A COMPREHENSIVE REVIEW ON SLEEP APNEA

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ABSTRACT

Background:
Sleep Apnea is a prevalent sleep disorder characterized by recurrent pauses in breathing during sleep, leading to fragmented sleep patterns and potential health risks. Despite its prevalence and impact on individuals' well-being, Sleep Apnea often goes undiagnosed and untreated. Understanding the causes, symptoms, and treatment options for Sleep Apnea is crucial for improving patient outcomes and reducing associated health risks.

Main body:
This review provides an overview of Sleep Apnea, including its epidemiology, pathophysiology, clinical manifestations, diagnostic methods, and treatment options. The prevalence of Sleep Apnea is increasing worldwide, with significant implications for public health. Risk factors for Sleep Apnea include obesity, age, gender, and anatomical abnormalities of the upper airway. Untreated Sleep Apnea is associated with numerous adverse health outcomes, including cardiovascular disease, hypertension, diabetes, cognitive impairment, and decreased quality of life. Diagnosis of Sleep Apnea typically involves polysomnography or home Sleep Apnea testing, followed by treatment with continuous positive airway pressure (CPAP) therapy, oral appliances, lifestyle modifications, or surgical interventions.

Conclusion:
In conclusion, sleep Apnea is a common and serious sleep disorder with significant health consequences. Early recognition and appropriate management of Sleep Apnea are essential for improving patients' quality of life and reducing the burden of associated comorbidities. Further research is needed to better understand the underlying mechanisms of sleep Apnea and to develop more effective treatments.

Key Words: Complex sleep Apnea syndrome, Central sleep Apnea, Continuous Positive Airway Pressure, Sleep Apnea, Obstructive Sleep Apnea.

BACKGROUND

Sleep Apnea can have significant health implications due to the interruption of normal breathing patterns during sleep. It's important to seek proper diagnosis and treatment if you suspect you may be experiencing sleep apnea. cessation of breathing during sleep is a defining characteristic of sleep apnea. These episodes result in hypoxemia; This means that a person with sleep apnea experiences periods where they temporarily stop breathing while asleep. This can lead to reduced oxygen levels in the blood and disrupt the normal sleep cycle. Thus, the consequences are both cardiorespiratory and neural.[1-6] Previous studies on sleep-related breathing disorders, particularly obstructive sleep apnea (OSA), have indeed emphasized its clinical features. OSA involves repetitive occurrences of either partial or complete obstruction of the upper airway during sleep, which leads to decreased levels of oxygen and increased levels of carbon dioxide. To counteract this obstruction and restore normal breathing, patients experience frequent awakenings, causing disruptions in their sleep patterns. This can result in fragmented and discontinuous sleep.[7] Central apnea is characterized by apnoeic events during sleep without associated ventilatory effort. Central sleep apnea syndrome involves repeated apneas during sleep due to a loss of respiratory effort. While the exact cause of central apnea is often unclear, ongoing research into the control of breathing during sleep and its association with certain diseases has identified potential mechanisms. It's important to note that the nonbehavioral control system plays a significant role in regulating ventilation during sleep. Therefore, any diseases affecting this control system can influence breathing patterns while the patient is asleep.[8] Complex sleep apnea syndromes (CompSAS), also known as treatment-emergent central sleep apnea, is a condition characterized by a combination of both obstructive and central apneas during sleep. In individuals with CompSAS, central apneas tend to become more prominent when they are exposed to continuous positive airway pressure (CPAP), which is a common treatment for obstructive sleep apnea. This means that individuals with CompSAS may initially present with obstructive events, but when treated with CPAP, they may experience an increase in central apneas. It's a complex condition that requires careful evaluation and management by healthcare professionals specializing in sleep disorders.[9]

HISTORY OF SLEEP APNEA

The history of sleep apnea is marked by significant milestones in understanding, diagnosing, and treating this condition. Here's a brief overview:

1. **Mid-19th Century:** Observations of periodic breathing in sleep were first reported in the mid-1850s.
2. **1870s:** British physicians described cases of obstructed apneas as "fruitless contractions of the inspiratory and expiratory muscles against glottic obstruction with accompanying cyanosis during sleep".
3. **Late 19th Century:** Doctors began to group together symptoms of sleep apnea under the term "Pickwickian syndrome," named after a character in Charles Dickens' novel "The Pickwick Papers."

4. **Early to Mid-19th Century:** Periodic breathing was reported in heart failure patients by British physician Hunter and Irish physicians Cheyne and Stokes. It was also observed in otherwise healthy subjects at high altitudes by British physiologists.
5. **Early 1960s:** Comprehensive studies by Bulow marked the first reports on the effects of sleep on ventilation and ventilatory stability in health.
6. **1970s:** Case reports of obstructive sleep apnea and the occasional use of chronic tracheostomy for treatment started to emerge.
7. **Mid to Late 1970s through Early 1980s:** Significant advancements in physiological research on sleep and breathing took place,
8. **Late 20th Century:** Sleep apnea was officially designated as a disorder and received more attention from the medical community.
9. **Recent Decades:** Continuous research, technological advancements, and the development of various treatment options, including positive airway pressure therapy, oral appliances, and surgical interventions, have significantly improved the management of sleep apnea.

It's important to note that the information provided is based on historical records up until my last training data in January 2022.[1, 5]

OBSTRUCTIVE SLEEP APNEA (OSA):

Breathing is regulated by centrally located respiratory centres in the brainstem, which control the muscles involved in respiration. Any dysfunction in these centres, as well as issues in the upper airway, can lead to abnormal breathing patterns, especially during sleep. This can result in disruptions in gas exchange and frequent awakenings during the night.[10] In obstructive sleep apnea (OSA), the primary Patho mechanism involves partial or complete obstruction of the upper airways during sleep, leading to decreased airflow and oxygen desaturation. This obstruction can be influenced by various factors, including anatomical abnormalities in the upper airways, altered neuromuscular control of pharyngeal muscles, and a general reduction in skeletal muscle tone during sleep. Additionally, external negative pressure applied to the mouth and nose can induce upper airway collapse, which aligns with the concept of the Starling resistor, a model used to understand collapsible tubes like the upper airways.[11]

PATHOPHYSIOLOGY OF OSA:

Obstructive sleep apnea (OSA) is a condition characterized by recurrent episodes of partial or complete upper airway obstruction during sleep, leading to disruptions in breathing and subsequent drops in blood oxygen levels. Here's a simplified overview of its pathophysiology:

1. **Upper Airway Obstruction:** During sleep, the muscles in the throat and tongue relax. In individuals with OSA, this relaxation can lead to a narrowing or complete closure of the upper airway.

2. **Airflow Obstruction:** As the airway narrows or closes, it becomes more difficult for air to flow into the lungs, resulting in reduced or absent airflow.
3. **Hypoxia and Hypercapnia:** Reduced airflow leads to a drop in blood oxygen levels (hypoxia) and an increase in carbon dioxide levels (hypercapnia). This triggers various physiological responses.
4. **Arousal Response:** The brain senses the drop in oxygen and increase in carbon dioxide, causing a brief arousal from sleep. This stimulates the upper airway muscles to contract and reopen the airway.
5. **Fragmented Sleep:** These recurrent arousals disrupt the normal sleep cycle, preventing individuals from reaching deeper stages of sleep, leading to fragmented and poor-quality sleep.
6. **Sympathetic Activation:** The repeated cycles of airway obstruction and arousal lead to an increase in sympathetic nervous system activity. This can result in elevated blood pressure and other cardiovascular changes.
7. **Systemic Effects:** OSA is associated with various systemic consequences, including hypertension, cardiovascular disease, metabolic disturbances, and cognitive impairment.
8. **Inflammatory Response:** OSA can trigger an inflammatory response in the body, which may contribute to the development or exacerbation of other health conditions.

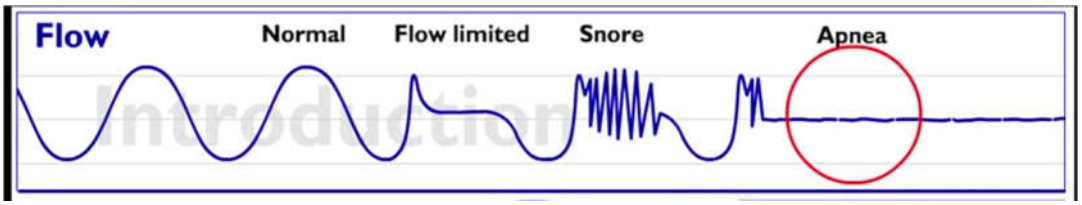


Figure 1. overview of its pathophysiology, characterized by recurrent episodes of partial or complete upper airway obstruction and flow limitations or airflow obstruction during sleep, leading to snoring and disruptions in breathing and subsequent hypoxia drops.[1]

It's important to note that the severity of OSA can vary widely, and not all individuals with OSA will experience the same degree of symptoms or complications. Additionally, OSA is a complex condition influenced by factors like obesity, genetics, and lifestyle. 10, 11, 46

Upper Airway Obstruction Pattern

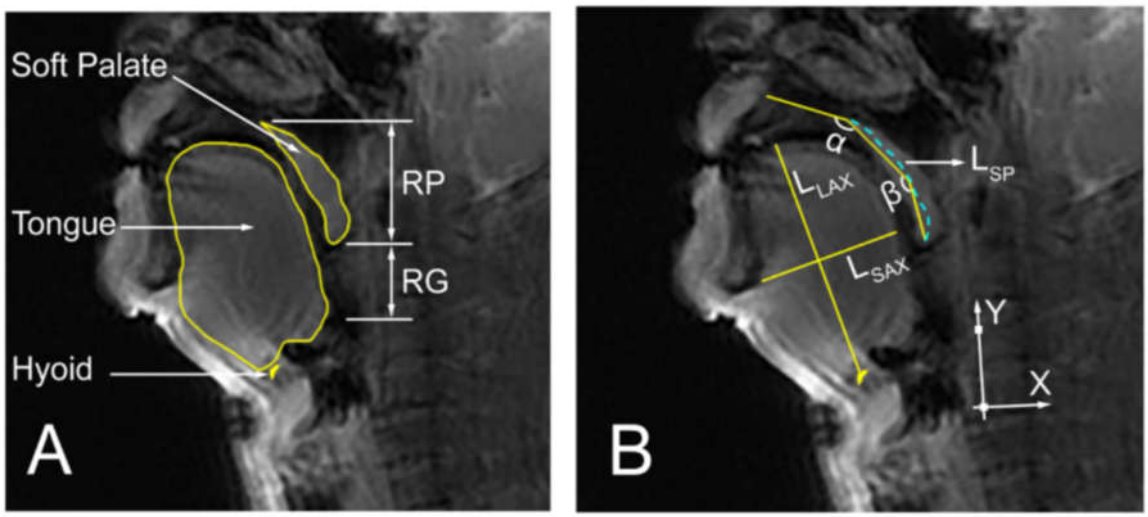
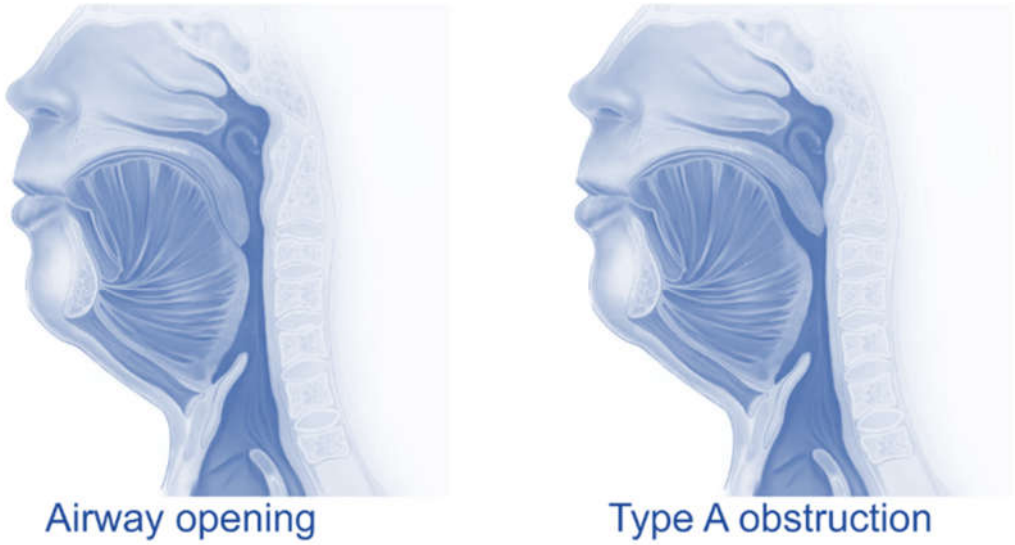


Figure 2. Schematic diagram of the tissues (A) and morphological parameters (B) to be extracted. RP: Retropalatal; RG: Retroglossal region; LLAX: The long axis of the tongue; LSAX: the short axis of the tongue; α: the angle between the hard palatal and the soft.[12]

Type for our statistical analysis. If a patient had multiple types of airway obstruction, the patient was classified based on the longest cumulative time for the type of obstruction. As well, we characterized the airway anatomical parameters in normal breathing status of the patients using the mean value of the parameters during airway opening.[12]

We first categorized airway obstruction into three major patterns based on dynamic MRI in the mid-sagittal plane, as shown in Figure 2.



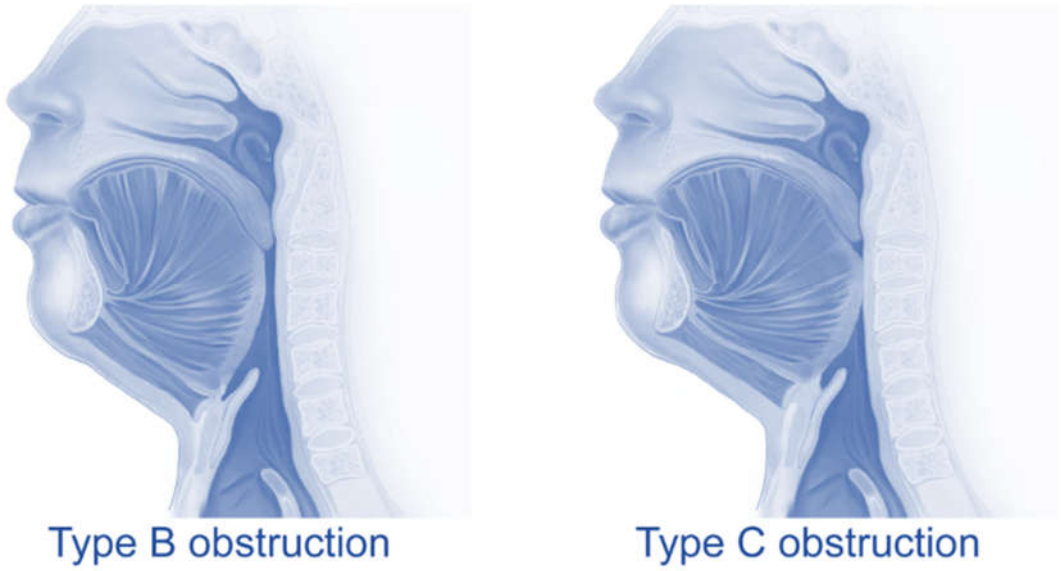


Figure 3: Schematic diagram of upper airway opening and different types of obstruction. [12]

These patterns included retropalatal obstruction caused by a backward movement of the soft palate separated from the tongue (Type A), retropalatal obstruction due to a backward movement of the soft palate attached to the tongue (Type B), and retropalatal and retroglossal obstruction arising from a combined backward movement of the soft palate and the tongue (Type C). However, there were two distinct tissue movement patterns within type B obstruction. This prompted us to further subdivide type B obstruction into type BI and type BII. Both subtypes were characterized by retropalatal obstructions resulted from tongue pushing against the soft palate, but they exhibited different tissue movements. Supplementary dynamic schematic diagrams of the four obstruction patterns are presented here, which can clearly distinguish between BI and BII obstruction.[12]

CENTRAL SLEEP APNEA:

Do you know what happens to our respiratory drive when we fall a sleep?

In central sleep apnea, the normal respiratory drive, which is controlled by the brain's respiratory centres, can be disrupted. Unlike obstructive sleep apnea, where there is a physical obstruction in the airway, central sleep apnea occurs when the brain fails to send the proper signals to the muscles that control breathing. This means that during central sleep apnea episodes, the body essentially forgets to breathe. This can lead to periods of interrupted or shallow breathing during sleep, which can cause a decrease in blood oxygen levels. In central sleep apnea, there can be a loss of behavioural control over breathing and a narrowing of the physical parameters that regulate respiration. This is because central sleep apnea is primarily a disorder of the central nervous system, where the brain's respiratory centres fail to maintain proper control over the breathing process. As a result, the body's ability to regulate breathing becomes compromised, leading to episodes of interrupted or shallow breathing during sleep.

This can have significant effects on the body's oxygen levels and overall physiological function.

Central sleep apnea (CSA) is characterized by a lack of drive to breathe during sleep, resulting in repetitive periods of insufficient ventilation and compromised gas exchange. These night time breathing disturbances can lead to important comorbidity and increased risk of adverse cardiovascular outcomes.

Central apnea is defined by a lack of respiratory effort during cessations of airflow. This means that during a central apnea episode, there is a pause in breathing without any associated physical effort to breathe. This can occur due to various reasons, including,

a) hypoventilation (abnormally slow or shallow breathing)
b) hyperventilation (excessive rapid breathing). (less commonly) 18, 49

In central sleep apnea, a common mechanism involves a condition known as high loop gain.

Loop gain refers to the feedback control system that regulates breathing. When the loop gain is high, it means that small disturbances in breathing can lead to exaggerated responses, potentially causing oscillations in breathing patterns. Loop gain is a concept borrowed from control theory and engineering, which can be applied to describe the stability of a feedback control system in central sleep apnea.

In the context of central sleep apnea, the feedback control system involves the body's regulation of breathing. This system includes sensors that monitor factors like blood oxygen and carbon dioxide levels, as well as neural pathways and muscles that control respiration. When there is a disturbance in breathing (such as an apnea episode), the feedback control system responds to correct the situation. Loop gain specifically quantifies how much the system responds to a disturbance. A high loop gain means that even small disturbances can lead to exaggerated responses, potentially causing oscillations in breathing patterns. In central sleep apnea with high loop gain, hyperventilation (excessive rapid breathing) can be a contributing factor. This leads to an excessive elimination of carbon dioxide from the body, resulting in low levels of carbon dioxide in the blood (hypocapnia). This, in turn, can disrupt the normal respiratory control system, leading to episodes of central apnea. In the context of respiratory physiology, loop gain is defined as the ratio of the ventilatory response to a ventilatory disturbance. It measures how much the system responds to a disturbance in ventilation. [18,49,50]

LOOP GAIN COMPRISES THREE PRINCIPAL COMPONENTS:

1. **Plant Gain (Gp):** This component represents the sensitivity of the respiratory system to changes in carbon dioxide levels. It indicates how much the ventilation rate changes in response to alterations in carbon dioxide concentration.[50]

2. **Controller Gain (Gc):** This component relates to the responsiveness of the central respiratory centres in the brainstem. It determines how much the central respiratory centres adjust the breathing rate in response to changes in carbon dioxide levels.[51]
3. **Delay (Td):** The delay component refers to the time it takes for changes in carbon dioxide levels to be detected by the central respiratory centres and for the response to be initiated.[52]

These three components together influence how the respiratory system responds to disturbances, such as apneas or hypopneas, in central sleep apnea. [18,50,51,52]

MECHANISMS COMPLEX SLEEP APNEA

The mechanism of complex sleep apnea, particularly in terms of CO2 levels, involves a complex interplay between the body's respiratory control system, feedback mechanisms, and the application of positive airway pressure (PAP) therapy**.**

1. **Pre-existing Obstructive Sleep Apnea (OSA):** Individuals with complex sleep apnea often have a history of OSA. In OSA, there are repeated episodes of partial or complete upper airway obstruction during sleep. This leads to a buildup of carbon dioxide (CO2) in the blood (hypercapnia) and a decrease in oxygen levels (hypoxia).
2. **Positive Airway Pressure (PAP) Therapy:** When individuals with OSA are treated with PAP therapy (such as CPAP or BiPAP), a continuous flow of air at a prescribed pressure is delivered through a mask, effectively stenting the airway open. This helps to prevent airway obstruction.
3. **Changes in Respiratory Control System:** In some cases, the application of positive pressure to the airway can lead to changes in the respiratory control system. This can include alterations in the sensitivity of chemoreceptors (which detect changes in CO2 levels) and the responsiveness of the brainstem's respiratory centres.
4. **Ventilatory Instability:** The introduction of PAP therapy may disrupt the normal feedback mechanisms that regulate breathing, particularly the response to CO2 levels. This can result in a state of ventilatory instability, where the body's breathing patterns become erratic and may shift between obstructive and central patterns.[20,54]

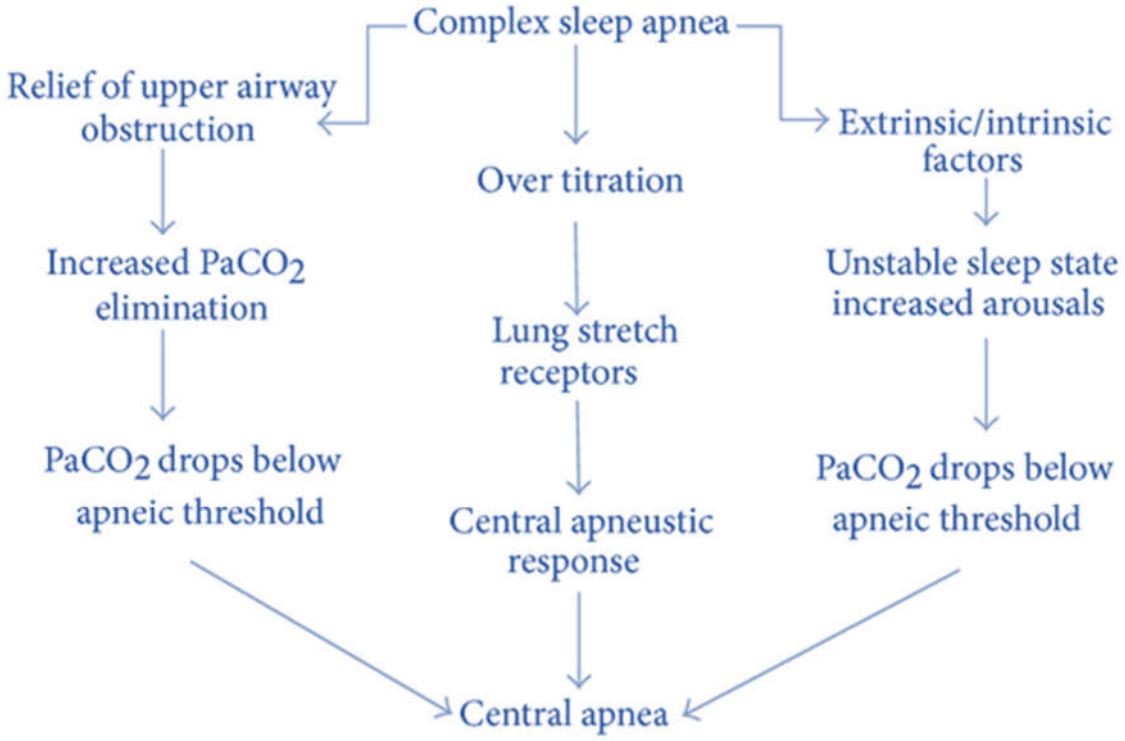


Figure 4. Schematic representation of pathogenesis of complex sleep apnea.[21]

SYMPTOMS:

Table 1. Night time and day time symptoms.

NIGHT TIME SYMPTOMS	DAY TIME SYMPTOMS
Loud persistence snoring	Early morning headache
Witness pauses in breathing	Daytime sleepiness
Choking or gasping for air	Poor concentration
Restless sleeping	Irritability
Frequent visits to the bathroom	Falling asleep during routine activities

TESTS THAT MAY HELP DIAGNOSE CENTRAL SLEEP APNEA OR ELIMINATE OTHER ISSUES INCLUDE:

- A sleep study, or polysomnography [22,23]
- An electrocardiogram, to observe the heart [24,25]

- lung function testing, to rule out other conditions [26,27]
- An MRI of the spine and brain, to check for structural issues [28,29]

RISK FACTORS: Sleep apnea can affect people regardless of sex, race, or age. However, risk factors include:

- Congestive heart failure[30]
- Diabetes[31]
- Cardiovascular disease[32,33]
- Obesity[34,35,36]
- Gender[37]
- Large neck circumference (greater than 16–17 inches)
- Enlarged tonsils or tongue[38]
- Narrow upper jaw[39]
- Nasal congestion[40]
- Allergies[41]
- gastroesophageal reflux[42]

Table 2. Treatment based on Severity.

	Mild OSA (AHI/RDI 5 – 14.9)	**Moderate OSA (AHI/RDI 15 – 29.9)**	**Severe OSA (AHI/RDI ≥30)**
Primary treatment	Observe (Asymptomatic) Positional Therapy Oral appliance Surgery – UPPP	PAP	PAP
Secondary treatment	PAP	Oral appliance Or Surgery – UPPP	Surgery – MMA Or Oral appliance
Adjunctive	Weight loss Positional Therapy	Weight loss Positional Therapy	Weight loss Positional Therapy

TREATMENT OPTIONS:

- Continuous fixed positive pressure (CPAP)
- Behavioural treatments
- Oral appliances (OA) or mandibular repositioning appliances (MRA)
- surgical procedure
- pharmacological drug therapies[47,50]

NEW AND NOVEL THERAPIES FOR OSA:

- Oral Pressure Therapy (OPT)
- Nasal Expiratory Positive Airway Pressure
- Upper Airway Stimulation[47]

PHARMACOTHERAPY

Pharmacotherapy is generally not the primary treatment for obstructive sleep apnea (OSA). Lifestyle changes, positional therapy, continuous positive airway pressure (CPAP), and oral appliances are commonly used first-line treatments. However, there are some medications that may be considered in specific cases:

1. **Modafinil or Armodafinil:** These medications are wakefulness-promoting agents and are sometimes prescribed to address daytime sleepiness associated with sleep apnea.
2. **Oxygen Therapy:** Supplemental oxygen may be used in certain cases, especially for individuals with central sleep apnea or those who have low blood oxygen levels during sleep.
3. **Acetazolamide:** This medication may be considered for individuals with central sleep apnea, as it stimulates breathing and can help normalize ventilation.[61]

Central Sleep Apnea (CSA) involves a lack of respiratory effort, unlike obstructive sleep apnea where the airway is physically blocked. Treatment for CSA often includes addressing underlying medical conditions and, in some cases, pharmacotherapy.

Here are some medications that may be considered for the management of central sleep apnea:

1. **Acetazolamide:** This medication helps stimulate breathing and is sometimes used for individuals with CSA, particularly those at high altitudes or with conditions like congestive heart failure.
2. **Adaptive Servo-Ventilation (ASV):** While not a medication, ASV is a device that adjusts airway pressure based on detected breathing patterns. It is a form of positive airway pressure therapy specifically designed for central sleep apnea.
3. **Theophylline:** This bronchodilator has respiratory stimulant effects and may be considered in certain cases of CSA.
4. **Oxygen Therapy:** Supplemental oxygen is sometimes used to treat central sleep apnea, especially if low oxygen levels are detected during sleep.62

BEHAVIORAL TREATMENTS:

Behavioral treatments can complement other therapies for sleep apnea, focusing on lifestyle changes and habits. Here are some behavioral strategies that may help manage sleep apnea:

1. Weight Management
2. Sleep Positioning
3. Avoiding Alcohol and Sedatives
4. Smoking Cessation
5. Regular Sleep Schedule
6. Positional Therapy[63, 64]

CONCLUSION

Sleep apnea is a common and serious sleep disorder with significant health consequences. Early recognition and appropriate management of sleep apnea are essential for improving patients' quality of life and reducing the burden of associated comorbidities. Further research is needed

to better understand the underlying mechanisms of sleep apnea and to develop more effective treatments.

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