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How sleep and depression are related: What does this contribute to interventions of sleep disorders and depression?

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Abstract:

This literature review explores the complex relationship between sleep and depression. Sleep disturbances, particularly insomnia, are commonly observed in individuals with depression, with 60% to 90% of depressed patients experiencing these issues. Physiological factors, such as disruptions in the sleep-wake cycle, irregularities in cortisol and melatonin secretion, and activity of the hypothalamic-pituitary-adrenocortical (HPA) axis, along with imbalances in neurotransmitters like serotonin and dopamine, are key contributors to this relationship. Neuroimaging studies have identified that brain regions such as the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), and amygdala are involved in both sleep regulation and depression, indicating shared neural pathways. Psychological factors, including stress, rumination, and anxiety, further intensify these problems. Effective treatments, such as antidepressants, cognitive behavioral therapy (CBT), and transcranial direct current stimulation (tDCS), show potential in addressing both sleep disorders and depression concurrently. However, challenges remain, including small sample sizes, reliance on self-reported data, and a lack of long-term follow-up, highlighting the need for further research. Future studies should investigate integrated treatment approaches to more effectively address the co-occurrence of sleep disorders and depression.

Keywords: sleep disorders, depression, bidirectional relationship.

1. Introduction

In recent decades, as society has progressed, there has been a growing awareness and recognition of mental health issues like depression, anxiety, and obsessive-compulsive disorder. Sleep disorders have emerged as a common concern among those affected. According to 2023 data from the World Health

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Organization (WHO), depression is estimated to affect 3.8% of the global population, impacting over 300 million people[27]. They were found to be especially likely to experience sleep disturbances and excessive daytime or nighttime sleepiness, or hypersomnia, affects around 20% of individuals with depression. According to Tsuno et al., between 60% and 90% of depressed patients report having insomnia, which manifests as trouble going asleep, numerous night wakings, or early awakenings[25]. Additionally, a large epidemiological survey, the National Co-morbidity Survey Replication (NCS-R) study, has shown similar findings that the prevalence of insomnia is significantly higher among individuals with depression than in the general population. Specific data in that survey showed that approximately 75% of individuals with major depression reported experiencing insomnia. According to Ettensohn et al., sleep disorders and problems can appear in some people before the onset of depression symptoms, but they can also co-occur with depressive symptoms or persist even after depression treatment[9]. Therefore, this review aims to investigate the relationship between sleep and depression, examining how sleep disorders can lead to the onset and exacerbation of depressive symptoms and, conversely, how depression can lead to various sleep disorders. A one-tailed hypothesis suggests that there may be a significant mutually reinforcing bidirectional relationship between sleep and depression, which can be mitigated by improving sleep and also by reducing depression. Specifically, it can be divided into 2 parts. First, sleep disorders like insomnia, excessive sleepiness, and sleep apnea are considered significant risk factors for the onset and worsening of depression. Second, depression plays a role in the development and persistence of these sleep disorders, creating a vicious cycle that intensifies both conditions.

2. Sleep Disorders as a biomarker to Depression

Firstly, what role does the sleep factor play in depression? Based on the findings of most studies and those made in the literature, it can be concluded that sleep is a biomarker of depression. These biomarkers have practical implications-they can help to diagnose and classify depression, offer insights into the underlying biological mechanisms of these disorders, guide the selection of the most appropriate treatment for an individual, increase the likelihood of treatment efficacy, and monitor the progress of treatment, and make necessary adjustments[24]. So, how is sleep a biomarker for depression?

Benca et al. found that polysomnographic sleep pattern changes in depressed patients could be classified into three categories: sleep continuity disorders, SWS (slow wave sleep) disorders, and REM sleep disorders[3]. This study revealed that individuals with depression experience longer times to fall asleep, shorter latency before entering REM sleep, fragmented sleep with frequent awakenings, reduced duration of N3 slow-wave sleep, and extended, disrupted REM sleep stages. In contrast, healthy controls displayed shorter times to fall asleep, normal REM sleep latency, more continuous sleep with fewer awakenings, sufficient N3 slow-wave sleep duration, and normal REM sleep periods, typically longer in the morning. This comparison underscores the significant differences in sleep patterns between those with depression and healthy individuals.

Additionally, Monteleone and Maj suggest that individuals suffering from depression exhibit disruptions not just in their psychological balance but also in the control of their sleep-wake cycle[15]. They show numerous other disruptions in the circadian physiological rhythm, including changes in cortisol secretion, melatonin, and core body temperature, in addition to anomalies in the circadian sleep-wake cycle. Additional clinical signs of circadian rhythm disruptions in depression include early morning awakening, sleep disturbance, delayed sleep onset, weariness during the day, and decreased or reversed normal morning peaks of subjective energy and alertness.

Meanwhile, Holsboer found that most people with depression show the activity of the HPA system increased[12]. Specifically, they found that a major mechanism in the pathophysiology of depression, impaired corticosteroid receptor (CR) signaling is associated with these conditions, manifesting as disrupted regulation of corticotropin (ACTH) and cortisol secretion. Certain alterations in sleep EEG are also attributed to hyperactivity of the HPA axis. A hormone that releases corticotropin (CRH) causes sleep disturbances and hypervigilance. Furthermore, they found that CRH encourages REM sleep. This implies a possible close relationship between HPA axis overactivity and depression, reveals how hormonal imbalances can lead to mood disorders and sleep disorders, and highlights the importance of endocrine function.

From a neurotransmitter perspective, imbalances in neurotransmitters, especially serotonin and dopamine, are crucial in both sleep regulation and mental disorders[21]. Sleep disturbances can disrupt the production and regulation of these neurotransmitters, contributing to depressive symptoms. For instance, serotonin is involved in regulating the sleep-wake cycle and influencing mood, and its dysregulation has been associated with insomnia and depression.

From a neuroimaging perspective, the structure and function of the anterior cingulate cortex (ACC), dorsolateral

prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), amygdala, and hippocampus may serve as biomarkers for predicting the response to antidepressant treatment and understanding the pathophysiology of major depressive disorder (MDD). Grimm et al. discovered that a significant causative component in major depressive illness is an imbalance between right- and left-side DLPFC activity, and that prefrontal cortex activity is pathologically changed in this condition[10]. The orbitofrontal region may also be impacted by this imbalance in activation, which is not exclusive to the dorsolateral prefrontal cortex. Meanwhile, some studies have found that these cortical regions are not only associated with depression but also with sleep. Muzur et al. found that the prefrontal cortex is sensitively involved when it comes to sleep physiology, dreaming, and sleep deprivation[16]. Specifically, Yamashita et al. found that astrocytic activity in the ACC can resemble mice's sleep disruption, which means that ACC is likely related to sleep disorders[28]. Similarly, Park et al. found that reduced GABA levels in the ACC/mPFC were linked to shorter sleep duration[18]. In addition to ACC, DLPFC has also been found to be associated with sleep disorders. Ding et al. use rTMS as a treatment of insomnia, and they found that the stimulation of the left dorsolateral prefrontal cortex (LDLPFC) can significantly enhance the insomnia patients' capacity for dispute resolution and quality of sleep, which can be evidence that DLPFC may be associated with sleep[7].

Therefore, sleep plays an important role as a biomarker in depression, revealing that the sleep patterns of people with depression are significantly different from those of healthy individuals through a variety of mechanisms, such as sleep continuity disorders, SWS disorders, and REM sleep disorders, as well as neurotransmitter imbalances and functional abnormalities in brain regions.

3. Depression is a cause of sleep disorders

Regarding the impact of depression on sleep, insomnia and other sleep disorders may be due to depression[23]. Most studies reflected that people with depression frequently suffer from insomnia, which is characterized as having trouble getting to sleep, staying asleep, or having non-restorative sleep[25]. As Calandra et al. suggest depression is regarded as a significant comorbid disease in patients with chronic insomnia of any origin, and depression symptoms are essential risk factors for insomnia[4]. They found, in particular, that 60% to 80% of people with depression may have symptoms of insomnia.

In addition, certain psychological elements like stress, rumination, and anxiety make these worse indirectly. Nolen-Hoeksema claimed that high levels of stress and anxiety can further impair sleep, and people with depression frequently have recurrent thoughts about unpleasant experiences or anxieties about the future[17].

Stress is one of the common psychological factors among people with depression[13]. They suggest that long-term high levels of stress can cause chronic insomnia, which makes it harder for people to have a deep sleep and worsens sleep quality and recovery by causing problems falling asleep, frequent nighttime awakeness, and sporadic sleep. It can trigger the body's stress response system, which involves the hypothalamus-pituitary-adrenal (HPA) axis and raises cortisol and other stress hormone levels[26]. Additionally, depression is frequently accompanied by ruminative thoughts or the recurrent recall of unpleasant experiences. It has been suggested by Pillai and Drake that this kind of thinking disrupts sleep by keeping the brain active through the night, which makes it hard to fall asleep[19]. Both naturally occurring and experimentally generated anxieties hampered the initiation and maintenance of subsequent sleep, and they discovered that trait worriers were more likely to experience sleep problems. Furthermore, high levels of anxiety are one of the main problems commonly faced by people with depression. Harvey found that anxiety causes the body to be in a constant state of 'fight or flight' response, resulting in increased heart rate, shortness of breath, and muscle tension, which are physiological responses that further impede the process of relaxation and falling asleep[11]. These physiological responses further impede the process of relaxation and sleep. Therefore, when anxiety is high, individuals may experience frequent awakenings during the night and have difficulty falling back to sleep after awakening. Prolonged anxiety can lead to decreased sleep quality, increased daytime fatigue and dysfunction[2].

Overall, depression significantly increases the risk of insomnia and other sleep disorders. Stress, ruminative thinking and high levels of anxiety may further indirectly exacerbate these sleep problems.

4. Bidirectional relationship between sleep and depression

Therefore, the cases mentioned above of insomnia among depressed patients and depression among sleep disorder patients can suggest a bidirectional relationship between the two, where insomnia can be both a biomarker of depression and a consequence of depression. The circular nature of this relationship can create a feedback loop in which poor sleep exacerbates depression and depressive

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symptoms further disrupt sleep.

In addition, Baglioni et al. suggest that insomnia leads to reduced cognitive functioning, which makes individuals more likely to fall into negative thinking patterns and thus may lead to difficulties in concentration, memory, and decision-making, which can exacerbate feelings of helplessness and hopelessness, further perpetuating the cycle of insomnia and depression[2]. Similarly, as mentioned above, Harvey suggests that depression often involves pervasive negative thinking, which can make individuals feel nervous and anxious[11]. This heightened state of arousal and anxiety can lead to difficulties in falling and staying asleep, thereby worsening the symptoms of both depression and sleep disturbances. In terms of emotion regulation ability, Riemann et al. found that sleep deprivation may cause increased irritability and anxiety, which can significantly contribute to the increase and decrease levels of depression[20]. The lack of restorative sleep heightens emotional reactivity and reduces the ability to manage stress, making individuals more vulnerable to depressive symptoms.

5. Discussion

Therefore, according to the above-mentioned studies, there is a good real-life application of investigating the relationship between sleep and depression that it can contribute to clinical treatments. Therapies such as antidepressants, cognitive behavioral therapy (CBT), and transcranial direct current stimulation (tDCS) are hypothesized to go from being effective in the treatment of depression and sleep disorders, respectively, to possibly being effective in both at the same time.

For example, several pharmacological treatments are suggested to target both depression and sleep disorders. For example, antidepressants, particularly SSRIs, improve sleep by normalizing neurotransmitter levels. However, some antidepressants may have effects that may exacerbate drowsiness. Additionally, cognitive behavioral therapy can be a type of treatment that improve patients' mood and sleep quality by helping them change negative thought patterns. For example, the study of Espie et al. found that the clinical effectiveness of CBT as a treatment for depression was slightly better than that of placebo on daytime outcomes, and it showed a significant improvement in sleep-wake function on sleep status indicators[8]. Similarly, Cunningham and Shapiro suggest that Cognitive Behavioral Therapy for Insomnia (CBT-I) can be one of the most effective treatments for insomnia co-occurring with depression, as reductions in insomnia brought about by CBT-I may also result in reductions in depressive symptoms[6]. Ashworth et al. have similar findings that CBT-I is a highly effective treatment for the difficulties associated with both insomnia and depression[1]. They claimed that it should be regarded as a crucial supplementary therapy for patients with depression who do not get relief from their symptoms after antidepressant treatment. Furthermore, Transcranial Direct Current Stimulation (tDCS) is a non-invasive technique used to alter the "excitability" of cortical tissues by applying a small direct current (DC) through electrodes positioned on the scalp over the specific cortical region, with currents typically ranging from 0.5 to 2 mA[14], which is an effective treatment for both depression and insomnia. Zhou et al. investigated the effects of tDCS on sleep quality and depressive symptoms in MDD patients with insomnia[29]. They found that in addition to reducing anxiety and depressive symptoms, tDCS enhances the quality of sleep for MDD patients. Cheng et al. have similar findings that significant effects of active stimulation were observed for depression, anxiety, total sleep time, efficiency of sleep, and latency of sleep[5]. According to their findings, tDCS has a substantial impact on sleep and depression that is consistent across demographics and treatment parameters.

Although the above study of the relationship between sleep and depression could be useful for clinical therapeutic applications, there are some limitations. Firstly, the sample size is limited, and the results produced by subjects in Western countries may not be representative of those in Eastern countries, thus making them low in generalisability. Secondly, the measurement tools for depression and sleep disorders are mostly self-report methods like Pittsburgh Sleep Quality Index (PSQI) and Beck Depression Inventory (BDI), which may be influenced by subjective interpretation and individual differences and thus low in validity. Thirdly, most of the trials did not have long-term follow-up, so the reliability and validity of the theory and treatment may be low.

6. Conclusion

To sum up, there is a complex bidirectional relationship between sleep and depression. Sleep disorders, particularly insomnia, are prevalent not only as a biomarker in patients with depression and sleep disorders but also as a symptom and risk factor for the onset and exacerbation of both depression and sleep disorders. Physiological and neurobiological factors play a crucial role in the sleep-depression relationship, including disturbances in the sleep-wake cycle, changes in cortisol and melatonin secretion, and increased hypothalamic-pituitary-adrenocortical (HPA) axis activity, among others. Neurotransmitter imbalances, particularly those involving serotonin and dopamine, further link sleep disorders to depressive symptoms.

Neuroimaging studies also show that brain regions such as the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), and amygdala play a role in sleep regulation and depression, suggesting that they may share neural pathways.

However, intriguing issues concerning their interrelated mechanisms are raised by the remarkable similarities between the cerebral cortex regions linked to depression and those involved in sleep regulation. This overlap raises the possibility that the brain substrates underpinning both illnesses may have similar pathways, which should be investigated more in future research into their precise cause-and-effect interactions. Recognizing the reasons behind the bidirectional influence of areas like the amygdala, dorsolateral prefrontal cortex (DLPFC), and anterior cingulate cortex (ACC) on depression symptoms and sleep disorders may provide important new insights. To address both problems simultaneously, future research endeavors to clarify these neurological connections and ascertain how therapies focusing on these regions might do so. Research on the possibility of using transcranial direct current stimulation (tDCS) to treat depression and sleeplessness at the same time need further investigation. Furthermore, assessing the efficacy of integrated intervention strategies, such as drug therapies, cognitive behavioral therapy (CBT), and tDCS should result in more thorough and efficient methods of treating these co-occurring diseases in the future.

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