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Sleep loss causes emotional dysregulations increasing depression and anxiety: A reciprocal relationship

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ABSTRACT

Introduction: Good quality sleep is essential for good neurocognitive performance, mental and physical health. However, changes in society have led to a worsening of sleep quality, which is associated with the development of anxiety and depression. Objective: Discuss and contribute for a better understanding of the association between sleep loss and anxiety and depression. Methodology: This article presents a narrative review of the literature based on the analysis of scientific articles published from 2014 to 2022, in PubMed, about sleep deprivation and its association with anxiety and depression. Two criterias were applied, titles that did not mention the thematic association between sleep deprivation and depression and anxiety and abstracts that did not address that theme. After the exclusion criterias, was obtained in total, 45 articles originally in English (including book chapters, guidelines and case reports) remained.
Discussion: Sleep deprivation is associated with an increase in cortisol levels, a reduction in testosterone and serotonin levels, and an increase in inflammatory markers. In this context, this condition is related to symptoms of depression and anxiety. Due changes in the pattern of society, such as increased use of the internet and a greater workload, have led a large part of the population to develop problems in sleep quality. Addictionaly, it is known that good quality sleep is essential for good neurocognitive performance, mental and physical health.
Conclusion: This study discussed the relation between sleep deprivation, depression and anxiety. It is added to its effect on good neurocognitive performance, mental and physical health. Overall, it was evidenced that there is an association of mechanisms between these disorders. In this context, there is an urgent need for more specific research and dissemination of data on the association of sleep deprivation and depression and anxiety.

Keywords: Neurocognitive, Depression.

1 INTRODUCTION

Good sleep quality plays an essential role in consolidating and maintaining learning, neurocognitive and psychomotor performance, physical and mental health (1). Thus, sleep deprivation is associated with an increase in cortisol levels, a reduction in testosterone and serotonin levels, and an increase in inflammatory markers. A recent study evaluated people between the ages of 25 and 45, demonstrating that 20% slept 90 minutes less than needed to maintain good health (2). The etiology of this condition is multifactorial and may be associated with sleep apnea, insomnia, parasomnias, mood disorders, psychosis and sleep deprivation (3). From this perspective, the recent increase in sleep abstention is associated with changes in the pattern of society, marked by greater use of the Internet, this situation was greatly worsened by the COVID-19 Pandemic (2, 4, 5).

From this perspective, sleep deprivation and daytime sleepiness are associated with a worsened quality of life and symptoms of depression and anxiety (1), studies report that 70% of people suffering from anxiety disorders are mostly multifocal, excessive and difficult to control, it is usually accompanied by other non-specific psychological and physical symptoms and its risk factors include female individuals, low socioeconomic status and exposure to childhood adversities (6). Furthermore, anxiety can often be associated with symptoms such as sleep disturbances, restlessness, muscle tension, gastrointestinal symptoms, and chronic headaches (7). In addition, patients with GAD are at increased risk of different mental and physical health disorders, with depression being one of the most common coexisting conditions (6).

Neurons, non-neuronal cells such as oligodendrocytes, astrocytes and microglia play a critical role in synaptic maintenance and homeostasis. With this, the chronic loss of sleep or its fragmentation creates a state of activation of these cells, thus influencing the individual's behavioral state. (8) In this context, findings suggest that sleep deprivation increases synaptic strength and cortical excitability, leading to synapse saturation in healthy individuals and inhibition of associative plasticity, which supports optimal neural functioning. (9) Other evidence suggests that the amygdala plays an important role in anxiety. Sleep deprivation increases the amygdala's response to subliminal signals of anxiety and fear. This is a brain region with the highest expression levels of neuropeptide S receptors (NPSR), being the main site of action of the anxiolytic effect of neuropeptide S (NPS). (10)

Depression is a widespread chronic illness that impacts thoughts, mood and physical health. It courses with physical symptoms, such as fatigue, pain, sleep disorders, and with mental symptoms like bad mood, depressed mood, sadness and insomnia, in addition to the feeling of inability to enjoy life. (11,12) This disease significantly limits psychosocial functioning and decreases quality of life. (13).

Major depressive disorder (MDD) is one of the most prevalent and debilitating psychiatric disorders(14), and is the leading cause of disability worldwide and will be present in one in five people throughout their lives. (15). This disease significantly impairs cognitive subdomains such as memory,

processing speed, executive functioning, concentration and attention, regardless of whether it is between or during its crises. (16) Its pathophysiology is not entirely clear, but it is known that several mechanisms are involved, such as alterations in the serotonergic, noradrenergic, dopaminergic, and glutamatergic systems, increased inflammation, abnormalities of the hypothalamic-pituitary-adrenal axis, vascular changes, and decreased of neurogenesis and neuroplasticity. (14)

Additionally, sleep deprivation is related to several psychiatric complications, such as depression (2). Depression is a chronic, widespread medical illness that can affect both physical and mental health. It is characterized by moodiness, lack of energy, sadness, insomnia, and an inability to enjoy life (12). Furthermore, the incidence of depression is steadily increasing worldwide and current epidemiological data reveal that depression is now the third leading contributor to the global burden of disease (9). Thus, sleep deprivation has a proven contribution to the increase in the occurrence of this pathology in the population, since a recent prospective study with 3,134 young people aged 11 to 17 years found that sleep deprivation during the week (defined as ≤ 6 h/night)) is associated with an almost 40% greater likelihood of reporting symptoms of depression one year later (OR 1.38 [1.02–1.85]), regardless of age, gender, family, income, and early depression (17).

Furthermore, good quality sleep is essential for good neurocognitive performance, mental and physical health. However, due to changes in the pattern of society, such as increased use of the internet and a greater workload, aggravated by the COVID-19 Pandemic, have led a large part of the population to develop problems in sleep quality. Thus, sleep deprivation has a proven contribution to the increase in the occurrence of psychiatric diseases.

2 METHODOLOGY

This article presents a narrative review of the literature based on the analysis of scientific articles published from 2014 to 2022, in PubMed, about sleep deprivation and and its association with anxiety and depression

In the application of the first set of criteria, titles that did not mention the theme, articles not included in the period of research 2014-2022 and articles that were not found in English were excluded. In the database of PubMed, 640 articles were found by the keywords “(sleep deprivation) AND (depression)” and 774 articles by the keywords "(sleep deprivation) AND (anxiety)" from which 389 were selected.

The second set of criteria was applied, from which were excluded the abstracts that did not address the theme sleep deprivation and depression and anxiety, which led to 344 articles being excluded.

Of total, 45 articles originally in English (including book chapters, guidelines and case reports) remained.

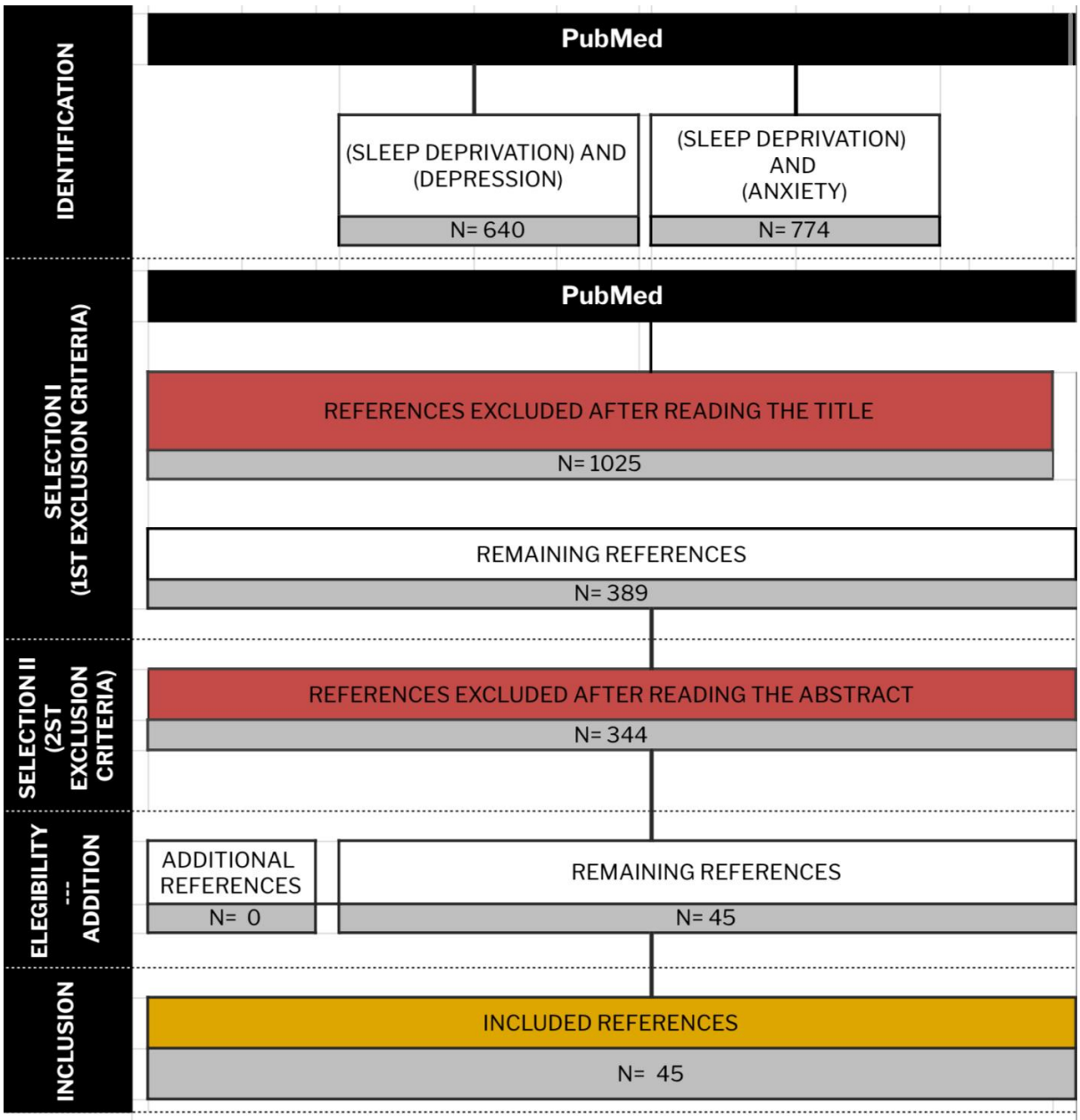

Figure 1. Articles addressing to Sleep Deprivation, Depression and Anxiety

3 RESULTS AND DISCUSSION

3.1 TYPES OF ANXIETY DISORDERS

Anxiety disorders are defined as debilitating psychological disorders characterized by a wide range of cognitive and somatic symptoms (18). In the current scenario, anxiety disorders are the most common type of mental illness in Europe, with a 12-month prevalence of 14% among people aged 14 to 65 years and usually with onset in adolescence or early adulthood (19). In this perspective of high prevalence in society, the World Health Organization classified anxiety disorders as the ninth most health-related cause of disability, affecting approximately 9.3% of the Brazilian population. (20). Furthermore, anxiety disorders are divided into generalized anxiety disorder, panic disorder, social anxiety disorder, specific phobia and separation anxiety disorder (21).

Generalized anxiety disorder (GAD) is a disorder characterized by anxiety and excessive worry about different events that are disproportionate to their actual probability, occurring on most days for at least six months (21). Its clinical picture is described by restlessness or feeling of "nerves on edge", fatigability, difficulty concentrating, irritability, sleep disturbance and muscle tension (21). These symptoms must cause significant suffering in the individual's social functioning, which is not caused by another medical condition or some type of intoxication (21).

Panic disorder is related to unexpected and recurrent panic attacks, being defined by none of these attacks having an obvious trigger at the time of recurrence, with at least 1 of the attacks followed by a month (or more) of their clinical picture (21) . Its clinical characteristics are palpitations, racing heart, tachycardia, sweating, tremors, dyspnea, chest pain, nausea, vertigo and fear of losing control or "going crazy" (21). This discarded the possibility of the psychological effects of a substance or a mental disorder (21). Furthermore, among the differential diagnoses of panic attacks, there is agoraphobia (21). Agoraphobia is characterized by a difficulty in exposing oneself in situations from which it is difficult to escape or obtain help in cases of embarrassment or during a panic attack (21). In this context, characteristic of the symptoms of agoraphobia is the disproportionate fear and/or anxiety of leaving home alone, using public transport, being in spaces (parking lots), being in crowds and staying in closed places (cinemas) for at least six months (21).

Furthermore, social anxiety disorder (social phobia) is reported by fear or exacerbated anguish of situations in which the individual is exposed to possible evaluation by another person (conversations, encounters with strange people, being observed eating or drinking, lectures) (21). Fear of a negative reaction when demonstrating anxiety symptoms, causing an avoidance behavior in these individual assessment situations for at least 6 months (21).

Besides that, the specific phobia is characterized by marked fear or anxiety about an object or situation (flying, heights, animals, taking an injection, seeing blood), the individual's reaction being almost immediate to the patient's fear, being known as a fear disproportionate to real life, requiring at least a duration of 6 months (21). Affecting more women and most with onset before age 10 (21).

In addition, excessive fear and distress involving separation from those with whom the patient is attached is characteristic of separation anxiety disorder (21). The individual reports excessive distress about moving away from important attachment figures, having excessive preoccupation with illness, injury, disasters or death, reporting repeated somatic complaints and repeated nightmares involving separation (21).

3.2 RELATIONSHIP BETWEEN ANXIETY AND SLEEP

Sleep deprivation and daytime naps are associated with poorer quality of life and may lead to anxiety symptoms such as feelings of worry and fear (1,22,23). Epidemiological studies reveal that

about 50% of individuals with anxiety have sleep disorders, especially insomnia, and that insufficient sleep can further stimulate or exacerbate this condition (24). Some factors that can trigger this bidirectional relationship between sleep and anxiety are low socioeconomic status, female gender and exposure to adversities in childhood. (6)

In this context, the symptomatic relationship of anxiety with the fear network that includes the limbic system and the network of importance involved in cognitive control, dorsal anterior cingulate cortex and anterior insula is highlighted. (24) One model suggests that anxiety and insomnia indicate different dimensions of a single dynamic neurobiological diathesis, where dysregulation in shared brain regions triggers problems in both anxiety and sleep. (25) Related to this association, sleep interruption has been reported to decrease the connection between the regulatory areas and abilities of the prefrontal cortex, leading to further dysregulation and thus reaffirming the lack of sleep quality as a predictor of accentuation anxiety and general mood dysregulation.

Furthermore, another factor that is related to the impairment of medial prefrontal cortex activity and the connectivity associated with extended limbic regions is the anxiogenic impact of nocturnal worry, negative thoughts and ruminant planning (25,26). These course with the excitability of the limbic system, which is already in a state of dysregulation due to deprivation, mainly chronic, of sleep, creating a vicious cycle (27). The effects of sleep disruption on the brain correlates underlying anxiety can be classified as either cognitive (worry) or somatic (physiological arousal), with higher cortisol levels reflecting greater somatic arousal associated with vigilance which interferes with feelings of necessary safety and relaxation. for sleep (24,27). Complaints of sleep disorders reported by anxious individuals are characterized by more nocturnal awakenings, less slow-wave sleep, more reports of night terrors and longer sleep latency when compared to those who do not suffer from anxiety. (28)

It is added that thousands of neurotransmitters and neuromodulators participate in the physiology of sleep and emotional regulation, such as serotonin, norepinephrine, GABA, acetylcholine, dopamine, glutamate and adenosine (22, 24). It is known that serotonin and norepinephrine present bidirectional connections with emotion processing and regulation centers and inhibitory projections, to a functioning sleep-wake regulation center, the preoptic ventrolateral nucleus (24). Also, GABA is responsible for an important role in the acquisition, storage and extinction of fear, which is considered one of the main symptoms of anxiety.(29) Acetylcholine, in turn, is an excitatory neurotransmitter, which during wakefulness and REM sleep it has cholinergic activity and during non-REM sleep its activity is reduced. (24) In conclusion, the bidirectional relationship between anxiety and sleep disorders is extremely important and can negatively impact quality of life. In light of this, there are effective treatments that include psychotherapy (often cognitive behavioral therapy) and pharmacotherapy, such as selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. (20.30)

3.3 SLEEP AND DEPRESSION: UNDERSTANDING THE CONNECTION

Adequate sleep is critical for long-term learning, neurocognitive and psychomotor performance, and physical and mental health (1). In the contemporary scenario, studies show that there has been a decline of up to 18 minutes in the amount of sleep per night in the last three decades (2). In this way, sleep deprivation is associated with the incidence of depression, insulin resistance, hypertension, diabetes, weight gain, stress and a tendency towards drug addiction and the use of tobacco and hypnotics (5). With regard to depression, irregular sleep-wake patterns and insufficient sleep have been highly correlated with depressive symptoms, as the risk of organic mental disorders increases by 106% in people who sleep little and 44% in people who sleep less than 5 hours/night compared to those sleeping 7-8 hours (8, 31).

Depression, in particular Major Depressive Disorder (MDD), is a generalized chronic medical illness that can affect thoughts, mood and physical health, and is characterized by lack of energy, sadness, insomnia and inability to enjoy life (12). WHO has ranked MDD as the third leading cause of disease burden worldwide and has projected that the disorder will rank first by 2030, in addition, it is estimated that approximately 300 million individuals suffer from this disease globally, equals 4.4% of the world's population (10, 13). Furthermore, these individuals exhibit a constellation of clinical symptoms not explained by a single unifying mechanism, it is likely that Th17 cells leverage neuroinflammation and activation of central nervous system cells, such as microglia and astrocytes, favoring neural damage. However, the precise neural mechanisms underlying the development of depression remain elusive (32, 33).

In patients with depression, sleep disturbance is a frequent complaint, being considered one of the main secondary manifestations of depression. However, currently, many studies describe insomnia as an independent risk factor for the development of emerging or recurrent depression (34). Prolonged sleep latency has been associated with symptoms such as loss of pleasure, feelings of punishment, dislike for oneself, loss of interest, irritability and fatigue (8). This association can be confirmed with the introduction of polysomnography in psychiatric research, which demonstrated a disturbance of sleep continuity in patients with depression, revealing decreased slow wave sleep and disinhibition of REM sleep (35). Thus , chronic sleep deprivation causes neurobehavioral changes by altering the inflammatory response and the neuroendocrine stress system, being associated with increased cortisol levels, leading to a state of stress, and decreased testosterone levels, with this an important role in enhancing the function of gamma-aminobutyric acid (GABA) and serotonin systems in the brain.Besides the, lack of sleep is related to reduced amygdala connectivity with the posterior cerebellar lobe, which is involved in emotional control and executive function (2, 36, 37).

From this perspective, the pathogenesis of depression involves several mechanisms, such as changes in noradrenergic, dopaminergic, serotonergic and glutamatergic systems, increased

inflammation, abnormalities of the hypothalamic pituitary adrenal (HPA) axis, vascular impairments and reduced neurogenesis and neuroplasticity. In this way, the regulation of the HPA axis involves the action of cortisol, sleep and circadian rhythmicity, thus, losses in these factors generate a maladaptive response to stress (14, 37). Furthermore, the increase in glucocorticoids affects the medial prefrontal cortex (mPFC), responsible for executive functioning and emotion processing, the hippocampus, which is involved in memory and learning, and the amygdala, which plays an essential role in memory processing. emotion (9, 14, 36). Chronic stress promotes neuroadaptive deformations in the mesolimbic dopaminergic pathway, generating significant impairments in the expression of brain-derived neurotrophic factor (BDNF) and in neuroplasticity (14, 38). It should be noted that the development of depression in patients suffering from insomnia is also related to additional environmental factors such as lifestyle, coping mechanisms, psychosocial stress burden, and early preventive treatments (35).

In conclusion, depression is a complex disorder that has a huge impact on quality of life (32). Thus, the associations between sleep and mental health have important implications for clinical interventions, through more effective and earlier approaches to sleep in medical and mental health environments as a way to reduce the possible consequences of sleep deprivation (39).

3.4 WHY A SLEEP LOSS MAKE US DEPRESSED?

Studies have shown that insomnia increases the severity of depression. In the general population, almost 20% of patients with insomnia also have depressive symptoms (41). Furthermore, in addition to the effects of decreased sleep time, reductions in sleep quality also affect emotional well-being. Fragmentation and poor sleep quality are associated with higher rates of anxiety, altered mood, and impaired emotional regulation (40). From this perspective, inflammation and endocrine hormones also play important roles in this process. There is a two-way connection between the gut microbiome, sleep and depression. Thus, it has been demonstrated that the interaction between the chronic interruption of normal sleep patterns and diet can cause metabolic diseases and aggravate depressive states in individuals with sleep deprivation (41).

Besides that, brain-derived neurotrophic factor (BDNF) modulates plasticity-related changes that are associated with memory processing during sleep. Chronic sleep deprivation and insomnia can act as external stressors and result in depression, characterized by downregulation of BDNF in the hippocampus, along with disrupted frontal-cortical BDNF expression, as well as reduced levels and impaired daytime changes in serum expression of this factor. (42). Furthermore, abnormalities in the functional connectivity of the amygdala with the frontal lobe, when observed, suggest that emotional dysregulation may contribute to clinically relevant psychopathological phenotypes. Under this

perspective, studies of sleep deprivation and insomnia disorders have shown that sleep loss can alter such connectivity, resulting in higher rates of depression in sleep-deprived individuals (43).

Also, the effects of sleep deprivation on the function of the hypothalamic-pituitary-adrenal axis were studied by measuring serum and cerebrospinal fluid (CSF) levels of corticosterone in rats and, at the end of the experiment, the brains were collected to measure the circadian oscillations of gene expression in the hypothalamus, activation of glial cells and changes in inflammatory cytokines. Results indicated that sleep deprivation for as little as 3 days resulted in both anxious and depressive-like behaviors (44).

In this context, the relationship between deprivation and irregular sleep patterns in the population and changes in mood were also evaluated, as it was seen that a deprivation of 1 hour less sleep during weekdays can trigger depressive symptoms. Thus, impaired sleep is one of the public health concerns in modern society, as it has a direct impact on both the physical and mental health of these individuals, and may be associated with anxiety and depressive symptoms (45).

4 CONCLUSION

The present article discussed the association of sleep deprivation with anxiety and depression. On account of the existing knowledge, it was evidenced that sleep deprivation and daytime sleepiness are associated with a worsened quality of life. Therefore, these factors are responsible for the increase in the risk of depression and anxiety. In this context, it is of extreme importance the adequate prevention of this neurological disorder, besides the knowledge and development of new treatment approaches. On that account, the necessity of more specific research and propagation of data regarding the relationship between migraine, specially with aura, and cerebrovascular and cardiovascular pathologies, by the health planners and formulators of policies.

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