# Bidirectional Relationship Between Sleep and Depression

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Review article

# Bidirectional relationship between sleep and depression

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ABSTRACT

Patients with depression almost inevitably exhibit abnormalities in sleep, such as shortened latency to enter rapid eye movement (REM) sleep and decrease in electroencephalogram delta power during non-REM sleep. Insufficient sleep can be stressful, and the accumulation of stress leads to the deterioration of mental health and contributes to the development of psychiatric disorders. Thus, it is likely that depression and sleep are bidirectionally related, i.e. development of depression contributes to sleep disturbances and vice versa. However, the relation between depression and sleep seems complicated. For example, acute sleep deprivation can paradoxically improve depressive symptoms. Thus, it is difficult to conclude whether sleep has beneficial or harmful effects in patients with depression. How antidepressants affect sleep in patients with depression might provide clues to understanding the effects of sleep, but caution is required considering that antidepressants have diverse effects other than sleep. Recent animal studies support the bidirectional relation between depression and sleep, and animal models of depression are expected to be beneficial for the identification of neuronal circuits that connect stress, sleep, and depression. This review provides a comprehensive overview regarding the current knowledge of the relationship between depression and sleep.

## 1. Introduction

Sleep is deeply related to mental health. Human sleep comprises 2 states, rapid eye movement (REM) sleep and non-REM (NREM) sleep. After falling asleep at night, we first enter NREM sleep and then transition into REM sleep, repeating this cycle several times. REM sleep is accompanied by vivid dreams and loss of muscle tone. NREM sleep accounts for 75–80% of the total sleep. Sleep plays crucial roles in the secretion of growth hormones, clearance of brain metabolites, and memory consolidation (Takahashi et al., 1968; Chauvette et al., 2012; Xie et al., 2013; Tsai et al., 2021). Sleep might also have roles in stress resilience. In humans, acute sleep deprivation leads to increased plasma cortisol levels (Leproult et al., 1997). The accumulation of stress leads to the deterioration of mental health and contributes to the development of psychiatric disorders and sleep disorders. For example, mice sleep-deprived for 1 or 3 h after acute stress exposure exhibit increased anxiety compared with mice allowed ad libitum sleep (Feng et al., 2020). In this review, we focus on depression, a common psychiatric disorder associated with stress. First, we summarize the close relationship between mental health and sleep, focusing especially on depression and sleep disorders. Next, we summarize the effects of stress on sleep in animals and the neuronal circuits that connect stress resilience and sleep. Finally, we discuss the relationship between sleep and depression with a focus on antidepressants and sleeping pills.

## 2. Sleep and depression are deeply related to each other

### 2.1. Overview of sleep abnormalities in patients with depression

Stressful events can lead to the onset of depression and have harmful effects on sleep. Approximately 90% of patients with depression suffer from sleep disturbances (Reynolds and Kupfer, 1987). Abnormalities in the sleep architecture are frequently observed in depressed individuals (summarized in Fig. 1). Patients with depression exhibit a prolonged sleep latency and an increased number of awakenings during sleep (Reynolds and Kupfer, 1987). During NREM sleep, reduced slow-wave activity (SWA), especially that in the low frequency range (0.25–2.50 Hz), is often observed (Borbély et al., 1984), and decreased delta power is more prominent in patients suffering a recurrence of depression than in those patients without recurrence (Buysse et al., 1997). Thus,

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decreased delta power is a risk factor for recurrence of depression. Patients with depression exhibit a shortened REM sleep latency (latency to enter the first REM sleep episode from sleep onset), increased REM density (frequency of eye movements during REM sleep), and increased mean duration of REM sleep episodes (Kupfer and Foster, 1972; Pillai et al., 2011; Wang et al., 2015; Riemann et al., 2020). Moreover, patients with depression have an increased amount of REM sleep (Reynolds et al., 1985). In contrast, patients with neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease typically exhibit a reduced REM sleep amount (Petit et al., 2004). Long-lasting shortened REM sleep latency is associated with a higher risk of recurrence of depression (Giles et al., 1987). Thus, these changes in the sleep architecture are recognized as a biomarker for depression (Steiger and Kimura, 2010; Wichniak et al., 2013).

### 2.2. Sleep deprivation as a treatment for depression

Acute sleep deprivation as a clinical therapy is often applied to patients with depression (Pflug and Tölle, 1971; Boland et al., 2017). In humans, self-rating scores of depression decreased after a single night of sleep deprivation compared with those on the previous day (Gerner et al., 1979), suggesting that acute sleep deprivation has a quick antidepressant effect. The effect is not long lasting, however, and symptoms relapse after rebound sleep (Gerner et al., 1979). The neurobiologic basis of this acute effect of sleep deprivation is not well understood. Acute sleep deprivation increases the activity of several brain regions, including the amygdala and ventral tegmental area, in response to pleasure-evoking stimuli presented using the International Affective Picture System, an experimental system in which subjects are shown various sets of photographs and asked to judge whether they feel positive, neutral, or negative (Gujar et al., 2011). Sleep-deprived humans tend to judge emotional stimuli as pleasant events, which might explain why patients with depression feel mood improvement after acute sleep deprivation.

Although the delta power is decreased in patients with depression, as described above, frontal SWA during sleep is increased in adolescents with major depression, and frontal SWA positively correlates with the Children's Depression Rating Scale-Revised (CDRS-R) subscore "morbid thoughts" (Tesler et al., 2016). Slow-wave deprivation intervention, in which an auditory tone is delivered whenever a slow-wave is detected in the subject's electroencephalogram (EEG), in non-medicated patients with major depression, reduced SWA by 37% overnight and depressive symptoms by 10% overnight (Landsness et al., 2011). In contrast, depression in adolescent boys is characterized by a more uniform distribution of SWA at night compared with that in healthy subjects, and reflects the severity of the symptoms of depression (Santangeli et al., 2017).

A more technique-demanding method of sleep intervention for the treatment of depression is selective REM sleep deprivation in which patients are woken up when they enter REM sleep based on encephalography. Because patients with depression exhibit an increased amount of REM sleep, REM sleep is thought to have adverse effects on depression. In fact, several weeks of REM sleep deprivation also decreases Hamilton Depression Rating Scale scores on the next day from the end of the REM sleep deprivation period (Vogel et al., 1973; Vogel, 1975). Thus, an increase in REM sleep might negatively affect recovery from depression. Although these previous studies raise the possibility that REM sleep is harmful for patients with depression, careful interpretation is necessary. REM sleep deprivation is usually followed by a large rebound of REM sleep that occurs during an uninterrupted night; thus, it might be the rebound sleep, and not REM sleep deprivation itself, that has an antidepressant effect. In addition, REM sleep in insomnia patients might qualitatively differ from natural REM sleep, with increased microarousals and eye movements (Riemann et al., 2012), and this low-quality REM sleep might have harmful effects for patients with depression, whereas natural REM sleep might have restorative functions. Even in healthy subjects, those with low-quality REM sleep, i.e., REM sleep interrupted by brief awakenings, exhibit a slower resolution

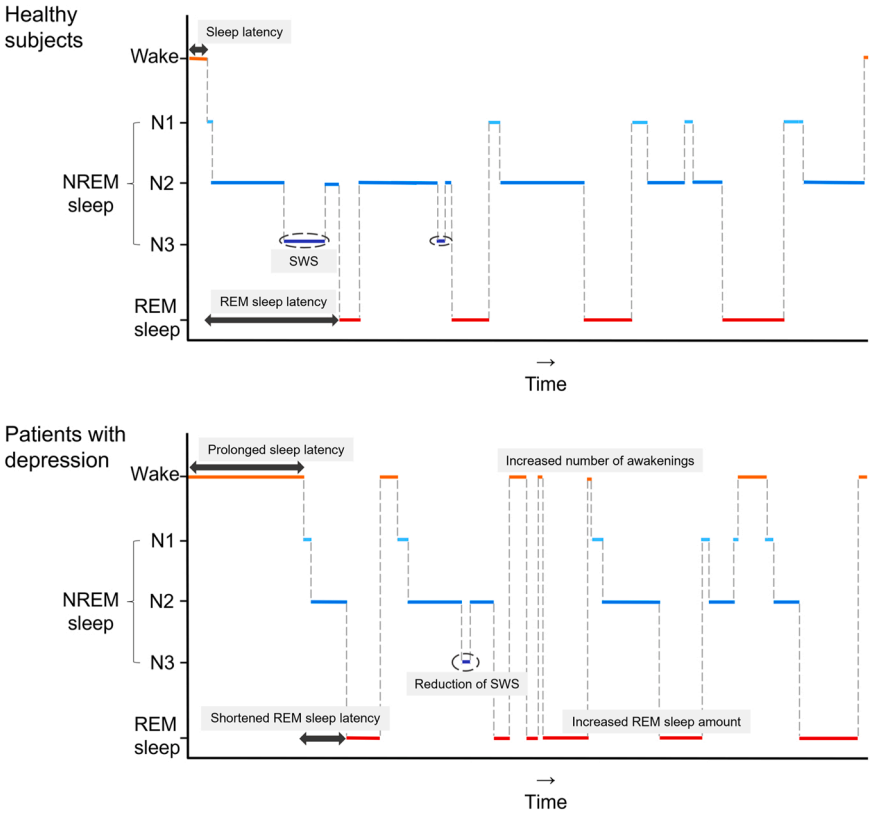


**Fig. 1.** Schematics of sleep architecture in healthy subjects and patients with depression Sleep abnormalities are observed in patients with depression.

of emotional distress on the basis of a questionnaire compared with those not experiencing these brief awakenings during REM sleep (Wassing et al., 2016). Thus, low-quality REM sleep might reduce stress resilience, and the therapeutic effect of REM sleep deprivation in patients with depression might be explained by the effects of reducing this low-quality REM sleep. The role of REM sleep in depression is controversial and there is currently no direct evidence that REM sleep contributes to either the worsening of depression or recovery from depression.

### 2.3. Molecular mechanisms of sleep dysregulation and depression

Various hypotheses regarding the biologic mechanisms that underlie the onset of depression are proposed. One hypothesis is the cholinergic-monoaminergic hypothesis (Mineur and Picciotto, 2010; Perez-Caballero et al., 2019), which postulates that depression is caused by an imbalanced production of cholinergic and monoaminergic neurotransmitters. In patients with depression, serotonin metabolites are decreased, and serotonin is a major target for antidepressant drugs. On the other hand, increasing the levels of acetylcholine by pharmacologically or genetically inhibiting acetylcholine esterase leads to depression-like symptoms in both humans and mice (Risch et al., 1981; Mineur et al., 2013; Dulawa and Janowsky, 2019). Monoamines and acetylcholine are also likely involved in regulating REM sleep. During the transition from NREM sleep to REM sleep, both noradrenergic neurons in the locus coeruleus in mice (Takahashi et al., 2010) and serotonergic neurons in the dorsal raphe nucleus in cats (Sakai and Crochet, 2001) decrease their firing, and cholinergic neurons in the pedunculopontine tegmentum in cats (Datta and Siwek, 1997) increase their firing (Pace-Schott and Hobson, 2002; Schwartz and Kilduff, 2015). Moreover, injection of the cholinergic receptor agonist carbachol into the pontine tegmentum induces REM sleep in cats (Vanni-Mercier et al., 1989), whereas monoamine oxidase inhibitors (MAOIs) suppress REM sleep (Akindele et al., 1970). Findings from recent genetic studies strongly suggest that the REM sleep switch comprises glutamatergic neurons in the sublaterodorsal nucleus (Krenzer et al., 2011) and GABAergic neurons in the ventrolateral periaqueductal gray/deep mesencephalic nucleus (Hayashi et al., 2015; Weber et al., 2015). Nevertheless, it remains likely that cholinergic/monoaminergic systems are strongly involved in the regulation of REM sleep. Another crucial regulator of REM sleep is orexin/hypocretin. Orexin/hypocretin is a neuropeptide crucial for maintaining arousal (Sakurai et al., 1998; Sakurai, 2007). Orexin/hypocretin is specifically produced in the lateral hypothalamus, and deficits in orexinergic neurons cause narcolepsy (Chemelli et al., 1999; Lin et al., 1999; Peyron et al., 2000). Patients with narcolepsy have difficulties maintaining wakefulness and often directly enter REM sleep without going through NREM sleep. In addition to sleep-wake regulation, orexin/hypocretin might be involved in mood regulation and depression (Shariq et al., 2019). In humans, the level of orexin/hypocretin in the amygdala increases in a manner coincident with positive feelings, anger, or social interactions (Blouin et al., 2013). Further, children with narcolepsy have a higher risk of depression (Stores, Montgomery and Wiggs, 2006; Inocente et al., 2014). On the other hand, studies in mice demonstrated that an orexin receptor antagonist reduces depression-like behavior (Nollet et al., 2012). On the basis of these studies, orexin/hypocretin not only regulates sleep-wake cycles, but might also be a crucial factor for mood regulation.

### 2.4. The genetic overlap between insomnia and depression

Sleep disturbance is a diagnostic criterion for depression. Sleep disturbance is also a risk factor for depression (Buysse et al., 2008; Jaussent et al., 2011) and insomnia is a risk factor for the recurrence of depression (Breslau et al., 1996; Chang et al., 1997; Perlis et al., 1997; Roberts et al., 2000; Jindal, 2004), suggesting that treatment of insomnia is crucial to the treatment of depression (Jindal, 2004). How sleep affects depression, however, is unclear. A one-year follow up study revealed that patients with insomnia are at a high risk of developing major depression (Weissman et al., 1997). These studies support a bidirectional relationship between insomnia and depression. Environmental factors including stressful social events are risk factors for developing insomnia and depression. In addition to environmental factors, genetic factors contribute to the development of both depression and insomnia. For example, patients with insomnia have a positive family history of sleep disturbances (Bastien and Morin, 2000), and depression in the mother or father is associated with an increased risk of depression in offspring (Klein et al., 2005). A genome-wide association study (GWAS) of insomnia revealed 202 genomic risk loci (Jansen et al., 2019) and a GWAS of depression identified 102 genetic variants (Howard et al., 2019). In addition to the heritability of risks for insomnia and depression, GWAS studies and conditional false discovery rate approaches revealed an overlap of high-risk genetic variances between depression and insomnia (Stein et al., 2018; Jansen et al., 2019; O'Connell et al., 2021). These studies support the close interrelation of depression and insomnia at the genetic level.

## 3. Sleep impairments in animal models of stress disorders

In animals, several models that exhibit depression-related phenotypes have been established, such as the learned helplessness model (Bali and Jaggi, 2015), the drug-induced withdrawal model (Harrison, Liem and Markou, 2001), genetic models (Clapcote et al., 2007), the corticotropin-releasing hormone (CRH)-overexpression or CRH-intracerebroventricular injection model (Stenzel-Poore et al., 1994; Holsboer, 2001), and stress-exposure models. Stress is an important factor which can cause depression-like phenotypes and sleep impairments. Although careful interpretation is required, exposure of rodents to chronic stress results in various phenotypes that appear to share characteristics with symptoms of depression, such as despair-like and anhedonia-like behaviors (Czéh et al., 2016; Slattery and Cryan, 2017; Wang et al., 2017; Yasugaki et al., 2019; Okamura et al., 2022). Administration of antidepressants effective in humans alleviates these phenotypes (Willner, 2005; Mahar et al., 2014; Hare et al., 2017; Ramaker and Dulawa, 2017). Thus, the use of rodent models will provide clues to the mechanisms underlying changes in sleep architecture induced by stress that are potentially involved in the development of psychiatric disorders.

### 3.1. Sleep phenotypes in rodent models of stress disorders

Various studies using rodents have examined the effects of stress on sleep (summarized in Fig. 2). For example, acute restraint stress exposure for 0.5–2 h increases REM sleep in rats (Rampin et al., 1991; Gonzalez et al., 1995; Bonnet et al., 1997; Marinesco et al., 1999; Koehl et al., 2002; Dewasmes et al., 2004) and mice (Meerlo et al., 2001; Rachalski et al., 2009). Exposure of mice to aggressive and dominant male mice is a well-established model of social stress that has effects similar to those of acute restraint stress on sleep (Meerlo and Turek, 2001; Henderson et al., 2017; Feng et al., 2020). Stress exposure during either the light or dark phase leads to an increase in the REM sleep amount during the dark phase, when mice or rats, which are nocturnal animals, usually exhibit little REM sleep (Koehl et al., 2002). While the exposure to stress is limited to approximately 10 days at maximum in most studies using applied restraint stress or social defeat stress (SDS), Yasugaki et al. (2019) focused on the effects of exposure to daily stress for up to 3 weeks. In their study, mice that underwent a combination of water immersion and restraint stress exhibited an increase in REM sleep similar to mice experiencing restraint stress or SDS, an effect that was maximal during the first week in the early phase of stress exposure and attenuated at the third week in the later phase of stress exposure (Yasugaki et al., 2019). Decreased body weight, another stress-induced phenotype, persisted throughout the 3 weeks, suggesting that it is

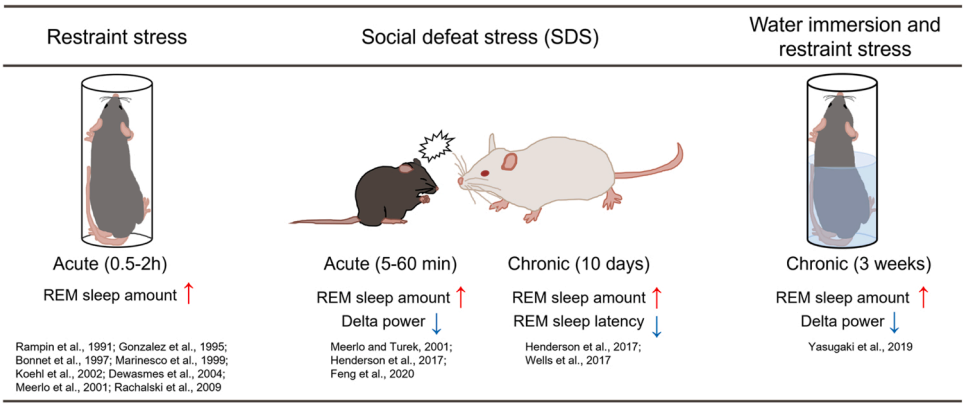


**Fig. 2.** Stress-induced changes in rodent sleep phenotypes.

unlikely that the mice adapted to the repeated stress. Thus, prolonged exposure to a stressful environment might attenuate the alterations in sleep occurring in response to that stressful environment. Further studies are necessary to determine whether attenuation of the sleep changes at later periods contributes to the emergence of depression-like behaviors.

Immediately after the stress exposure, REM sleep is initially strongly suppressed (Meerlo and Turek, 2001; Henderson et al., 2017; Yasugaki et al., 2019). Stress exposure evokes the release of CRH from the paraventricular nucleus of the hypothalamus, which exerts its effect both by increasing the circulating levels of corticosteroids such as cortisol released from the adrenal gland and by directly acting on various brain areas. The initial suppression of REM sleep can be explained by an increase in corticosterone levels, as a systemic increase in cortisol is suggested to suppress REM sleep (Born et al., 1991). The subsequent large increase in REM sleep might be, in part, a homeostatic response to the prior decreased REM sleep amount, whereas there may be other contributing mechanisms considering that the increased amount of REM sleep exceeded the immediate reduction in the REM sleep amount (Yasugaki et al., 2019). The increased amount of REM sleep might be due to the REM sleep-promoting effect of CRH in the forebrain (Kimura et al., 2010). Chronically stressed animals also exhibit altered brain oscillatory activity manifested in the EEG power spectrum. In NREM sleep, the delta power is decreased both after acute SDS (Feng et al., 2020; but also see Henderson et al., 2017; Fujii et al., 2019 which oppositely reported increased delta power) and chronic water-immersion and restraint stress (Yasugaki et al., 2019), consistent with reduced slow-wave sleep (SWS) in patients with depression (Hubain et al., 2006; Armitage, 2007; Lopes et al., 2007; Nutt et al., 2008; Steiger and Kimura, 2010; Palagini et al., 2013; Medina et al., 2014). SWS is accompanied by decreased levels of plasma cortisol (Gronfier et al., 1997), and SWA itself may contribute to reducing cortisol levels (Besedovsky et al., 2017), suggesting that the decreased delta power contributes to an increase in cortisol levels and the emergence of depression-like phenotypes. Notably, in mice that were exposed to chronic unpredictable stress, no effect on delta power was detected (Nollet et al., 2019), suggesting that the effects on EEG delta power differ depending on the type on stress. Patients with chronic insomnia show enhanced high-frequency EEG activity during sleep (Freedman, 1986; Merica et al., 1998; Perlis et al., 2001; Riedner et al., 2016). Under healthy states, high-frequency oscillatory activity is increased during wake and REM sleep. The pathologically heightened wake-like EEG activity during NREM sleep is a representative core symptom of insomnia and might reflect hyperarousal of the brain during sleep.

In the SDS model, defeated mice are divided into 2 groups based on their level of social avoidance, i.e., “susceptible mice” and “resilient mice”. Notably, even when similarly stressed, the effects on social behavior appear in some subjects but not in others. Interestingly, resilient mice exhibit higher levels of EEG activity in the theta (5–10 Hz) and alpha (10–13 Hz) bands during NREM sleep compared with susceptible mice (Henderson et al., 2017). Thus, application of the SDS model might help to effectively decipher the differences in the EEG activity among individuals with different levels of stress susceptibility.

In addition to the increase in REM sleep, patients with depression exhibit some other features of sleep: shortening of the REM sleep latency (Reynolds et al., 1985; Papadimitriou et al., 1988; Hubain et al., 2006; Armitage, 2007; Nutt et al., 2008; Steiger and Kimura, 2010; Palagini et al., 2013; Medina et al., 2014) and sleep fragmentation (Rotenberg et al., 2000; Lopes et al., 2007; Nutt et al., 2008; Steiger and Kimura, 2010; Palagini et al., 2013; Medina et al., 2014). In rodents, 10 days of repeated SDS results in shortened REM sleep latency (Wells et al., 2017) and long-term unpredictable mild stress exposure leads to fragmented sleep (Nollet et al., 2019). On the other hand, no significant difference in the REM sleep latency was observed in mice exposed to chronic water immersion and restraint stress (Yasugaki et al., 2019), and it appears that each model has its own advantages for replicating human diseases. Some human studies also report no significant difference in the REM sleep latency in patients with depression (Rotenberg et al., 2000; Lopes et al., 2007), and thus depression itself might be a disorder with a spectrum of diverse sleep characteristics.

Studies using rats showed that continued REM sleep deprivation induced depressive-like behavior, such as increased anxiety-like behavior in the open field test, anhedonia-like symptoms in the sucrose preference test, and increased immobility time in the forced swim test and tail suspension test (Ma et al., 2019). These findings suggested that REM sleep might be necessary to prevent depression. By contrast, REM sleep deprivation in a rat model of depression induced by chronic unpredictable stress alleviated anhedonia-like symptoms in the sucrose preference test, suggesting that REM sleep deprivation has a therapeutic effect (Ju et al., 2021). In both studies, the flowerpot method was applied for REM sleep deprivation, which requires careful interpretation. This method is highly stressful considering that rats are housed on a small platform placed over water for days. Release from the platform immediately evokes a REM sleep rebound, which might also have various physiologic effects. Thus, the effects of REM sleep on depression remain controversial.

### 3.2. *Sleep phenotypes in non-rodent animal models of stress*

Animal species other than rodents are also used for studies of stress or depression. Zebrafish (*Danio rerio*) is well known for its usefulness as an animal model in the field of drug discovery research. In zebrafish, chronic restraint stress or unpredictable stress results in increased anxiety-like behavior, which is evaluated by a preference for staying at the bottom of the tank or entering a black compartment, and elevated cortisol levels (Piato et al., 2011; Chakravarty et al., 2013; Manuel et al., 2014). Despite the limitations of technical and ethical considerations,

some studies have attempted to investigate if stress and sleep are co-related in non-rodent animal stress models. The increase in cortisol levels in zebrafish caused by acute stress is inhibited by melatonin administration, which simultaneously induces a sleep-like state (Lunkes et al., 2021). The tree shrew (*Tupaia belangeri*), a non-rodent species, responds to social stress exposure (i.e., daily social confrontations with dominant individual) with both endocrine and behavioral changes including an increase in urinary cortisol levels and a decrease in locomotor activity and self-grooming, which are changes that are also induced in rodents by centrally administered CRH, and those alterations can be reverted by the administration of antidepressants (Fuchs et al., 1996). In addition, tree shrews exposed to stress exhibit increased awake phases with immobility and reduced SWS (Fuchs and Flügge, 2002). Thus, the tree shrew might be a suitable experimental paradigm to study the causal mechanisms of depression.

## 4. Depression treatment and sleep

As described above, sleep in patients with depression is typically characterized by changes in REM sleep, i.e., shortened REM sleep latency, increased total REM sleep amount, and increased REM density (Kupfer and Foster, 1972; Kupfer, 1976; Riemann et al., 2020). Antidepressants such as tricyclic antidepressants (TCAs), tetracyclic antidepressants, MAOIs, selective noradrenaline reuptake inhibitors (NARIs), selective serotonin reuptake inhibitors (SSRIs), and serotonin and noradrenaline reuptake inhibitors (SNRIs) affect REM sleep (Wang et al., 2015) (summarized in Fig. 3). These drugs cause prolonged REM sleep latency, reduce the total amount of REM sleep, decrease REM sleep frequency, and reduce REM density (Wang et al., 2015). It is difficult, however, to conclude that the effect of these antidepressants on REM sleep is beneficial for recovery from depression, considering that these drugs have diverse effects.

Some drugs do not reduce REM sleep and yet are effective for depression treatment. Agomelatine, an agonist of melatonin receptors and antagonist of a serotonin receptor subtype, is approved as an antidepressant in the European Union, with demonstrated efficacy in double-blind clinical trials (Lôo, Hale and D'haenen, 2002). In a rodent model of chronic mild stress, the administration of agomelatine reverses reduced sucrose water consumption (Papp et al., 2003). Because long-term treatment with agomelatine in patients with depression shortens sleep latency (San and Arranz, 2008) and increases sleep efficiency and the amount of SWS without affecting REM sleep (Quera Salva et al., 2007), the antidepressant effects can be dissociated from the REM-sleep reducing effects of this drug.

Reduction of SWS and sleep fragmentation are also characteristic sleep abnormalities in depressive patients (Riemann et al., 2020). Ketamine, which is a non-competitive N-methyl-D-aspartate receptor antagonist, is effective for treating patients with both insomnia and depression (Liu et al., 2021). Ketamine has acute antidepressant effects. For example, suicidal ideation in patients with depression is improved within 40 min of ketamine treatment (DiazGranados et al., 2010; Daly et al., 2018; Corriger and Pickering, 2019). Administration of ketamine increases SWA and NREM sleep in addition to REM sleep (Duncan et al., 2013, 2017).

Recently, cognitive behavioral therapy for insomnia (CBT-I) is becoming a major treatment for insomnia. CBT-I includes sleep restriction, stimulus control to overcome the conditioning between the bedroom environment and wakefulness, cognitive therapies regarding dysfunctional attitudes and beliefs towards sleep, sleep hygiene, and relaxation training (Taylor and Pruiksma, 2014). Notably, CBT-I is effective for alleviating symptoms not only in insomnia (Smith et al., 2005; Franzen and Buysse, 2008) but also in depression comorbid with insomnia, both independently of and as a compliment to antidepressant medications (Cunningham and Shapiro, 2018). Thus, CBT-I is expected as an effective treatment especially for patients that co-suffer from insomnia and depression and are resistant to antidepressants.

| Antidepressants | Changes in sleep |
|---|---|
| TCAs, MAOIs, NARIs, SSRIs, SNRIs | REM sleep latency ↑<br>REM sleep amount ↓<br>REM sleep frequency ↓<br>REM density ↓<br>Wang et al., 2015 |
| Agomelatine | Sleep latency ↓<br>San and Arranz et al., 2008<br>Sleep efficiency ↑<br>SWS amount ↑<br>Quera Salva et al., 2007 |
| Ketamine | REM sleep amount ↑<br>NREM sleep amount ↑<br>SWA ↑<br>Duncan et al., 2013; Duncan et al., 2017 |

**Fig. 3.** Antidepressants have diverse effects on sleep in humans.

## 5. Conclusion

Although depression and sleep are deeply related, it remains controversial whether sleep, particularly REM sleep, plays beneficial or harmful roles in the recovery from depression. Caution is required when discussing this point with reference to antidepressants, because antidepressants have diverse effects on behaviors other than sleep. Given that CBT-I is effective for patients with depression, not only improving their sleep but also their depressive symptoms (Cunningham and Shapiro, 2018), it might also become an important treatment approach and provide novel findings regarding the roles of sleep in the recovery from depression.

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## Data Availability

No data was used for the research described in the article.

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