REVIEW ARTICLE

Psychiatry and Clinical Psychopharmacology 2020;30(4):449-457
DOI: 10.5455/PCP.20201207094228

Exploring the Complex Relationship Between Sleep, Depression and the Immune System

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Abstract

Sleeping has a critical function to promote health. Studies over the past ten years has documented that sleeping disorders has a strong influence on the risk of infectious diseases and in particular occurrence and progression associated with several major health issues including depression. Recent studies have focused on elucidating the underlying mechanisms that play a role in this situation. This article has been written to review the dynamics of sleep disturbance, sleep restriction, and insomnia on depression and the immune system. Also aimed to discuss the multi-faceted relationship that connect sleep disorder and immunity in terms of the neurobiology of sleep, inflammation and depression. In this context, what is known about the role of sleep on the immune system and the relationship between sleep disorder and depression and the immune system of depression will be reviewed.

ARTICLE HISTORY

Received: Dec 07, 2020
Accepted: Dec 14, 2020

KEYWORDS: sleep, depression, immune system, cytokines

INTRODUCTION

Although depression is a psychiatric disorder, it is closely related to many mental disorders and also physical illnesses. The results of studies conducted for more than twenty years reveal the relationship between sleep, psychiatric disorders and the immune system. These studies have also shown the existence of bi-directional communication between the sleep regulating networks in the central nervous system and the cells of the immune system. Normally, sleep is related to circadian rhythm and it may not be easy to find the exact components of this two-way relationship. For example, many studies have been published showing that depressed individuals have a 60% higher risk of developing type II diabetes than those without depression, and that coronary heart disease also plays a role in the etiology of diseases such as obesity, stroke, hypertension, cancer, dementia and sleep disorders. Insomnia is a common symptom of depression that it is often accompanied by sleep changes, and patients with major depressive disorder (MDD) experience problems falling asleep, maintaining sleep, and waking up early in the morning. Immune system/inflammatory pathologies have found to be related to sleep. This bidirectional relationship between depression and sleep is now becoming to be considered as a tripartite relationship; depression, sleep and immune system [1-3](Figure 1).

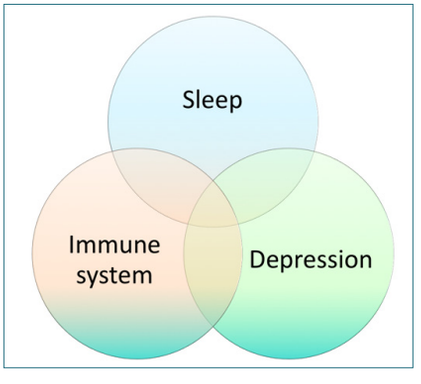

Figure 1. The relationships between sleep, immune system and depression

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To cite this article: Aricioglu F, Cetin M. Exploring the Complex Relationship Between Sleep, Depression and the Immune System. Psychiatry and Clinical Psychopharmacology 2020;30(4):449-457, DOI: 10.5455/PCP.20201207094228

Functions of Sleep

Sleep is a common feature and need in almost all living things. It is a condition that occurs naturally in the brain and body, characterized by the altered state of consciousness, reduced response to external stimuli, and the absence of voluntary movements. Contrary to popular belief, sleep is not a state dominated by passive inactivity, it is a daily rhythm with complex functions. As is known, sleep consists of two main stages: rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. The first document between infectious diseases and sleep belongs to Hippocrates in the 4th century BC. The general idea that sleep is increased during an infectious disease, and the widespread belief that poor sleep leads to increased susceptibility to pathogens have supported the hypothesis that sleep has a restorative function. There has been a dramatic increase in scientific interest in the interaction between sleep and immunity, which has led to recent advances in this field [4].

A master circadian pacemaker is located in the hypothalamus, the suprachiasmatic nucleus which increases production of the hormone melatonin in order to trigger sleep is important for matching the body's circadian rhythm to the external cycle of light and darkness through pineal gland. In communication with the brain stem, especially the pons and medulla, thalamus, cerebral cortex, basal forebrain and midbrain regulates sleep, wakefulness, clock genes and immune system (Figure 2).

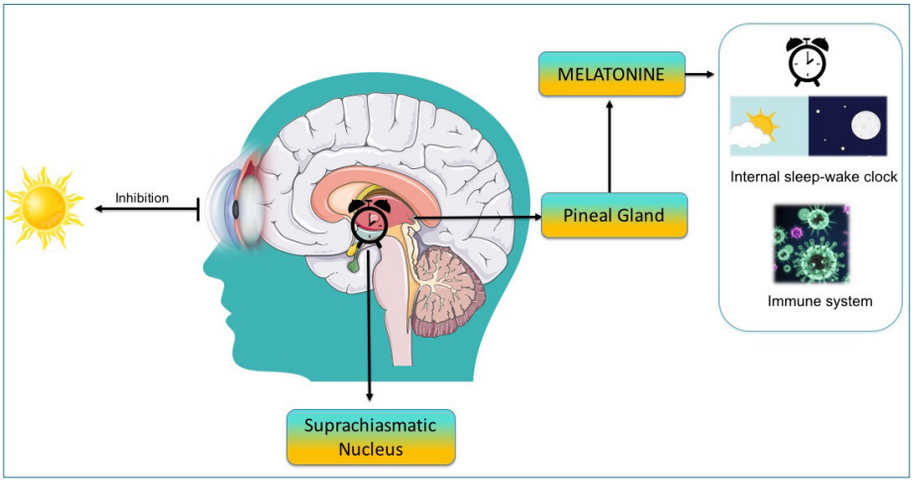

Figure 2. Biological clock, sleep regulation and immune system.

The suprachiasmatic nucleus contains neurons that exhibit a circadian pattern of activity and regulate melatonin secretion by the pineal gland in response to the environmental light/dark cycle. Blood levels of melatonin are high at night and low during the day and its primary function is regulating the circadian rhythm and synchronize our sleep-wake cycle with night and day. Therefore, melatonin facilities a transition to sleep and promotes consistent, quality rest. Apart from that, it is a hormone that can control cell cycle and immune system due to its strong antioxidant properties. Besides, serotonin, the precursor of melatonin helps to wake up, can modulate feelings and a deficiency in serotonin can result in depression. Sleep has many properties that affect the nervous system. Staying without sleep for one night negatively affects mood and cognitive functions including the basic cognitive functions such as memory, language, visual functions, and executive functions such as attention, planning, programming, regulation. There are many functions of sleep on memory, learning new information and storing it in long-term memory, endocrine functions, cardiovascular system, immune system, mood state [5].

Sleep and Aging

Research results in the last 35 years show that the body's biological clock deteriorates with aging, and this has been associated with the development of neurodegeneration, obesity, and type 2 diabetes. It has also been shown that sleep disorders increase the number of aging-related diseases and the number of deaths from these diseases. Even experiencing partial insomnia overnight can cause differentiation in genes that cause aging at the cellular level, shortening of telomeres and a change called "epigenetic methylation". In a study comparing those who slept less than 5 hours and more than 7 hours a night, it was shown that less sleep affects cognitive functions negatively and the process is associated with inflammation [6].

The results of recent studies show that glial cells such as microglia and astrocyte actively contribute to sleep and immune system interactions, rather than neurons. Studies conducted in this context also show that the changes in sleep-wake behavior observed during the aging process and the suppression of the immune system are made by

microglia and astrocytes. Increasing age-related changes in the function of the immune system with insufficient sleep brought the definition of "Inflammaging". The dynamics are different from those observed in young people, although decreased sleep in older individuals increases immunomodulators and similarly inflammation alters sleep. These data show that the potential interaction between sleep and immunity is irregular in aging. One of the features of aging is the morphological changes of microglia and astrocytes. Therefore, these cells are the most important members of synaptic homeostasis and may be the most important cause of age-related changes in sleep and immune function. Undoubtedly, the rapid increase of the population aged 65 and over in the world suggests the need for studies to understand these interactions [7].

Sleep, Gender and Mood Disorders

Women are more likely to suffer from depression, inflammation, and sleep disorders than men. Consistent with this information, decreased sleep quality, inflammation and heart disease have been found in women a lot more than in men. Sleep disturbances are the most common symptoms of depression and increases the likelihood of depression recurrence. Having sleep disorders due to psychological stress also increases the risk of developing depression. In addition, the presence of an underlying inflammatory disease increases the development of sleep disturbance and depression caused by the common denominator inflammatory reaction [8].

In bipolar disorder and depression, it is known that disruption in circadian rhythms, an irregularity in the internal clock of the body, can cause new disease periods. The recurrence is one of the most prominent clinical features of bipolar disorder. While mood episodes usually follow a seasonal rhythm, significant disturbances are observed in circadian rhythm and sleep-wake cycles. Circadian rhythm affects not only body temperature, hormone release, sleep-wake cycles, but also psychomotor performance, cognitive functions, and mood. Therefore, depending on circadian rhythm irregularities, the susceptibility of the person to transition from depression to hypomania-mania may increase. The clock gene, which is considered to be responsible for the regulation of circadian rhythm, has been shown to affect behaviors similar to those observed during manic periods, such as hyperactivity, decreased need for sleep, and unusual talkative. This highlights the relationship between the development of bipolar spectrum disorders and the clock gene [9-12].

Interpersonal Relationships Social Rhythm Therapy is a psychotherapy which was developed in the 1990s to be applied to patients with bipolar disorder and later, it was demonstrated that this therapy has a protective proporties. With the Social Rhythm Metric application, moods can be regulated mainly by interfering with the sleep pattern. It has been shown that bipolar disorder can be triggered by shift work. The onset and recovery of bipolar disorder can be achieved by providing sleep patterns and regulating social rhythms, helping to solve interpersonal problems and increasing support system with this therapy. It is known that adding psychotherapies to drug therapy provides better biopsychosocial recovery. Interpersonal Relationships Social Rhythm Therapy aims to facilitate the treatment processes of irregularities in social timings such as sleep, wake time, meal time, and the disruption of the regular functioning of the working body over time [13-15].

Sleep Stress and Immune System

Over the past century, there has been a dramatic increase in the scientific interest in the interaction between sleep and immunity, which has led to recent advances in the field. This chapter aims to contribute to this growing area of research by exploring the reciprocal relations between sleep and the immune system by means of two basic experimental approaches that are currently being adopted in research of the field: one is the increased sleep induced either by spontaneous or experimental inflammation/ infection, and the other is how sleep deprivation modulates immune responses (16). Investigation of the environmental and personalized genomic inputs that influence sleep and inflammatory biological mechanisms is needed to understand how distinct aspects of sleep map onto immunological signatures. Sleep is not homogeneous, and multiple factors including circadian rhythms, homeostatic drive to sleep, and physical activity, can all impact sleep quality, sleep duration, and sleep depth, yet the vast majority of human research linking sleep disturbance to inflammation has not considered the over-lapping influences of these additional factors on sleep processes. It is necessary to understand how different aspects of sleep are regulated immunologically, affecting sleep and inflammatory biological mechanisms. It has been suggested that circadian rhythms of sleep and wakefulness may be related to the oxidant / antioxidant balance. It has been suggested that free radicals and reactive oxygen species formed during wakefulness are removed by sleep [17,18].

Cytokines, which are immunological signaling molecules, are the most important members of brain-immune system communication. It is generally accepted that sleep loss increases the production of proinflammatory molecules, REM sleep deprivation increases circulating levels of interleukin (IL)-6, IL-1β, IL-2, IL-18, and tumor necrosis factor alpha (TNF-α), and some of them may remain high for a week (19). As a result of bidirectional communication between the central nervous system and the immune system, if sleep is altered, there is a deterioration in the response to invading immune system and likewise immune response is capable of inducing sleep changes. It is known that proinflammatory cytokine release increases especially in sleep disorders such as sleep deprivation and chronic restriction. In accordance with this, as a result of the activation of the peripheral immune system, circulating cytokines can reach the brain

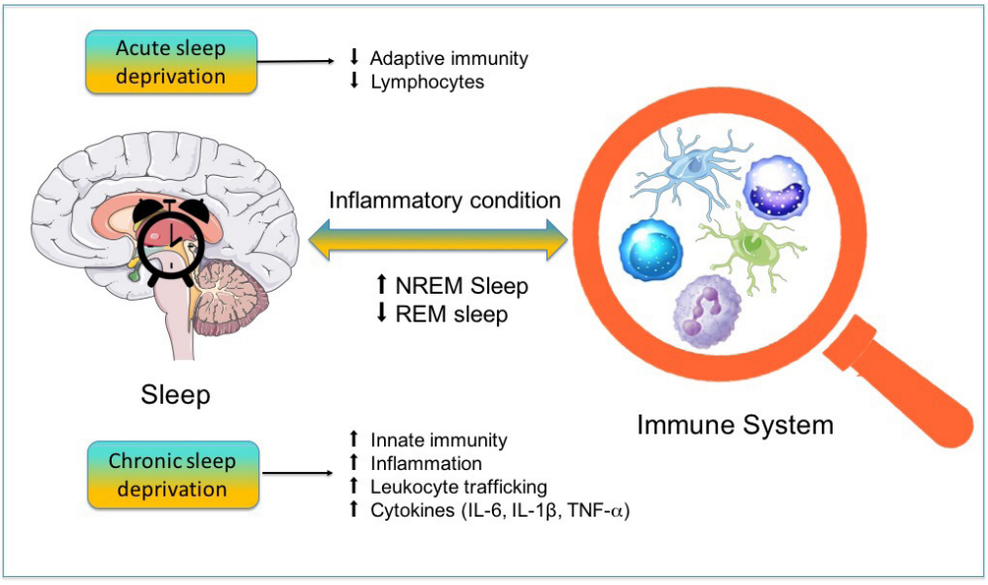

Figure 3. Sleep and immune system interaction

by crossing the blood-brain barrier and are also produced within the brain [20](Figure 3).

Cytokines are synthesized and released in the brain by both neurons and glia. In particular, neurons immunoreactive to IL-1 and TNF-α - are found in regions of the brain involved in sleep / wake cycle regulation such as the hypothalamus, hippocampus, brainstem, and neocortex, in which cytokine receptors are found in both neurons and astrocytes. Studies have shown that especially the proinflammatory cytokines (IL-1β, IL-2, IL-6, IL-18 and TNF-α) support NREM sleep while anti-inflammatory cytokines (IL-4, IL-10, IL-13 and TGF) inhibit NREM sleep [20].

The putative mechanism includes changes in the action and secretion of neurorotransmitters (such as monoamines, acetylcholine, and glutamate), hormones (CRH, ACTH, MSH, and GH), and changes in synaptic flexibility in neurocircuits that regulate mood, motor activity, motivation, anxiety, and alertness. Under physiological conditions, IL-1, IL-6, and TNF-α play a role in the regulation of the circadian rhythm; It is highest during the night and decreases to lowest during wakefulness [20-23]. As is well known, peripheral monocytes, macrophages or dendritic cells and glia in the brain are the innate immune system cells. These cells form the first line of defense that protects the body against tissue damage and microbial infection. These cells, which can be activated within minutes to hours in the presence of an organism-threatening situation, initiate a series of inflammatory processes to help infection control and support healing when necessary [24].

Pathogen-associated molecular patterns are recognized as highly conserved receptors of innate immune cells. When these pattern recognition receptors (PRRs) are activated, both local and systemic increase in inflammatory activity occurs. It occurs through toll-like receptors (TLRs), which are found in macrophages, neutrophils, and dendritic cells. In general, TLRs recognize conserved components of microbes, including bacteria, viruses, and fungi.

It is essential to understand how sleep disturbances play an important role in the dynamics of innate responses and the cases that govern the innate author responses. Direct communication from the peripheral immune system to the CNS occurs through the action of cytokines and pathogen-related molecular models on the vagus nerve. Vagal afferents innervate brainstem nuclei, including the core of the solitary tract, ventrolateral medulla, paraventricular and supraoptic nuclei of the hypothalamus, and amygdala. Each of these brain regions plays an important role in regulating sleep [25].

Inflammation and Depression

Sleep disturbances are the symptoms which are known to be independently associated with depression. It is well documented that changes in sleep in MDD patents is different from those whose experience problems with sleep onset, sleep maintenance and early morning awakenings. In fact, sleep disturbance is a diagnostic feature of depression, but it is also common in most people with sleep problems [26,27].

Inflammation occurs widely in psychiatric diseases including depression. Inflammation is due to the innate immune cells in the brain, particularly the microglia which are the resident macrophages, are activated to produce cytokines, chemokines and other inflammatory factors in response to the stimulus. While transient inflammatory stimuli are generally considered as a protective and beneficial process for the brain, chronic inflammation is a damaging process that deeply affects neuronal plasticity and homeostasis of the brain [28]. Common biological pathways have been proposed to explain the link between sleep and depression. Especially in terms of changes in sleep structure

neurobiological processes including REM sleep and changes in monoaminergic and neuroendocrine systems have been described [29]. However, there are only a limited number of studies that investigate the prospective relationship between sleep, depression, and other physical illness, and examine the role of depression and sleep problems, especially at the onset of the disease [30].

There is clinical evidence that proinflammatory cytokines such as IL-1β, IL-6 and TNF-α are elevated in the serum of MDD patients. Supporting this information, there is evidence that the therapeutically use of the inflammatory cytokine interferon-alpha to treat hepatitis C and malignant melanoma accelerates the formation of a depressive state [31,32]. Numerous evidence suggests that depression is accompanied by activation of the inflammatory pathway in increasing blood and CSF concentrations of IL-1β, IL-6 and TNF-α [33].

Inflammatory changes accompanying depression occur in peripheral organs and brain parenchyma. As a result of chronic exposure of the brain to inflammation, structural changes associated with depression occur, particularly in the frontal cortex and subcortical areas, raising the question of whether it is possible to prevent or even reverse these changes with pharmacological intervention [34].

Toll-like receptors (TLRs) located in the membrane of microglia and macrophage cells are activated by stress / depression. One of the important regulators of the innate immune system, NOD-like receptors (NLRs) are cytosolic receptors and can be activated due to activation of TLRs. NLRs consists of three components, one sensor molecule, one adapter protein, and one effector component. Following activation, these subunits combine to form a pro-inflammatory, multiprotein complex called inflammasome [35]. This interesting protein complex exists in an inactive form in the cytoplasm and is transformed into the active forms IL-1β and IL-18, which are potent proinflammatory cytokines that are inactive intracellularly in the form of pro-IL-1β and pro-IL-18 when activated, as well as to pro – It also converts caspase-1 to active caspase-1. Activated IL-1β and IL-18 are then can be secreted from cells [36] (Figure 4).

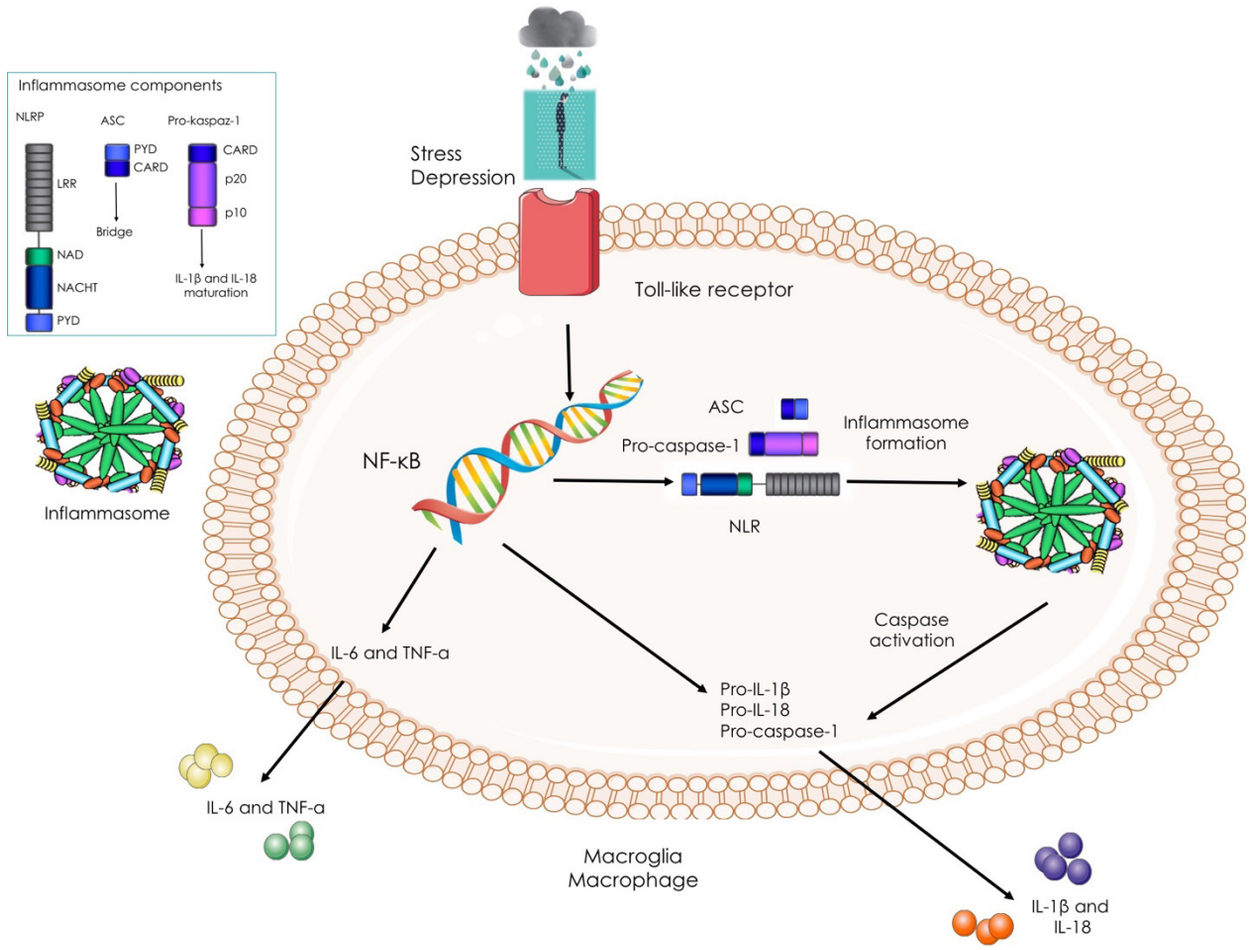

Figure 4. Activation of NLRP3 inflammasome. Inflammasomes contains NOD-like receptor (NLR) family, such as NLRP3. The NLR protein recruits the inflammasome-adaptor protein ASC, which in turn interacts with caspase-1 leading to its activation. When activated it promets maturation of caspase-1 and proinflammatory cytokines such as interleukin (IL)-1β and IL-18.

In addition to the large family of cytokines responsible for inflammation and thus modulation of the immune response, a protein complex with intracellular Pro – and even anti-inflammatory functions has recently been identified and named NLRs. NLRP3 inflammasome is the most studied member of this family so far. The NLRP3 protein is linked by a CARD (ASC) bridge to procaspase-1 responsible for apoptosis [37-38]. Activation of the NLRP3 inflammasome, which consists of the NLRP3 protein, the adapter protein ASC, and caspase-1, leads to the maturation of the proinflammatory cytokines IL-1β and IL-18. Increased concentration of IL-1β and IL-18 is closely linked to inflammatory disorders. Recently, the importance of ROS to activate NLRP3 inflammasome has been demonstrated because ROS reduction inhibits NLRP3 inflammasome activation [39].

The first depression study related with NLRP3 was published in 2014. In peripheral blood mononuclear cells isolated from depressive patients, NLRP3 and caspase-1 expressions and associated IL-1β and IL-18 serum levels were found to be higher than in healthy individuals. In the same study, it was shown that NLRP3 activation and related cytokine responses decreased in patients treated with amitriptyline for at least 10 months [40,41]. In another clinical study conducted on patients with depression, it was shown that ASC levels, which act as a bridge, in the NLRP3 inflammatory complex, increased [42]. In addition to monitoring NLRP3-inflammasome and IL-1β / IL-18 release, it is recommended as a biomarker for antidepressant therapy in MDD patients. It has been suggested that NLRP3 expression levels and proinflammatory cytokines may have a clinical value in drug selection, demonstrating that antidepressant-mediated autophagy may play a role in the restoration of certain metabolic and immunological pathways in MDD patients [43].

A better knowledge of the objective aspects of sleep disturbance on inflammatory disease risk will inform what specific aspects of sleep might be targeted to moderate the associations between sleep disturbance, inflammation, and adverse health outcomes including depression. A limited number of polysomnography studies have been conducted to investigate the effects of these drugs on patients' sleep when cytokine antagonists are used for the treatment of inflammatory diseases. In a study conducted on 36 treatment-resistant depression patients, it was shown that the use of TNF-α antagonist infliximab may be effective in reducing inflammation, improving depressive symptoms and enhancing sleep. Infliximab therapy has been shown to reduce spontaneous stimulation during the night and improve sleep efficiency. They also found that TNF-α blockade improved sleep continuity and increased sleep depth in patients with romatoid artritis. TNF-α antagonism has been found to reduce daytime sleepiness in patients with sleep apnea and possibly improve other depressive symptoms in those with high levels of inflammation [44,45]. There are various treatment options for patients with sleep disorders; pharmacological, psychological and behavioral approaches (Cognitive Behavioral Therapy-CBT) and relaxation-based therapies (eg Tai chi and Yoga). There is evidence that CBT is as effective as pharmacological treatments in patients with insomnia complaints. These studies indicate that the basis of the potency of CBT is its effects on the immune system, including the innate immune response components [46,47]. Where nuclear factor kappa B (NF-κβ) decreases and reverses the activation of inflammatory signaling pathways during the control of insomnia with CBT [48]. In addition, the alleviation of insomnia in parallel with its treatment, reduced the high CRP levels of the 16-month application, and provided additional benefits such as 50% reduction in sleep problems, physical activity and weight loss after one year. During the control of insomnia with CBT, it has been found that NF-κβ decreases and reverses the activation of inflammatory signaling pathways. The findings of some studies supporting their findings have shown that insomnia treatment can reverse the increase of IL-6 and TNF-α and suppress proinflammatory gene expression. The relationship between sleep and immunity has been debated since 2400 years ago when the increase in sleep during acute infection was mentioned in ancient Greece [46,49].

Today it is well known that this relation is mediated not only by neurotransmitters but also with intercellular signals like cytokines and chemokines. For example, we know that the production of pro-inflammatory cytokines such as IL-1β and TNF-α in certain brain regions plays a role in the regulation of both physiological functions and behavioral processes including sleep-wake status. This information indicates an increase in CRH, ACTH and NF-κβ due to activation of the sympathetic system and hence the HPA axis. The findings of shift workers examining the changes that both acute and chronic sleep deprivation impact on the immune system confirming the innate immune response as well as the inflammatory response may be an increased risk for viral infection [50].

Sleep Deprivation in Treatment of Depression

Even though it may seem paradoxical with the aforementioned information, sleep deprivation is the most widely recommended antidepressant treatment, with both partial and total sleep deprivation providing clinical improvement in symptoms of depression within 24 hours. Considering the accumulated research results on this subject, it has been shown that sleep deprivation provides rapid antidepressant effects in approximately 40-60% of the cases, this rate is 45% in studies using control group and 50% in studies that do not use it. In addition, the response to insomnia is significantly influenced by the type of sleep deprivation, the nature of the clinical sample, the medication, the definition of the response used, the age and gender of the case [51,52].

In a study investigating the effects of late partial sleep deprivation and antidepressant medication on regional cerebral blood flow in patients with depression, an antidepressant drug was administered immediately after the first SPECT. A second SPECT was performed at the

second, fourth and sixth weeks of treatment, after being evaluated using HAM-D and BDI. In the late partial sleep deprivation procedure, the subjects who slept between 09:00 and 02:00 were awakened at 02:00 AM and were not allowed to sleep until the morning SPECT application. In the study, the positive response criterion for insomnia was accepted as a minimum 30% decrease in HAM-D scores and it was observed that these scores were 75% in depressive cases [53].

COVID-19, Immune System and Depression

Today, COVID-19 is on the agenda of the whole world. COVID-19 infection was also named "cytokine storm" because it is an aggressive inflammatory reaction against the SARS-CoV-2 virus caused by excessive release of the pro-inflammatory cytokine. We have recently begun to experience a process we had no knowledge of before. COVID-19 has been a process that affects the entire world population and affects the daily routine and sleep quality with it. On the other hand, this process increases the importance of the immune system, cytokine storm and thus the activity of cytokines which are inflammatory markers such as IFN, TNF-α, IL-1β, C-reactive protein.

The COVID-19 process was once again pointed out to the relationship under insomnia. This relationship is also closely linked to the psychosocial impact of the pandemic and confirms the link between sleep, the immune system and psychology. As a result of the analysis of cytokine profiles from COVID-19 patients, high levels of IL-1β, IL-7, IL-8, IL-9, IL-10, FGF, G-CSF, GM-CSF, IFN, TNF-α in plasma were revealed. We do not yet know exactly how cytokines, one of the most emphasized hypotheses in psychiatric diseases and especially depression neurobiology, will affect the world population depending on the situation defined as cytokine storm like COVID-19. There is a need for a better understanding of this mechanism, which underlies psychiatric illnesses, whether or not due to COVID-19 [54].

Our experience in this short period made us think once again about the power of cytokines, sleep and immune system relationship. The COVID-19 epidemic has clearly demonstrated the damage caused on the mental health of the society in China and the United States in January and February 2020, and the relationship between increased levels of depression and poor sleep quality. With the progress of the epidemic, the widespread increase in depression and anxiety has brought the role of sleep in emotional stabilization as risk factors associated with the onset of insomnia. In patients with depression who naturally experience great psychological stress, the common denominator of immunity, sleep and depression is especially CRP and IL-6 as a pro-inflammatory cytokine, and these parameters known to increase inflammation in terms of inflammation also increase depressive symptoms. Moreover, sleep disturbances such as insomnia also increase inflammation and cytokine storm, which is directly linked to the incidence of depression [55].

CONCLUSION

In this review article, we have tried to review the interaction between sleep, MDD and the immune system. occur with depression. Accumulated evidence pointing the close relationship between sleeping disorders, infectious diseases and MDD which connect sleep disorders and immunity. Sleep influences both HPA axis and sympathetic nervous system, which regulate adaptive and innate immune responses. Besides circadian factors play a predominant role in regulating the distribution of immune cells while modulating internal clock and sleep cycles. Studies support a bidirectional relationship between these pro – inflammatory cytokines and sleep. Increases in these cytokines lead to increased sleep, and conversely, sleep deprivation and disruption can increase these cytokines. On the other hand, insomnia is not simply a symptom of depression but may play a role in predicting depression incidence. It seems that COVID-19 and its effects on the immune system, the importance of sleep and its possible relationships with psychiatric diseases will be in our focus for a long time. Perhaps the only positive contribution of this process will be a much better understanding of the effects of cytokine storm and thus changes in cytokine balance on our health. The biggest expectation is, of course, to transform this experience into products for the benefit of human health. Further research is necessary for better understanding this phenomenon from the clinical perspective and to develop novel therapeutic strategies for patients suffering from both sleep disturbances and MDD.

Author contributions: MC and FA equally contributed in writing and FA drew figures.

REFERENCES

[1] Benca RM, Peterson MJ. Insomnia and depression. Sleep Med. 2008;9 (Suppl 1):S3-9. doi: 10.1016/S1389-9457(08)70010-8.

[2] Pan A, Keum N, Okereke OI, Sun Q, Kivimaki M, Rubin RR, Hu FB. Bidirectional association between depression and metabolic syndrome: A systematic review and meta-analysis of epidemiological studies. Diabetes Care. 2012; 35:1171–1180. doi:10.2337/dc11-2055.

[3] Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. Br. J. Psychiatry 2013; 202, 329–335. doi:10.1192/bjp.bp.112.118307.

[4] Zielinski MR, McKenna JT, McCarley RW. Functions and mechanisms of sleep. AIMS Neurosci. 2016; 3(1): 67-104. doi: 10.3934/Neuroscience.2016.1.67.

[5] Carley DW, Farabi, SS. Physiology of sleep. Diabetes Spectr. 2016; 29(1):5-9. doi: 10.2337/diaspect.29.1.5

[6] Prather AA, Janiki-Deverts D, Hall MH, Cohen S. Behaviourally assessed sleep and susceptibility to the common cold. Sleep 2015;38(9):1353-1359. doi: 10.5665/sleep.4968.

[7] Ingiosi AM, Opp MR, Kruege JM. Sleep and immune function: glial contributions and consequences of aging. Current Opinion in Neurobiology 2013, 23:806–811.

[8] Gliske SV. A new theory of gender dysphoria incorporating the distress, social behavioral, and body-ownership networks. eNeuro. 20;6(6):ENEURO.0183-19.2019. doi: 10.1523/ENEURO.0183-19.2019.

[9] Rainville JR, Hodes GE. Inflaming sex differences in mood disorders. Neuropsychopharmacology 2019;44(1):184-199. doi: 10.1038/s41386.018.0124-7.

[10] Subramaniapillai M, Carmona NE, Rong C, McIntyre RS. Inflammation: Opportunities for treatment stratification among individuals diagnosed with mood disorders. Dialogues Clin Neurosci. 2017;19(1):27-36. doi: 10.31887/DCNS.2017.19.1/rmcintyre.

[11] Vadnie CA, McClung CA. Circadian rhythm disturbances in mood disorders: Insights into the role of the suprachiasmatic nucleus. Neural Plast. 2017;2017:1504507. doi: 10.1155/2017/1504507.

[12] Gao L, Li P, Hu C, To T, Patxot M, Falvey B, Wong PM, Scheer FAJL, Lin C, Lo MT, Hu K. Nocturnal heart rate variability moderates the association between sleep-wake regularity and mood in young adults. Sleep. 2019;42(5):zsz034. doi: 10.1093/sleep/zsz034.

[13] Frank E. Treating bipolar disorder-A clinician's guide to interpersonal and social rhythm therapy, The Guilford Press, New York, 2005.

[14] Frank E, Soreca I, Swartz HA, Fagiolini AM, Mallinger AG, Thase ME, Grochocinski VJ, Houck PR, Kupfer DJ. The role of interpersonal and social rhythm therapy in improving occupational functioning in patients with bipolar I disorder. Am J Psychiatry. 2008;165(12):1559-65. doi: 10.1176/appi.ajp.2008.071.21953.

[15] Lipsitz JD, Markowitz JC. Mechanisms of change in interpersonal therapy (IPT). Clin Psychol Rev. 2013;33(8):1134-47. doi: 10.1016/j.cpr.2013.09.002.

[16] Poole L, Jackowska M. The association between depressive and sleep symptoms for predicting incident disease onset after 6-year follow-up: findings from the English Longitudinal Study of Ageing. Psychological Medicine 2019; 49, 607–616. doi:10.1017/S003.329.1718001290.

[17] Aytac B, Kayhan A,Devrim E, Durak I, Erguder S. The effects of sleep deprivation on oxidant/antioxidant status. Klinik Psikofarmakoloji Bulteni-Bulletin of Clinical Psychopharmacology 2007;17:130-133 (Turkish).

[18] Yehuda S, Sredni B, Carasso RL, Kenigsbuch-Sredni D. REM sleep deprivation in rats results in inflammation and interleukin-17 elevation. J. Interf. Cytok. Res. 2019;29: 393–398.

[19] Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008;9: 46–56.

[20] Kapsimalis, F, Richardson G, Opp MR, Kryger M. Cytokines and normal sleep. Curr. Opin. Pulm. Med. 2005;11: 481–484.

[21] Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. Pharmacol. Ther. 2011; 130: 226–238.

[22] Petrovsky N, McNair P, Harrison LC. Diurnal rhythms of proinflammatory cytokines: regulation by plasma cortisol and therapeutic implications. Cytokine 1998; 10: 307–312.

[23] Medzhitov R. Origin and physiological roles of inflammation. Nature 2008;454: 428–435.

[24] Besedovsky L, Lange T, Born J. Sleep and immune functions. Pflugers Arch. 2012; 463(1):121-137. doi: 10.1007/s00424.011.1044-0.

[25] Asarnow LD, Soehner AM, Harvey AG. Basic sleep and circadian science as building blocks for behavioral interventions: a translational approach for mood disorders. Behav Neurosci. 2014;128(3):360-70. doi: 10.1037/a0035892.

[26] Taylor DJ, Lichstein KL, Durrence HH, Reidel BW, Bush AJ. Epidemiology of insomnia, depression, and anxiety. Sleep 2005;28(11):1457-1464. doi: 10.1093/sleep/28.11.1457.

[27] Lyman M, Lloyd DG, Ji X, Vizcaychipi MP, Ma D. Neuroinflammation: the role and consequences. Neurosci Res. 2014; 79:1-12.

[28] Baglioni C, Riemann D. Is chronic insomnia a precursor to major depression? Epidemiological and biological findings. Curr Psychiatry Rep 2012;14(5):511-518. doi: 10.1007/s11920.012.0308-5.

[29] Mezick EJ, Hall M, Matthews KA. Are sleep and depression independent or overlapping risk factors for cardiometabolic disease?. Sleep Med Rev 2011;15(1):51-63. doi: 10.1016/j.smrv.2010.03.001.

[30] Maes M, Meltzer HY, Bosmans E, Bergmans R, Vandoolaeghe E, Ranjan R, Desnyder R. Increased plasma concentrations of IL-6, soluble IL-6, soluble IL-2 and transferrin receptor in major depression. J Affect Dis. 1995; 34:301-309.

[31] Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 2006; 27:24-31.

[32] Hosoda S, Takimura H, Shibayama M, Kanamura H, Ikeda K, Kumada H. Psychiatric symptoms related to interferon therapy for chronic hepatitis: clinical features and prognosis. Psychiat Clin Neurosci. 2000;54:565-572.

[33] Dolati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctot KL. A meta analysis of cytokines in major depression. Biological Psychiatry 2010; 67: 446-457.

[34] Leonard BE. Inflammation and depression: a causal or co-incidental link to the pathophysiology? Acta Neuropsychiatrica 2018;30:1-16.

[35] Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. Mol Cell. 2002;10:417–26.

[36] Jo EK, Kim JK, Shin DM, Sasakawa C. Molecular mechanisms regulating NLRP3 inflammasome activation. Cell Mol Immunol. 2016;13:148–59.

[37] Iwata M, Ota KT, Duman RS. The inflammasome: pathways linking psychological stress, depression, and systemic illnesses. Brain Behav Immun. 2013;31: 105-114.

[38] Evavold C, Kagan JC. How inflammasomes inform

adaptive immunity. J Mol Biol. 2018; 430(2): 217–237. doi: 10.1016/j.jmb.2017.09.019.

[39] Carta S, Penco F, Lavieri R, Martini A, Dinarello CA, Gattorno M, Rubartelli A. Cell stress increases ATP release in NLRP3 inflammasome-mediated autoinflammatory diseases, resulting in cytokine imbalance. Proc Natl Acad Sci 2015;112:2835–2840. doi:10.1073/pnas.142.474.1112.

[40] Alcocer-Gomez E, de Miguel M, Casas-Barquero N, Nunez-Vasco J, Sanchez-Alcazar JA, Fernandez-Rodriguez A, Cordero MD. NLRP3 inflammasome is activated in mononuclear blood cells from patients with major depressive disorder. Brain Behav Immun. 2014;36: 111-117.

[41] Alcocer-Gomez E, Ulecia-Moron C, Marin-Aguilar F, Rybkina T, Casas-Barquero N, Ruiz-Cabello J, Ryffel B, Apetoh L, Ghiringhelli F, Bullon P, Sanchez-Alcazar JA, Carrion AM, Cordero MD. Stress-induced depressive behaviors require a functional NLRP3 inflammasome. Mol Neurobiol. 2016;53(7): 4874-4882.

[42] Momeni M, Ghorban K, Dadmanesh M, Khodadadi H, Bidaki R, Kazemi Arababadi M, Kennedy D. ASC provides a potential link between depression and inflammatory disorders: a clinical study of depressed Iranian medical students. Nord J Psychiatry. 2016;70(4): 280-284.

[43] Alcocer-Gomez E, Casas-Barquero N, Williams MR, Romero-Guillena SL, Canadas-Lozano D, Bullon P, Sanchez-Alcazar JA, Navarro-Pando JM, Cordero MD. Antidepressants induce autophagy dependent-NLRP3-inflammasome inhibition in Major depressive disorder. Pharmacol Res. 2017;121: 114-121.

[44] Weinberger JF, Raison CL, Rye DB, Montague AR, Woolwine BJ, Felger JC et al. Inhibition of tumor necrosis factor improves sleep continuity in patients with treatment resistant depression and high inflammation. Brain Behav Immun 2015;47: 193–200.

[45] Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry 2013;70: 31–41.

[46] Irwin MR, Olmstead R, Carrillo C, Sadeghi N, Breen EC, Witarama T et al. Cognitive behavioral therapy vs Tai chi for late life insomnia and inflammatory risk: a randomized controlled comparative efficacy trial. Sleep 2014; 37: 1543–1552.

[47] Morin C, Cholecchi C, Stone J, Sood R, Brink D. Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. JAMA 2019;281: 991–999.

[48] Irwin MR, Opp MR. Sleep health: Reciprocal regulation of sleep and innate immunity. Neuropsychopharmacology Rewiews 2017;42:129–155.

[49] Opp MR, Krueger JM. Sleep and immunity: a growing field with clinical impact. Brain Behav Immun 2015;47:1–3.

[50] Almeida CMO, Malheiro A. Sleep, immunity and shift workers: A review. Sleep Science 2016; 9:164–168.

[51] Hines DJ, Schmitt LI, Hines RM, Moss SJ, Haydon PG. Antidepressant effects of sleep deprivation require astrocyte-dependent adenosine mediated signaling. Transl Psychiatry 2013;3(1):e212. doi: 10.1038/tp.2012.136.

[52] Elaine M. Boland, Hengyi Rao, David F. Dinges, Rachel V. Smith, Namni Goel, John A. Detre, Mathias Basner, Yvette I. Sheline, Michael E. Thase, Philip R. Gehrman. Meta-Analysis of the antidepressant effects of acute sleep deprivation. Journal of Clinical Psychiatry 2017;78(8):e1020-e1034. doi: 10.4088 / JCP.16r11332.

[53] Ebrinc S, Basoglu C, Yilmaz V, Cetin M, Narin Y, Agargun MY. The effects of late partial sleep deprivation and antidepressant drug treatment to regional cerebral blood flow in patients with major depressive disorder: a SPECT study. Klinik Psikofarmakoloji Bulteni-Bulletin of Clinical Psychopharmacology 2001;11:242-250 (Turkish).

[54] Silva ESM, Ono BHVS , Souza JC. Sleep and immunity in times of COVID-19. Rev Assoc Med Bras 2020; 66(Suppl 2):143-147. doi:10.1590/1806-9282.66.S2.143.

[55] Patrick PerettI-Watel, Alleaume C, Léger D, Beck F, Verger P. Anxiety, depression and sleep problems: a second wave of COVID-19. General Psychiatry 2020;33:e100299. doi:10.1136/ gpsych-2020-100299.