REVIEW

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Current Updates on Pharmacotherapy for Obstructive Sleep Apnea

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Obstructive sleep apnea (OSA) is a common sleep disorder associated with substantial cardiovascular morbidity and mortality. Although positive airway pressure (PAP) remains the gold-standard treatment, poor long-term adherence often limits its clinical effectiveness, underscoring the need for safe and effective pharmacological alternatives. Advances in the understanding of OSA endotypes, including anatomical collapsibility, upper airway muscle responsiveness, arousal threshold, and loop gain, have shifted research toward precision pharmacotherapy. Early studies of single-agent therapies, such as protriptyline and acetazolamide, were limited by modest efficacy or clinically significant adverse effects. More recent dual-drug combinations and anti-obesity medications have shown greater promise. In particular, atomoxetine plus oxybutynin has demonstrated significant reductions in the apnea–hypopnea index (AHI) by enhancing upper airway muscle tone across sleep stages. In parallel, glucagon-like peptide-1 receptor agonists have substantially changed the management of obesity-related OSA. Tirzepatide, in particular, has produced marked weight loss of nearly 20% and an AHI reduction of more than 50%, leading to its recent U.S. Food and Drug Administration approval for OSA. Despite earlier skepticism, the shift from broad-spectrum agents toward endotype-specific and metabolic-targeted therapies may improve the management of selected patients with OSA. However, long-term safety and cost-effectiveness require further evaluation before these emerging pharmacological options can be broadly integrated into care for patients who cannot tolerate conventional PAP therapy.

Keywords: Drug therapy; Obesity; Phenotype; Sleep apnea, obstructive.

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repetitive narrowing or complete collapse of the upper airway during sleep, resulting in reduced blood oxygen saturation and frequent arousals that impair sleep quality. More than 900 million people worldwide are estimated to have at least mild OSA [1]. OSA causes chronic fatigue, daytime sleepiness, impaired concentration, and cognitive dysfunction related to poor sleep quality and has also been associated with increased mortality through cardiovascular complications, including hypertension, arrhythmia, ischemic heart disease, and stroke [2]. Positive airway pressure (PAP) therapy is the standard treatment for OSA and safely and effectively relieves airway obstruction by delivering positive pressure through a nasal or oronasal mask. In the Republic of Korea, PAP prescriptions have increased steadily, particularly since national health insurance coverage began in 2018 [3]. However, long-term adherence remains challenging because of discomfort during sleep and the burden of maintaining the equipment [4]. Oral appliances and surgical interventions can be used as alternatives, but both have limitations in efficacy and safety compared with PAP. These limitations have created a continuing need for safe and effective pharmacological treatments for OSA.

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OSA ENDOTYPE-BASED PHARMACOTHERAPY

In 2013, investigators at Harvard University identified four OSA endotypes that have since provided a framework for understanding the major physiological mechanisms underlying the disorder [5]. These endotypes are 1) airway collapsibility, defined as the anatomical predisposition to upper airway closure and represented by the critical closing pressure; 2) upper airway muscle responsiveness; 3) arousal threshold; and 4)

loop gain, which reflects the stability of central respiratory control. For example, OSA can occur even when anatomical upper airway collapse is not severe if the arousal threshold is low, because even slight negative pressure during inspiration can trigger arousal. In the Harvard group's study, anatomical collapsibility was identified as a major factor in approximately 46% of patients with OSA, whereas low upper airway muscle responsiveness and high loop gain were key factors in 36% of patients each, including overlapping endotypes [5]. Similarly, marked instability in central respiratory control, reflected by high loop gain, can cause OSA even without substantial anatomical airway obstruction: a slight decrease in airflow can trigger hyperventilation, which then suppresses the respiratory center and leads to apnea. These findings indicate that the relative contribution of each endotype varies among patients, suggesting that the most effective pharmacological treatment may also differ by endotype. PAP therapy is effective across endotypes because it maintains airway patency through a positive-pressure splinting effect. By contrast, pharmacological treatment requires accurate identification of the patient's dominant endotype so that the appropriate medication can be selected. Current clinical polysomnography (PSG), however, cannot directly diagnose these endotypes; endotype assessment requires laboratory-based PSG with positive pressure delivered through a mask. Nevertheless, studies are evaluating whether routine PSG data can be used as surrogate markers for endotype classification [6-10]. If these approaches are validated, endotype identification from routine PSG may become clinically feasible.

CONSIDERATIONS IN EVALUATING THE EFFICACY OF PHARMACOTHERAPY FOR OSA

When the efficacy of novel OSA treatments, including pharmacological therapy, is compared with that of PAP, the current standard of care, one important distinction must be considered. Clinical trials commonly assess efficacy by measuring improvements in OSA severity indices, such as the apnea–hypopnea index (AHI) and blood oxygen saturation. In practice, however, patients may remove a PAP mask during sleep or be unable to use the device during business trips or travel, leaving a meaningful portion of sleep time untreated. By contrast, a pharmacological agent taken once daily before sleep may provide treatment throughout the entire sleep period if it has sustained efficacy and acceptable tolerability. Mean disease alleviation is a metric that incorporates adherence and efficacy to estimate real-world effectiveness [11]. Therefore, comparisons among treatments should be based on effectiveness rather than efficacy alone. Given the low adherence rates associated with PAP, a treatment that reduces the AHI to below 10 events/h, or even to a higher residual AHI, could achieve effectiveness similar to that of PAP with a residual AHI below 5 events/h if adherence is substantially better. For example, consider a patient with OSA, an AHI of 30 events/h, and an average sleep duration of 8 hours. If the patient uses PAP therapy 5 days per week for 4 hours each night and has a residual AHI of 3 events/h during use, PAP achieves a 90% reduction in AHI-based disease burden during treated sleep. However, because the device is used on only 5 of 7 days and for only 4 of 8 hours of sleep, the overall effectiveness becomes:

$$90\% \times \frac{5}{7} \times \frac{1}{2} = 32.1\%$$

By comparison, if the same patient takes a medication that reduces the AHI to 15 events/h, the efficacy is only 50%. If the medication is taken daily and remains effective throughout the sleep period, however, overall effectiveness would be 50%, which is higher than that achieved with PAP in the example above. In addition, most OSA treatments are currently evaluated using the AHI, but the AHI does not account for the depth or duration of individual respiratory events, correlates weakly with subjective symptoms such as fatigue or daytime sleepiness [12], and is not strongly associated with health-related outcomes such as cardiovascular complications [13]. For this reason, alternative indices, including hypoxic burden (HB), have recently been studied. Recent pharmacological studies have increasingly reported HB and other indices alongside the AHI [14]. Thus, even when AHI reduction is smaller than expected, drug efficacy should also be assessed using indices such as HB, which may correlate more closely with cardiovascular outcomes.

EARLY STAGES OF PHARMACOLOGICAL RESEARCH

Early reports suggested that protriptyline, a tricyclic antidepressant, reduced apnea in some patients. Animal studies in cats further showed that protriptyline stimulates the hypoglossal and recurrent laryngeal nerves [14]. A placebo-controlled study was later conducted to evaluate whether protriptyline reduced OSA severity. The drug did not significantly reduce apnea duration or frequency, although 2 weeks of administration significantly suppressed rapid eye movement (REM) sleep and reduced both REM apnea time and total apnea time [15]. Its clinical use was also limited by anticholinergic adverse effects, including urinary retention, xerostomia, and palpitations. Acetazolamide, which stimulates the respiratory center by inducing metabolic acidosis, was also evaluated for apnea treatment. This drug reduced the frequency of

apnea and associated arousal responses, particularly in patients with central sleep apnea [16]. In a prospective, randomized, double-blind clinical trial of patients with OSA, acetazolamide significantly improved indices such as the AHI compared with placebo. However, despite improvements in objective metrics, OSA-related symptoms did not improve [17]. These drugs may benefit patients with high loop gain by lowering loop gain through respiratory center stimulation, but their clinical use remains limited because they have not improved subjective symptoms and raise long-term safety concerns, particularly regarding metabolic acidosis.

AGENTS ACTING ON THE AROUSAL THRESHOLD

Upper airway obstruction during sleep leads to a progressive increase in epiglottic pressure, reflecting the magnitude of negative pressure within the pharyngeal cavity during inspiration. The arousal threshold is the level of epiglottic pressure at which excessive negative pressure triggers arousal. An excessively high arousal threshold can be dangerous because it may allow severe oxygen desaturation and hypercapnia, but an abnormally low arousal threshold can also worsen OSA by inducing frequent arousals. Under normal conditions, increased CO_2 levels and negative pharyngeal pressure help stabilize breathing by stimulating the respiratory muscles and dilating the upper airway. In patients with a low arousal threshold, however, arousal occurs before the upper airway dilator muscles are sufficiently stimulated, compromising airway stability and contributing to OSA [18]. Pharmacological agents known to increase the arousal threshold include ethanol, pentobarbital, trazodone, and benzodiazepines such as flurazepam and triazolam. Although these agents may alleviate OSA by raising the arousal threshold, they may also promote airway collapse by reducing upper airway dilator muscle responsiveness. Eszopiclone, a non-benzodiazepine agent, has therefore become an important focus of OSA drug research because it does not appear to adversely affect the upper airway dilator muscles. In a double-blind crossover clinical trial, eszopiclone increased the arousal threshold during stage 2 non–rapid eye movement (NREM) sleep by 18% (±4%) and reduced the AHI by 23% (±9%). Although no significant AHI reduction was observed in patients with high arousal thresholds, the AHI decreased by 43% (±9%) in the subgroup of patients with low arousal thresholds, defined as 0 to -15 cmH_2O (34.8%, n=8) [18]. In addition, a study in patients with mild-to-moderate anatomical airway collapsibility found that oxygen, which lowers loop gain, combined with eszopiclone significantly reduced the mean AHI from 49.3/h at baseline to 26.5/h [19].

Calculating the arousal threshold requires more than standard PSG. It requires a specialized setup in which airflow and pressure changes are quantitatively measured while the patient wears a mask connected to a PAP device, along with esophageal pressure measurement using a catheter. As noted above, however, if low arousal thresholds can eventually be identified using routine PSG data as surrogate markers [6], agents such as eszopiclone may become useful therapeutic options for selected patients.

AGENTS ACTING ON UPPER AIRWAY MUSCLE ACTIVATION

In the brain, neurotransmitter systems that promote arousal and sleep generally inhibit one another. In healthy sleep–wake regulation, arousal and sleep function like an "on–off" switch and are not active simultaneously (Fig. 1). When this balance is disrupted and arousal-promoting neurotransmitters, such as acetylcholine, histamine, dopamine, serotonin, and norepinephrine, increase, insomnia may occur. Conversely, increased sleep-promoting neurotransmitter activity during wakefulness can manifest as narcolepsy or idiopathic hypersomnia. Upper airway muscle activation is fundamentally more closely linked to arousal than to sleep [20]. For this reason, early research on pharmacological OSA treatment that

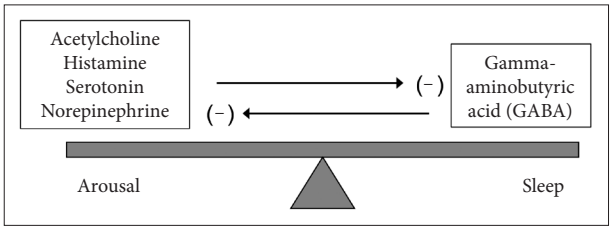

Fig. 1. Schematic diagram of sleep–wake regulation and the mechanisms of investigational pharmacotherapies for obstructive sleep apnea. The normal sleep–wake system functions as an "on–off" switch through reciprocal inhibitory circuitry. When arousal-promoting centers release neurotransmitters such as acetylcholine, histamine, serotonin, and norepinephrine, they inhibit sleep-promoting neurons in the VLPO and MnPN. Conversely, activation of the VLPO and MnPN leads to gamma-aminobutyric acid secretion, which suppresses the arousal system. Pharmacological approaches to OSA target this circuit to enhance upper airway muscle tone, which is primarily linked to arousal. Selective serotonin reuptake inhibitors, such as paroxetine, and noradrenergic and specific serotonergic antidepressants, such as mirtazapine, aim to increase synaptic serotonin and norepinephrine to stimulate airway dilator muscles. Cholinesterase inhibitors, such as donepezil, increase acetylcholine levels to promote muscle activity but may disrupt sleep architecture, for example by inducing nightmares. More recently, dual-drug combinations such as atomoxetine and oxybutynin have been developed to increase muscle tone through complementary mechanisms. Atomoxetine, a selective norepinephrine reuptake inhibitor, stimulates the hypoglossal nerve via norepinephrine during non–rapid eye movement sleep, whereas oxybutynin counteracts norepinephrine-induced sleep disruption and prevents genioglossus inhibition during rapid eye movement sleep by blocking muscarinic receptors. MnPN, median preoptic nucleus; OSA, obstructive sleep apnea; VLPO, ventrolateral preoptic nucleus.

aimed to activate the upper airway muscles focused on arousal-related neurotransmitters, initially excluding norepinephrine because of concern that it could substantially disrupt sleep. Selective serotonin reuptake inhibitors (SSRIs) were early targets for OSA therapy because they were already used to treat depression and were generally well tolerated. In a prospective, randomized, double-blind clinical trial, paroxetine reduced the AHI during NREM sleep by 35% but did not lower the AHI during REM sleep [21]. Among antidepressants, mirtazapine, a noradrenergic and specific serotonergic antidepressant, increases both norepinephrine and serotonin release. In a trial comparing low-dose mirtazapine (4.5 mg once daily) with high-dose mirtazapine (15 mg once daily), both doses reduced the AHI during NREM and REM sleep, with the high-dose group showing a 54% reduction compared with placebo. However, this reduction was mainly attributable to fewer hypopnea events resulting from the arousal-suppressing effect of mirtazapine. The drug did not improve blood oxygen saturation or subjective symptoms such as daytime sleepiness; therefore, mirtazapine was not recommended as an OSA treatment [22]. Another trial of fluoxetine combined with ondansetron reported a 40.5% reduction in the AHI with the high-dose combination, consisting of 10 mg and 24 mg, respectively [23]. Although these SSRI-related studies demonstrated some AHI reduction, the magnitude of efficacy was generally considered insufficient to support clinical recommendations.

Donepezil, a cholinesterase inhibitor used to treat Alzheimer's disease, has also been studied in patients with mild-to-moderate Alzheimer's disease. Although donepezil significantly increased the proportion of REM sleep, it markedly lowered the REM AHI and significantly improved OSA severity indices, including the overall AHI, minimum oxygen saturation, and T90, defined as the percentage of sleep time with SpO_2 below 90% [24]. Subsequent studies in patients with OSA who did not have dementia reported similar therapeutic effects. However, the reduction was modest, from a mean baseline AHI of 42.2/h to 32.8/h after treatment, and adverse effects such as insomnia and nightmares limited its use as an OSA treatment [25].

Studies that attempted to increase upper airway muscle tone by promoting arousal-related neurotransmitters, including serotonin and acetylcholine, have generally produced disappointing results. More recently, dual-drug combinations have been investigated to overcome these limitations. A phase 1 clinical trial of atomoxetine plus oxybutynin reported a significant reduction in mean AHI from 28.5/h to 7.5/h and an improvement in mean minimum oxygen saturation from 84% to 94% [26]. Atomoxetine, a selective norepinephrine reuptake inhibitor used to treat attention-deficit/hyperactivity disorder, dilates the upper airway by stimulating the hypoglossal nerve during NREM sleep. However, as noted above, increased norepinephrine can disrupt sleep by lowering the arousal threshold. Oxybutynin, an anticholinergic used to treat overactive bladder, counteracts the arousal-promoting effects of atomoxetine through its sedative effects and may also increase upper airway muscle tone during REM sleep by blocking muscarinic receptors involved in genioglossus inhibition. Although this mechanism appears to conflict with the muscle-activating role of acetylcholine, animal studies have shown that anticholinergic agents can increase genioglossus activity during REM sleep [27]. These findings suggest that a neurotransmitter may have different effects in the central and peripheral nervous systems and may act differently across NREM and REM sleep.

Because the anticholinergic adverse effects of oxybutynin are not well suited to long-term OSA treatment, a combination using its isomer, R-oxybutynin, was developed to reduce adverse effects. This formulation, AD109 (2.5 mg aroxybutynin plus 75 mg atomoxetine), was tested in a phase 3 clinical trial (NCT05813275, SynAIRgy), and the results were recently published [28]. Although AD109 demonstrated statistically significant therapeutic efficacy compared with placebo, the reductions in the AHI and oxygen desaturation index were only 3.3/h and 3.7/h, respectively. In addition, 70.8% of participants who received AD109 reported adverse events, compared with 46.7% in the placebo group. Common adverse events included dry mouth, nausea, insomnia, and urinary hesitation. Although no serious treatment-related adverse events occurred, 21.2% of participants in the AD109 group discontinued the trial because of adverse events, compared with 3.1% in the placebo group. These findings suggest that long-term tolerability and safety may remain challenging [28]. A similar trial combining reboxetine with oxybutynin instead of atomoxetine also did not show a clear therapeutic effect [29], indicating that similar drug classes may produce different outcomes when used in combination.

OBESITY MEDICATIONS AND OSA

Obesity is a distinct risk factor for the development and exacerbation of OSA, with OSA prevalence reported to reach nearly 50% among people with obesity [30]. Accordingly, OSA treatment guidelines explicitly state that weight loss is essential for patients with obesity [31]. The relationship between the degree of weight loss and the reduction in OSA severity can be estimated from meta-analyses of bariatric surgery outcomes [32]. Bariatric surgery resulted in an average weight loss of 28%, which was associated with a 68% reduction in the AHI among patients with severe OSA. This finding suggests that the percentage reduction in the AHI is approximately 2.4 times the percentage of weight lost. Similarly,

Table 1. Overview of investigational pharmacotherapies for obstructive sleep apnea

Drug (class)	Main mechanism	Study type (no. of participants)	Outcomes	Limitations
Protriptyline (tricyclic antidepressant)	Stimulation of upper airway motor activity	Parallel-group RCT (n=5)	No significant reduction in AHI; suppressed REM sleep	Anticholinergic adverse effects, including xerostomia, urinary retention, and palpitations
Acetazolamide (carbonic anhydrase inhibitor)	Respiratory center stimulation through loop gain reduction	Parallel-group RCT (n=10)	Significant reductions in AHI and arousal responses	No improvement in subjective symptoms; risk of metabolic acidosis
Eszopiclone (non-benzodiazepine)	Increased arousal threshold	Crossover RCT (n=17)	43% AHI reduction in the low-arousal-threshold subgroup	Requires specific endotype diagnosis; potential risk of airway collapse
Paroxetine (selective serotonin reuptake inhibitor)	Upper airway muscle activation	Parallel-group RCT (n=36)	35% reduction in NREM AHI; no reduction in REM AHI	Insufficient efficacy to support clinical recommendations
Mirtazapine (noradrenergic and specific serotonergic antidepressant)	Upper airway muscle activation	Parallel-group RCT (n=12)	54% AHI reduction with the high dose, primarily through reduced hypopnea events	No improvement in oxygen saturation or subjective symptoms
Donepezil (acetylcholinesterase inhibitor)	Cholinergic stimulation and muscle activation	Parallel-group RCT (n=21)	Modest AHI reduction, from 42.2/h to 32.8/h; improved SpO_2 and T90	Insomnia and nightmares; modest efficacy in patients without dementia
Atomoxetine plus oxybutynin (combination drug)	Norepinephrine reuptake inhibition plus anticholinergic-mediated muscle activation	Crossover RCT (n=22)	Mean AHI decreased from 28.5/h to 7.5/h; mean minimum SpO_2 improved from 84% to 94%	Long-term safety concerns related to anticholinergic exposure; phase 1 trial
Liraglutide (glucagon-like peptide-1 receptor agonist)	Weight loss	Parallel-group RCT (n=359)	5.7% weight loss; AHI reduction of 12.2/h	Insufficient AHI reduction as a s tandalone treatment
Phentermine/topiramate	Weight loss	Parallel-group RCT (n=45)	10.2% weight loss; 71% reduction in AHI	Long-term tolerability
Semaglutide (glucagon-like peptide-1 receptor agonist)	Weight loss	Parallel-group RCT and meta-analysis	Approximately 15% weight loss and AHI reduction	Gastrointestinal adverse events; less potent weight loss than tirzepatide
Tirzepatide (glucagon-like peptide-1/ glucose-dependent insulinotropic polypeptide dual agonist)	Weight loss	Parallel-group RCT (n=469)	Approximately 20% weight loss; AHI reduction of approximately 25–29/h, corresponding to more than 50% from baseline	Gastrointestinal adverse events, including diarrhea and nausea

AHI, apnea-hypopnea index; NREM, non-rapid eye movement; RCT, randomized controlled trial; REM, rapid eye movement; SpO_2, peripheral oxygen saturation; T90, percentage of sleep time with SpO_2 below 90%.

meta-analyses of lifestyle modification programs, excluding medication and surgery, showed that an average weight loss of 13% was associated with a 48% reduction in the AHI among patients with moderate OSA [33].

Although the importance of weight loss in OSA management is well established, achieving and maintaining clinically meaningful weight loss is difficult in practice. A U.S. meta-analysis of systematic weight loss programs found that, over 5 years of follow-up, patients maintained an average weight loss of only 3 kg or at least 3% of total body weight [34]. A 3% reduction in body weight is unlikely to be sufficient to meet therapeutic goals for OSA. Therefore, interest has grown in the development of safe and effective anti-obesity medications, particularly in the United States, where the prevalence of obesity is high.

Sibutramine, marketed under the brand name Reductil, inhibits the reuptake of serotonin, norepinephrine, and dopamine, thereby activating satiety centers and suppressing appetite. In middle-aged patients with obesity and OSA, sibutramine achieved a 35% reduction in weight from baseline over 6 months and improved subjective sleepiness [35]. However, in a comparative study of PAP users with a body mass index (BMI) of 30 kg/m^2 or higher, sibutramine produced only a 5.4-kg weight loss over 1 year. The PAP group showed significant improvements in cardiovascular and OSA severity indices, including sleep oxygen saturation and blood pressure, whereas the sibutramine group did not [36]. Sibutramine was subsequently withdrawn from the global market because of an increased risk of cardiovascular adverse events, including myocardial infarction and stroke. Liraglutide (Saxenda), a glucagon-like peptide-1 receptor agonist (GLP-1 RA), was initially approved for the treatment of type 2 diabetes. It induces weight loss by reducing hunger, increasing satiety through hypothalamic effects, and delaying gastric emptying. In a 32-week randomized controlled trial (RCT) involving patients with moderate-to-severe OSA who refused or could not tolerate PAP therapy (mean baseline AHI, 49.2/h; 63% with prediabetes), liraglutide achieved 5.7% weight loss and an AHI reduction of 12.2/h. Although this reduction was statistically greater than that with placebo, the magnitude of AHI reduction was insufficient for liraglutide to be considered a robust standalone treatment [37]. Qsymia, a combination of phentermine and topiramate, was designed to maximize weight loss while minimizing adverse effects. Phentermine suppresses appetite by increasing norepinephrine in the hypothalamus, whereas topiramate, a sedative that acts on gamma-aminobutyric acid receptors, enhances satiety. In an RCT of patients with obesity and moderate-to-severe OSA (BMI, 30–40 kg/m^2), this combination achieved 10.2% weight loss and a 71% reduction in the AHI from baseline (44.2/h) over 28 weeks, demonstrating significant improvement compared with placebo [38]. The more recently developed agents semaglutide (Wegovy) and tirzepatide (Mounjaro) have produced even greater weight loss. Tirzepatide, marketed as Zepbound for obesity and Mounjaro for diabetes in the U.S., became the first medication to receive U.S. Food and Drug Administration approval specifically for OSA. In the Republic of Korea, tirzepatide was approved as a single brand, Mounjaro, for type 2 diabetes, obesity management, and OSA in patients with a BMI of 30 kg/m^2 or higher. Although semaglutide and liraglutide share the same GLP-1 RA mechanism, semaglutide has a longer half-life, requires only once-weekly injection, and produces greater weight loss. Tirzepatide acts as a dual agonist of both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors, resulting in greater weight loss and fewer gastrointestinal adverse effects. In the 52-week SURMOUNT-OSA RCTs, tirzepatide reduced body weight by 17.7% in non-PAP users (Trial 1) and 19.6% in PAP users (Trial 2). Correspondingly, the AHI decreased by 25.3/h and 29.3/h, respectively, demonstrating a clear therapeutic effect compared with placebo [39]. Recent meta-analyses have confirmed that GLP-1 RAs, particularly tirzepatide, significantly reduce the AHI [40-42]. However, because adverse events were significantly more frequent with these agents than with placebo, long-term safety requires careful monitoring [41]. Table 1 summarizes investigational pharmacotherapies for OSA.

CONCLUSION

Past studies with limited efficacy and tolerability led to skepticism about pharmacological treatment development for OSA. However, expectations have increased as combination therapies with distinct mechanisms, such as atomoxetine plus oxybutynin, have advanced to phase 3 clinical trials. Although tirzepatide is currently the only U.S. Food and Drug Administration-approved medication for OSA, it is expected that OSA-directed pharmacotherapy unrelated to weight loss that is effective for patients who refuse or discontinue PAP therapy may become available in the near future. In addition, because a substantial proportion of patients with OSA are overweight or have obesity, the introduction of medications such as tirzepatide, which can produce weight loss of nearly 20% and an AHI reduction exceeding 50%, represents an important therapeutic development. In the Republic of Korea, where the prevalence of severe obesity is lower than in Western countries, tirzepatide has been explicitly approved for patients with OSA and a BMI of 30 kg/m^2 or higher. Although its overall clinical impact remains to be determined, clinicians now have an additional therapeutic option for this challenging condition. Ultimately, OSA treatment may move toward a comprehen-

sive strategy that combines conventional PAP therapy with emerging pharmacological interventions selected according to each patient's physiological endotype.

Ethics Statement

Not applicable

Availability of Data and Material

All data generated or analyzed during the study are included in this published article.

Conflicts of Interest

The author has no potential conflicts of interest to disclose.

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