

REVIEW ON AWAKENING INNOVATION: A COMPREHENSIVE REVIEW OF THERAPEUTIC ADVANCES, SURGICAL INNOVATIONS, AND EMERGING TECHNOLOGIES IN SLEEP APNEA MANAGEMENT

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ABSTRACT:

Sleep apnea is a common sleep related breathing disorder characterized by repeated episodes of partial or complete cessation of breathing during sleep, causing intermittent hypoxemia, sleep fragmentation, and reduced quality of life. Obstructive sleep apnea (OSA) is the most prevalent form and is associated with cardiovascular, metabolic, neurocognitive, and psychological complications. Continuous positive airway pressure (CPAP) remains a standard treatment, but adherence and individual treatment response can be challenging. This review, “Awakening Innovation: A Comprehensive Review of Therapeutic Advances, Surgical Innovations, and Emerging Technologies in Sleep Apnea Management,” summarizes recent advances in sleep apnea diagnosis and management. It covers conventional and emerging pharmacological therapies, weight management approaches, surgical procedures, and device based interventions, including hypoglossal nerve stimulation and maxillomandibular advancement. Emerging technologies such as artificial intelligence, machine learning, wearable devices, home sleep testing, and telemedicine are also discussed. The integration of therapeutic, surgical, and digital innovations may support more personalized and effective approaches to sleep apnea management and improve patient care.

KEYWORDS:

Sleep apnea; Obstructive sleep apnea; Central sleep apnea; Surgical innovations; Hypoglossal nerve stimulation; Maxillomandibular advancement; Artificial intelligence; Wearable technologies; Telemedicine; Digital health; Precision medicine.

1. INTRODUCTION:

Sleep is an essential physiological process that plays a critical role in maintaining physical health, cognitive performance, emotional well being, metabolic regulation, and cardiovascular function. Adequate sleep is necessary for tissue repair, memory consolidation, immune system modulation, and energy restoration. Disturbances in normal sleep architecture can adversely affect multiple organ systems and contribute to significant morbidity and mortality

[1].

Sleep-related breathing disorders (SRBDs) represent a heterogeneous group of conditions characterized by abnormal respiratory patterns, impaired ventilation, or recurrent episodes of airflow limitation during sleep. These disorders include obstructive sleep apnea (OSA), central sleep apnea (CSA), mixed sleep apnea, obesity hypoventilation syndrome (OHS), upper airway resistance syndrome (UARS), and sleep related hypoxemia disorders [1]. Among these conditions, OSA is the most prevalent and extensively studied form, affecting millions of individuals worldwide and posing a substantial public health burden [2].

Recent epidemiological studies indicate that nearly one billion adults worldwide may suffer from OSA, with a considerable proportion remaining undiagnosed. The prevalence of OSA has increased over recent decades owing to rising rates of obesity, aging populations, sedentary lifestyles, and improved disease recognition. The disorder is more common in men, older adults, and individuals with obesity; however, women and children are also affected, particularly in the presence of specific anatomical or genetic predispositions [8]. Untreated sleep-related breathing disorders have been associated with cardiovascular diseases, hypertension, stroke, diabetes mellitus, metabolic syndrome, cognitive impairment, depression, and reduced quality of life [3].

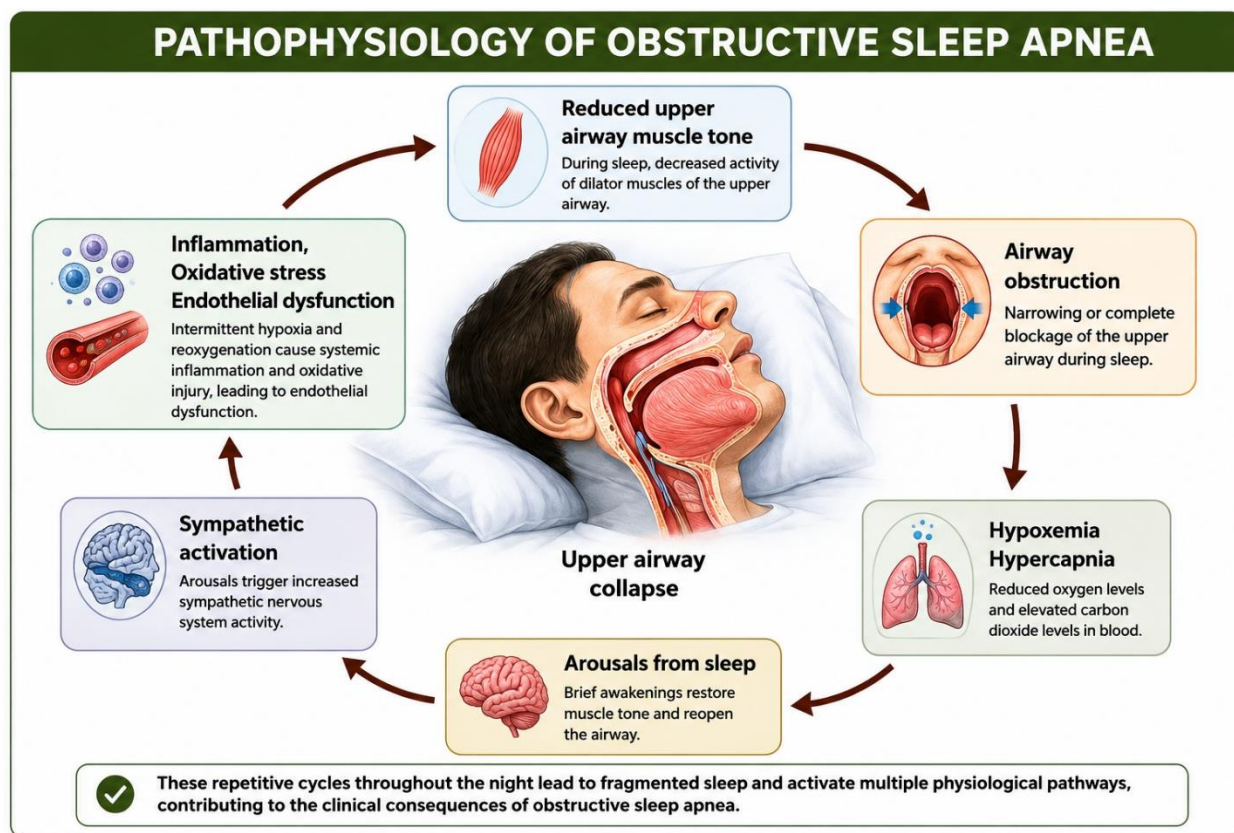


Fig:1 PATHOPHYSIOLOGY OF OBSTRUCTIVE APNEA

The pathophysiology of sleep related breathing disorders is complex and multifactorial. In obstructive sleep apnea, repetitive collapse of the upper airway during sleep results in intermittent hypoxia, hypercapnia, sleep fragmentation, and fluctuations in intrathoracic pressure. These events activate sympathetic nervous system activity, induce oxidative stress, promote systemic inflammation, and contribute to endothelial dysfunction, thereby increasing cardiovascular risk [4]. In contrast, central sleep apnea is characterized by a temporary reduction or cessation of respiratory drive from the central nervous system, leading to impaired respiratory effort and recurrent breathing pauses during sleep.

Accurate diagnosis of sleep related breathing disorders is essential for preventing disease progression and associated complications. Polysomnography remains the gold standard diagnostic method, providing comprehensive

information regarding sleep stages, respiratory events, oxygen saturation, and cardiovascular parameters [1]. In recent years, home sleep apnea testing devices, wearable sensors, and digital monitoring technologies have emerged as valuable tools for improving accessibility and facilitating early diagnosis. Advances in artificial intelligence (AI) and machine learning (ML) have further enhanced diagnostic accuracy through automated sleep-stage classification and respiratory event detection.

Continuous positive airway pressure (CPAP) therapy remains the first line treatment for moderate-to-severe obstructive sleep apnea due to its effectiveness in maintaining upper airway patency and reducing apnea-hypopnea events [18]. However, long term adherence to CPAP remains a significant challenge, with many patients experiencing discomfort, intolerance, or poor compliance [5]. Consequently, alternative therapeutic approaches have gained increasing attention.

Recent years have witnessed remarkable progress in surgical management strategies for sleep related breathing disorders. Surgical innovations such as uvulopalatopharyngoplasty (UPPP), barbed reposition pharyngoplasty, transoral robotic surgery (TORS), maxillomandibular advancement (MMA), and hypoglossal nerve stimulation (HGNS) have demonstrated encouraging outcomes in carefully selected patients. These procedures aim to address specific sites of upper airway obstruction and provide individualized treatment options when conventional therapies fail or are poorly tolerated.

In addition to surgical advancements, emerging pharmacological therapies targeting upper airway muscle function, ventilatory control instability, and obesity related mechanisms are being investigated as potential treatment modalities. Furthermore, technological innovations including wearable monitoring devices, telemedicine platforms, implantable sensors, and AI-assisted decision support systems are transforming the diagnosis, monitoring, and long-term management of sleep-related breathing disorders [6].

Given the growing prevalence of sleep-related breathing disorders and the rapid evolution of therapeutic technologies, a comprehensive understanding of current evidence is essential for healthcare professionals and researchers. Therefore, this review aims to provide an updated overview of sleep related breathing disorders, emphasizing their epidemiology, pathophysiology, clinical manifestations, diagnostic approaches, surgical innovations, pharmacological developments, and emerging technologies that are shaping the future of sleep medicine.

2. RELAXATION OF THE HUMAN BODY:

2.1 Rest and Work Hours

The human body functions through a complex interaction of physiological processes that require an appropriate balance between periods of activity and rest. Regular cycles of work and rest are essential for maintaining physical performance, cognitive function, emotional stability, and overall health. During periods of activity, the body consumes energy, generates metabolic waste products, and experiences varying degrees of physical and mental stress. Adequate rest allows recovery of physiological systems, restoration of energy reserves, and maintenance of homeostasis.

The regulation of work and rest is closely linked to the circadian rhythm, an endogenous biological clock located within the suprachiasmatic nucleus of the hypothalamus. Circadian rhythms synchronize physiological functions such as hormone secretion, body temperature regulation, metabolism, and the sleep–wake cycle with environmental light-dark patterns . Disruption of these rhythms due to prolonged working hours, shift work, irregular sleep schedules, or excessive occupational stress can impair sleep quality and increase the risk of metabolic, cardiovascular, and neuropsychiatric disorders [7].

Work-related fatigue develops when the demands placed on the body exceed its capacity for recovery. Physical fatigue results from depletion of energy stores and accumulation of metabolic by products, whereas mental fatigue is associated with prolonged cognitive effort and reduced attentional capacity. Rest periods facilitate muscle recovery, glycogen replenishment, tissue repair, and restoration of cognitive performance. Research indicates that regular breaks during work improve productivity, reduce stress, and enhance overall well-being.

International health organizations recommend balancing work and rest through structured schedules that allow sufficient recovery time. Adults are generally encouraged to maintain consistent sleep wake patterns, limit excessive overtime work, and incorporate regular periods of relaxation into daily routines. Occupational health studies have demonstrated that excessive work hours exceeding 55 hours per week are associated with increased risks of cardiovascular disease, hypertension, anxiety, depression, and sleep disorders.

Furthermore, modern lifestyles characterized by prolonged screen exposure, sedentary behavior, and increased occupational demands may interfere with normal circadian regulation and sleep initiation. Maintaining healthy work rest schedules, engaging in regular physical activity, and practicing good sleep hygiene are therefore critical strategies for preserving physiological health and preventing sleep related disorders [8].

2.2 Rest, Relaxation, and Sleep Duration

Rest and relaxation are fundamental biological processes that contribute to physical recovery, psychological well being, and optimal functioning of multiple organ systems. Relaxation refers to a state of reduced physiological and psychological arousal characterized by decreased sympathetic nervous system activity and enhanced parasympathetic activity. Techniques such as meditation, deep breathing exercises, yoga, mindfulness practices, and leisure activities can promote relaxation and improve sleep quality.

Chronic stress has profound effects on sleep regulation. Activation of the hypothalamic pituitary adrenal (HPA) axis during periods of stress leads to increased secretion of cortisol and other stress hormones, which can interfere with sleep initiation and maintenance. Persistent stress may result in insomnia, fragmented sleep, reduced sleep efficiency, and excessive daytime sleepiness. Conversely, effective relaxation strategies can lower stress hormone levels, improve emotional resilience, and facilitate healthy sleep patterns [9].

Sleep duration is a critical determinant of overall health. Adequate sleep supports cognitive performance, memory consolidation, immune function, metabolic regulation, cardiovascular health, and emotional stability . The National Sleep Foundation recommends that healthy adults obtain approximately 7–9 hours of sleep per night, while adolescents require 8–10 hours and school aged children require 9–11 hours for optimal development and functioning.

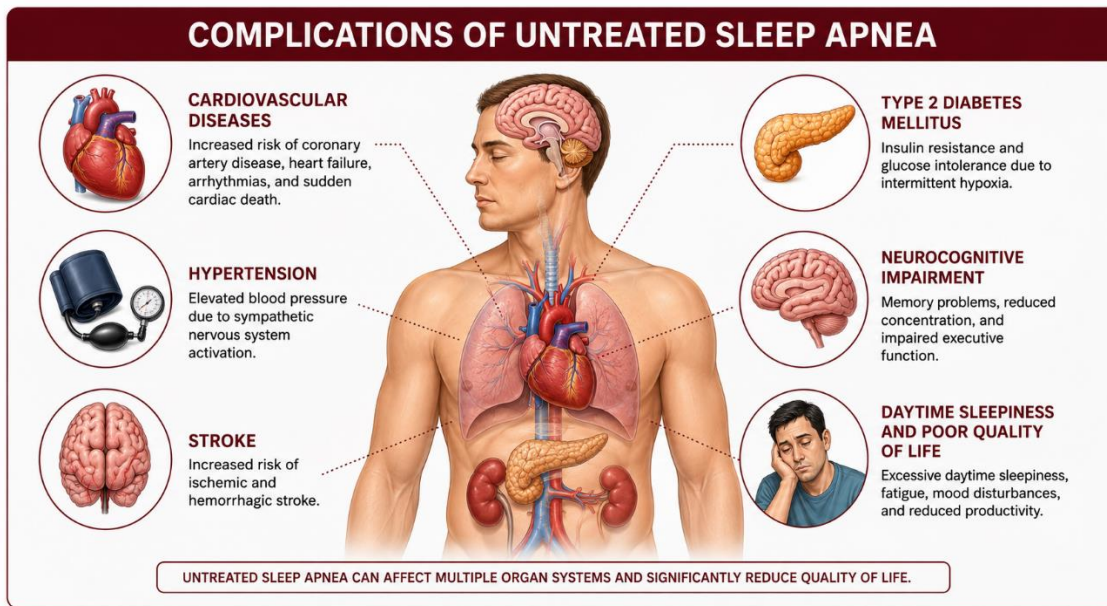


Fig:2 COMPLICATIONS OF UNTREATED SLEEP APNEA

Insufficient sleep has become a significant public health concern worldwide. Sleep deprivation is associated with impaired attention, reduced learning capacity, increased accident risk, obesity, diabetes mellitus, hypertension, cardiovascular disease, depression, and decreased quality of life. Long-term sleep restriction may also contribute to immune dysfunction, chronic inflammation, and accelerated biological aging [10]. Excessive sleep duration may likewise be associated with adverse health outcomes, including metabolic disturbances, cardiovascular disease, and increased mortality risk. Therefore, both sleep quantity and sleep quality are important determinants of health. Establishing regular sleep schedules, minimizing exposure to electronic devices before bedtime, reducing caffeine intake during evening hours, and maintaining a comfortable sleep environment can help promote healthy sleep duration and restorative rest. Overall, adequate rest, effective relaxation practices, and appropriate sleep duration are essential components of healthy living. These factors contribute significantly to physiological recovery, disease prevention, mental health maintenance, and improved quality of life, while also reducing the risk of sleep-related breathing disorders and other sleep disturbances [11].

3. SLEEP:

Sleep is a naturally recurring physiological state characterized by reduced consciousness, diminished responsiveness to external stimuli, and altered neurological activity. It is a highly organized biological process essential for maintaining physical health, cognitive performance, emotional regulation, immune function, and metabolic homeostasis. Far from being a passive state, sleep involves complex interactions among neural networks, neurotransmitters, hormones, and circadian regulatory mechanisms.

The sleep wake cycle is regulated by two major physiological processes: the circadian timing system and the homeostatic sleep drive. The circadian system, controlled primarily by the suprachiasmatic nucleus (SCN) of the hypothalamus, synchronizes sleep patterns with the environmental light dark cycle. Simultaneously, the homeostatic process increases the pressure to sleep as wakefulness is prolonged, ensuring adequate recovery and restoration [12].

Human sleep is broadly divided into two major states: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. These stages occur cyclically throughout the night, with each cycle lasting approximately 90–110 minutes. A typical adult experiences four to six sleep cycles during a normal night's sleep. NREM sleep generally occupies about 75–80% of total sleep time and is associated with physical restoration and energy

conservation, whereas REM sleep accounts for approximately 20–25% of sleep and plays a crucial role in memory processing, emotional regulation, and neural development.

Sleep serves numerous physiological functions, including tissue repair, protein synthesis, immune regulation, hormonal balance, memory consolidation, and maintenance of cardiovascular and metabolic health. Insufficient or poor-quality sleep can impair cognitive function, increase susceptibility to chronic diseases, and contribute to the development of sleep related breathing disorders [13,14]. Consequently, understanding normal sleep physiology is essential for comprehending the mechanisms underlying sleep disorders and their clinical management.

3.1 Rapid Eye Movement (REM) Sleep

Rapid eye movement (REM) sleep is a distinct stage of sleep characterized by rapid conjugate eye movements, heightened brain activity, vivid dreaming, and profound skeletal muscle relaxation. REM sleep typically begins approximately 90 minutes after sleep onset and recurs several times throughout the night, with longer REM periods occurring during the latter half of the sleep episode .

Electroencephalographic (EEG) recordings during REM sleep demonstrate low amplitude, high-frequency brain waves that closely resemble those observed during wakefulness. Because of this similarity, REM sleep is often referred to as paradoxical sleep, as the brain remains highly active while voluntary skeletal muscles are largely paralyzed. This muscle atonia is mediated by inhibitory neural pathways originating in the brainstem and serves to prevent individuals from physically acting out their dreams [15].

REM sleep plays a vital role in cognitive and emotional functions. Numerous studies suggest that REM sleep contributes to memory consolidation, learning processes, emotional adaptation, and neural plasticity. During this stage, the brain processes information acquired during wakefulness and integrates newly learned experiences into long-term memory networks. REM sleep is also believed to facilitate creativity, problem-solving abilities, and emotional resilience.

Physiological changes occurring during REM sleep include increased cerebral blood flow, fluctuations in heart rate and blood pressure, irregular respiratory patterns, and enhanced autonomic nervous system activity [16]. These respiratory changes are clinically significant because airway muscle tone decreases substantially during REM sleep, making individuals with obstructive sleep apnea particularly vulnerable to upper airway collapse and respiratory events during this stage.

Abnormalities in REM sleep have been associated with several neurological and psychiatric disorders, including depression, anxiety disorders, narcolepsy, REM sleep behavior disorder, and neurodegenerative diseases such as Parkinson's disease [17]. Therefore, REM sleep is considered an essential component of healthy sleep architecture and overall neurological function.

3.2 Non-Rapid Eye Movement (NREM) Sleep

Non-rapid eye movement (NREM) sleep constitutes the largest proportion of total sleep time and is primarily associated with physical restoration, energy conservation, and physiological recovery. NREM sleep is divided into three stages: N1, N2, and N3, each characterized by distinct neurophysiological features and levels of sleep depth.

Stage N1 represents the transition from wakefulness to sleep and is considered the lightest stage of sleep. During this phase, muscle activity decreases, eye movements become slow and rolling, and individuals can be easily awakened. N1 typically accounts for approximately 5% of total sleep time [18].

Stage N2 is characterized by the appearance of sleep spindles and K-complexes on EEG recordings. Sleep spindles are bursts of rhythmic neural activity believed to support memory consolidation and neural communication, whereas

K-complexes are thought to protect sleep from external disturbances. N2 sleep comprises approximately 45–55% of total sleep duration and serves as an important intermediate stage between light and deep sleep [19].

Stage N3, also known as slow-wave sleep (SWS) or deep sleep, is characterized by high amplitude, low frequency delta waves. This stage is considered the most restorative phase of sleep and is associated with tissue repair, immune system enhancement, growth hormone secretion, and metabolic recovery. During N3 sleep, heart rate, blood pressure, respiratory rate, and body temperature decrease significantly, reflecting reduced physiological demands and enhanced restorative processes.

NREM sleep plays a crucial role in memory consolidation, particularly for declarative memory and learning. Research has demonstrated that slow-wave sleep facilitates synaptic remodeling, removal of metabolic waste products from the brain through the glymphatic system, and restoration of neuronal function [20]. These processes are essential for maintaining cognitive performance and long-term neurological health.

Disruptions in NREM sleep can impair immune function, increase fatigue, reduce cognitive efficiency, and contribute to various sleep disorders. Furthermore, certain sleep-related breathing disorders, including obstructive sleep apnea, may occur during NREM sleep, although respiratory events are often more pronounced during REM sleep due to greater reductions in upper airway muscle tone.

Overall, NREM and REM sleep work together to maintain optimal physiological, cognitive, and emotional functioning. Preservation of normal sleep architecture is therefore critical for health, disease prevention, and overall quality of life.

4. BREATHING DISORDERS DURING SLEEP:

Sleep-related breathing disorders (SRBDs) comprise a group of conditions characterized by abnormalities in respiration, ventilation, and gas exchange that occur during sleep. These disorders result in recurrent episodes of airflow limitation, oxygen desaturation, sleep fragmentation, and disturbances in normal sleep architecture. SRBDs are among the most common sleep disorders worldwide and are associated with substantial cardiovascular, metabolic, neurocognitive, and psychological consequences [21].

Normal breathing during sleep is regulated through complex interactions between the respiratory centers of the brainstem, upper airway musculature, lung mechanics, and chemoreceptor responses to oxygen and carbon dioxide levels. During sleep, particularly during rapid eye movement (REM) sleep, physiological reductions in upper airway muscle tone and ventilatory drive occur. In susceptible individuals, these changes may lead to airway obstruction, impaired respiratory effort, or inadequate ventilation, resulting in various forms of sleep related breathing disorders.

The clinical manifestations of SRBDs include loud snoring, witnessed breathing pauses, nocturnal choking or gasping, fragmented sleep, excessive daytime sleepiness, fatigue, impaired concentration, morning headaches, mood disturbances, and reduced quality of life. If left untreated, these disorders may increase the risk of hypertension, coronary artery disease, stroke, heart failure, insulin resistance, type 2 diabetes mellitus, and premature mortality.

Accurate diagnosis typically involves comprehensive clinical evaluation, overnight polysomnography, home sleep apnea testing, pulse oximetry, and advanced respiratory monitoring techniques. The severity of respiratory events is commonly quantified using the Apnea Hypopnea Index (AHI), which measures the number of apnea and hypopnea episodes occurring per hour of sleep [22].

4.1 Types and Timing of Sleep Related Breathing Disorders

Sleep related breathing disorders may occur during different stages of sleep and vary according to the underlying pathophysiological mechanism. Respiratory disturbances are often influenced by changes in upper airway muscle

tone, ventilatory control, arousal thresholds, and autonomic nervous system activity occurring throughout the sleep cycle [23].

Obstructive respiratory events frequently worsen during REM sleep because this stage is associated with profound skeletal muscle relaxation and reduced activity of the pharyngeal dilator muscles. The resulting decrease in upper airway stability increases the likelihood of airway collapse and recurrent apnea episodes. Patients with REM predominant obstructive sleep apnea may exhibit relatively normal breathing during NREM sleep but experience severe respiratory disturbances during REM sleep.

In contrast, certain forms of central sleep apnea are more common during transitions between wakefulness and sleep or during lighter stages of NREM sleep. Instability in ventilatory control mechanisms, fluctuations in carbon dioxide levels, and impaired respiratory drive contribute to the development of central respiratory events [24].

Sleep related hypoventilation disorders and obesity hypoventilation syndrome may occur throughout the night but often worsen during REM sleep because respiratory muscle activity decreases significantly, leading to inadequate ventilation and progressive carbon dioxide retention. Consequently, understanding the timing and sleep stage distribution of respiratory events is important for diagnosis, treatment planning, and assessment of disease severity.

4.2 Types of Sleep-Related Breathing Disorders

4.2.1 Obstructive Sleep Apnea (OSA)

Obstructive sleep apnea (OSA) is the most prevalent sleep-related breathing disorder and is characterized by recurrent episodes of complete or partial upper airway obstruction during sleep despite continued respiratory effort. These episodes result in intermittent hypoxemia, hypercapnia, sleep fragmentation, and repeated arousals from sleep.

Globally, OSA affects hundreds of millions of adults and represents a major public health concern. Risk factors include obesity, male sex, advancing age, craniofacial abnormalities, enlarged tonsils, nasal obstruction, smoking, alcohol consumption, and family history^[25]. Common clinical manifestations include loud habitual snoring, witnessed apneas, nocturnal choking, excessive daytime sleepiness, impaired cognitive performance, and decreased quality of life.

Diagnosis is primarily based on overnight polysomnography, which evaluates respiratory events, oxygen saturation, sleep stages, and the apnea–hypopnea index. Untreated OSA is strongly associated with hypertension, cardiovascular disease, arrhythmias, stroke, metabolic syndrome, insulin resistance, and neurocognitive impairment.

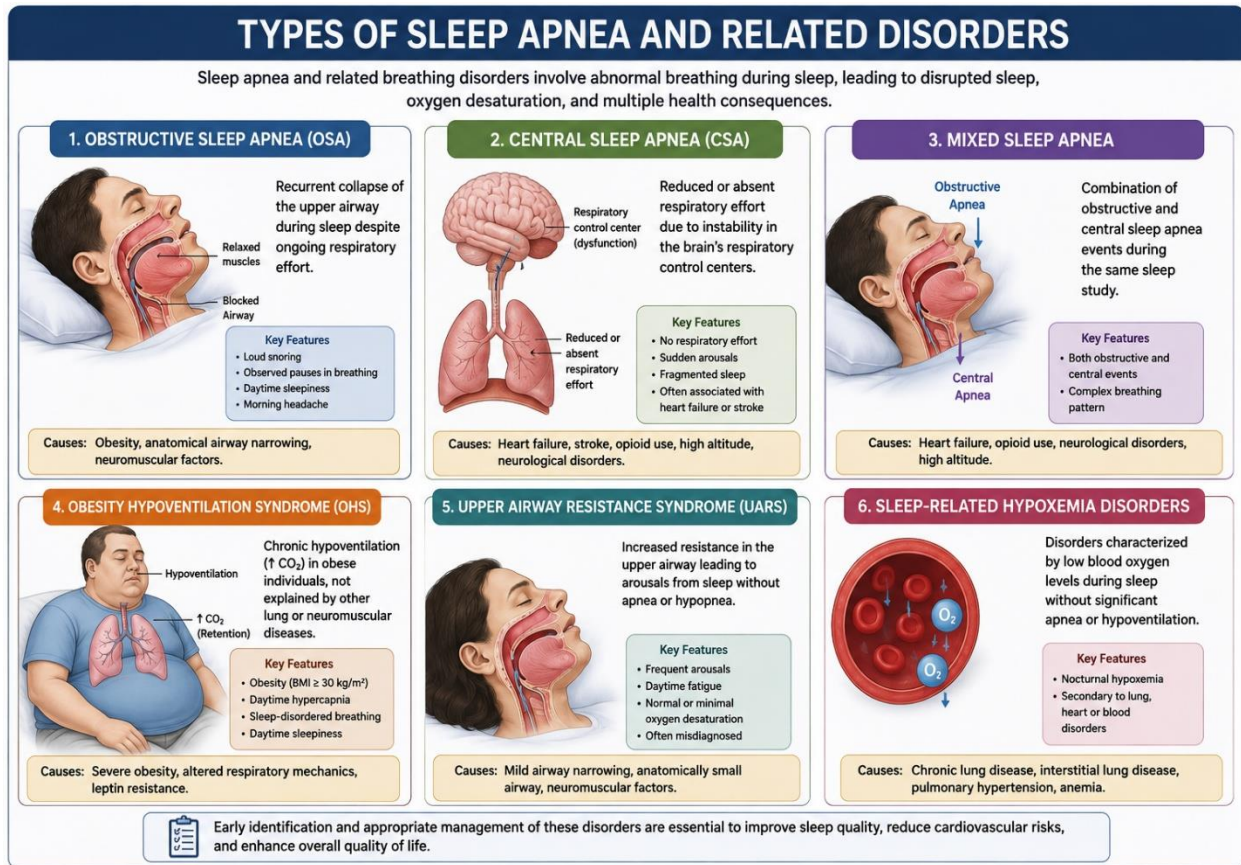


Fig:3 TYPES OF SLEEP APNEA AND RELATED DISORDERS

4.2.2 Central Sleep Apnea (CSA)

Central sleep apnea (CSA) is characterized by repetitive episodes of absent or reduced airflow caused by a temporary loss of respiratory drive from the central nervous system. Unlike OSA, respiratory effort is absent during central apnea events [26].

CSA is commonly observed in patients with heart failure, neurological disorders, chronic opioid use, high altitude exposure, and certain neuromuscular diseases. Cheyne Stokes respiration, a characteristic pattern of cyclic breathing and apnea, is frequently associated with heart failure-related CSA.

Clinical symptoms include insomnia, nocturnal awakenings, excessive daytime fatigue, poor sleep quality, and cognitive dysfunction. Diagnosis requires polysomnographic identification of central respiratory events. Potential complications include worsening cardiovascular disease, impaired quality of life, and increased mortality in susceptible populations [27].

4.2.3 Mixed Sleep Apnea

Mixed sleep apnea, also referred to as complex sleep apnea, involves features of both obstructive and central sleep apnea. Respiratory events typically begin as central apneas with absent respiratory effort and subsequently evolve into obstructive events characterized by upper airway collapse. This disorder may occur spontaneously or emerge during treatment of obstructive sleep apnea with continuous positive airway pressure therapy. The exact mechanisms remain incompletely understood but likely involve ventilatory instability combined with upper airway dysfunction. Management often requires individualized therapeutic approaches, including positive airway pressure therapy, adaptive servo-ventilation, oxygen supplementation, or treatment of underlying medical conditions [28].

4.2.4 Obesity Hypoventilation Syndrome (OHS)

Obesity hypoventilation syndrome is a disorder characterized by obesity, chronic daytime hypercapnia, and sleep disordered breathing in the absence of alternative causes of hypoventilation [88]. The condition results from a combination of impaired respiratory mechanics, reduced ventilatory responsiveness, increased work of breathing, and obesity related physiological changes.

OHS predominantly affects individuals with severe obesity and is frequently associated with obstructive sleep apnea. Common manifestations include excessive daytime sleepiness, fatigue, dyspnea, morning headaches, and impaired exercise tolerance.

Untreated OHS can lead to pulmonary hypertension, right sided heart failure, respiratory failure, and increased mortality. Early diagnosis and treatment are therefore essential for improving long-term outcomes [29].

4.2.5 Upper Airway Resistance Syndrome (UARS)

Upper airway resistance syndrome is characterized by increased resistance within the upper airway that causes repeated arousals from sleep without meeting the diagnostic criteria for obstructive sleep apnea. Patients experience increased respiratory effort and sleep fragmentation despite relatively preserved oxygen saturation levels [30].

Individuals with UARS commonly report excessive daytime sleepiness, fatigue, unrefreshing sleep, difficulty concentrating, headaches, and reduced quality of life. The condition is often underdiagnosed because standard sleep studies may not detect subtle respiratory abnormalities. Although generally considered less severe than OSA, untreated UARS may contribute to chronic sleep deprivation, neurocognitive dysfunction, and progression to more severe forms of sleep-disordered breathing [31].

4.2.6 Sleep-Related Hypoxemia Disorders

Sleep-related hypoxemia disorders are characterized by abnormal reductions in blood oxygen saturation during sleep that are not fully explained by obstructive or central apnea events. These conditions commonly occur in patients with chronic obstructive pulmonary disease (COPD), interstitial lung disease, pulmonary vascular disorders, neuromuscular diseases, and severe obesity.

Persistent nocturnal hypoxemia may result in oxidative stress, systemic inflammation, pulmonary hypertension, cardiac dysfunction, impaired cognitive performance, and reduced survival. Continuous monitoring of oxygen saturation through polysomnography or overnight oximetry is important for diagnosis and treatment planning [32].

Overall, sleep-related breathing disorders encompass a diverse group of conditions with distinct pathophysiological mechanisms but overlapping clinical consequences. Early recognition and appropriate management are essential to reduce disease burden, improve sleep quality, and prevent long-term complications.

5. SURGICAL, PHARMACOLOGICAL AND EMERGING THERAPEUTIC APPROACHES:

The management of sleep-related breathing disorders (SRBDs) has evolved substantially over the past decade. Although continuous positive airway pressure (CPAP) remains the standard treatment for many patients with obstructive sleep apnea (OSA), long-term adherence remains suboptimal. Consequently, significant efforts have been directed toward developing alternative therapeutic strategies, including innovative surgical procedures, pharmacological interventions, and advanced digital technologies. These approaches aim to improve patient outcomes through individualized and precision-based treatment methods [33].

5.1 Surgical Innovations

Surgical treatment is generally considered for patients who are unable to tolerate CPAP therapy, have specific anatomical abnormalities contributing to airway obstruction, or require multimodal treatment approaches. Recent advances in sleep surgery emphasize personalized interventions guided by anatomical and physiological assessment techniques such as drug-induced sleep endoscopy (DISE) [34].

5.1.1 Uvulopalatopharyngoplasty (UPPP)

Uvulopalatopharyngoplasty (UPPP) is one of the most frequently performed surgical procedures for OSA. The procedure involves removal or reshaping of excess tissue from the soft palate, uvula, and surrounding pharyngeal structures to enlarge the upper airway and reduce airflow obstruction [99]. Modern modifications of UPPP focus on preserving functional tissues while improving airway patency. Contemporary studies demonstrate that patient selection based on anatomical evaluation significantly enhances surgical success rates and reduces postoperative complications [35].

5.1.2 Barbed Reposition Pharyngoplasty (BRP)

Barbed reposition pharyngoplasty is a relatively recent advancement in sleep surgery that utilizes barbed sutures to reposition and stabilize pharyngeal tissues without extensive tissue excision. The technique aims to enlarge the retropalatal airway and reduce pharyngeal collapse during sleep.

Compared with traditional UPPP, BRP is associated with reduced postoperative pain, shorter recovery periods, preservation of normal anatomy, and improved airway stability. Several studies have reported significant reductions in apnea–hypopnea index (AHI) and improvement in subjective sleep quality following BRP [36].

5.1.3 Transoral Robotic Surgery (TORS)

Transoral robotic surgery represents a major technological advancement in the surgical management of OSA. TORS employs robotic systems to provide enhanced visualization, precision, and access to difficult anatomical regions such as the tongue base and hypopharynx.

The procedure is particularly useful for patients with tongue-base obstruction, a common contributor to airway collapse. Clinical investigations have demonstrated significant reductions in respiratory events, improved oxygenation, and favorable long-term outcomes in carefully selected patients undergoing TORS [37].

5.1.4 Maxillomandibular Advancement (MMA)

Maxillomandibular advancement is considered one of the most effective surgical interventions for moderate-to-severe OSA. The procedure involves simultaneous forward repositioning of the maxilla and mandible, thereby enlarging the upper airway and reducing pharyngeal collapsibility [105]. Numerous studies have reported substantial reductions in AHI, improvements in daytime functioning, and durable long-term efficacy. Surgical success rates frequently exceed those observed with other upper airway procedures, making MMA an important option for patients with craniofacial abnormalities or severe disease [38].

5.1.5 Hypoglossal Nerve Stimulation (HGNS)

Hypoglossal nerve stimulation has emerged as one of the most innovative treatments for OSA. This implantable system delivers electrical stimulation to the hypoglossal nerve during inspiration, promoting activation of tongue muscles and preventing airway collapse. Recent clinical trials have demonstrated sustained improvements in sleep parameters, quality of life, and daytime sleepiness. Advances in implant technology, sensing mechanisms, and patient-selection criteria have further expanded the clinical applicability of HGNS [39].

5.1.6 Radiofrequency Ablation (RFA)

Radiofrequency ablation utilizes controlled thermal energy to reduce tissue volume within the soft palate, tongue base, or nasal structures. The procedure induces localized fibrosis and tissue contraction, resulting in increased airway dimensions. RFA is minimally invasive, can often be performed in outpatient settings, and is associated with low complication rates. It may be used alone or as part of multilevel surgical approaches for selected patients with mild to moderate OSA^[40].

5.2 Pharmacological Approaches

5.2.1 Treatment and Pharmacological Advances

Pharmacological treatment of sleep apnea has traditionally had a limited role because obstructive sleep apnea (OSA) is a heterogeneous disorder involving upper airway collapsibility, impaired upper airway dilator muscle function, ventilatory control instability, arousal responses, and, frequently, obesity. Consequently, positive airway pressure (PAP) therapy remains the principal evidence-based treatment for clinically significant OSA, particularly in patients with excessive daytime sleepiness or impaired sleep related quality of life. Pharmacological approaches have instead developed as adjunctive or phenotype-specific interventions aimed at modifying individual pathophysiological mechanisms or treating persistent symptoms.

Recent advances in understanding the biological heterogeneity of OSA have encouraged the development of mechanism directed pharmacological therapies. These approaches include weight-reduction therapies, drugs that enhance upper airway neuromuscular activity, agents that modify ventilatory control, and wake promoting medications for residual excessive daytime sleepiness. Such therapies are particularly relevant because conventional treatment does not produce equivalent benefits in every patient, and treatment selection may increasingly depend on the predominant physiological mechanism contributing to sleep disordered breathing ^[41].

A major recent development is the introduction of tirzepatide, a dual glucose-dependent insulintropic polypeptide (GIP) and glucagon like peptide-1 (GLP-1) receptor agonist. Tirzepatide produces substantial weight reduction through effects on appetite, energy intake, and metabolic regulation. Because obesity contributes importantly to upper-airway narrowing and collapsibility, reduction in body weight can consequently improve the severity of OSA. In two phase 3 trials, tirzepatide produced significant reductions in the apnea hypopnea index (AHI), body weight, hypoxic burden, and sleep-apnea-related outcomes in adults with obesity and moderate-to-severe OSA ^[42]. The United States Food and Drug Administration subsequently approved tirzepatide for adults with obesity and moderate-to-severe OSA in combination with a reduced-calorie diet and increased physical activity, making it the first medication specifically approved for OSA. Nevertheless, tirzepatide should be regarded as a treatment option for an appropriately selected obese OSA population rather than as a universal replacement for PAP therapy.

Pharmacological strategies directed toward the upper airway dilator muscles represent another important area of development. Atomoxetine, a norepinephrine reuptake inhibitor, increases noradrenergic activity at upper airway motor neurons and can enhance genioglossus muscle responsiveness during sleep. Oxybutynin, an antimuscarinic agent, may further augment this response by reducing cholinergic inhibition. The combination of atomoxetine and oxybutynin has therefore been investigated as a mechanism based treatment for OSA. A randomized crossover study demonstrated a substantial reduction in OSA severity following combination treatment, supporting the concept that pharmacological enhancement of upper airway neuromuscular activity may be beneficial in selected patients. Subsequent repeated dose studies have provided additional evidence of physiological efficacy, although anticholinergic adverse effects, cardiovascular considerations, and the absence of sufficient long-term safety data currently limit routine clinical use.

Alterations in ventilatory control are another pharmacological target, particularly in patients with central sleep apnea (CSA) or a prominent high loop gain respiratory phenotype. Acetazolamide, a carbonic anhydrase inhibitor, induces a mild metabolic acidosis that increases ventilatory drive and may stabilize breathing during sleep. Clinical studies and meta analyses have demonstrated reductions in AHI and improvements in oxygenation with acetazolamide in selected forms of sleep disordered breathing. Its clinical role is more established in CSA and high altitude sleep apnea than in uncomplicated OSA. The current AASM clinical practice guideline conditionally recommends oral acetazolamide for several forms of CSA, including primary CSA, CSA associated with heart failure, medication- or substance-related CSA, treatment emergent CSA, and high altitude CSA [43].

Sultiame, another carbonic anhydrase inhibitor, represents an emerging pharmacological approach for OSA. Its proposed effects include enhancement of ventilatory drive and modulation of upper-airway muscle activity. The phase 2 flow trial reported significant reductions in OSA severity with once-daily sultiame treatment, supporting further evaluation of carbonic-anhydrase inhibition as a therapeutic strategy for selected patients. However, the available evidence remains insufficient to establish sultiame as a routine treatment, and longer term studies are required to determine its efficacy, safety, optimal dosing, and appropriate patient phenotype.

A separate pharmacological objective is the management of residual excessive daytime sleepiness despite appropriate treatment of the underlying sleep disordered breathing. Solriamfetol, a dopamine and norepinephrine reuptake inhibitor, has demonstrated significant improvements in objective wakefulness and subjective sleepiness among patients with OSA. Pitolisant, an inverse agonist/antagonist of the histamine H3 receptor, enhances histaminergic neurotransmission and has also demonstrated clinically meaningful improvements in excessive daytime sleepiness in patients with OSA. These agents are important because persistent sleepiness may remain even when PAP adherence is adequate; however, they do not directly correct upper airway obstruction and therefore should be considered symptom-directed therapy rather than primary treatment of OSA.

Overall, pharmacological development in sleep apnea is moving from nonspecific drug treatment toward precision and phenotype oriented therapy. Weight directed treatment currently has the strongest evidence for reducing OSA severity among pharmacological interventions, particularly in patients with obesity. Upper airway neuromuscular agents and ventilatory control modifiers represent promising approaches for physiologically selected patients, whereas wake promoting agents have an established role in managing residual daytime sleepiness. Continued research is required to determine which pharmacological combinations provide durable improvements in respiratory events, nocturnal hypoxemia, cardiovascular risk, symptoms, and long term clinical outcomes [44]. Pharmacotherapy should therefore be integrated with established treatments and individualized according to disease severity, obesity status, physiological phenotype, comorbidities, treatment tolerance, and patient preference.

5.2.2 Comparison of Medicines Used in Sleep Apnea Management

Pharmacological agents investigated for sleep apnea differ substantially in their therapeutic targets, clinical indications, strength of evidence, and safety profiles. Importantly, these medicines should not be considered interchangeable. Some agents can reduce the severity of obstructive sleep apnea by addressing an underlying physiological mechanism, whereas others primarily improve excessive daytime sleepiness without correcting nocturnal upper airway obstruction. Therefore, pharmacological treatment should be selected according to the patient's phenotype, comorbidities, treatment tolerance, and whether the therapeutic objective is reduction of respiratory events or control of residual daytime symptoms [45].

Tirzepatide currently represents the most important pharmacological advance for patients with obesity associated moderate to severe OSA. It is a dual GIP/GLP-1 receptor agonist that produces substantial weight reduction and consequently decreases the anatomical burden contributing to upper airway collapse. In the SURMOUNT-OSA

trials, tirzepatide significantly reduced the apnea-hypopnea index and body weight compared with placebo in adults with obesity and moderate to severe OSA. Its principal clinical advantage is therefore its ability to address both obesity and OSA severity. However, gastrointestinal adverse effects, particularly nausea, diarrhea, vomiting and constipation, can occur, and treatment requires appropriate patient selection and monitoring. Tirzepatide should consequently be regarded as an obesity directed treatment with demonstrated OSA benefits rather than as a direct airway opening drug.

Acetazolamide has a different pharmacological profile. By inhibiting carbonic anhydrase, it produces a mild metabolic acidosis that increases ventilatory drive and can reduce instability of respiratory control. Evidence indicates that acetazolamide can decrease the AHI and improve oxygenation in selected patients, with its clinical relevance being particularly evident in central sleep apnea and high altitude sleep disordered breathing. Its advantages include an established mechanism and relatively extensive clinical experience; however, paresthesia, increased urination, electrolyte abnormalities and metabolic disturbances may limit tolerability. Consequently, acetazolamide is better regarded as a phenotype specific treatment than as a routine pharmacological therapy for uncomplicated OSA.

Atomoxetine combined with oxybutynin represents an upper airway neuromuscular strategy. Atomoxetine increases noradrenergic stimulation of upper airway motor neurons, while oxybutynin reduces muscarinic-mediated inhibition. Their combined action can increase genioglossus activity and improve upper airway stability during sleep. Controlled studies have reported marked reductions in OSA severity with this combination. Nevertheless, anticholinergic effects such as dry mouth, urinary symptoms and potential cardiovascular effects, together with limited long term safety data, currently restrict its use to an investigational or highly selected setting. It should therefore not be presented as equivalent to established outpatient treatments.

Sultiame is another emerging carbonic anhydrase inhibitor. Its proposed benefit is mediated through increased ventilatory drive and modulation of upper airway muscle activity. Recent phase II evidence demonstrated reductions in OSA severity following once-daily treatment, supporting further investigation of this approach. However, evidence regarding long term clinical outcomes, comparative effectiveness and safety remains limited. Sultiame therefore currently occupies an emerging rather than established position in OSA pharmacotherapy.

In contrast, solriamfetol and pitolisant are primarily used to address excessive daytime sleepiness rather than the underlying obstruction. Solriamfetol inhibits dopamine and norepinephrine reuptake, producing a wake-promoting effect. In the tones 3 randomized trial, solriamfetol significantly improved both objective wakefulness and subjective sleepiness in patients with OSA. The most frequently reported adverse effects included headache, nausea, decreased appetite and anxiety, with most events being mild to moderate. Thus, solriamfetol may be useful when clinically significant sleepiness persists despite appropriate management of OSA, but it should not be used as a substitute for treatment directed at the respiratory disorder.

Pitolisant acts principally through histaminergic pathways as a selective histamine H₃-receptor inverse agonist/antagonist. Clinical trials have demonstrated reductions in excessive daytime sleepiness among patients with OSA, including patients receiving CPAP and those who were unable or unwilling to use CPAP [46]. Headache and insomnia are among the commonly reported adverse effects. Recent phase III evidence also demonstrated significant improvement in Epworth Sleepiness Scale scores with pitolisant in patients with moderate to severe OSA, irrespective of CPAP use. Similar to solriamfetol, however, pitolisant primarily improves wakefulness and should not be interpreted as eliminating nocturnal airway obstruction.

The comparison demonstrates that tirzepatide differs fundamentally from wake promoting agents because its principal effect is on an important underlying risk factor for OSA, namely obesity. In contrast, solriamfetol and

pitolisant primarily improve daytime alertness. Consequently, improvement in subjective sleepiness with these agents should not be interpreted as resolution of nocturnal respiratory events. Similarly, acetazolamide and emerging agents such as atomoxetine, oxybutynin and sultiame are most appropriately considered within a phenotype directed framework rather than as universal treatments.

Medicine	Main Mechanism of Action	Principal Clinical Use	Effect on Sleep Apnea	Important Tolerability Considerations
Tirzepatide	GIP/GLP-1receptor agonism;decreases appetite and promotes substantial weight loss	Moderate-to-severe OSA associated with obesity	Reduces AHI and overall disease severity primarily through weight reduction	Mainly gastrointestinal adverse effects; monitoring is required for contraindications and metabolic effects
Acetazolamide	Carbonicanhydrase inhibition→bicarbonate loss → mild metabolic acidosis→increased ventilatory drive	Selected CSA, high-altitude periodic breathing, and selected OSA phenotypes	Improves ventilatory stability and may reduce AHI	Paresthesia, dysgeusia, increased urination,and electrolyte disturbances; caution in renal disease
Atomoxetine+ Oxybutynin/ Aroxybutynin	Increases noradrenergic upper-airway drive and reduces muscarinic inhibition	Emerging treatment for selected OSA phenotypes	Directly enhances upper-airway muscle responsiveness and may reduce AHI	Dry mouth, insomnia, urinary effects, and cardiovascular effects; not yet established as routine first-line therapy
Solriamfetol	Inhibits dopamine and norepinephrine reuptake	Residual excessive daytime sleepiness (EDS) in treated OSA	Improves wakefulness but does not eliminate upper-airway obstruction	Headache, nausea, decreased appetite, anxiety, and possible increases in blood pressure; cardiovascular monitoring may be required

Pitolisant	HistamineH3receptor antagonism/inverse agonism,increasing histaminergic neurotransmission	Excessive daytime sleepiness associated with OSA in selected patients	Improves daytime alertness rather than directly correcting airway obstruction	Headache, insomnia, nausea, and potential drug interactions; QT-related considerations should be assessed
Modafinil	Wake-promoting activity involving dopaminergic and other central neurotransmitter systems	Residual EDS despite effective OSA treatment	Improves daytime sleepiness but has little direct effect on airway obstruction	Headache, nausea, insomnia, anxiety, and potential drug interactions
Armodafinil	R-enantiomer of modafinil with wake-promoting activity	Residual EDS in effectively treated OSA	Improves wakefulness and functional outcomes without directly correcting airway obstruction	Headache, nausea, insomnia,and anxiety may occur;drug interactions should be considered

Table:5.2.2 Comparison of Medicines Used in Sleep Apnea Management

From a safety perspective, no pharmacological option can currently be considered completely free of clinically relevant adverse effects. The most appropriate treatment is therefore one in which the anticipated benefit is balanced against the patient's comorbidities, concomitant medications and individual risk factors. Current evidence supports a selective and individualized pharmacological approach, with weight directed therapy having the strongest evidence for reducing OSA severity and wake promoting therapy having an established role in selected patients with persistent excessive daytime sleepiness.

5.2.3 Mechanisms of Action of Pharmacological Therapies

Pharmacological therapies investigated for sleep apnea act through different physiological pathways, including weight reduction, enhancement of upper airway dilator muscle activity, stabilization of ventilatory control, and promotion of wakefulness. The mechanism of action of the principal pharmacological agents is described separately below.

5.2.3.1 Tirzepatide

Tirzepatide is a dual agonist of the glucose-dependent insulintropic polypeptide (GIP) and glucagon like peptide-1 (GLP-1) receptors. Activation of these receptors influences appetite and energy intake, resulting in substantial reduction in body weight. In patients with obesity associated obstructive sleep apnea (OSA), weight reduction can

decrease fat deposition and mechanical loading surrounding the upper airway, thereby reducing pharyngeal collapsibility during sleep. Tirzepatide therefore acts primarily through a weight mediated mechanism rather than directly stimulating the upper airway dilator muscles. Clinical trials have demonstrated that reductions in body weight are accompanied by reductions in apnea-hypopnea index (AHI) and other measures of OSA severity [47].

5.2.3.2 Acetazolamide

Acetazolamide is a carbonic-anhydrase inhibitor that alters renal bicarbonate handling and produces a mild metabolic acidosis. The resulting reduction in blood bicarbonate and increase in ventilatory drive stimulate respiration during sleep. This increased respiratory drive can reduce fluctuations in ventilation and stabilize breathing, particularly in patients with central sleep apnea (CSA) or elevated loop gain. Acetazolamide may consequently reduce the frequency of central and, in selected circumstances, obstructive respiratory events while improving nocturnal oxygenation. Its mechanism is therefore primarily related to modulation of ventilatory control rather than direct mechanical opening of the upper airway [48].

5.2.3.3 Sultiame

Sultiame is another carbonic-anhydrase inhibitor that can influence respiratory control through mild metabolic acidosis and increased ventilatory stimulation. In addition to increasing ventilatory drive, experimental evidence suggests that carbonic anhydrase inhibition may influence upper airway motor activity and respiratory stability. By modifying these physiological traits, sultiame may reduce the tendency toward repetitive respiratory events during sleep. The phase II flow trial demonstrated a reduction in OSA severity following once daily sultiame treatment, supporting further investigation of this mechanism directed approach [49].

5.2.3.4 Atomoxetine

Atomoxetine

is a selective norepinephrine reuptake inhibitor. During sleep, reduced noradrenergic activity can contribute to diminished activity of upper airway dilator muscles, particularly the genioglossus. By inhibiting norepinephrine reuptake, atomoxetine increases noradrenergic neurotransmission and can enhance activation of upper airway motor pathways. This may improve the ability of the pharyngeal dilator muscles to compensate for negative intraluminal pressure and maintain airway patency. Atomoxetine therefore primarily targets the impaired upper-airway muscle responsiveness endotype of OSA [50].

5.2.3.5 Oxybutynin

Oxybutynin is an antimuscarinic drug that inhibits muscarinic acetylcholine receptors. Cholinergic mechanisms can influence upper-airway motor activity during sleep, and reduction of muscarinic activity may decrease inhibitory influences on upper airway dilator muscle function. Oxybutynin has therefore been investigated in combination with atomoxetine to enhance upper airway muscle responsiveness. The combination is intended to produce complementary noradrenergic stimulation and antimuscarinic modulation, thereby improving upper-airway stability during sleep [51].

5.2.3.6 Atomoxetine And Oxybutynin Combination

The combination of atomoxetine and oxybutynin targets two complementary pathways involved in upper airway neuromuscular control. Atomoxetine increases norepinephrine availability and promotes activation of upper-airway motor neurons, whereas oxybutynin reduces muscarinic cholinergic activity. The combined effect can increase genioglossus activity and improve the ability of the upper airway to resist collapse. Randomized clinical studies have demonstrated substantial reductions in OSA severity with this combination, although treatment response varies among patients and long term safety remains incompletely established.

5.2.3.7 Solriamfetol

Solriamfetol is a dopamine and norepinephrine reuptake inhibitor that increases extracellular concentrations of these neurotransmitters in the central nervous system. Enhanced dopaminergic and noradrenergic signaling increases wake promoting activity and improves the ability to maintain wakefulness during the daytime. Solriamfetol therefore primarily addresses excessive daytime sleepiness associated with OSA rather than the underlying upper airway obstruction. Its mechanism does not directly prevent apnea or hypopnea during sleep and consequently should be distinguished from disease modifying treatments [52].

5.2.3.8 Pitolisant

Pitolisant is a selective histamine H3-receptor inverse agonist/antagonist. H3 receptors function as presynaptic autoreceptors that regulate histamine release. Their blockade increases histaminergic neurotransmission in the brain and promotes wakefulness. In patients with OSA, this mechanism can reduce excessive daytime sleepiness and improve daytime alertness. Similar to solriamfetol, pitolisant primarily provides symptomatic treatment of residual sleepiness and does not directly eliminate upper-airway obstruction or replace primary OSA therapy [53].

5.2.3.9 Mechanistic Comparison of Pharmacological Agents

The principal pharmacological agents used or investigated in sleep apnea can therefore be differentiated according to their primary biological targets. Tirzepatide acts predominantly through weight reduction and metabolic pathways; acetazolamide and sultiame primarily modify ventilatory control and respiratory drive; atomoxetine and oxybutynin enhance upper airway neuromuscular function through complementary pathways; while solriamfetol and pitolisant act predominantly on central wake promoting systems to reduce excessive daytime sleepiness. This distinction is clinically important because reduction in daytime sleepiness and reduction in nocturnal respiratory events represent different therapeutic outcomes. Wake promoting agents may improve daytime functioning without correcting the underlying sleep disordered breathing, whereas weight directed and physiological therapies have the potential to modify disease severity in appropriately selected patients. Consequently, pharmacological treatment should be selected according to the predominant pathophysiological mechanism and the specific therapeutic objective for each patient.

5.2.4 Pharmacological Treatment According to Patient Phenotype

Obstructive sleep apnea (OSA) is a heterogeneous disorder in which the relative contribution of anatomical and non-anatomical mechanisms differs substantially between individuals. Although increased upper airway collapsibility remains a major determinant of OSA, additional physiological traits include impaired upper-airway dilator muscle responsiveness, a low respiratory arousal threshold, and unstable ventilatory control or high loop gain. These differences provide a rationale for selecting pharmacological therapy according to the predominant phenotype or endotype rather than applying the same medication to all patients with OSA [54].

Patients with obesity-associated OSA. Obesity is one of the most important modifiable risk factors for OSA because increased adipose deposition around the upper airway can increase pharyngeal collapsibility. In patients with moderate to severe OSA and obesity, weight directed pharmacotherapy may therefore provide dual benefits by reducing body weight and improving the physiological factors contributing to airway obstruction. Tirzepatide, a dual GIP/GLP-1 receptor agonist, has demonstrated significant reductions in AHI and body weight in adults with obesity and moderate to severe OSA [55]. This approach may be particularly relevant for patients in whom excess body weight represents a major contributor to disease severity. However, pharmacological weight reduction should complement, rather than automatically replace, established OSA therapies when these remain clinically indicated.

Patients with impaired upper airway muscle responsiveness. Some patients have relatively inadequate activation of the pharyngeal dilator muscles during sleep despite an airway that is not maximally anatomically compromised. In such individuals, therapies designed to increase upper airway neuromuscular activity may be particularly relevant. The combination of atomoxetine and oxybutynin has been investigated for this purpose. Atomoxetine increases noradrenergic stimulation of upper airway motor pathways, whereas oxybutynin reduces muscarinic inhibition. Clinical studies have demonstrated improvements in upper airway collapsibility and muscle compensation with the combination. Recent physiological analyses further suggest that patients with less severe baseline OSA and relatively less severe airway collapsibility may have a greater probability of responding to this treatment [56]. Nevertheless, this combination remains an emerging approach and is not currently equivalent to established first line OSA treatment.

Patients with high loop gain or unstable ventilatory control. High loop gain refers to an exaggerated ventilatory response to changes in blood gases, resulting in repeated oscillations between excessive and insufficient respiratory drive. This instability can contribute to recurrent respiratory events and may be particularly important in patients with a substantial non anatomical component to their sleep apnea. Carbonic anhydrase inhibitors such as acetazolamide and sultiame can increase ventilatory drive through mild metabolic acidosis and thereby stabilize respiratory control. Acetazolamide has demonstrated reductions in AHI and improvements in oxygenation in selected patients with sleep disordered breathing. Sultiame has also demonstrated reductions in OSA severity in clinical trials and is being investigated as a mechanism-directed treatment [57]. These agents may therefore be considered in appropriately selected patients with ventilatory control instability, although their precise role in routine OSA management continues to evolve.

Patients with a low arousal threshold. The respiratory arousal threshold represents the degree of respiratory disturbance required to awaken an individual from sleep. Patients with a low arousal threshold may awaken in response to relatively modest airway narrowing or respiratory disturbances. Frequent premature arousals can fragment sleep and prevent the sustained activation of upper airway dilator muscles that might otherwise restore airway patency. Pharmacological modulation of the arousal threshold has consequently been investigated as a potential treatment strategy [58]. However, increasing the arousal threshold is not universally beneficial because excessive suppression of arousal may prolong obstructive events and worsen nocturnal hypoxemia. For this reason, pharmacological manipulation of this trait requires careful physiological selection and remains predominantly investigational.

Patients with persistent excessive daytime sleepiness. A separate phenotype consists of patients who continue to experience clinically significant daytime sleepiness despite appropriate management of the underlying OSA. In these patients, wake promoting agents may be considered when residual sleepiness has been appropriately evaluated. Solriamfetol increases dopaminergic and noradrenergic neurotransmission through inhibition of dopamine and norepinephrine reuptake and has demonstrated significant improvements in objective and subjective measures of wakefulness. Pitolisant enhances histaminergic neurotransmission through inverse agonism/antagonism of the histamine H3 receptor and has similarly demonstrated improvements in excessive daytime sleepiness in patients with OSA [59]. These agents are symptom directed and do not eliminate upper-airway obstruction; therefore, they should not be used as substitutes for effective treatment of the underlying sleep disordered breathing.

Patients with predominantly anatomical upper-airway obstruction. Patients whose OSA is dominated by marked anatomical airway collapsibility may derive less benefit from pharmacological approaches directed primarily at non anatomical traits. In these individuals, treatment selection should continue to emphasize established interventions such as positive airway pressure, oral appliance therapy in appropriately selected patients, positional interventions, weight management, or anatomical procedures where indicated. Pharmacological treatment may be

considered as an adjunct when a relevant treatable trait, such as obesity, ventilatory instability, or persistent sleepiness, is also present [60].

Patients with multiple physiological abnormalities. Many individuals do not exhibit a single isolated endotype. Instead, OSA may result from a combination of anatomical collapsibility, impaired muscle compensation, ventilatory instability, and altered arousal responses. Such patients may theoretically benefit from combination pharmacotherapy targeting more than one mechanism. Experimental studies combining drugs that enhance upper airway muscle activity with agents that stabilize ventilatory control have provided preliminary evidence supporting this concept. However, combination pharmacotherapy remains an emerging area and requires confirmation through larger, longer duration clinical trials before it can be incorporated routinely into clinical practice.

Phenotype guided pharmacotherapy therefore provides a framework for moving from a generalized treatment model toward individualized management. In practical terms, obese patients may be candidates for weight directed pharmacotherapy, patients with impaired upper airway muscle responsiveness may be investigated for neuromuscularly targeted approaches, patients with unstable ventilatory control may be considered for carbonic-anhydrase inhibition, and patients with persistent excessive daytime sleepiness may require wake-promoting therapy after adequate treatment of the underlying OSA. Importantly, these categories can overlap within the same patient. The future clinical application of pharmacotherapy is consequently likely to involve identification of dominant physiological traits followed by selection or combination of treatments that address those specific mechanisms [61,62].

At present, phenotype guided pharmacological treatment should be considered complementary to established OSA management rather than a universal replacement for positive airway pressure. The strongest evidence for a disease modifying pharmacological approach currently exists for weight directed therapy in appropriately selected patients with obesity, whereas several endotype specific treatments remain under investigation. Further development of practical methods for identifying OSA endotypes in routine clinical settings will be essential for translating precision pharmacotherapy from physiological research into everyday outpatient care.

5.2.5 Comparison of Established and Emerging Pharmacological Approaches

Pharmacological treatment of sleep apnea is undergoing a transition from predominantly symptomatic management toward disease-modifying and mechanism directed therapy. Historically, pharmacological agents have had a limited role in obstructive sleep apnea (OSA), as no conventional medicine could reliably overcome upper airway obstruction during sleep. Consequently, positive airway pressure (PAP), oral appliance therapy, positional interventions, weight management, and selected surgical procedures have remained the principal therapeutic approaches. The emergence of weight directed and endotype specific pharmacological therapies has, however, expanded the potential treatment options for selected patients [63].

Among currently established pharmacological approaches, wake promoting agents occupy an important but specific role. Solriamfetol and pitolisant can improve excessive daytime sleepiness in patients with OSA, particularly when clinically significant sleepiness persists despite appropriate management of the underlying sleep disordered breathing. Their major advantage is the ability to improve daytime functioning without requiring mechanical airway support. However, these medications primarily treat a consequence of OSA rather than the airway obstruction itself. Therefore, they should not be regarded as substitutes for effective treatment of nocturnal respiratory events.

Acetazolamide represents another relatively established pharmacological option, although its application is more restricted. Its ability to increase ventilatory drive through carbonic anhydrase inhibition makes it particularly relevant to central sleep apnea and selected forms of ventilatory instability. Evidence from systematic reviews demonstrates reductions in respiratory event frequency and improvements in oxygenation in appropriately selected patients. The 2025 American Academy of Sleep Medicine guideline conditionally recommends acetazolamide for several forms

of central sleep apnea, demonstrating that its clinical role is more established in central rather than uncomplicated obstructive sleep apnea [64].

A major change in the pharmacological landscape has been the development of **weight directed therapy for obesity associated OSA**. Tirzepatide provides a disease modifying approach by producing substantial weight loss, which can subsequently reduce the anatomical and physiological factors contributing to upper airway obstruction. The SURMOUNT OSA trials demonstrated significant reductions in AHI, body weight, hypoxic burden and sleep-apnea-related outcomes in adults with obesity and moderate to severe OSA. The subsequent regulatory approval of tirzepatide for moderate to severe OSA in adults with obesity represents an important milestone because it established pharmacological treatment specifically directed at OSA in an appropriately defined patient population. Unlike wake promoting agents, therefore, tirzepatide has the potential to modify an important underlying driver of OSA rather than simply treating daytime symptoms.

Emerging upper airway neuromuscular therapies represent a second major development. The combination of atomoxetine and oxybutynin has demonstrated substantial reductions in OSA severity in controlled clinical studies by increasing noradrenergic activation and reducing muscarinic inhibition of upper airway dilator activity. Its principal advantage is that it directly targets an important non anatomical contributor to airway obstruction. Nevertheless, adverse anticholinergic effects, cardiovascular considerations, limited long term evidence and uncertainty regarding regulatory approval restrict its current clinical application. Recent physiological studies have further emphasized that treatment response may depend strongly on patient characteristics, supporting its future use within an endotype-guided treatment model [65].

Sultiame represents another emerging therapy with a different but related physiological target. As a carbonic anhydrase inhibitor, it can increase ventilatory drive and influence respiratory stability. The flow phase II trial demonstrated clinically relevant reductions in OSA severity with once daily sultiame treatment [66]. These findings suggest that pharmacological manipulation of ventilatory control may become an important component of future OSA treatment. Nevertheless, phase III confirmation, longer term safety data, and evidence regarding patient-important outcomes are required before widespread routine use can be recommended.

The distinction between established and emerging therapies is summarized in Table 5.2.5

Treatment approach	Principal target	Current evidence	Major advantage	Major limitation	Current position
Solriamfetol	Dopaminergic and noradrenergic wake pathways	Multiple randomized controlled trials	Effective improvement of excessive daytime sleepiness	Does not directly correct airway obstruction; cardiovascular and other adverse effects require consideration	Established symptom-directed therapy

Pitolisant	Histamine H3 receptor and wake-promoting pathways	Randomized clinical trials	Improves daytime sleepiness, including in selected patients unable to use or adhering to CPAP	Does not directly eliminate nocturnal obstruction; medication-specific safety considerations	Established/symptom-directed therapy
Acetazolamide	Ventilatory control through carbonic-anhydrase inhibition	Systematic reviews and clinical guidelines, particularly for CSA	Can stabilize breathing and improve oxygenation	Electrolyte, metabolic and sensory adverse effects; limited role in uncomplicated OSA	Established for selected CSA indications
Tirzepatide	GIP/GLP-1 pathways and weight reduction	Large phase III trials	Reduces body weight and OSA severity; disease-modifying potential in obesity	Gastrointestinal adverse effects, contraindications and need for long-term monitoring	Established pharmacological option for selected adults with obesity and moderate-to-severe OSA
Atomoxetine + oxybutynin	Upper-airway neuromuscular activation	Early randomized trials	Directly targets impaired upper-airway muscle responsiveness	Anticholinergic /cardiovascular adverse effects and limited long-term evidence	Emerging/investigational
Sultiame	Carbonic-anhydrase inhibition and ventilatory stability	Phase II clinical evidence	Mechanism-directed reduction in OSA severity	Limited long-term and comparative evidence	Emerging
Combination endotype-directed therapy	Multiple physiological traits	Early clinical/experimental evidence	Potentially addresses several	Complex patient selection, safety and insufficient	Investigational

	simultaneously		interacting mechanisms	long-term evidence	
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Table:5.2.5 Comparison of established and emerging pharmacological approaches in sleep apnea

An important distinction between established and emerging pharmacological approaches is the level of clinical evidence. Established therapies generally have evidence from multiple randomized trials, established prescribing frameworks, or clinical practice recommendations for defined indications. Emerging therapies may demonstrate promising reductions in AHI or improvements in physiological measures but may lack sufficient evidence concerning long term cardiovascular outcomes, mortality, sustained adherence, or comparative effectiveness against established treatments.

Another important consideration is the therapeutic endpoint. Weight directed therapy aims to reduce the severity of OSA by modifying an underlying risk factor, whereas solriamfetol and pitolisant principally improve daytime consequences. Acetazolamide and sultiame attempt to modify ventilatory instability, while atomoxetine–oxybutynin targets upper airway neuromuscular compensation. Consequently, comparison based solely on AHI reduction can be misleading because the biological targets and intended clinical outcomes differ among therapies.

The **safety profile and treatment burden** also distinguish these approaches. Pharmacological therapy may avoid some of the practical disadvantages associated with mechanical devices, but this does not mean that medicines are inherently free of adverse effects. Tirzepatide is associated primarily with gastrointestinal adverse effects and requires consideration of important contraindications and warnings. Wake-promoting agents may produce headache, gastrointestinal symptoms, insomnia or cardiovascular effects, whereas carbonic-anhydrase inhibitors can cause paresthesia, diuresis and metabolic or electrolyte abnormalities. Atomoxetine–oxybutynin additionally raises concerns related to anticholinergic and cardiovascular effects. Thus, medication selection should involve individualized assessment rather than a general assumption that pharmacological therapy is better tolerated than non-pharmacological treatment.

The future distinction between established and emerging therapies is likely to become increasingly dependent on precision medicine. Conventional OSA management largely categorizes patients according to disease severity, whereas emerging pharmacological approaches attempt to identify the dominant physiological mechanism responsible for respiratory events. Such an approach could permit patients with obesity to receive weight-directed therapy, patients with impaired upper airway muscle responsiveness to receive neuromuscularly targeted treatment, and patients with ventilatory instability to receive therapies that stabilize respiratory control. Combination treatment may eventually be considered for individuals in whom multiple endotypes contribute substantially to disease severity [67].

Overall, established pharmacological treatments currently have relatively specific roles, particularly the treatment of residual excessive daytime sleepiness and selected forms of central sleep apnea. Tirzepatide has expanded this landscape by providing a pharmacological option that can directly reduce OSA severity in adults with obesity. In contrast, atomoxetine, oxybutynin, sultiame and other mechanism directed agents remain promising but require additional evidence before routine widespread adoption. The progression from symptomatic treatment toward disease modifying and phenotype-specific pharmacotherapy represents an important development in sleep medicine, but pharmacological approaches should continue to complement rather than indiscriminately replace established OSA therapies until sufficient long term evidence is available.

5.2.6 Safety and Tolerability of Pharmacological Treatment

The safety and tolerability of pharmacological treatment are important considerations in the management of sleep apnea because the currently available and emerging agents have substantially different mechanisms, adverse effect profiles, contraindications, and levels of clinical evidence. Pharmacotherapy should therefore be prescribed only after consideration of disease phenotype, comorbidities, concomitant medications, treatment objectives, and the potential risks associated with long term exposure. Current clinical guidance does not support routine pharmacological treatment for all adults with obstructive sleep apnea (OSA); rather, pharmacological agents are considered for selected treatable traits such as obesity or excessive daytime sleepiness [68].

Tirzepatide and metabolic therapies. Tirzepatide has demonstrated clinically important reductions in body weight and OSA severity in adults with obesity and moderate to severe OSA. However, its safety profile requires appropriate monitoring. Gastrointestinal adverse effects, including nausea, diarrhea, vomiting, constipation, abdominal discomfort and dyspepsia, are among the most frequently reported reactions. More serious but less frequent concerns include severe gastrointestinal reactions, acute kidney injury associated with volume depletion, gallbladder disease, pancreatitis and hypersensitivity reactions [69]. The current prescribing information also contains a boxed warning concerning thyroid C-cell tumors observed in rats and contraindicates use in individuals with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2 . Tirzepatide should therefore not be described as a medication with minimal adverse effects. Its risk benefit profile is most favorable when the expected OSA and weight management benefits are clinically meaningful and the patient is appropriately screened.

Carbonic anhydrase inhibitors. Acetazolamide and sultiame can produce adverse effects associated with carbonic anhydrase inhibition. Acetazolamide commonly causes paresthesia, increased urinary frequency and gastrointestinal symptoms and may produce electrolyte disturbances or metabolic acidosis. These effects can influence adherence, particularly when prolonged treatment is required. The available evidence supports acetazolamide mainly for selected forms of central sleep apnea and ventilatory control instability rather than routine treatment of uncomplicated OSA [70]. Sultiame has demonstrated promising efficacy in clinical trials, but its long-term safety profile in OSA remains less well established because clinical experience is considerably more limited than that of acetazolamide.

Atomoxetine and oxybutynin. The combination of atomoxetine and oxybutynin has shown potential to reduce OSA severity by enhancing upper airway neuromuscular activity. Nevertheless, tolerability is an important limitation. Atomoxetine may produce cardiovascular and central nervous system effects, including increases in heart rate or blood pressure, insomnia and other adrenergic symptoms. Oxybutynin can produce anticholinergic adverse effects such as dry mouth, constipation, urinary difficulties and blurred vision. These considerations become particularly relevant in older patients and in individuals with cardiovascular, urological or other conditions that may be aggravated by anticholinergic treatment [71]. Recent repeated dose research supports a physiological treatment effect, but the available duration of treatment remains relatively short and long term safety data are still required.

Wake-promoting medications. Solriamfetol and pitolisant are primarily used to control excessive daytime sleepiness rather than to correct nocturnal airway obstruction. Solriamfetol may cause headache, nausea, decreased appetite, anxiety and insomnia, and its noradrenergic activity requires consideration of cardiovascular status and blood pressure. Pitolisant is generally used as a wake promoting treatment through histaminergic modulation, with headache, insomnia and gastrointestinal symptoms among reported adverse effects [72]. The clinical benefit of these agents should therefore be weighed against the possibility of adverse effects, particularly when treatment is prolonged or when patients have multiple comorbidities. An important safety principle is that improvement in daytime sleepiness should not be interpreted as adequate control of OSA itself. Wake-promoting medications can

improve alertness while the underlying episodes of upper airway obstruction and nocturnal hypoxemia continue. Consequently, patients receiving these agents should continue appropriate treatment of the underlying sleep disordered breathing whenever possible. Current clinical guidance emphasizes evaluation and optimization of standard OSA treatment before pharmacological treatment of residual excessive daytime sleepiness is initiated^[73].

Risk of inappropriate pharmacological treatment. The use of sedative medications requires particular caution in patients with sleep apnea. Drugs that substantially depress respiratory drive or alter upper airway muscle activity may potentially worsen sleep disordered breathing in susceptible individuals. Benzodiazepines are therefore generally not recommended as treatment for comorbid insomnia in OSA when safer alternatives are available, and sedative therapy should be individualized and closely monitored. Similarly, pharmacological treatment should not be selected solely on the basis of a reduction in subjective sleepiness without evaluating its effects on respiratory events, oxygenation and overall sleep quality.

Long-term safety and monitoring. Most emerging pharmacological therapies for OSA have been evaluated over relatively short periods compared with the lifelong treatment requirements of chronic sleep apnea. Consequently, important questions remain regarding sustained efficacy, weight regain after discontinuation of weight loss medications, long term cardiovascular outcomes, adherence, drug interactions and cumulative adverse effects ^[74]. Monitoring should therefore extend beyond short term symptom improvement and include treatment adherence, adverse events, blood pressure where relevant, weight and metabolic parameters when weight-directed therapy is used, and objective measures of OSA control when clinically indicated.

The safety profile of pharmacological treatment is summarized in Table 5.2.6

Pharmacological approach	Common adverse effects	Major safety considerations	Monitoring considerations
Tirzepatide	Nausea, diarrhea, vomiting, constipation, abdominal symptoms	Thyroid C-cell tumor warning; severe GI reactions; gallbladder disease; pancreatitis; hypersensitivity	Weight, gastrointestinal tolerance, hydration, relevant metabolic parameters and clinical warning symptoms
Acetazolamide	Paresthesia, diuresis, gastrointestinal symptoms	Electrolyte disturbances, metabolic acidosis and renal considerations	Electrolytes and renal function when clinically appropriate
Sultiame	Carbonic-anhydrase-related adverse effects	Long-term OSA safety experience remains limited	Clinical tolerance and laboratory monitoring according to treatment protocol
Atomoxetine + oxybutynin	Dry mouth, constipation, urinary symptoms, insomnia, cardiovascular/adrenergic effects	Anticholinergic burden and cardiovascular risk	Blood pressure, heart rate and anticholinergic symptoms
Solriamfetol	Headache, nausea, decreased appetite, anxiety, insomnia	Blood-pressure and cardiovascular considerations	Blood pressure, heart rate, sleepiness and treatment response

Pitolisant	Headache, insomnia, gastrointestinal symptoms	Drug interactions and patient-specific cardiac considerations	Clinical response, adverse effects and concomitant medications
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Table:5.2.6 safety and tolerability of pharmacological treatment

Overall, the safety of pharmacological therapy depends strongly on appropriate patient selection rather than on the medication alone. Tirzepatide currently has the strongest disease modifying evidence for obesity associated OSA, but it also has clinically important contraindications and adverse effects. Wake-promoting agents have a more established symptomatic role but do not directly treat airway obstruction. Atomoxetine–oxybutynin and sultiame remain promising mechanism directed approaches, although their long-term safety and tolerability require further evaluation [74,75].

Thus, pharmacological treatment should be incorporated into a risk-benefit framework in which the expected improvement in OSA severity or daytime functioning is balanced against adverse effects, comorbidities, drug interactions, treatment burden and the availability of established non pharmacological therapies. Future studies should place greater emphasis on longterm safety, cardiovascular outcomes, quality of life, treatment adherence and identification of patients most likely to obtain clinically meaningful benefit from individual pharmacological interventions.

CONCLUSION:

Sleep related breathing disorders (SRBDs) constitute a significant group of sleep disorders that adversely affect respiratory function, sleep quality, and overall health. These conditions, which include obstructive sleep apnea (OSA), central sleep apnea (CSA), mixed sleep apnea, obesity hypoventilation syndrome (OHS), upper airway resistance syndrome (UARS), and sleep-related hypoxemia disorders, are increasingly recognized as major public health concerns due to their high prevalence and association with cardiovascular, metabolic, neurocognitive, and psychological complications . Despite advances in awareness and diagnostic capabilities, a substantial proportion of affected individuals remain undiagnosed and untreated.

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