Ciencia Latina Revista Científica Multidisciplinar, Ciudad de México, México.
ISSN 2707-2207 / ISSN 2707-2215 (en línea), marzo-abril 2025,
Volumen 9, Número 2.

https://doi.org/10.37811/cl_rcm.v9i2

SLEEP, OBSTRUCTIVE SLEEP APNEA AND CIRCADIAN RHYTHMS

SUEÑO, APNEA OBSTRUCTIVA DEL SUEÑO Y RITMOS CIRCADIANOS

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DOI: https://doi.org/10.37811/cl_rcm.v9i2.17006

Sleep, Obstructive Sleep Apnea and Circadian Rhythms

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ABSTRACT

A non-reversible obstructive inflammatory process of the small airways and destruction of the alveolar walls characterizes Chronic Obstructive Pulmonary Disease (COPD). One of the direct consequences is poorer quality sleep. It has also been proven that sleep-related symptoms correspond to significant changes in the respiratory center, airway resistance, and muscle contractility. The main sleep disorder that these patients may present is Obstructive Sleep Apnea Syndrome (OSAS), which is characterized by repetitive airway obstruction during sleep with complete or partial cessation of airflow. This alteration can have effects on the circadian rhythm of the sleep-wake cycle, such as a desynchronization of the light-dark cycle or endogenously desynchronized, resulting in: insomnia, fatigue, and poor performance in daily activities and symptoms such as insomnia or hypersomnia, common in patients with circadian sleep disorders, although there are other causes to which they can be attributed and that must be excluded before making the diagnosis of a circadian sleep disorder. In a patient without another sleep pathology, a daily record of activities, meals, exercise, naps, and bedtime is an essential tool to evaluate circadian sleep disorders.

Keywords: sleep, circadian rhythms, apnea, melatonin

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RESUMEN

La Enfermedad Pulmonar Obstructiva Crónica es un proceso inflamatorio obstructivo no reversible de las vías aéreas. Una de las consecuencias directas es la peor calidad del sueño. También se ha comprobado que los síntomas relacionados con el sueño corresponden a cambios significativos en el centro respiratorio, la resistencia de las vías aéreas y la contractilidad muscular. El principal trastorno del sueño que pueden presentar estos pacientes es el Síndrome de Apnea Obstructiva del Sueño (SAOS), que se caracteriza por la obstrucción repetitiva de las vías aéreas durante el sueño con cese completo o parcial del flujo aéreo. Esta alteración puede tener efectos sobre el ritmo circadiano del ciclo sueño-vigilia, como una desincronización del ciclo luz-oscuridad o desincronizarse endógenamente, dando como resultado: insomnio, fatiga y bajo rendimiento en las actividades diarias y síntomas como insomnio o hipersomnia, comunes en pacientes con trastornos circadianos del sueño, aunque existen otras causas a las que se pueden atribuir y que deben excluirse antes de realizar el diagnóstico de un trastorno circadiano del sueño. En un paciente sin otra patología del sueño, un registro diario de actividades, comidas, ejercicio, siestas y hora de acostarse es una herramienta esencial para evaluar los trastornos circadianos del sueño.

Keywords**:** sueño, AOS, ritmos circadianos, apnea, melatonina

Artículo recibido 20 febrero 2025
Aceptado para publicación: 25 marzo 2025

INTRODUCTION

The prevalence of Obstructive Sleep Apnea (OSA) has increased due to the aging of the population and the risk factors acquired by bad habits developed in daily life, which predispose to diseases such as obesity. Sleep is essential for human beings. It is regulated by two processes, one circadian and one homeostatic. Therefore, if sleep disturbances occur, essential functions of the body are affected. It has demonstrated that circadian rhythms are involved in functions of the body and intervene in the form of expression of chronic diseases, making it interesting to investigate the relationship that the deregulation of these rhythms could have with OSA, one of the principal sleep disorders.

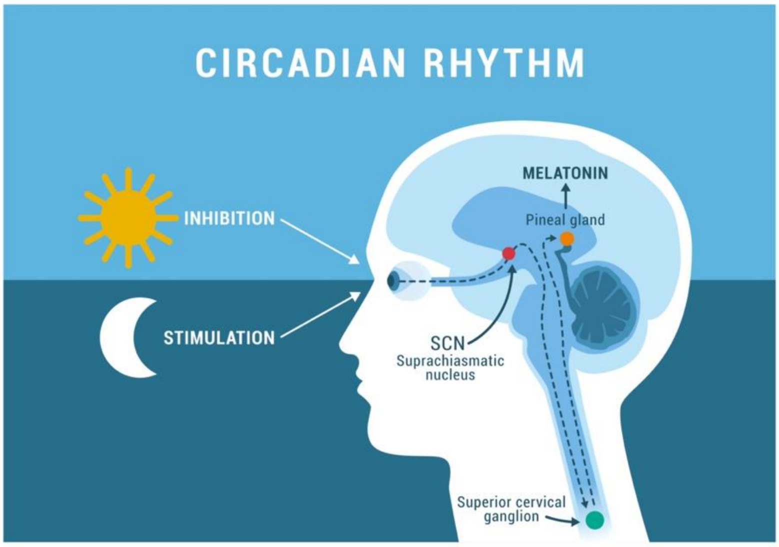
Neurobiology of sleep

Sleep is a natural, reversible state of reduced response to stimuli, relative neuronal inactivity, and loss of consciousness. It hasn't been possible to have a specific definition that explains all the mechanisms involved in sleep but now that it is a cyclical process essential for the optimal health and well-being of human beings as well as for maintaining the homeostasis of the body. The time a person sleeps is equivalent to a third of their life. We could think that it is only a period of rest but while we sleep, many meaningful physiological processes happen, for example, memory, learning, moods, and behavior, as well as immune responses, metabolic processes, hormone levels, digestion, among others (Acosta, 2019).

Sleep is regulated by the circadian system, imposing a sleep-wake cycle with 24 hours synchronized mainly by the light-dark cycle. In this process, different interactions occur that include multiple neuronal circuits, neurotransmitters, and hormones (Foster, 2020). Melatonin is one of the main hormones that, due to its chronobiotic capacity, influences the suprachiasmatic nucleus and functions as a central pacemaker that coordinates all circadian rhythms. Melatonin release is a phototransduction process that is stimulated in the dark through the eye, sending nerve signals which, via the retinohypothalamic tract, stop at the suprachiasmatic nucleus, which it inhibits, releasing the sympathetic system via a direct projection to the paraventricular nucleus of the hypothalamus, which projects to the intermediate lateral column of the spinal cord, terminating in the superior cervical ganglion which projects its sympathetic fibers directly to the pineal gland. Melatonin usually peaks during the dark phase of the day (Poza et al., 2022).

Regarding neuronal circuits and neurotransmitters, it is important to know that while we sleep, the brain is still active regulating sleep from various structures in the brain stem, hypothalamus, thalamus, and forebrain. Sleep and awakening are regulated through the participation of the ascending reticular activation system and nuclei in the hypocretinergic, GABAergic, histaminergic, adrenergic, and cholinergic systems (Telias & Wilcox, 2019). When we are awake, neurons in the lateral hypothalamus project and excite different populations of neurons that promote wakefulness within the mid-hindbrain, among these neurons are monoaminergic neurons that release histamine, dopamine, and serotonin, as well as cholinergic neurons that release acetylcholine in the hindbrain and neurons that release glutamate. This set of neurotransmitters projects inhibits the ventrolateral preoptic nucleus, activating wakefulness and consciousness in the cortex. In the case of sleep periods, the ventrolateral preoptic nucleus is activated by the release of neurotransmitters gamma-aminobutyric acid and galanin that inhibit orexin neurons in the lateral hypothalamus and monoaminergic, cholinergic, and glutamatergic neuronal populations (Saper & Fuller, 2017).

Figure 1. Circadian sleep-wake rhythm. Release of melatonin in the dark phase of the day.



Sleep stages

Sleep is divided into two stages: rapid eye movement (REM) and non-REM sleep (NREM). In REM sleep, high-frequency, low-amplitude electroencephalographic activity like wakefulness occurs, along with a decrease in muscle tone. NREM sleep is divided into three stages: N1, N2 and N3;

electroencephalographic activity is high amplitude, synchronized and low frequency (Kohtala et al., 2021). Stage N1 occurs when the individual feels sleepy and marks the change from the awake state. In the N2 stage, the dynamics of vital signals, such as eye movements, heart rate, body temperature, and brain activity, begin to attenuate. Stage N3 is considered deep or slow wave sleep; no eye or muscle movement occurs (Hussain et al., 2022).

Sleep stages alternate, presenting four to five sleep cycles per night. The first sleep cycle has a longer duration of NREM sleep and a shorter duration of REM. In subsequent sleep cycles, the duration of NREM sleep progressively shortens while the proportion of REM sleep increases (Kohtala et al., 2021).

Recapitulating, two basic processes are considered to regulate the time and duration of sleep: a circadian one that defines the alternation of periods, independent of wakefulness and sleep but linked to oscillations in core body temperature and melatonin secretion and a homeostatic process determined by sleep-wake that allows an increase in sleep pressure when restricted or absent and a reduction in sleep pressure in response to excess sleep. It's meaningful to remember that the circadian process determines the quantity of sleep, while homeostasis determines the quality. When the two systems are in a state of balance, the individual can stay awake for a long time in the day (approximately 16 hours) and maintain long, stable sleep at night (approx. 8 hours) (Sun & Chen, 2021).

Sleep disorders

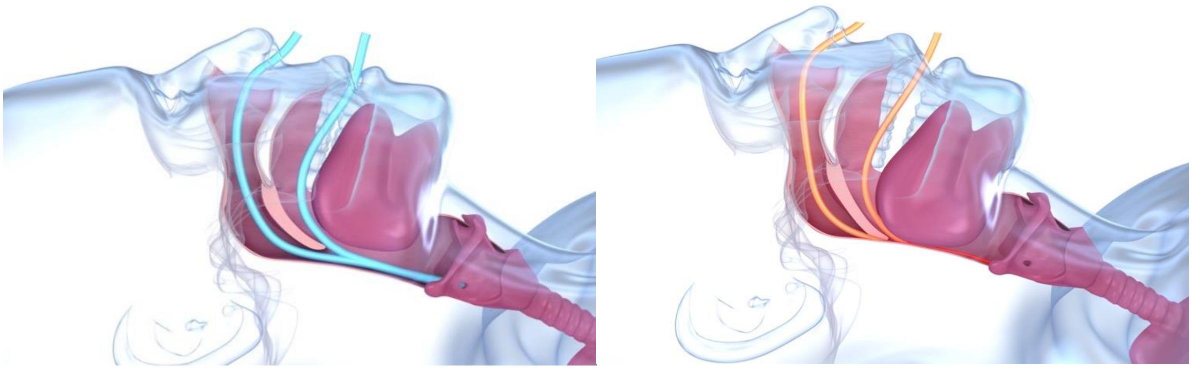
Due to the importance of the sleep process for human beings, the disorders that can occur during this process and that will cause more than one of the main functions of the body to be affected have been to be investigated. The American Academy of Sleep Medicine has made the third edition of the classification of sleep disorders, establishing them as: insomnia, sleep-related breathing disorders, central hypersomnolence disorders, sleep-wake circadian rhythm disorders, parasomnias, sleep-related movement disorders and other sleep disorders (Sateia, 2014).

Although all the disorders mentioned above are important, in this case, we will focus on sleep-related breathing disorders: obstructive sleep apnea (OSA), central sleep apnea, and non-obstructive hypoventilation, because in recent years, it's prevalence has increased. Specifically, we will talk about OSA since its prevalence records previously ranged between 2% in women and 4% in men. However, they have increased abruptly, registering a prevalence of 23 to 26% in women and 40.6% to 49.7% in men in 2018 (Guerrero et al., 2018). This is derived from the increase in obesity, the aging of the population and the accessibility of tests that detect the disease.

Obstructive sleep apnea (OSA)

OSA is a common, chronic, sleep-related respiratory disorder characterized by recurrent moments of upper airway obstruction, precisely during sleep. It is an age-dependent disease, that is the older the age, the greater the prevalence, reaching a plateau around the age of 65 (Chiu et al., 2022). The most important clinical symptoms are loud snoring, night waking, increased respiratory effort, daytime sleepiness and fatigue. Furthermore, it is associated with several comorbidities affecting different systems, including cardiovascular, metabolic, psychiatric, and neurological complications (Gabryelska et al., 2022).

Figure 2. Airflow obstruction. In the image on the left, you can see how the airflow is normal. When the muscles relax, the uvula and soft palate collapse simultaneously with the tongue over the pharyngeal portion of the airway, preventing the normal flow of air and becoming even more accentuated in the REM sleep stage due to muscle atony (right image).



The obstruction is produced by pharyngeal collapse that can be complete (apnea) or partial (hypopnea). During wakefulness, the upper airways are kept open by the constant activity of the muscles that dilate but after the onset of sleep, when muscle activity is reduced, the airways collapse. Intermittent airway obstruction generates hypoxia that can lead to autonomic activation and repeatedly cause transient awakening. This leads to sleep fragmentation which in turn leads to somnolence, anxiety, poor work performance, and increased risk of car and work accidents. A significant factor for the development of OSA is morphological abnormalities such as reduced length of the mandible, low setting of the hyoid bone, posterior displacement of the maxilla, narrowing of the pharyngeal space, enlargement of the soft structures in and around the airways, for example lengthening of the soft palate, increased soft tissue in the neck and redundant pharyngeal mucosa (Lv et al., 2023). Deviation of the nasal septum, turbinate hypertrophy, reduction of the oropharynx caused by palatine toncillary hypertrophy, macroglossia or changes in dental occlusion can also contribute to the development of OSA (Laratta et al., 2017).

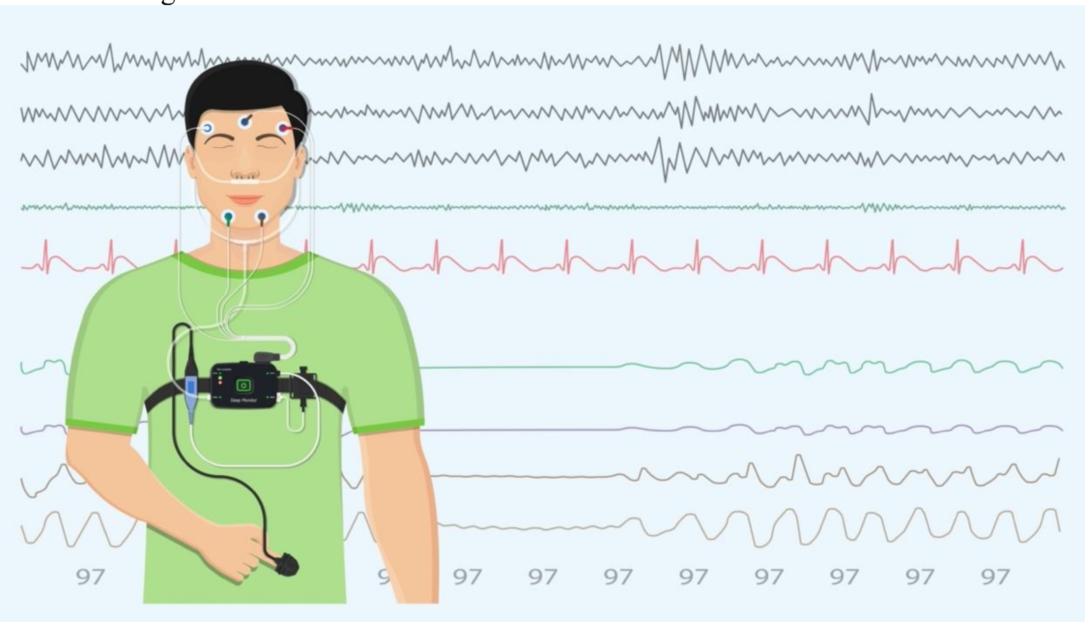
Risk factors

Risk factors can be divided into two categories - modifiable and non-modifiable. Non-modifiable risk factors include male gender, age, race, genetic risk, family history of OSA, and craniofacial anatomy that results in narrow airways. On the other hand, modifiable factors include obesity which is closely correlated with body mass index. Obesity contributes to airway compression by increasing the volume of fat in the throat, upper airways, and around the sinuses. Additionally, muscle relaxants such as benzodiazepines, opiates, or alcohol can cause airway narrowing, which is also a risk factor (Chiu et al., 2022; Lv et al., 2023).

Diagnosis

Polysomnography is the gold standard for diagnosing OSA. During the study, the patient spends the night at a sleep clinic or lab, where several sensors are used to record electrophysiological data while they sleep. The electroencephalogram provides neurophysiological data that helps detect different stages of sleep, identify normal brain activity, and differentiate between wakefulness and sleep. Electrooculography and electromyography can detect REM sleep by monitoring eye movements and muscle tone changes. The test also includes electrocardiography, body position, and movement sensors, as well as airway-related signals such as airflow, thoracic, abdominal movement. This comprehensive approach enables accurate diagnosis and effective treatment, snoring, and oxygen saturation.

Figure 3. Polysomnography is currently the gold standard for diagnosing obstructive sleep apnea. It is performed in a sleep laboratory where the patient undergoes a real-time analysis, electrical and mechanical signals are obtained from the different clinical variables that can be affected during sleep.



It is important to detect the frequency of obstructive respiratory events in patients with OSA (Obstructive Sleep Apnea) as they can have various types of respiratory abnormalities. These events include apneas (when breathing stops for more than 10 seconds) and hypopneas (when there is a decrease in oxygen saturation by 3% or more or sleep arousal). The apnea-hypopnea index (AHI) is calculated by adding all apneas and hypopneas and then dividing them by the total sleep time. The severity of OSA is determined by the AHI, where an AHI of 5 to 15 indicates mild OSA, 16 to 30 indicates moderate OSA and more than 30 events per hour indicate severe OSA (Benjafield et al., 2019;).

Polysomnography is a diagnostic tool for sleep disorders, but it is expensive, requires trained personnel, and is not easily accessible for mass diagnoses. To overcome these limitations, respiratory polygraphy has been introduced as a simplified version of polysomnography. Respiratory polygraphy records four to seven signals, mainly cardiorespiratory, without measuring brain activity or sleep staging information. It is a more comfortable option for patients as it does not require the presence of a technician (Kissow Lildal et al., 2023).

Several studies have compared the results of polysomnography and respiratory polygraphy for diagnosing obstructive sleep apnea (OSA). They have reported that respiratory polygraphy is a viable alternative to polysomnography with a correlation of 0.98, sensitivity of 98%, and specificity of 88%.

This means that respiratory polygraphy offers not only qualitative but also quantitative tests for more accessible diagnoses and adequate statistics to improve treatments. It is important to note that OSA is not only an adult disease, but it can also affect children (Kissow Lildal et al., 2023).

Circadian rhythms and OSA

Circadian rhythms are generated by the circadian system with periods of approximately 24 hours, where central structures and peripheral organs participate and coordinate endogenous rhythms of behavior, physiology, and hormonal environment. There are physiological and pathophysiological patterns dependent on daily responses to behavioral changes in the environment, for example, night and day that promote the daily sleep-wake cycle (Thosar et al., 2018).

OSA is not classified as a circadian rhythm disorder but has been linked to its alternation. Some authors have proposed that the interaction between OSA and circadian dysregulation is bidirectional because the circadian system influences the pattern of respiratory events in OSA, promoting circadian dysregulation through hypoxia and hypoxia signaling sleep fragmentation. When deregulation of circadian rhythms occurs, several homeostatic processes involved in the development of comorbidities related to OSA, such as metabolic syndrome, cardiovascular disease, and cancer, are altered (Li et al., 2022).

There have been studies conducted on the circadian secretion of hormones in patients with Obstructive Sleep Apnea (OSA), but the results have been conflicting. Unlike the control group, patients with OSA do not have a maximum peak of melatonin at 02:00 am. Instead, the maximum peak occurs at 06:00 am, and the concentration is much lower than the controls. One study found that the rhythm of melatonin secretion was altered in 25.4% of OSA patients. However, other studies report that the circadian waveforms of melatonin, heart rate, and cortisol are not affected by OSA, but blood pressure is, and the circadian system contributes to the prolongation of apneas (Butler MP et al., 2020).

Patients with OSA are at a higher risk of developing circadian rhythm disruption. Recurrent apnea and related nocturnal hypoxemia can affect pineal gland function as the expression of circadian rhythm genes is disrupted. The main mechanism of interaction is probably mutual transcriptional regulation between HIF-1 and BMAL1: CLOCK. The Per1, Cry1, and CLOCK genes have hypoxia response elements, so they may be targets for HIF-1. An increased level of HIF-1 α subunits in OSA patients is associated with overexpression of clock gene proteins (Gabryelska et al., 2022).

CONCLUSIONS

Sleeping properly has great benefits for our body. However, we do not give it importance, or we are not aware of these benefits. Now that we know the importance of sleeping well and some diseases that negatively participate in the sleep-wake cycle and alterations in circadian rhythms, for example, Chronic Obstructive Pulmonary Disease as one of the main causes of morbidity and mortality in the world, since it generates significant changes in the respiratory center, resistance of the airways, which can result in the development of Obstructive Sleep Apnea Syndrome, associated with a sleep disorder that is characterized by repetitive obstruction of the airway during sleep with complete or partial cessation of air. The symptoms of both pathologies can be confused with polygraphy or polysomnography in patients where symptoms of sleep apnea are accentuated, such as persistent snoring, witnessed apneas, episodes of suffocation and excessive daytime sleepiness, in order to provide the patient with correct clinical management, which includes management of the sleep disorder as well as personalized attention in the temporary reorganization of activities such as eating, locomotor activity and the use of chronobiotics such as melatonin as chronotherapeutic support. Finally, it is recommended to visualize in an integrated manner the patient with sleep disorders and sleep apnea syndrome.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgment

This study was partially supported by grants PAPIIT-IN216623-UNAM to Manuel Angeles-Castellanos.

REFERENCES

Acosta, M. T. (2019). Sleep, memory and learning. *Medicina*, *79*, 29–32.

Benjafield, A. V., Ayas, N. T., Eastwood, P. R., Heinzer, R., Ip, M. S. M., Morrell, M. J., Nunez, C. M., Patel, S. R., Penzel, T., Pépin, J. L., Peppard, P. E., Sinha, S., Tufik, S., Valentine, K., & Malhotra, A. (2019). Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *The Lancet. Respiratory medicine*, *7*(8), 687–698. https://doi.org/10.1016/S2213-2600(19)30198-5

Butler MP, SS, T., C, S., DeYoung PN, H, W., MV, H., … K, H. (2020). Effects of obstructive sleep apnea on endogenous circadian rhythms assessed during relaxed wakefulness; an exploratory analysis. *Chronobiology international*, *37*(6), 856–866. https://doi.org/10.1080/07420528.2020.1740723.Effects

Chiu, H. Y., Chou, K. T., Su, K. C., Lin, F. C., Liu, Y. Y., Shiao, T. H., & Chen, Y. M. (2022). Obstructive sleep apnea in young Asian adults with sleep-related complaints. *Scientific Reports*, *12*(1), 1–8. https://doi.org/10.1038/s41598-022-25183-5

Foster, R. G. (2020). Sleep, circadian rhythms and health. *Interface Focus*, *10*(3). https://doi.org/10.1098/rsfs.2019.0098

Gabryelska, A., Turkiewicz, S., Karuga, F. F., Sochal, M., Strzelecki, D., & Białasiewicz, P. (2022). Disruption of Circadian Rhythm Genes in Obstructive Sleep Apnea Patients—Possible Mechanisms Involved and Clinical Implication. *International Journal of Molecular Sciences*, *23*(2). https://doi.org/10.3390/ijms23020709

Guerrero, S., Gaona, E., Cuevas, L., Torre, L., Reyes, M., Shamah, T., & Perez, R. (2018). Prevalencia de síntomas de sueño y riesgo de apnea obstructiva del sueño en México. *Salud Pública de México*, *60*(3), 347–355.

Hussain, I., Hossain, M. A., Jany, R., Bari, M. A., Uddin, M., Kamal, A. R. M., Ku, Y., & Kim, J. S. (2022). Quantitative Evaluation of EEG-Biomarkers for Prediction of Sleep Stages. *Sensors (Basel, Switzerland)*, *22*(8), 3079. https://doi-org.pbidi.unam.mx:2443/10.3390/s22083079Jordan , A., McSharry, D., &

Kissow Lildal, T., Boudewyns, A., Kamperis, K., Rittig, S., Bertelsen, J. B., Otto, M., Nørregaard, O., & Ovesen, T. (2023). Validity of in-lab and home respiratory polygraphy for detecting obstructive sleep apnea in children. *Sleep medicine*, *103*, 195–203. https://doi-org.pbidi.unam.mx:2443/10.1016/j.sleep.2023.01.016

Kohtala, S., Alitalo, O., Rosenholm, M., Rozov, S., & Rantamäki, T. (2021). Time is of the essence: Coupling sleep-wake and circadian neurobiology to the antidepressant effects of ketamine. *Pharmacology and Therapeutics*, *221*. https://doi.org/10.1016/j.pharmthera.2020.107741

Laratta, C. R., Ayas, N. T., Povitz, M., & Pendharkar, S. R. (2017). Diagnosis and treatment of obstructive sleep apnea in adults. *Cmaj*, *189*(48), E1481–E1488. https://doi.org/10.1503/cmaj.170296

Li, X., Liu, X., Meng, Q., Wu, X., Bing, X., Guo, N., … Li, H. (2022). Circadian clock disruptions link oxidative stress and systemic inflammation to metabolic syndrome in obstructive sleep apnea patients. *Frontiers in Physiology*, *13*(August), 1–13. https://doi.org/10.3389/fphys.2022.932596

Lv, R., Liu, X., Zhang, Y., Dong, N., Wang, X., He, Y., Yue, H., & Yin, Q. (2023). Pathophysiological mechanisms and therapeutic approaches in obstructive sleep apnea syndrome. *Signal transduction and targeted therapy*, *8*(1), 218. https://doi-org.pbidi.unam.mx:2443/10.1038/s41392-023-01496-3

Mejía Avellaneda, C. A., & Garciandia, J. A. (2021). Algunas reflexiones sobre apnea obstructiva del sueño, ansiedad y consumo de alcohol. *Universitas Médica*, *62*(1), 1–16. https://doi.org/10.11144/javeriana.umed62-1.aods

Poza, J. J., Pujol, M., Ortega-Albás, J. J., & Romero, O. (2022). Melatonina en los trastornos de sueño. *Neurología*, *37*(7), 575–585. https://doi.org/10.1016/j.nrl.2018.08.002

Saper,C.B., & Fuller, P.M. (2017). Wake-sleep circuitry: an overview. *Curr Opin Neurobiol*, 44:186-192. doi:10.1016/j.conb.2017.03.021

Sateia, M. J. (2014). International classification of sleep disorders-third edition highlights and modifications. *Chest*, *146*(5), 1387–1394. https://doi.org/10.1378/chest.14-0970

Sun, S.-Y., & Chen, G.-H. (2021). Treatment of Circadian Rhythm Sleep–Wake Disorders. *Current Neuropharmacology*, *20*(6), 1022–1034. https://doi.org/10.2174/1570159x19666210907122933

Telias, I., & Wilcox, M. E. (2019). Sleep and Circadian Rhythm in Critical Illness. *Critical Care*, *23*(1), 2–5. https://doi.org/10.1186/s13054-019-2366-0

Thosar, S. S., Butler, M. P., & Shea, S. A. (2018). Role of the circadian system in cardiovascular disease. *Journal of Clinical Investigation*, *128*(6), 2157–2167. https://doi.org/10.1172/JCI80590