
58. Kajaste, S., et al., *Effects of a cognitive-behavioural weight loss programme on overweight obstructive sleep apnoea patients.* J Sleep Res, 1994. **3**(4): p. 245-249.
59. Kansanen, M., et al., *The effect of a very low-calorie diet-induced weight loss on the severity of obstructive sleep apnoea and autonomic nervous function in obese patients with obstructive sleep apnoea syndrome.* Clin Physiol, 1998. **18**(4): p. 377-85.
60. Noseda, A., et al., *Sleep apnea after 1 year domiciliary nasal-continuous positive airway pressure and attempted weight reduction. Potential for weaning from continuous positive airway pressure.* Chest, 1996. **109**(1): p. 138-43.
61. Suratt, P.M., et al., *Effect of very-low-calorie diets with weight loss on obstructive sleep apnea.* Am J Clin Nutr, 1992. **56**(1 Suppl): p. 182S-184S.

62. Schwartz, A.R., et al., *Effect of weight loss on upper airway collapsibility in obstructive sleep apnea.* Am Rev Respir Dis, 1991. **144**(3 Pt 1): p. 494-8.
63. Smith, P.L., et al., *Weight loss in mildly to moderately obese patients with obstructive sleep apnea.* Ann Intern Med, 1985. **103**(6 (Pt 1)): p. 850-5.
64. Foster, G.D., et al., *A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study.* Arch Intern Med, 2009. **169**(17): p. 1619-26.
65. Tuomilehto, H.P., et al., *Lifestyle intervention with weight reduction: first-line treatment in mild obstructive sleep apnea.* Am J Respir Crit Care Med, 2009. **179**(4): p. 320-7.
66. Johansson, K., et al., *Effect of a very low energy diet on moderate and severe obstructive sleep apnoea in obese men: a randomised controlled trial.* BMJ, 2009. **339**: p. b4609.
67. Kajaste, S., et al., *A cognitive-behavioral weight reduction program in the treatment of obstructive sleep apnea syndrome with or without initial nasal CPAP: a randomized study.* Sleep Med, 2004. **5**(2): p. 125-31.
68. Tuomilehto, H., J. Seppa, and M. Uusitupa, *Obesity and obstructive sleep apnea--clinical significance of weight loss.* Sleep Med Rev, 2013. **17**(5): p. 321-9.
69. Araghi, M.H., et al., *Effectiveness of lifestyle interventions on obstructive sleep apnea (OSA): systematic review and meta-analysis.* Sleep, 2013. **36**(10): p. 1553-62, 1562A-1562E.
70. Kuna, S.T., et al., *Long-term effect of weight loss on obstructive sleep apnea severity in obese patients with type 2 diabetes.* Sleep, 2013. **36**(5): p. 641-649A.
71. Verhulst, S.L., et al., *The effect of weight loss on sleep-disordered breathing in obese teenagers.* Obesity 2009. **17**(6): p. 1178-83.
72. Siegfried, W., et al., *Snoring and Sleep Apnea in Obese Adolescents: Effect of Long-term Weight Loss-Rehabilitation.* Sleep Breath, 1999. **3**(3): p. 83-88.
73. Alfaris, N., et al., *Effects of a 2-year behavioral weight loss intervention on sleep and mood in obese individuals treated in primary care practice.* Obesity (Silver Spring), 2015. **23**(3): p. 558-64.
74. Tan, X., et al., *Effect of Six-Month Diet Intervention on Sleep among Overweight and Obese Men with Chronic Insomnia Symptoms: A Randomized Controlled Trial.* Nutrients, 2016. **8**(11).
75. Buysse, D.J., et al., *The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research.* Psychiatry Res, 1989. **28**(2): p. 193-213.
76. Wing, R.R. and S. Phelan, *Long-term weight loss maintenance.* Am J Clin Nutr, 2005. **82**(1 Suppl): p. 222S-225S.
77. Andrade, F.M. and R.P. Pedrosa, *The role of physical exercise in obstructive sleep apnea.* J Bras Pneumol, 2016. **42**(6): p. 457-464.
78. Lang, C., et al., *The relationship between physical activity and sleep from mid adolescence to early adulthood. A systematic review of methodological approaches and meta-analysis.* Sleep Med Rev, 2016. **28**: p. 32-45.
79. Kredlow, M.A., et al., *The effects of physical activity on sleep: a meta-analytic review.* J Behav Med, 2015. **38**(3): p. 427-49.
80. Rubio-Arias, J.A., et al., *Effect of exercise on sleep quality and insomnia in middle-aged women: A systematic review and meta-analysis of randomized controlled trials.* Maturitas, 2017. **100**: p. 49-56.
81. Youngstedt, S.D. and C.E. Kline, *Epidemiology of exercise and sleep.* Sleep Biol Rhythms, 2006. **4**(3): p. 215-221.

82. Phillips, C.L., et al., *Changes in regional adiposity and cardio-metabolic function following a weight loss program with sibutramine in obese men with obstructive sleep apnea.* J Clin Sleep Med, 2009. **5**(5): p. 416-21.
83. Yee, B.J., et al., *The effect of sibutramine-assisted weight loss in men with obstructive sleep apnoea.* Int J Obes (Lond), 2007. **31**(1): p. 161-8.
84. Yanovski, S.Z. and J.A. Yanovski, *Long-term drug treatment for obesity: a systematic and clinical review.* JAMA, 2014. **311**(1): p. 74-86.
85. Svendsen, M. and S. Tonstad, *Orlistat after initial dietary/behavioural treatment: changes in body weight and dietary maintenance in subjects with sleep related breathing disorders.* Nutr J, 2011. **10**: p. 21.
86. Maahs, D., et al., *Randomized, double-blind, placebo-controlled trial of orlistat for weight loss in adolescents.* Endocr Pract, 2006. **12**(1): p. 18-28.
87. Ozkan, B., et al., *Addition of orlistat to conventional treatment in adolescents with severe obesity.* Eur J Pediatr, 2004. **163**(12): p. 738-41.
88. Hong, K., et al., *Naltrexone/Bupropion extended release-induced weight loss is independent of nausea in subjects without diabetes.* Clin Obes, 2016. **6**(5): p. 305-12.
89. CONTRAVE (naltrexone HCL and Bupropion HGl) Extended-Release, P.I. 2014 [cited 2017 June 20]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/200063s000lbl.pdf.
90. Martin, C.K., et al., *Lorcaserin, a 5-HT(2C) receptor agonist, reduces body weight by decreasing energy intake without influencing energy expenditure.* J Clin Endocrinol Metab, 2011. **96**(3): p. 837-45.
91. Fidler, M.C., et al., *A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial.* J Clin Endocrinol Metab, 2011. **96**(10): p. 3067-77.
92. Smith, S.R., et al., *Multicenter, placebo-controlled trial of lorcaserin for weight management.* N Engl J Med, 2010. **363**(3): p. 245-56.
93. Henry, R.R., et al., *Clinical Impact of ITCA 650, a Novel Drug-Device GLP-1 Receptor Agonist, in Uncontrolled Type 2 Diabetes and Very High Baseline HbA1c: The FREEDOM-1 HBL Study.* Diabetes Care, 2018.
94. Lau, D.C. and H. Teoh, *Current and Emerging Pharmacotherapies for Weight Management in Prediabetes and Diabetes.* Can J Diabetes, 2015. **39 Suppl 5**: p. S134-41.
95. Stonehouse, A.H., T. Darsow, and D.G. Maggs, *Incretin-based therapies.* J Diabetes, 2012. **4**(1): p. 55-67.
96. Winslow, D.H., et al., *A randomized, double-blind, placebo-controlled study of an oral, extended-release formulation of phentermine/topiramate for the treatment of obstructive sleep apnea in obese adults.* Sleep, 2012. **35**(11): p. 1529-39.
97. Blackman, A., et al., *Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial.* Int J Obes (Lond), 2016. **40**(8): p. 1310-9.
98. Gomez-Peralta, F., et al., *An association between liraglutide treatment and reduction in excessive daytime sleepiness in obese subjects with type 2 diabetes.* BMC Endocr Disord, 2015. **15**: p. 78.
99. Reames, B.N., et al., *Changes in bariatric surgery procedure use in Michigan, 2006-2013.* JAMA, 2014. **312**(9): p. 959-61.
100. Haines, K.L., et al., *Objective evidence that bariatric surgery improves obesity-related obstructive sleep apnea.* Surgery, 2007. **141**(3): p. 354-8.

101. Del Genio, G., et al., *Sleeve gastrectomy improves obstructive sleep apnea syndrome (OSAS): 5 year longitudinal study.* Surg Obes Relat Dis, 2016. **12**(1): p. 70-4.
102. Peromaa-Haavisto, P., et al., *Obstructive sleep apnea: the effect of bariatric surgery after 12 months. A prospective multicenter trial.* Sleep Med, 2017.
103. Ibrahim, A.M., J.R. Thumma, and J.B. Dimick, *Reoperation and Medicare Expenditures After Laparoscopic Gastric Band Surgery.* JAMA Surg, 2017. **152**(9): p. 835-842.
104. Buchwald, H. and D.M. Oien, *Metabolic/bariatric surgery worldwide 2011.* Obes Surg, 2013. **23**(4): p. 427-36.
105. Zou, J., et al., *Effect of Laparoscopic Roux-en-Y Gastric Bypass Surgery on Obstructive Sleep Apnea in a Chinese Population with Obesity and T2DM.* Obes Surg, 2015. **25**(8): p. 1446-53.
106. Malhotra, A., et al., *Upper-airway collapsibility: measurements and sleep effects.* Chest, 2001. **120**(1): p. 156-161.
107. Marcus, C.L., et al., *Developmental changes in upper airway dynamics.* Journal of Applied Physiology, 2004. **97**(1): p. 98-108.
108. Toor, P., K. Kim, and C.K. Buffington, *Sleep quality and duration before and after bariatric surgery.* Obes Surg, 2012. **22**(6): p. 890-5.
109. Kalra, M., et al., *Effect of surgical weight loss on sleep architecture in adolescents with severe obesity.* Obes Surg, 2008. **18**(6): p. 675-9.
110. Tuomilehto, H., et al., *Sustained improvement in mild obstructive sleep apnea after a diet- and physical activity-based lifestyle intervention: postinterventional follow-up.* Am J Clin Nutr, 2010. **92**(4): p. 688-96.
111. Johansson, K., et al., *Longer term effects of very low energy diet on obstructive sleep apnoea in cohort derived from randomised controlled trial: prospective observational follow-up study.* BMJ, 2011. **342**: p. d3017.
112. Barnes, M., et al., *A diet and exercise program to improve clinical outcomes in patients with obstructive sleep apnea--a feasibility study.* J Clin Sleep Med, 2009. **5**(5): p. 409-15.
113. Nerfeldt, P., et al., *A two-year weight reduction program in obese sleep apnea patients.* J Clin Sleep Med, 2010. **6**(5): p. 479-86.
114. Kemppainen, T., et al., *Effect of weight reduction on rhinometric measurements in overweight patients with obstructive sleep apnea.* Am J Rhinol, 2008. **22**(4): p. 410-5.
115. Fredheim, J.M., et al., *Obstructive sleep apnea after weight loss: a clinical trial comparing gastric bypass and intensive lifestyle intervention.* J Clin Sleep Med, 2013. **9**(5): p. 427-32.
116. Rao, A., et al., *Obstructive sleep apnoea (OSA) patterns in bariatric surgical practice and response of OSA to weight loss after laparoscopic adjustable gastric banding (LAGB).* Ann Acad Med Singapore, 2009. **38**(7): p. 587-7.
117. Varela, J.E., M.W. Hinojosa, and N.T. Nguyen, *Resolution of obstructive sleep apnea after laparoscopic gastric bypass.* Obes Surg, 2007. **17**(10): p. 1279-82.
118. Poitou, C., et al., *Serum amyloid A and obstructive sleep apnea syndrome before and after surgically-induced weight loss in morbidly obese subjects.* Obes Surg, 2006. **16**(11): p. 1475-81.

Highlights

- Three modalities of obesity therapies exist: 1) lifestyle modification of eating and activity habits, along with behavioral interventions; 2) weight loss medications; and 3) bariatric surgery.
- Initial lifestyle, pharmacological and surgical studies suggest weight loss is associated with improvements in obstructive sleep apnea syndrome (OSAS), sleep duration, and sleep quality, although there is a high degree of variability.
- Large, well-controlled studies examining the efficacy of weight loss modalities and their impact on long-term treatment of OSAS and other sleep parameters, particularly in youth, are needed.