REVIEW

Sleep patterns and the risk for unipolar depression: a review

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Abstract: Psychological disorders, particularly mood disorders, such as unipolar depression, are often accompanied by comorbid sleep disturbances, such as insomnia, restless sleep, and restricted sleep duration. The nature of the relationship between unipolar depression and these sleep disturbances remains unclear, as sleep disturbance may be a risk factor for development, an initial manifestation of the disorder, or a comorbid condition affected by similar mechanisms. Various studies have examined the impact of sleep deprivation on the presence of (or exacerbation of) depressive symptoms, and have examined longitudinal and concurrent associations between different sleep disturbances and unipolar depression. This review examines the evidence for sleep disturbances as a risk factor for the development and presence of depression, as well as examining common underlying mechanisms. Clinical implications pertaining to the comorbid nature of various sleep patterns and depression are considered.

Keywords: sleep, depression, insomnia, sleep deprivation, development

Introduction

Sleep difficulties are often comorbid with psychological conditions, particularly mood disorders, such as unipolar depression.[1] To what extent sleep problems are a risk for development of unipolar depression or are an outcome of depression is, however, unclear. Evidence suggests that, for depression, there is a bi-directional relationship, such that sleep problems contribute to increased manifestation of depressive symptoms (eg, mood dysregulation), and depressive psychopathology contributes to worsened sleep.[2] Therefore, this review will examine (1) evidence for various sleep aspects being risk factors for both development and exacerbation of unipolar depression; (2) common underlying mechanisms between sleep disturbance and depression; and (3) clinical implications of the interplay between sleep and depression.

Methods

A search using PubMed, Google Scholar, and PsycInfo® databases was carried out. Combinations of the following keywords were used: "sleep", "psychopathology", "depression", "risk factor", "predictor", "development", "sleep restriction", "sleep deprivation", "sleep patterns", "insomnia," and "sleep problems". Other relevant articles were obtained by examining the reference sections of appropriate articles. Articles were kept that directly assessed variables of interest (sleep patterns and unipolar depression). Precedence was given to studies that showed a directional relationship between sleep and psychopathology. Studies with the elderly were excluded, due to the presence of additional complications, such as increased risk of illness and injury,

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which may contribute to the development of sleep problems and/or depression. Two articles pertaining to experimental sleep deprivation and depression were found and reviewed, along with twelve articles examining the longitudinal relationship between sleep disturbance and depression, and 14 articles which examined sleep phenotype and risk for depression. Although definitions of sleep terminology varied between different studies, for the purposes of this review, insomnia refers to the clinical condition of non-restorative sleep, usually due to difficulties initiating and/or maintaining sleep, which interferes with daily functioning and lasts for a period of at least 1 month;[3] sleep deprivation refers to the purposeful elimination of sleep, during at least one 24-hour period;[4] and sleep disturbance refers to dysfunctions of sleep, including diagnosable sleep disorders, such as insomnia, parasomnias, and other sleep disorders, as well as dysfunctions of sleep architecture and continuity.[5]

Sleep and unipolar depression

Unipolar depression is a common psychological condition, consisting of feelings of low self-worth, sadness, lack of interest or pleasure in normally enjoyable activities, with an adverse effect on relationships and everyday functioning.[3] It has a prevalence of approximately 4%–11% in children and adolescents,[6,7] and 3%–3.5% in adults.[8] Given that almost 90% of individuals who experience depression have comorbid sleep disorders,[9] the following section will examine the influence of sleep deprivation, insomnia, and sleep phenotypes on the development and/or exacerbation of depressive symptoms. It is followed by consideration of common pathophysiological mechanisms. Finally, clinical implications regarding the interplay between sleep and depression are discussed.

Sleep deprivation as a risk factor for depressive symptoms

Studies that examined the impact of sleep deprivation on depressive symptomology show an interesting phenomenon: sleep deprivation can be beneficial in reducing symptoms,[10] or it can aggravate or precipitate a negative mood state.[11] Such phenomena make it more difficult to understand the nature of the relationship between sleep and depression.

Studies that experimentally manipulate the amount of sleep healthy participants receive have found a relationship between sleep deprivation and increased depressive symptoms.[11] In a study by Kahn-Greene and colleagues,[11] healthy military participants were asked to complete a baseline assessment of the Personality Assessment Inventory,[12]

which examines symptoms of various psychological disorders, and were required to stay awake for 56 hours before again completing the Personality Assessment Inventory. The researchers found that, following sleep deprivation, scores on the affective psychological disorder components of the inventory were significantly increased. Of note is that physical aspects of depressive symptoms did not change from baseline to post-deprivation, but the cognitive and affective aspects did. Although values fell within a normal range, the researchers noted that the increases for depressive scores would be considered clinically significant.[11,12]

In another study, by Bernier and colleagues,[13] healthy women and women experiencing unipolar depression were restricted to 2.5 hours in bed for 1 night. Participants completed the Profile of Mood States assessment[14] at baseline and following sleep restriction. Although negative mood states were not exacerbated for the women experiencing depression, healthy women experienced a significant increase in anhedonia ratings, from baseline to post-restriction. This finding is important, as it suggests that, while healthy women may not develop unipolar depression following sleep restriction, they are prone to developing depressive-like symptoms following acute sleep restriction.

These experimental studies provide insight into the effect that acute sleep deprivation or restriction can have on depressive symptoms. However, it is unclear from these studies how chronic sleep problems may contribute to developing depressive symptoms, or depression itself. Therefore, it is important to examine longitudinal studies that investigate the effects of chronic sleep disturbance, such as encountered with insomnia, and how they relate to the risk of developing depression.

Insomnia as a risk factor for developing depression

Accumulating evidence suggests that sleep problems, such as insomnia, are risk factors for the development of depression.[15] Longitudinal associations have been examined over different time periods, from 1 to 45 years, and age groups (Table 1). Although some studies have failed to find an association between sleep problems and the development of depression,[16,17] more generally, the presence of insomnia has been associated with 2.1[18] to 39.8[15] greater odds of developing depression at follow-up, compared to those not suffering from insomnia.

An initial study to examine the ability of sleep problems to predict future development of major depression was conducted by Ford and Kamerow.[15] In this study, adults aged

Table I Studies examining the risk of developing depression based on sleep disturbances

Author	Sample size	Age at TI	Sleep measures	Diagnostic measures	Time-frame	Main findings
Ford and Kamerow[15]	10,534 at TI; 7954 at T2	18+ years	Diagnostic interview schedule[63]	Diagnostic interview schedule[63]	I year	If insomnia was present at both interviews, there were 39.8 greater odds of developing depression; These odds were reduced to 1.6 if insomnia resolved by the follow-up
Vollrath et al[17]	457	21 years	Psychiatric interview	DSM-III[64] criteria	7 years	Depression levels were elevated for insomniacs at follow-up, but not significantly so
Breslau et al[65]	1007 at TI; 979 at T2	21–30 years	DIS-III-R[66]	DIS-III-R[66]	3.5 years	Insomnia predicted 2.1 greater odds of developing depression
Chang et al[18]	1053 men	~26 years	Habit survey questionnaire[67]	Questionnaires and medical reports	1–45 years (median, 34 years)	Presence of insomnia in medical school was related to 2.1 greater odds of developing depression
Johnson et al[24]	823 at TI; 717 at T2	6 years	Child behavior checklist[68]	Child behavior checklist[68] and teacher report form[68]	5 years	Trouble sleeping was related to 6.9 greater odds of increased Anxious/Depressed scores; Relationships were stronger at 11 years than at 6 years
Gregory and O'Connor[22]	490 at TI; 360 final	4 years	Child behavior checklist[68]	Child behavior checklist[68]	11 years	Sleep problems at age 4 predicted mid-adolescent Anxious/Depressed scores; Early Anxious/Depressed scores did not predict later sleep problems
Gregory et al[16]	943 children	Five time points: 5, 7, 9, 21, and 26 years	Self-developed measure of persistent sleep problems	Rutter child behaviour scale[69], diagnostic interview schedule[63]	21 years	Sleep problems did not predict development of depression, although 46% of children with persistent sleep problems developed anxiety problems
Johnson et al[20]	1014 adolescents	13–15 years	Computerized diagnostic interview schedule for children-IV[70]	Computerized diagnostic interview schedule for children-IV[70]	Based on self-reported age of onset	Insomnia occurred before depression in 69% of cases; Prior depression was not related to future insomnia
Ong et al[21]	220 at TI; 164 final	6–23 years	Restrospective report for the dimensions of temperament survey[71]	SADS-L[72] and K-SADS-E[73]	20 years	Irregular sleep schedules related to 1.3 greater odds of adolescent onset of major depressive disorder
Gregory et al[23]	2076 at TI; 1615 at T6	4–16 years	Child behavior checklist[68]	Child behavior checklist[68] and young adult self-report[74]	14 years	Sleeping less than others, overtiredness, and trouble sleeping were related to increased odds for higher Anxious/Depressed scores at follow-up (1.43, 1.37, and 1.39 greater odds, respectively)
Roane and Taylor[39]	4494 at TI; 3582 at T2	12–18 years	Nonvalidated questionnaire	Nonvalidated questionnaire	6–7 years	If insomnia was present in adolescence, there were 2.3 greater odds of developing depression
Gregory et al[19]	300 twin pairs at TI; 250 at T2	8 years	Children's sleep habits questionnaire[75]	Children's depression inventory[76]	~2 years	Sleep problems at age 8 predicted development of depression by age 11, while the opposite was not true

Abbreviations: T1, time 1 (first assessment); T2, time 2; T6, time 6; DIS-III-R, Diagnostic Interview Schedule Version 3, Revised; DSM, Diagnostic and Statistical Manual of Mental Disorders; SADS-L, Schedule for Affective Disorders and Schizophrenia-Lifetime version; K-SADS-E, Schedule for Affective Disorders and Schizophrenia in School-age children.

18 years and older were interviewed at baseline and 1 year later, using clinical diagnostics for sleep problems and major depression. It was found that adults who experienced insomnia both at baseline and follow-up were 39.8 times more likely to develop depression than those who never experienced insomnia. These odds were reduced to 1.6 times greater risk if insomnia symptoms resolved during the intervening period. At the time of this study, these findings were ground-breaking; they have led the way to many more studies that examine the relationship between sleep problems and future development of depression.

One area that has received particular attention is the association between childhood sleep problems, defined in various ways (Table 1), and the subsequent development of depression or anxiety/depression in adolescence or adulthood. It has been found generally that the presence of insomnia, or sleep problems, predicts later development of unipolar depression[19–21] or anxious/depressive symptoms,[22–24] while the converse is not true.[19,20,22] This suggests that sleep problems are either an initial symptom of depression or that they increase vulnerability to developing depression later in life, which emphasizes the importance of examining insomnia and trouble sleeping from an early age.

Sleep phenotypes as risk factors for development and recurrence of depression

In a meta-analysis of 177 adult studies, which examined the association between various psychiatric disorders and sleep phenotypes, Benca et al[25] found that REM sleep pressure, which refers to shorter rapid eye movement (REM) sleep latency, as well as to an overall increased duration and density of REM during the night, was related to increased risk for the development and presence of affective disorders such as depression.[26–29] Other common sleep phenotype characteristics that indicated increased risk for developing depression included increased sleep onset latency, and reduced slow-wave activity.[26–29]

Developmental considerations

Although findings regarding sleep architecture and its relation to depression are fairly consistent in adults, associations between sleep architecture and depression are not as consistent in children and adolescents.[30] While some researchers find that at-risk children and adolescents present with increased sleep onset latency, decreased sleep efficiency, and increased REM sleep pressure,[31–33] others have shown no relationship with REM sleep characteristics,[30] or limited relations with other sleep aspects common to depressed adults.[34,35] This suggests there may be a developmental aspect in the way that sleep and depression are related, which is consistent with findings that sleep physiology undergoes significant changes from pre-pubescence, through puberty, and into adulthood.[36,37]

Further examination of sleep architecture with children and adolescents, either experiencing depression or at risk for developing major depression, has found that such individuals display reduced sleep spindle activity during Stage 2 sleep, compared to healthy controls.[38] Additionally, this relationship was stronger in girls than in boys,[38] suggesting that girls who display reduced sleep spindle activity may be particularly vulnerable for developing unipolar depression – or that those girls most likely to develop depression show more pronounced differences in sleep characteristics.

Given the evidence supporting the increased risk of developing depression, or having recurrence of depression, when certain sleep characteristics are present, understanding the common pathophysiology of sleep disturbance and depression is important for recognizing how we can treat both these disorders.

Methodological considerations

Although a number of studies have examined the relationship between various sleep patterns and risks for depression and depressive symptomology, several methodological considerations need to be addressed. First, depression and sleep problems, such as insomnia, have been defined in different ways among the studies. Especially in pediatric literature, depression is often combined with anxiety,[22–24] and diagnosis is based on a questionnaire, rather than through the use of strict diagnostic criteria. Furthermore, sleep measurements are obtained from parent-report or self-report,[16,18,19,21–24,39] rather than being objective measures, such as polysomnography or actigraphy. Research shows that parents may not be as aware of sleep difficulties experienced by their children,[40–42] and that what is considered a problem to one person may not be viewed as the same by another. In addition, estimates of sleep quality have been found to have low correlation with objective measures, particularly in individuals that experience unipolar depression,[43] which suggests that studies' findings may differ, depending on the type of measure used.

Another problem arising from the use of subjective measures is the lack of standardization in their use.

Sleep problems are often defined by a small number of questions, with different studies using different questionnaires (Table 1). As such, it is unclear how various sleep problems may relate to the risk of developing depression, and how sleep problems found in one study compare with those defined in another study.

Finally, although some longitudinal studies have provided very interesting and relevant information, the majority of studies are both subjective and correlational by nature. Although the use of objective measurements can be relatively costly, longitudinal work would benefit from the use of objective measures, on a sub-sample of participants, over the period of examination. The use of objective measures, in conjunction with a longitudinal design, would both strengthen findings and help us to better understand the nature of the relationship between various disordered sleep patterns and the development of depression.

Common underlying pathophysiology of sleep disturbance and depression

Several hypotheses have been put forth to explain a mechanism that might underlie the interplay between the sleep/wake system and depression, including regulation by the prefrontal cortex (PFC) and the serotonergic system. These hypotheses are not mutually exclusive, and may provide a better explanation of the reasons that sleep disturbance and depression co-occur.

Prefrontal cortex

The PFC is involved in both arousal control and mood regulation; therefore, it has been proposed as a brain area underlying the relationship between sleep disturbance and depression.[44] In particular, it is thought that the PFC plays a significant role in the coordination of sleep and wakefulness, such that higher activity in the PFC promotes wakefulness, while reduced activity or metabolic levels in the PFC may promote sleep.[45] Evidence for this comes from studies that examined metabolic activity in the PFC; with the greatest change in activity being from wakefulness (when PFC function is highest) to sleep (when the PFC displays the lowest levels of activity).[46] Moreover, sleep deprivation leads to both an increased need to sleep and an associated decrease in the level of activity in the PFC,[11] further suggesting that the PFC is involved in regulation of the sleep/wake system.

The PFC is not only linked to regulation of sleep and arousal, but also to other higher-order processes, including the regulation of affect. The orbital and medial PFC are connected, either directly or indirectly, with the amygdala and hypothalamus structures in the limbic system, which are important for affect regulation.[47] Sleep deprivation has been shown to lead to weaker functional connectivity between these areas,[48] suggesting that impairment due to sleep problems affects mood regulation. In evidence of this, studies indicate that impairment of the PFC, such as reduced volume and metabolic activity,[49,50] can lead to affective disorders, such as depression.[45] Given the evidence for the PFC's role in regulating arousal and affect, as well as the links found between sleep deprivation and connectivity with areas important for mood regulation, the PFC appears to be an area likely to be responsible for the co-occurrence of sleep disturbance and depression.

Serotonergic system

Serotonin is a neurotransmitter that decreases in level during sleep, and is implicated in the pathophysiology of unipolar depression.[51] Despite serotonin's implication in both sleep and affective disorders, research has only recently begun to examine links between serotonin, sleep impairment, and depression. In two recent studies, the effect of sleep restriction on serotonin receptor sensitivity was experimentally tested.[52,53] It was hypothesized that the sensitivity of serotonin receptor 1A, a receptor with decreased sensitivity in depressed individuals, would decrease following chronic sleep restriction. Rats were restricted to 4 hours of sleep per day for either 2 or 8 days, and were subjected to a serotonin challenge. It was found that there was no change in the sensitivity of serotonin receptor 1A following 2 days of sleep restriction.[53] However, following 8 days of sleep restriction, both studies reported significant desensitization of the serotonin receptor, with responses similar to those found in depressed individuals.[25,26] These findings suggest that sleep restriction leads to a decreased response to the presence of serotonin, thereby limiting the brain's ability to optimally use the serotonin available to it, and creating a situation that has also been found to be present for individuals suffering from unipolar depression.

In the study by Roman et al,[53] a follow-up experiment was conducted which examined how long desensitization lasted once recovery sleep was allowed. They found that even after 7 days of recovery sleep, receptor sensitivity was still not back to baseline levels. The authors suggested that chronic sleep restriction, such as occurs commonly within Western society, and is experienced by insomniacs, may make individuals more vulnerable to the development of depression.

Further evidence for serotonin's role in the association between sleep disturbance and depression comes from animal[54,55] and human[56,57] studies, which show that expression of the short allele of the serotonin transporter gene is related both to the presence of insomnia[56] and to a greater vulnerability for developing depression.[54,55,57,58] This is important, as the short allele variant is related to decreased efficiency of serotonin transcription and expression,[59] leading to reduced levels of serotonin available for transmission. As the presence of the short allele variant affects sleep disturbance and increases vulnerability to depression, there is strong support for the role of serotonin as a common underlying mechanism.

Clinical implications

The presence of sleep disturbances prior to depressive episodes, especially insomnia and increased REM pressure, provide a warning sign of the impending onset of depression, or the possible recurrence of a depressive episode. As such, clinicians and health care providers should pay special attention to the sleep patterns of individuals who are at particular risk for developing depression. Moreover, the occurrence of sleep difficulties prior to the onset of depression may provide a possible timeframe within which depression can be prevented. It is possible that by treating the sleep problem, the risk of having a future depressive episode may be reduced. Evidence from a study by Ford and Kamerow[15] supports this idea; individuals whose sleep problems resolved over the course of the study also had a decreased risk of developing depression. Following diagnosis of depression, it is important to ensure treatment of depression and any sleep problem that may be present, as alleviating sleep problems can accelerate the rate of recovery from depressive symptoms.[60] Additionally, if the resolution of sleep problems can reduce the risk of developing depression,[15] it suggests that treating a sleep problem during depression can reduce the likelihood of relapse following successful treatment of the depressive episode.

As sleep deprivation has been found to have beneficial effects in patients who experience major depression,[10,13] it has been thought that this may be a means of intervention in treating depression. However, it remains a controversial method, and has been shown to be a very temporary solution for depression management. Although patients improve following a night of total or REM sleep deprivation, the beneficial effects disappear following 1 night of recovery sleep.[13] Also, since sleep deprivation can exacerbate a negative mood state, it is also possible that, in some individuals,

using sleep deprivation may actually worsen depressive symptoms. Furthermore, although sleep deprivation may prove feasible in a clinical setting, where much help is available for keeping the patient from sleeping, such a treatment method becomes much harder for the outpatient, who must rely on his or her own means for staying awake when the drive to sleep is at its highest.

Despite the limitations of using sleep deprivation as a treatment method, it can be beneficial when used in conjunction with other treatment options, such as antidepressant medications, sleep phase advancement (advancing the time of day when one normally goes to sleep and wakes up), and light therapy (using bright light early in the morning to reset one's circadian rhythm earlier).[61] In particular, while most antidepressant treatments take weeks for effects to be seen,[62] sleep deprivation can be used to accelerate relief from depressive symptoms, usually within 1 day. Medication, sleep phase advancement, and light therapy have been found to sustain the positive treatment effects of sleep deprivation.[61]

Finally, when pharmacological interventions are required, it is important to consider the effect on comorbid sleep problems. Medications that may increase insomnia symptoms, such as certain selective serotonin reuptake inhibitors,[60] are likely to impair response to treatment. Therefore, it is important to monitor sleep following pharmacological intervention.

Summary and future directions

Current evidence clearly shows that sleep and depression are strongly interrelated. Sleep deprivation studies show that sleep can increase depressive symptoms, while longitudinal studies suggest that insomnia and trouble sleeping can be among initial manifestations of unipolar depression. In addition, certain sleep phenotypes, such as prolonged sleep onset latencies, reduced latency to REM sleep, and reduced sleep spindle activity may represent an increased vulnerability to developing depressive episodes. The relationships between sleep phenotypes and depression seem to change according to developmental stage, providing different markers for increased vulnerability in pre-pubertal and post-pubertal individuals. Sleep phenotype has also been related to increased risk of recurrence of depressive episodes, and to decreased responsiveness to intervention. As such, it is important to take sleep into consideration when identifying individuals at risk for developing depression, when choosing appropriate interventions, and while monitoring the effects of treatment for depression over time.

In order to provide the best possible treatments for comorbid sleep problems and unipolar depression, it is important to better understand the mechanisms underlying these disorders. Evidence suggests that the PFC may be involved in the manifestation of both sleep disturbance and depression, and that serotonin plays an important role in this relationship.

Future research would benefit from closer examination of the relationship between sleep in prepubescent individuals and depression, to better understand the changes that occur during development. Additionally, understanding the impact of puberty on sleep's relationship with depression is important for determining whether interventions that are suitable for adults may be suitable for youth. Given the findings of Ford and Kamerow,[15] future studies are needed that examine to what extent treating sleep problems may reduce the risk of developing unipolar depression.

Further elucidation of the ways in which the PFC and serotonergic systems relate both to sleep and to the presence of psychological disorders during development can help improve interventions, by appropriately targeting both the disorder and the sleep disturbances involved at particular developmental stages. By examining and monitoring sleep disturbances that may be present in depression, more efficacious intervention treatments can be created, with the aim of improving both sleep quality and psychological condition.

Disclosure

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