Psychiatric Illness and Obstructive Sleep Apnea

23

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23.1 Introduction

Despite multiple meta-analyses and articles that have addressed the issue of psychiatric illness and obstructive sleep apnea for decades, there is an inconsistent correlation between these medical conditions that persists, causing significant bias handling guidelines of both, not only in clinical practice but more significantly in the information that students receive in medical schools worldwide.

The purpose of this chapter is to emphasize that the chronic presence of undiagnosed sleep apnea in the presence of certain mental illness can increase the severity of the condition and provide poor pharmacological treatment that worsens both medical conditions. Thus, I will address the most related psychiatric conditions, like depression, attention-deficit disorder and hyperactivity, eating disorders, and insomnia.

23.2 Depression

The WHO defines depression as a disorder characterized by persistent sadness and a lack of interest or pleasure in previously rewarding activities. In addition, it can alter sleep and appetite, often accompanied by tiredness and lack of concentration. It is a significant cause of disability worldwide and significantly impacts morbidity.

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It is estimated that at least 322 million people worldwide suffer from depression, up 18% from a decade ago. Depression and anxiety increased by more than 25% only during the first year of the pandemic [1, 2].[1]

In the DSM V, the term depression is used primarily to refer to any depressive disorder.

For the diagnosis of major depression, ≥5 of the following symptoms must have been present almost every day for a given period of 2 weeks, and one of them should be depressed mood or loss of interest or pleasure:

Depressed mood most of the day.

A marked decrease in interest or pleasure in all or almost all activities most of the day.

Significant increase or loss (>5%) of weight, or decrease or increase in appetite.

Insomnia (often sleep-maintaining insomnia) or hypersomnia.

Agitation or psychomotor delay observed by others (not reported by the same patient).

Fatigue or loss of energy.

Feelings of worthlessness or excessive or inappropriate guilt.

Decreased ability to think or concentrate, or indecision.

Recurrent thoughts of death or suicide, attempted suicide, or a specific plan to commit suicide [3].

The ICD currently defines obstructive sleep apnea (OSA), when one of these two criteria is met

1. The presence of an apnea–hypopnea index (AHI) ≥15 h, predominantly obstructive.
2. The presence of an AHI 5 and 15 accompanied by one or more of the following factors: excessive daytime sleepiness, nonrestorative sleep, excessive tiredness, and/or sleep-related deterioration of quality of life, not justifiable by other causes [4].

OSA is a disease characterized by total or partial occlusion of the upper airway of patients during sleep. Because of this, breathing stops until a microarousal occurs that reactivates the muscles and reopens the airways. Apnea occurs when the elements that tend to close the airway cannot be compensated by the ability of the dilator muscles of the pharynx and/or respiratory centers to keep it open.

Due to these apneas, which produce hypoxia and sleep fragmentation, patients cannot sleep and rest properly and, during the day, they usually suffer from daytime sleepiness or tiredness [4].

In physiological terms, several symptoms of a depressed mood are the consequence of sleep apnea, and the impact of hypoxemia and hypoxia at the cellular level is considered a result of a neuro inflammatory process [5] (Fig. 23.1).

[1] American Psychiatric Association, DSM V Diagnostic Criteria Consultation Guide, Arlington, VA, American Psychiatric Association, 2013.

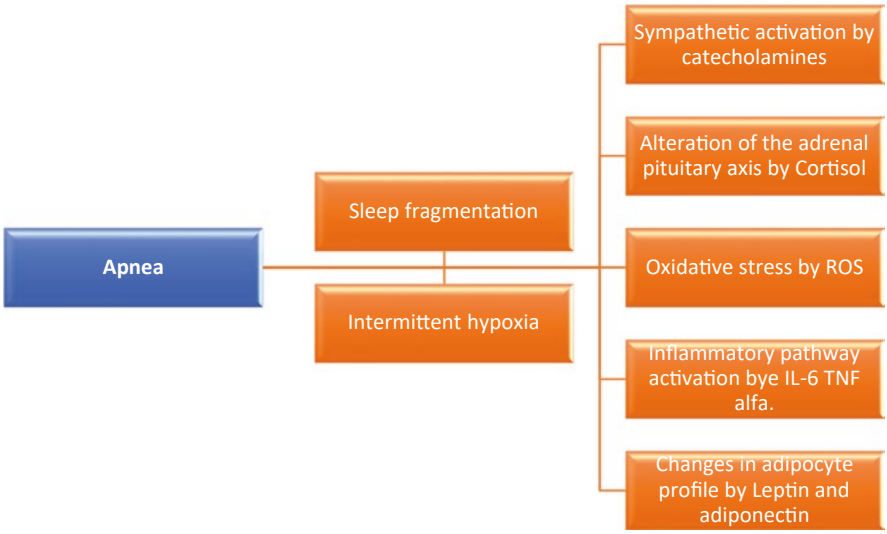

Fig. 23.1 Effects of apnea on cellular metabolism

23.3 Neuroinflammation Theory

Neuroinflammation is defined as the brain's response to injury, infection, or disease. In general, the purpose of inflammation is to remove or inactivate potentially harmful agents or damaged tissue. This response is mainly mediated through two cellular systems: the central nervous system glia and the hematopoietic system's lymphocytes, monocytes, and macrophages.

The results of studies suggest that patients with a major depressive disorder show changes in immunological markers, including an increase in proinflammatory cytokines activity [6].

In addition, chronic low-grade inflammation can lead to changes in brain structure and synaptic plasticity that led to neurodegeneration. Therefore, it should be added that neuronal repair due to increased glucocorticoid levels may be the initial markers of depression and a prelude to dementia in older people [7].

Significantly, chronic stress can exacerbate the release of proinflammatory cytokines and thus precipitate depressive episodes. It has been shown that stress, through its interaction with the immune system, can increase levels of proinflammatory cytokines such as **tumor necrosis factor TNF-α, interleukin IL-1β, IL-6, and IL-2R** [8, 9].

Inflammatory markers, such as IL-6, IL-1β, CRP, and TNF-α, are increased in inflammatory diseases and otherwise healthy people with MDD.

23.3.1 Relation Between Inflammatory Process and Depression

Cytokines make changes to the central nervous system through four pathways [10, 11]

1. Cytokines can activate primary afferent neurons.
2. Cytokines, released by macrophage-like cells in response to disease-causing agents, diffuse through the cerebral circumventricular organs.
3. Cytokine transporters saturate the blood–brain barrier.
4. Cytokine IL-1 activates receptors on perivascular macrophages and endothelial cells of brain venules and generates the local release of prostaglandin E2.

23.3.2 Analysis

After reviewing the contexts of global nomenclature of both medical conditions and the physiology of the inflammatory processes that occur in OSA, the correlation between the two can be appreciated, which must be included in every patient's clinical history. Both in people with depressive symptoms and respiratory alterations should be intentionally explored. In people with the already assigned diagnosis of OSA, the presence of depression or depressive symptoms should be explored since this causes depression that ends up being classified as resistant or poorly addressed. On the other hand, the results in the approaches to OSA will not be those expected by the health professional due to the omission of the condition of depression in the patient's medical history [12].

The most common symptoms shared by both medical conditions are shown in Table 23.1.

23.3.3 Conclusions

It is essential that the curricula of medical schools are updated and devote more hours/class, in sleep medicine, since the panorama reported by the WHO is worrying in the issue of the incidence and prevalence of depression in the last year, and if the problem continues to be addressed as before, the numbers will only continue to be exposed (Fig. 23.2).

Table 23.1 Most common symptoms shared by both medical conditions

Cognitive and emotional symptoms	Physical symptoms
Difficulty in the ability to acquire	Excessive daytime sleepiness
Decreased memory capacity	Hypersomnia
Decreased attention span	Fragmented sleep
Loss of interest in conducting activities	Alterations in appetite
Labile mood	Low libido
Apathy	Impotence

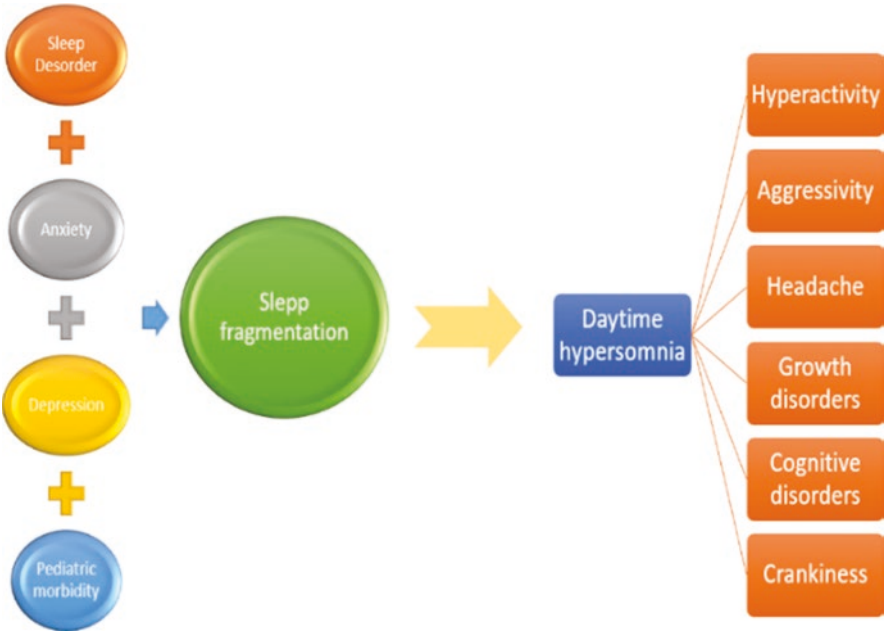

Fig. 23.2 Common consequences of fragmented sleep

Multidisciplinary work is needed in the treatment of major depressive disorder, a medical condition of multifactorial origin, ranging from the molecular, the genetic, the cellular, the systemic, including to the environment, and is not reduced only to "a neurochemical imbalance of certain substances in the brain".

It is key to prove solid foundations of physiology and understand the concept of general systems theory, taking it to clinical practice, to be able to see the real picture and not just a part of it.

Returning to the term "allostasis" would help a lot to understand that many conditions that we classify as "diseases" are simply the way in which the body, after being subjected to situations of stress, makes physiological changes to readapt and maintain its viability.

23.4 Insomnia

Most people are not adequately informed about what it is to sleep well and therefore do not know how to distinguish between sleeping well and poor sleeping or sleeping poorly and the consequences of not doing so.

Sleeping well is one of the healthiest and most fruitful habits, but unfortunately one of the least practiced and is treated as a "great luxury."

The WHO considers insomnia the difficulty in falling asleep or maintaining sleep; or the complaint feeling of nonrestorative sleep that generates a significant

discomfort or interference with social and work activities and occurs on at least three nights a week [1].

Excessive daytime sleepiness is a condition that makes the person feel very sleepy during the day and is considered a continuum of insomnia or sleep disturbances.

Without the presence of insomnia or any disorder that affects the quantity and quality of sleep, there is no presence of excessive daytime sleepiness [13].

According to the World Health Organization, lack of sleep represents one of the most common problems in people: 40% of the world's population has insomnia [1].

23.4.1 Statistical Impact

In the United States, according to the Sleep Foundation [14], with data updated to May 2022, between 10 and 30% of adults struggle with chronic insomnia. Women have a lifetime risk of insomnia that is up to 40% higher than men. As many as 15–30% of men and 10–30% of women meet a broad definition of obstructive sleep apnea. The second sleep disorder with the highest incidence and prevalence is obstructive sleep apnea. It has a prevalence of 10–30%, which together with insomnia represent 80% of the causes of poor sleep (Fig. 23.3).

The impact of insomnia on during the pandemic was that the incidence and prevalence rate increased more than any other mental health condition [15].

The body takes insomnia as an inflammatory process, which will have repercussions at the genetic, cellular, systemic, and environmental levels.

23.4.2 Aftermath of COVID-19

Insomnia is the most common sequelae of persistent COVID-19. U.S. researchers have found that moderate to severe sleep disturbances are prevalent among the post-acute sequelae of SARS-CoV-2 infection.

As per a team of researchers from the Cleveland Clinic (USA) who presented at the SLEEP 2022 meeting, almost 40% of people with persistent COVID-19 suffer from a sleep-related problems.

They analyzed data collected from 962 patients with long COVID-19 or persistent COVID-19 between February 2021 and April 2022. Patients recovered from COVID-19 and completed sleep disturbance and fatigue questionnaires.

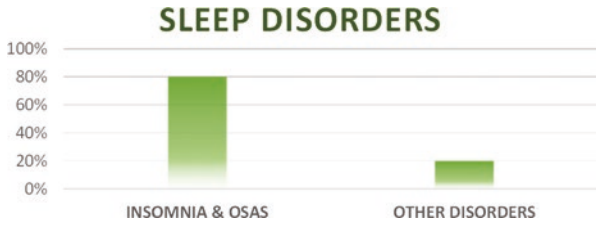

Fig. 23.3 Sleep disorders

Eight percent of patients reported severe sleep disturbances, while 41.3% reported moderate sleep disturbances [16].

23.4.3 Conclusions

Normalizing insomnia will make us contract a sleep debt that will not recover anymore and will result in conditions like cardiovascular and metabolic diseases, for examples, addictive behaviors, risk of certain cancer types, endocrine diseases, and be prone to occupational and traffic accidents.

23.5 Attention-Deficit Hyperactivity Disorder and Obstructive Sleep Apnea

According to the DSM V, attention-deficit hyperactivity disorder (ADHD) is a persistent or continuous pattern of inattention and/or hyperactivity and impulsivity that is maladaptive and incoherent concerning the child's level of development and can continue through adolescence and adulthood. It can be classified into three subtypes: inattentive predominance (20–30%), hyperactive-impulsive predominance (10–15%), and combined predominance (50–70%) [3].

The World Health Organization estimates that there is a prevalence of 5% worldwide.

ADHD is a public health problem that affects people's development and quality of life. It begins before the age of six, with an incidence of 5–7% in boys and a little less in girls; during adolescence, symptoms prevail, and in adulthood, it persists by up to 50% [17].

Both obesity and mental illness have increased among young people since the beginning of this century. Researchers have long observed a connection between obesity and ADHD, depression, and eating disorders, but it has rarely been studied [18].

One study involved 48 adolescents (73% girls) with an average age of 15 and an average BMI of 42, which is severe obesity. Half of the participants received medical treatment for obesity, while the other half underwent surgery.

Parents of the teens completed questionnaires to measure their children's ADHD symptoms. In addition, the teens themselves answered questions about binge eating and symptoms of depression.

Results showed that more than half of the parents estimated that their teenage children had difficulties resembling ADHD, even though only some had been previously diagnosed with these conditions [19].

23.5.1 Analysis, Theories, and Proposals

In several publications and articles, two aspects of ADHD are continuously discussed: on the one hand, if it is underdiagnosed, and on the other hand, if it is overdiagnosed.

And if it is misdiagnosed for not considering the variable presence of obesity and sleep apnea in the initial evaluation?

Not all is ADHD. The presence of some respiratory disorders that was never explored or the presence of some type of apnea or snoring may emulate a picture of ADHD in many situations (Table 23.2; Fig. 23.4).

A multidisciplinary approach is needed when we talk about diagnosing ADHD.

A misdiagnosis or a bad approach will decide the quality of life in the child, until adulthood.

Rather than discussing the underdiagnosis or overdiagnosis of ADHD, let's focus on updating health professionals and sharing our knowledge with evidence and numbers.

Sleep medicine is such a critical area and, at the same time, remains so unknown to many.

Table 23.2 Some ADHD symptoms

Emotional symptoms	Cognitive symptoms	Behavioral symptoms
Depressive mood	Inattention	Impulsiveness
Anxious mood	Deconcentration	Hyperactivity
Low frustration tolerance	Memory difficulties	Concern
Irritability	Difficulty measuring risks	Not finishing most activities
Emotional lability	Difficulty in planning	Risk of drug exposure

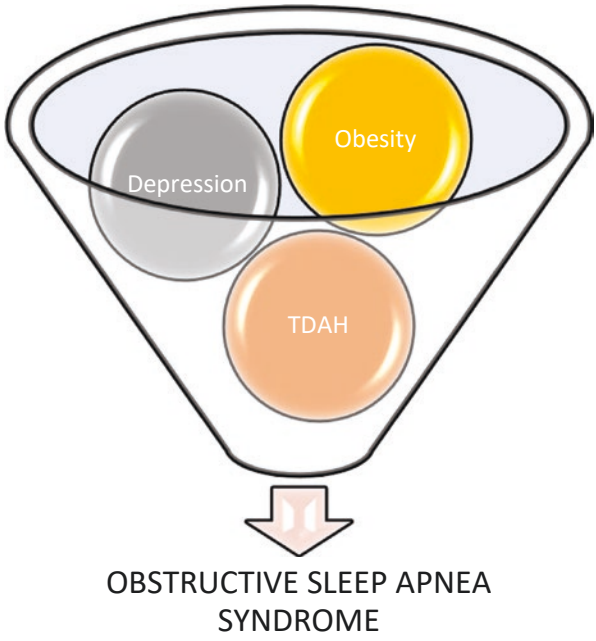

Fig. 23.4 Symptoms that occur in both ADHD and OSA

The only professional "interest" that there should be is to do our professional work as well as possible.

> What we know is a drop of water; what we ignore is the ocean.
> —ISAAC NEWTON

23.6 Eating Disorders in Obstructive Sleep Apnea

According to the WHO, eating disorders are severe mental health conditions. They involve serious problems about how the patient manages food and their eating behavior. They are considered a medical disease [1].

Globally, the number of cases of eating disorders has doubled in the last 18 years: Prevalence has doubled from 3.4% of the population to 7.8% between 2000 and 2018 [20].

Eating disorder prevalence ranges from 0.3 to 2.3% in teenage females and 0.3 to 1.3% in adolescent males. Eating disorders are associated with short-term and long-term adverse health outcomes, including physical, psychological, and social problems [21].

In particular, a type of disorder that is more associated with OSA is a binge-eating disorder with a nocturnal predominance and an eating behavior pattern that occurs in day-after-day pattern, more pronounced in the afternoon, eating small amounts of some food rich in carbohydrates and fats, intermittently.

23.6.1 How Common Is Binge-Eating Disorder?

Binge-eating disorder is the most common eating disorder in the United States [22].

Out of every 100 women, just over 3 will have binge-eating disorder at some point in their lives.

In men, 2% will have binge-eating disorder at some point in their lives [23].

Binge disorders occur in people of any weight; however, it is more frequent in obese or overweight patients [24], and there is a close correlation between OSA and eating disorders [25].

Poor sleep quality is associated with a decrease in leptin (an appetite-suppressing hormone) and an increase in ghrelin (an appetite-stimulating hormone), which can increase cravings for high-calorie foods (Fig. 23.5).

Studies show that lack of sleep directly affects how we eat.

This is mainly explained by a hormonal disturbance. Hunger and satiety are sensations regulated by ghrelin and leptin, respectively.

Ghrelin is responsible for hunger, and leptin tells our body that we have eaten enough [26].

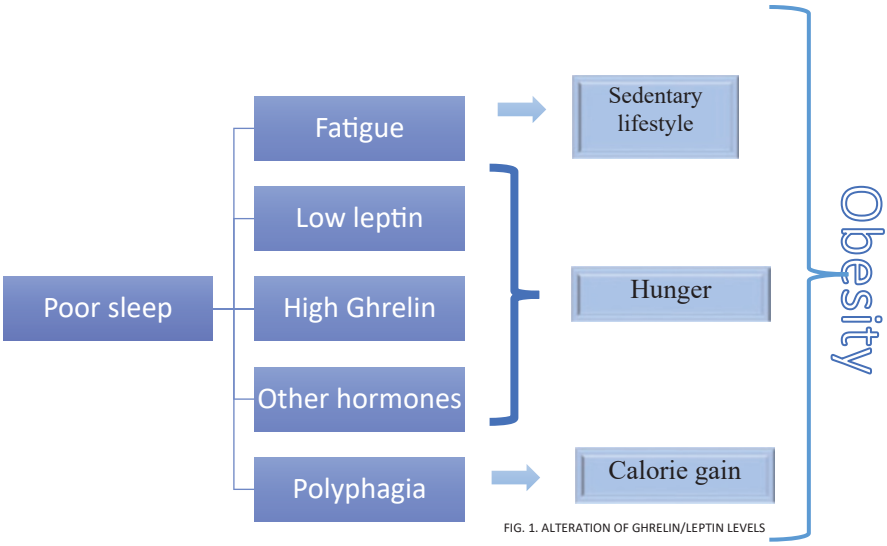

Fig. 23.5 Alteration of ghrelin/leptin levels

When we don't get enough sleep, the levels of these hormones are disturbed, and while ghrelin is produced in excess, leptin production doesn't reach the levels it should.

According to studies, 2 days of poor sleeping and without rest are enough to alter these hormones.

The consequences of this hormonal imbalance translate into a greater appetite and a considerable drop in energy [27].

23.7 Endocannabinoid System and Fat

Recent discoveries concerning cannabinoids have begun to shed light on these processes. Current knowledge indicates that the endocannabinoid system plays a vital role in the appetite and consummatory phases of food motivation, possibly mediating cravings and pleasure for the most desired meals that are generally highly calorically dense foods. In addition, endocannabinoid system appears to modulate central and peripheral components associated with fat and glucose metabolism [28, 29].

23.8 Relationship with High Cortisol Levels

Cortisol should not be high during the night, although prolonged stress can lead to high cortisol levels. Hyperactivity of the main stress response system (HPA axis) is associated with sleep disturbances, such as chronic insomnia. People with OSA have elevated cortisol levels at night and before bedtime.

Cortisol causes an increase in insulin, and this raise triggers an increase of appetite, mainly for consumption of sweets and starches. This favors the storage of fat, generating high levels of inflammatory substances in the liver.

On the other hand, the brain is also affected, because when trying to relieve stress with food, we activate the reward center; for example, eating ice cream or chips creates a sense of well-being, but once the effect has passed, we feel the need to consume more of those foods that, supposedly, relax us [30, 31].

23.9 Malfunction or Degeneration of the Orexinergic/Hypocretinergic System

The orexinergic system is composed of two different neuropeptide hormones, which are secreted in the hypothalamus, and neuron cells of the intestine, stomach, and pancreas. They participate in the modulation of multiple functions such as the regulation of the sleep–wake cycle, energy homeostasis, the regulation of temperature, neuroendocrine and autonomic regulation, regulation of muscle tone, and locomotion and have as main function of giving intestinal responses to the brain; therefore, they have an enormous influence on nutrition, intake, and appetite control. It has been called the brain–intestinal axis [32].

1. Orexin A or hypocretin 1
2. Orexin B or hypocretin 2

Generally speaking, any alteration that affects the hypothalamus in any way will result in loss of orexinergic/hypocretinergic neurons and, therefore, clinically in low or absent concentrations of orexin A/hypocretin 1 in CSF.

Orexins are essential in stabilizing the awake state and have been studied mainly concerning the increase in alertness and motivation by positive reinforcers. Thus, the orexinergic system participates in appetitive learnings in which an association occurs between a relevant stimulus and rewards such as food.

Orexin levels in an individual also depend on the demands of the environment, intrinsic or extrinsic, so it promotes appetite or aversive responses based on the body's previous experience. In this sense, orexin can intervene in the state of hypervigilance that underlies anxiety and stress states and that increases the salience of environmental stimuli. In these circumstances, the role of orexin would be to orchestrate the components of the stress response as an increase in activation, attention, and anxiety [33].

Take-Home Message

- Chronic undiagnosed sleep apnea in the presence of a specific mental illness can increase the severity of the condition.
- The most frequent conditions associated are depression, insomnia, attention deficit hyperactivity disorder (ADHD), and eating disorders.
- Poor pharmacological treatment worsens both medical conditions (mental illness and OSA).

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