Biological Psychiatry

Review

Sleep Neurophysiology in Depression

Yevgenia Rosenblum, Juan Nakagawa, Timo van Hattem, Elena Krugliakova, Bagmish Sabhapondit, Leonore Bovy, Thorsten Mikoteit, Axel Steiger, Marcel Zeising, and Martin Dresler

ABSTRACT

Sleep disturbances are both a primary symptom of and risk factor for major depressive disorder (MDD). Sleep alterations in MDD include the presence of insomnia or hypersomnia and aberrations in sleep macro- and microstructure, including a reduced latency until and prolonged duration of the first rapid eye movement (REM) episode, decreased slow-wave sleep (SWS), disturbed sleep continuity, and decreased steepening of aperiodic neural activity. MDD sleep is also characterized by dysfunctional autonomic cardiac activity as reflected by decreased heart rate variability. Sedating and novel antidepressants may improve sleep continuity and SWS while activating antidepressants tend to suppress REM sleep. Cognitive processing during sleep may contribute to MDD symptomatology; however, empirical research in this direction is still inconclusive. The rapid effects of antidepressants on sleep structure and of acute sleep deprivation on MDD symptoms suggest an intimate association between sleep and MDD neuropathology; however, the underlying mechanisms still need to be elucidated. This narrative review aims to provide a comprehensive overview of our current understanding of the physiology of sleep alterations in MDD and to discuss how sleep may play a role in current therapeutic approaches while also identifying novel strategies for modulating sleep in the context of depression. It seeks to offer a well-rounded foundation of the current knowledge on sleep and depression to guide basic and clinical scientists in future investigations related to improving existing and developing novel sleep-based therapeutic interventions.

https://doi.org/10.1016/j.biopsych.2025.07.023

SLEEP DISTURBANCES

Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders and one of the leading causes of disability in developed countries, where approximately 20% of people experience MDD at some point during their lifetime, with a 12-month prevalence rate of about 5% (1,2).

Up to 80% to 100% of patients with MDD report insomnia symptoms (3–5), and approximately 45% of patients with MDD meet DSM-5 criteria for insomnia (6) compared with a prevalence of ∼10% in the general population (7). Clinically, MDD with insomnia is associated with the melancholic (typical) MDD type. Notably, both patients with insomnia and patients with MDD show physiological markers of hyperarousal, such as an increased sympathetic (norepinephrine) and endocrine (cortisol) outflow, alterations in heart rate, overactivation of the brainstem arousal system (orexin), and an increase in fast (beta) electroencephalogram (EEG) oscillations (8). Hyperarousal may be a common pathophysiological mechanism of insomnia and MDD and a neurobiological correlate of suicidal ideation, a symptom of MDD (9,10).

Insomnia is not only a prominent symptom after the onset of MDD but also one of the key risk factors for depression; a majority of patients with MDD already experienced insomnia before the onset of other depressive symptoms (11). Longitudinal epidemiological studies have shown that nondepressed individuals with insomnia have a twofold risk of developing depression (12). In a recent large-scale study, sleep disturbances emerged as the most influential predictor of mental health risk in adolescents, surpassing even adverse childhood experiences and family mental health history (13). In particular, difficulty initiating and maintaining sleep predicted future depression (14). Consistent with longitudinal human studies, animal research suggests that chronically restricted or disrupted sleep may be a causal factor in the development of depression (15). Insomnia treatment may reduce the risk of developing MDD (16). Interventions for insomnia such as cognitive behavioral therapy also ameliorate depressive symptoms (17).

Symptoms of hypersomnia affect fewer patients with MDD, with a reported prevalence of 37% to 57% (5,18), and in some studies as low as 11% (19), compared with 19% to 27% in the general population (20,21). Characteristics of MDD-related hypersomnia include prolonged sleep time; long nonrefreshing naps, occurring almost daily; and sleep inertia. MDD patients with hypersomnia show sleep efficiency comparable to that seen in healthy individuals with and without hypersomnia despite an increased total sleep duration (22). Clinically, MDD with hypersomnia is associated with the atypical MDD type, but hypersomnia (together with sedation) may also be a side effect of benzodiazepines, Z-drugs, and antidepressants prescribed for MDD (23). Overall, hypersomnia in MDD is understudied and misdiagnosed, possibly

ISSN: 0006-3223

because of the confounding effect of MDD symptoms such as loss of energy and fatigue (1).

Interestingly, insomnia and hypersomnia (together with fatigue and poor concentration) are overlapping symptoms of depression and obstructive sleep apnea (OSA), a sleep-related breathing disorder. In patients with OSA, the prevalence of comorbid MDD ranges from 0% to 66%, comparable to that of comorbid anxiety disorders or schizophrenia (24). Both OSA and MDD show abnormal serotonergic neurotransmission and cortisol hyperarousal. Notably, OSA results in greater depression severity, and depression results in poor OSA treatment adherence (25). Many studies have suggested that MDD and OSA have bidirectional associations and should be treated concurrently for the best outcome. The comorbid prevalence of depression or anxiety in another common sleep disorder, restless legs syndrome (RLS), is 13% to 30% (26,27). Notably, RLS is sometimes induced by antidepressants (28).

Finally, MDD has been linked to specific circadian rhythms/chronotypes; the evening chronotype has been associated with MDD severity and a higher occurrence of suicidal thoughts and mood symptoms in MDD, bipolar, and anxiety disorders (29). This is consistent with the fact that bright light therapy is effective in treating depressive symptoms and highlights the importance of considering individual differences in chronotype when treating psychiatric disorders.

Overall, altered sleep has been linked to an increased risk of suicidal ideation and attempts (30); poorer overall functioning, quality of life, and treatment response; prolonged recovery time; and higher rates of nonremission (31) and relapses (32). The relationships between sleep disturbances and depressive symptoms are bidirectional and affect patients' everyday lives through a positive feedback loop. For example, insomnia may cause, maintain, or worsen symptoms such as fatigue, loss of energy, or decreased concentration (33). In turn, some symptoms, particularly those associated with cognitive hyperarousal and ruminative thoughts, may interfere with falling or staying asleep (34), especially if linked to hyperarousal. Intriguingly, fatigue has been linked to nonefficient waste clearance by the glymphatic system (35), which in turn has been associated with inflammation, oxidative stress, metabolic abnormalities within the brain, and Alzheimer's disease (36,37). All those factors have been linked to MDD. Sleep disturbances in depression also relate to adverse general health outcomes, including endocrine dysfunctions, a higher risk for cardiometabolic diseases (hypertension, obesity, diabetes, hypercholesterolemia), and an altered microbiota-gut-brain axis (36).

In the following sections, we will review our current understanding of sleep alterations in depression, discuss conventional and novel therapeutic approaches that modulate both depression symptoms and sleep, and raise open questions with broad implications for future studies. See Table 1 for a glossary of terms.

SLEEP MACROSTRUCTURE

Besides behaviorally disordered sleep, many patients with MDD also show neurophysiological alterations in sleep macrostructure such as sleep cycle duration, time spent in each sleep stage, sleep stage latency, or the rate of transitions between stages (38). Most previous sleep research in MDD has focused on rapid eye movement (REM) sleep, the sleep stage most closely associated with affective regulation (39). Reported alterations include shortened REM sleep latency or sleep onset REM periods and prolonged first REM sleep periods in patients, especially patients with the melancholic MDD subtype, compared with control participants (38,40–44). While not all these findings have been replicated (43–46), a recent meta-analysis confirmed that a shortened REM latency is a relatively robust feature of MDD (47). Generally, dysregulation of REM sleep may be considered not only as a symptom of MDD but also as a pathway to depression already before its onset, due to its role in affective regulation (48).

Non-REM (NREM) sleep in MDD has been studied less, with several reports on reduced amounts of N2 and slow-wave sleep (SWS) in patients versus control participants (49,50). A meta-analysis showed a further decrease in SWS percentage after MDD remission and in individuals at high risk for depression (40). It has been suggested that a decrease in SWS may be explained by excessive amounts of acetylcholine, the neurotransmitter crucially involved in REM sleep regulation (38). Overall, whether the primary sleep disturbance in MDD is one of REM or SWS regulation is still being debated.

A recent study developed a rat model of sleep in depression using social defeat stress. The authors observed that at baseline, vulnerable rats exhibited reduced stability of the sleep stage homologous to human SWS. During recovery after social defeat, instability of the sleep stage homologous to the human N1 stage was associated with the onset of microarousals (51). In humans, more time spent in N1 has been associated with a higher incidence of MDD symptoms (52).

Other parameters of sleep macrostructure known to be altered in MDD include increased sleep latency and wake after sleep onset (WASO), decreased sleep efficiency and total sleep time (TST), and early morning awakenings, specifically in the melancholic MDD subtype, all of which reflect impaired sleep continuity (40,41). Interestingly, a study that stratified patients by their MDD subtype (melancholic, atypical, and remitted) found that decreased sleep efficiency and increased WASO were associated with the melancholic MDD subtype only (44). Participants with atypical subtype may show increased TST and normal sleep efficiency compared with healthy control participants (53).

Sleep macrostructure also varies with age and sex. For example, the sleep findings in adolescents with MDD are known for notable inconsistencies in the literature regarding the direction of changes in almost all macrostructural sleep characteristics (54). Some alterations in sleep macrostructure, such as decreased SWS, increased REM sleep time, and shorter REM sleep latency, are observed in younger (40,41) but not in older (46,55) patients (Table 2).

However, it should be emphasized that disturbed sleep is the leading transdiagnostic symptom in psychiatry, such that many disorders show poor sleep continuity. For example, bipolar mania is characterized by drastically reduced need for sleep (56), and schizophrenia by disrupted NREM sleep and reduced spindle density (57). On the other hand, shortened REM sleep latency and increased REM density are less common in schizophrenia, anxiety, and bipolar disorders, suggesting that these may be the hallmarks of MDD (58,59).

Table 1. Glossary of Terms

Term	Explanation
Activating Antidepressants	Antidepressants that stimulate the central nervous system; mostly suppress REM sleep. Examples: imipramine, desipramine, fluoxetine, paroxetine, venlafaxine, reboxetine, bupropion. Side effects: anxiety, agitation, irritability, insomnia, and restlessness.
Agomelatine	A novel antidepressant, agonist of melatonergic receptors M_1 and M_2 and antagonist of 5-HT_{2C} receptors; enhances the brain's sensitivity to existing melatonin, which helps to regulate circadian rhythms.
Atypical MDD Subtype	An MDD subtype with predominant mood reactivity (i.e., mood improves in response to positive events) and at least 2 of the following: hypersomnia, increased appetite or weight gain, leaden paralysis (heavy limbs), and interpersonal rejection sensitivity.
Chronotype	Individual variation in the preferred timing of the sleep-wake cycle; an expression of circadian rhythms of body temperature, cortisol secretion, cognitive functions, eating and sleeping patterns; is influenced by genetics, light exposure, etc. Types: morning, evening, and intermediate.
CLAS	A noninvasive technique that uses soft auditory stimuli (most commonly, brief bursts of pink noise) presented to target the up phase of slow waves during SWS. In health, CLAS has the potential to increase SWA, slow oscillation–associated spindles, and HRV without disturbing natural sleep.
Cordance	An EEG metric that combines information from absolute and relative EEG spectral power. Prefrontal cordance in the theta range reflects the activity of the prefrontal cortex and anterior cingulate cortex and probably differentiates between antidepressant responders and nonresponders.
Fractal Cycles of Sleep	A time interval during which the time series of the slopes of fractal (aperiodic) power component of the EEG signal descend from the local maximum to the local minimum with amplitudes higher than |0.9| z and then lead back from that local minimum to the next local maximum; possibly reflect classical NREM-REM sleep cycles.
HRV	Fluctuations in the time interval between consecutive heartbeats. A measure of autonomic activity; reflects the regulation of autonomic balance; blood pressure; gas exchange; and gut, heart, and vascular tone. Its high-frequency component is primarily modulated by parasympathetic activity to the heart through the vagus nerve. Its low-frequency component reflects the influence of both sympathetic and parasympathetic activity.
Hyperarousal	Increased emotional, cognitive, and physiological/somatic activity that negatively affects the natural disconnection from the environment needed to fall asleep.
Latency (of a Sleep Stage)	The interval between sleep onset and the occurrence of the first period of a given stage.
Melancholic (Typical) MDD Subtype	An MDD subtype characterized by significant anhedonia (i.e., loss of pleasure in all or almost all activities and absence of reactivity to usually pleasurable stimuli) and at least 3 of the following symptoms: distinct quality of depressed mood, regular worsening in the morning, early morning awakening, psychomotor agitation or retardation, significant anorexia or weight loss, excessive guilt.
Melatonin	An endogenous hormone produced by the pineal gland at night; regulates the sleep-wake cycle.
NREM Sleep	A sleep state characterized by progressively slowing cortical neural activity, reduced eye movement, and decreased muscle tone relative to wakefulness. NREM time: 75%–80% of total sleep. Stages: N1, N2, N3. Typical EEG features: sleep spindles, K-complexes, slow waves. Functions: physical tissue restoration, memory consolidation, metabolic regulation, brain clearance.
OSA	Sleep-related breathing disorder that causes sleep fragmentation due to repetitive arousals with or without hypoxemia (oxygen desaturations); a risk factor for cardiovascular disease, metabolic disease, neurocognitive disorders, and MDD. Prevalence in the general population: 9%–38%.
(Neural/EEG) Oscillations	Rhythmic patterns of large-scale activity generated by large groups of neurons and measured by EEG; are usually linked to cognitive states. The best-known frequency bands (in Hz): alpha (8–12), beta (13–30), gamma (30–70), delta (1–4), theta (4–8), slow-wave (<4).
Remitted MDD	Individuals who had a major depressive episode in the past but no longer meet the full diagnostic criteria for MDD.
REM Sleep	A sleep state characterized by activated (wake-like) cortical neural activity, rapid eye movements, and atonia. REM time: 20%–25% of total sleep. Stages: phasic, tonic. Functions: emotional (memory) processing/regulation.
REM Sleep Rebound	A compensatory response usually observed after REM sleep deprivation/suppression that is characterized by a shorter REM sleep latency and increased REM sleep duration.
REM Sleep Suppression	Longer REM sleep latency and reduced amount and density of REM sleep.
rTMS	A brain stimulation approach that generates a series of consecutive magnetic field pulses administered with a fixed frequency that pass through the cranium and induce a weak electrical current in the cortical region underneath the coil. Depending on the frequency of stimulation, reversibly increases or decreases cortical excitability in the targeted region. Its effects can outlast the duration of stimulation.
RLS	A sleep-related sensorimotor disorder characterized by an urge to move the legs accompanied by uncomfortable and unpleasant sensations in the legs; appears/worsens at rest; occurs exclusively or predominantly in the evening or at night; is relieved by movement. Prevalence in the general population: 5%–13%.
Sedating Antidepressants	Antidepressants that slow/depress the activity of the central nervous system; promote sleep not through a sedative action but through resynchronization of the circadian rhythm. Examples: doxepin, mirtazapine, trazodone, trimipramine. Some of them are also used in the treatment of primary insomnia.
Sleep Cycle	A period that comprises an episode of NREM sleep followed by an episode of REM sleep; a physiological unit of sleep; lasts for ~90 minutes. Night sleep comprises 4–6 cycles.
Sleep Macrostructure	The timing and distribution of sleep cycles and sleep stages across the sleep period.

Table 1. Continued

Term	Explanation
Sleep Microstructure	Transient/phasic electrophysiological features/events below the time dimension of the conventional 30-s scoring epoch occurring within sleep stages; appears to determine the organization of sleep cycles and regulate the balance and alternation between the various stages of sleep.
Sleep Spindles	An EEG metric, 11–15 Hz oscillations typically seen during N2. Function examples: memory processing, maintaining disconnection from the external environment during sleep.
SWA	An EEG metric, slow (<4 Hz) oscillations, typically seen during SWS and to a lesser extent in N2; reflects sleep homeostasis.
Treatment-Resistant Depression	A failure to respond to at least 2 antidepressant treatments, augmentation, or behavioral therapies, often requiring interventions such as electroconvulsive therapy, rTMS, or neuromodulation with varying success rates.

CLAS, closed-loop auditory stimulation; EEG, electroencephalography; HRV, heart rate variability; MDD, major depressive disorder; NREM, non-REM; OSA, obstructive sleep apnea; REM, rapid eye movement; RLS, restless legs syndrome; rTMS, repetitive transcranial magnetic stimulation; SWA, slow-wave activity; SWS, slow-wave sleep.

SLEEP MICROSTRUCTURE

Sleep microstructure parameters reviewed here include REMs and aperiodic and oscillatory (e.g., sleep spindles, slow-wave activity [SWA], cordance) EEG activity (Table 3). The most prominent of them is an increased number of REMs within a given REM sleep bout (47,60), particularly during the first REM episodes (42). Increased REM density typically normalizes when patients remit (50).

Findings on slow (<4 Hz) oscillatory activity have shown some heterogeneity. Several studies showed lower relative delta power during SWS and a reduction of SWA and impairments in its regulation in patients with MDD compared with control participants (50,61–66). In particular, patients showed an abnormal distribution of SWA across a night, with inadequate homeostatic dissipation across the night (50,61). However, one study reported that women, but not men, with MDD experienced increased SWA (67). Another study found associations between decreased absolute delta power and the melancholic, but not the atypical, MDD subtype (44). An additional study reported that reduced all-night parieto-occipital SWA is the feature that distinguishes patients with MDD with versus without hypersomnia (45). Finally, SWA impairments have not been observed in older adults with MDD (46,61). However, this may be explained by a floor effect because SWA generally decreases with aging; therefore, a difference may be undetectable even if it exists.

Reduced oscillations in the theta range (4–8 Hz) have been reported in patients with MDD, particularly at the beginning of the night (64). Intriguingly, cordance in the theta range has been used to predict therapy response: During tonic REM sleep, prefrontal theta cordance is higher after the first week of antidepressant medication in responders compared with nonresponders and positively correlated with improvement in depression severity (68). Another study observed that prefrontal theta cordance during REM sleep may identify nonresponders and increase response rates owing to therapy decisions informed by such sleep measures (69).

Table 2. Sleep Macrostructural Parameters in MDD

Sleep Parameter	Findings	Reported Modulations by Medication, Age, Depression Subtype, and Sleep Disorder
Sleep Cycles, NREM-REM/Fractal Duration	↑	↑ in medicated, 0 in unmedicated
N2, Time/Proportion	↓	–
SWS, Time/Proportion	↓	↓ in younger, 0 in older
REM Sleep, Density/Time/Proportion	↑	↑ in younger, 0 in older ↑ in melancholic 0 in MDD with insomnia
REM Sleep, Latency	↓	↓ in younger, 0 in older 0 in MDD with insomnia
Sleep Latency and Wake After Sleep Onset	↑	↑ in melancholic
Total Sleep Time	↓	↑ in atypical
Sleep Efficiency	↓	↓ in melancholic 0 in atypical 0 in MDD with hypersomnia
Early Morning Awakenings	↑	↑ in melancholic

0 indicates no difference compared with healthy control participants, ↓ indicates decreased, and ↑ indicates increased.

MDD, major depressive disorder; NREM, non-REM; REM, rapid eye movement; SWS, slow-wave sleep.

Table 3. Sleep Microstructural Parameters in Major Depressive Disorder

Sleep Parameter	Findings	Reported Modulations by Medication, Gender, and Depression Subtype
Slow-Wave Activity/Delta Power	↓	↑ in females, 0 in males ↓ in younger, 0 in older ↓ in melancholic, 0 in atypical
Theta Cordance	–	↑ in responders
Spindles	↓, 0, ↑	↑ in females, 0/↓ in males
Alpha, Beta, Gamma Oscillations	↑	–
Steepening of Aperiodic Neural Activity	↓	↓ in medicated ↓ in unmedicated in N2 only
Rapid Eye Movement Density	↑	–
Heart Rate Variability	↓	–

0 indicates no difference compared with healthy control participants, ↓ indicates decreased, and ↑ indicates increased.

Findings on MDD alterations in sleep spindles remain scarce and mixed. Early studies reported decreased spindle activity (70), while others observed no changes (46,54,66,71) or even increased spindle amplitude (67) and density (72) or sigma band power during both NREM and REM sleep (73) in patients versus control participants.

Findings on alpha, beta, and gamma oscillations, the bands generally associated with wakefulness, are scarce. Some studies have observed increased oscillatory activity in these bands during sleep in individuals with MDD (74,75), suggesting that this may reflect increased worry, rumination, and arousal (75). Increased gamma oscillations in all sleep stages are further associated with clinical symptoms (74).

The last parameter to be addressed here is the aperiodic activity. Steepening the decay of the aperiodic component is one of the prominent characteristics of sleep, where SWS shows the steepest decay compared with other stages (76). Both healthy individuals and individuals with depression show such steepening, but in the latter, its magnitude is diminished. Specifically, unmedicated patients show decreased aperiodic steepening in the low-frequency band (2–20 Hz) during NREM sleep compared with control participants (77). Patients who are treated with antidepressants show decreased aperiodic steepening in both low- and high-frequency bands during both NREM and REM sleep compared with their own unmedicated states and healthy control participants (77). This alteration may reflect more activated brain states and noisier neural background activity (76) stemming (among other factors) from the activating effect of antidepressants. Furthermore, altered aperiodic activity in the high-frequency band (30–50 Hz) may reflect a shift in the excitation-inhibition ratio in favor of excitation (78); however, this hypothesis remains to be validated further (79). If confirmed, this theory would be consistent with the hyperarousal hypothesis of MDD.

Importantly, altered sleep parameters seen in MDD may interfere with sleep functions (e.g., restorative, metabolic, emotional processing), which in turn would cause, maintain, or worsen some MDD symptoms. Likewise, it is not entirely clear whether sleep structure is more impacted by antidepressant treatment or by pathophysiological processes related to depression (80,81).

AUTONOMIC CARDIAC ACTIVITY DURING SLEEP

Sleep has a marked effect on heart rate and blood pressure, and altered sleep has been linked to cardiometabolic risk (82,83), which is higher in individuals with depression, particularly in older women (84). Given the role of the sympathetic and parasympathetic nervous systems in REM and NREM sleep, respectively, and the autonomic dysfunction observed during wakefulness in MDD (85,86), several studies have sought to measure heart rate variability (HRV) in MDD sleep. One study explored HRV during REM sleep and found decreased HRV in patients with depression compared with control participants at week 4 of medication treatment (68). Because HRV and REM density negatively correlated in both patients and control participants but were comparable in responders and nonresponders, the authors suggested that HRV was a biomarker of depression and not of treatment response (68). Another study reported reduced HRV complexity during REM sleep in patients, which positively correlated with depression severity (87). Lower HRV measures have been observed during all sleep stages in patients compared with control participants (88), similar to those reported during wakefulness (85,86). However, sleep-related low-frequency components of HRV and ratios between low and high components of HRV were higher in the individuals with depression than in control individuals (88,89), the opposite of the findings reported in wakefulness. Notably, autonomic cardiac dysregulation in individuals with depression is more prominent during sleep, especially during NREM sleep, which suggests less parasympathetic modulation and is consistent with the hyperarousal theory of MDD (88). Furthermore, one study explored associations between HRV measured at rest, sleep disturbances, and depressive symptoms in the context of chronic stress in mothers of adolescents with autism spectrum disorder or intellectual disabilities (90). The authors suggest that lower HRV measures are a physiological biomarker for sleep reactivity (i.e., an individual's predisposition to experience sleep disturbances in response to stressful situations), which is also associated with an increased risk of developing depressive symptoms in the context of chronic stress. These associations reinforce the need to address sleep health not only for mood improvement but also to mitigate cardiometabolic complications in MDD.

ANTIDEPRESSANTS AND SLEEP

While the mood-enhancing effects of antidepressants often take several weeks to emerge, their effects on sleep are typically immediate. In general, these effects can be either activating or sedating (Table 4), but it should be kept in mind that each individual responds uniquely to a given medication.

Activating antidepressants mainly suppress REM sleep through the activation of serotonergic 5-HT_2 receptors and increased neurotransmission of norepinephrine and dopamine (80). REM sleep suppression tends to peak after a few days of treatment but diminishes significantly during long-term treatment (91). The long-term effects of chronic REM sleep suppression remain unclear (92). REM sleep rebound has been observed for days or weeks after withdrawal from tricyclic antidepressants (TCAs), monoamine oxidase inhibitors, and serotonin norepinephrine reuptake inhibitors (42,91,93–95). Most of these effects have been observed in both healthy individuals and individuals with depression (28).

Sedating antidepressants include sedating TCAs and tetracyclic antidepressants, both of which block histaminergic H_1 receptors, and serotonin antagonists and reuptake inhibitors, which block serotonergic 5-HT_2 receptors (Table 4) (28). They are mainly associated with improvements in sleep initiation and continuity and increases in SWS (96). For example, amitriptyline, doxepin, and trimipramine have been found to decrease sleep onset latency and WASO and increase sleep efficiency and TST (80,97). Likewise, multiple studies have shown that mirtazapine increases TST, sleep efficiency, and amounts of N2 and SWS and decreases sleep onset latency and WASO in patients with MDD (98,99). The effects of sedating antidepressants on REM sleep tend to be inconsistent. For example, while amitriptyline and doxepin suppress

Table 4. Effects of Antidepressants on Sleep

Effect on Sleep	Examples	Examples of Sleep Alterations
Activating, REM Sleep Suppressing	Activating TCA Imipramine Desipramine Activating SSRI Fluoxetine MAOI Tranylcypromine Moclobemide SNRI and NRI Venlafaxine Duloxetine Reboxetine	↑ REM sleep latency ↓ REM sleep amount ↓ REM density RLS (e.g., venlafaxine, SSRI) Sleep bruxism and REM sleep without atonia (e.g., SSRI, SNRI, TCA)
Activating, REM Sleep Nonsuppressing	NDRI Bupropion	↓/0 REM sleep latency ↑/0 REM density
Sedating	Sedating SSRI Paroxetine Fluvoxamine Sedating TCA Amitriptyline Doxepin Nortriptyline Trimipramine Clomipramine TeCA Mianserin Mirtazapine SARI Trazodone Nefazodone	↑ Sleep initiation ↑ Sleep continuity ↑ SWS ↓ Sleep onset latency ↓ WASO ↑ Sleep efficiency ↑ TST ↑/0/↓ REM sleep: conflicting/ inconclusive findings RLS (e.g., mianserin, mirtazapine) Nightmares (e.g., mirtazapine)
Novel/Atypical	Agomelatine Ketamine Tianeptine Vortioxetine	Agomelatine: ↑ sleep efficiency, ↑ TST, ↑ SWS, resynchronization of circadian rhythms Some novel/atypical antidepressants (e.g., vortioxetine): neutral/inconsistent effects on sleep

↓ indicates decrease, ↑ indicates increase, and 0 indicates no effect.

MAOI, monoamine oxidase inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor; NRI, norepinephrine reuptake inhibitor; REM, rapid eye movement; RLS, restless legs syndrome; SARI, serotonin antagonist and reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; SWS, slow-wave sleep; TCA, tricyclic antidepressant; TeCA, tetracyclic antidepressant; TST, total sleep time; WASO, wake after sleep onset.

REM sleep in patients with MDD, trimipramine does not (80,100,101). Zheng *et al.* (102) found no effect of trazodone on REM sleep, but they explored patients with insomnia with no comorbid MDD.

Finally, some novel antidepressants such as agomelatine have been found to improve sleep by increasing sleep efficiency, TST, and SWS through the resynchronization of circadian rhythms, as it enhances the brain's sensitivity to endogenous melatonin (28,103,104). Other novel antidepressants are neutral or have shown inconsistent findings (e.g., vortioxetine).

SLEEP DEPRIVATION

Paradoxically, while chronic sleep disturbances are a leading MDD symptom, acute sleep deprivation can serve as a rapid and effective therapeutic intervention that improves depressive symptoms in about half of patients with MDD (105). Proposed mechanisms of therapeutic sleep deprivation include changes in circadian-related gene expression (106), enhanced amygdala connectivity to the anterior cingulate cortex (107), and reduced consolidation of negative emotional memories during REM sleep (108). Responses to sleep deprivation have been linked to the distribution of SWA across successive NREM episodes (109) and shortened REM sleep latency (110).

Notably, the antidepressant effects of acute sleep deprivation are transient, with studies showing that a full night of recovery sleep leads to a partial or complete relapse of symptoms in ~80% of responders (105). Subjectively unrecognized episodes of microsleep may considerably interfere with the positive effects of acute sleep deprivation (111), further highlighting the close association between sleep neurophysiology and depressive symptomatology. However, deprivation of single sleep stages such as SWS (112) or REM sleep (113) may be an option that requires more investigation.

While it is insufficient as a stand-alone intervention, sleep deprivation is often combined with antidepressants or nonpharmacological treatments such as bright light therapy and cognitive behavioral therapy (114). Importantly, a recent meta-analysis of 29 articles found no robust evidence for the added benefit of sleep deprivation to the whole treatment package for eventual clinical outcomes (115). While the acute antidepressant effects of sleep deprivation may help elucidate the fundamental physiological mechanisms of depressed mood, large, well-structured randomized control trials are needed to establish whether there is a clinically relevant role for sleep deprivation in the treatment of depression as an addition to other treatment options (115).

COGNITIVE PROCESSING DURING SLEEP

Despite its overt inactivity, sleep is a state of rich mental activity. It has been hypothesized that emotional processing during sleep may contribute to depressive symptomatology (39,116,117); however, empirical research has been somewhat inconclusive so far (108,118). In contrast to intact sleep-associated consolidation of neutral declarative memories, consolidation of newly acquired motor skills during sleep was impaired in MDD, which appears to be related to hypothalamic-pituitary-adrenal dysfunction rather than dysregulation or pharmacological suppression of REM sleep (39,66,119,120).

Intriguingly, awareness of the ongoing sleep state, also known as lucid dreaming, has been shown to be facilitated by fragmented sleep and hypersomnia, characteristics of individuals with depression (121–123). Frequent lucid dreaming may in turn exacerbate depressive symptoms (120), where increased depressive symptoms together with the presence of lucid dreaming are associated with a higher frequency of nightmares (124). Nightmares are, in turn, associated with insomnia, hypersomnia, depression, and

higher suicide risk (123,125). Notably, both nightmares and lucid dreaming typically occur during REM sleep (123), which is altered in MDD. While yet another study found no association between lucid dreaming frequency and depression severity (126), an induction of lucid dreaming in patients with insomnia reduced their depression parameters and improved sleep (127). Notably, most of the therapeutic potential of lucid dreaming is probably driven by dream control and not dream awareness (123).

NONINVASIVE BRAIN STIMULATION

Noninvasive brain stimulation (37) has gained popularity as an effective MDD treatment. Two studies observed improvements in self-reported and objective sleep quality following repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation in patients with MDD (128,129). A combined therapy of rTMS and agomelatine increased the proportion of SWS and reduced the proportion of N1 in patients with MDD (130). On a microstructural level, rTMS over the left dorsolateral prefrontal cortex decreased local alpha band power during REM sleep, which correlated with the clinical outcomes (131). It remains unclear whether improvements in sleep quality following rTMS are a direct result of the intervention itself or are due to the relief of depressive symptoms. One study suggests that rTMS treatment independently influences mood and sleep quality in patients with MDD (129).

A more recent experimental technique is closed-loop auditory stimulation (CLAS) (132), i.e., the enhancement of ongoing sleep slow oscillation with precisely timed acoustic stimuli. While preliminary evidence suggests that the CLAS-induced SWA increase may benefit morning mood (133), to our knowledge, CLAS has not been tested in MDD yet.

FUTURE DIRECTIONS

Between-Patient Heterogeneity

Patients with MDD differ considerably in their symptoms (134), which has led to the proposal of different depressive subtypes such as melancholic, atypical, psychotic, seasonal, postpartum depression, or depression dominated by anxiousness. More recently, symptom heterogeneity has resulted in developments toward more data-driven transdiagnostic approaches using imaging data and machine learning strategies or other advanced statistics (134,135), considering mental health problems as systems instead of neatly separated syndromes (136). Because sleep disturbances are a leading transdiagnostic symptom in psychiatric diseases, elucidating the specific role of sleep physiology in such complex syndrome networks or diagnostic clusters/subtypes is an important direction for future research. Such a refined description will help capture MDD heterogeneity and enhance the clinical utility of symptom networks or MDD subtypes, eventually leading to more personalized interventions.

Within-Patient Heterogeneity

Beyond between-patient heterogeneity in MDD symptoms, the role of within-patient heterogeneity in sleep physiology remains understudied. For example, while REM sleep is traditionally scored as a single sleep stage, substates with frequent versus sparse eye movement activity have been differentiated into phasic versus tonic substates, which differ in both oscillatory and aperiodic EEG activity (137,138). Another REM substate, REM0, has been proposed recently, defined by the presence of low-frequency sequences of heart rate surges and avalanches of high-amplitude events (139). Also, the possibility of mixed/hybrid/local REM sleep phenomena has been discussed, from regional delta waves during REM sleep (140) to the phenomenon of lucid dreaming (123,141). Given the discussed role of REM sleep in MDD, future studies should explore how this REM sleep heterogeneity maps onto depressive processes and symptoms.

Beyond single sleep stages, medicated, but not unmedicated, patients with MDD differ from control participants in the duration of sleep cycles, based on both hypnograms and fluctuations of aperiodic neural activity (so-called fractal cycles), with the largest differences being observed for the first cycles of the night (81). Despite representing the most obvious building blocks of sleep, the role of sleep cycles in MDD remains relatively underexplored. Zooming further out of within-night heterogeneity and the traditional sleep medicine approach of polysomnographic snapshots of single nights, night-to-night variability of sleep structure has emerged in recent years as an important factor for mental and physical health (142,143). While simple measures of sleep regularity based on actigraphy have been shown to be reduced in MDD (144,145), taking the full richness of sleep electrophysiology into account for sleep regularity in MDD remains a promising future research direction.

Wearable Sleep Recordings

While the repeated measurement of sleep electrophysiology is constrained by the costs of laboratory-based polysomnography, recent innovations in wearable neurotechnology have opened avenues for low-cost sleep EEG measurement of larger samples in clinical or home settings (146). Longitudinal sleep EEG measurements of longer timeframes will allow not only assessment of more complex sleep regularity measures but also the use of machine learning to define depression subtypes or symptom patterns/networks based on sleep characteristics. This will help increase our understanding of the heterogeneity of sleep alterations in MDD; improve diagnostics, screening and monitoring; and pave the way for a more personalized form of health care for patients with MDD. Given that 30% to 50% of patients with MDD do not respond to antidepressant treatment, wearable sleep EEG recordings may help more broadly apply sensitive predictive sleep biomarkers to monitor and modify treatment plans.

Immunologic Processes

MDD has been associated with immunological dysregulation for many years (147). More recently, a potential inflammatory subtype of MDD has been proposed, considering that inflammation plays a causal role in the development and persistence of depressive symptoms in up to one third of patients (148). The immunological model tries to explain some MDD symptoms (e.g., anhedonia, fatigue, psychomotor slowing, reduced food intake, sleep problems) as a nonspecific reaction of the organism to infection and inflammation

(148). Importantly, inflammation and sleep show a close bidirectional relationship (149). Given that patients with the inflammatory subtype often show resistance to traditional antidepressant treatments such as selective serotonin reuptake inhibitors, alternative treatments targeting the sleep-immune system link, e.g., with CLAS (149), may be an intriguing option to test. Furthermore, given that sleep deprivation increases the production of proinflammatory cytokines (that cause inflammation but also alter neurotransmission), an interesting future direction would be to test whether the nonresponse to sleep deprivation is somehow related to the presence of the inflammatory subtype of depression.

Glymphatic Brain Clearance

It has been suggested that one of the causes of neuroinflammation could be a dysfunction of the glymphatic system, i.e., the sleep-associated waste clearance pathways in the brain, which is impaired in some patients with MDD (35,36). Markers and mechanisms of glymphatic brain clearance can be studied by combining polysomnography with either functional magnetic resonance imaging (fMRI) (150) or water-based functional near-infrared spectroscopy (fNIRS) (151). Future studies should evaluate whether (and how) fluctuations in brain fluid dynamics during sleep are affected in patients with MDD, while taking into account the effects of different sleep stages, time of night, MDD subtypes (with the main focus on the inflammatory type of depression) and the general health of patients. Also, for the assessment of glymphatic clearance, recent innovations in sleep wearables including wearable water-sensitive fNIRS (151) now allow investigators to conduct studies in naturalistic home environments across several nights.

Rapid Antidepressant Effects

The discovery of a rapid-acting antidepressant effect of ketamine in MDD added a second option for rapid intervention after decades of clinical practice when it was assumed that such rapid action was restricted to acute therapeutic sleep deprivation (152,153). Whether this resemblance reflects more than a coincidence remains to be determined; however, emerging evidence from multiple lines of research suggests the possibility of shared underlying mechanisms. For example, an association between ketamine's clinical antidepressant effects and circadian homeostasis has been shown (154), as it has an overlap of 64 genes whose expression is common in ketamine and sleep deprivation (155). EEG oscillatory activity in the delta range predicts ketamine effects on mood (154) and is changed after ketamine administration in patients with MDD (156). To test this association further, combined EEG-fMRI studies may test the acute response of patients with MDD to either ketamine or brief periods of microsleep under sleep deprivation, which frequently occur in resting-state fMRI scanning and have been suggested to counteract the antidepressant effects of sleep deprivation (157). A particular region of interest for such studies would be the lateral habenula, which has been associated with effects of both ketamine and sleep deprivation (158,159).

CONCLUSIONS

While sleep disturbances are becoming increasingly established as a leading symptom of and predictive risk factor for MDD, the measurement and modulation of sleep neurophysiology has a still underutilized potential for the diagnosis, treatment, outcome prediction, and monitoring of the disease. Large-scale longitudinal measurements that help map the heterogeneity of sleep neurophysiology to different biological functions of sleep both between and within patients have the potential to advance a truly personalized form of health care in MDD.

ACKNOWLEDGMENTS AND DISCLOSURES

YR and MD were supported by the Dutch Research Council (NWO). TvH is supported by the European Research Council (ERC Synergy) under the European Union's Horizon 2020 research and innovation program (ConnectToBrain, Grant No. 810377).

The authors reported no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Radboud University Medical Center, Donders Institute for Brain, Cognition and Behavior, Nijmegen, the Netherlands (YR, JN, EK, LB, MD); Hertie Institute for Clinical Brain Research and Department of Neurology and Stroke, University of Tübingen, Tübingen, Germany (TvH); Freie Universität Berlin, Berlin, Germany (BS); Psychiatric Services Solothurn and Faculty of Medicine of University of Basel, Solothurn, Switzerland (TM); Max Planck Institute of Psychiatry, Munich, Germany (AS); and Psychiatric and Sleep Medicine Practice Munich-Schwabing, Munich, Germany (MZ).

Address correspondence to Yevgenia Rosenblum, Ph.D., at yevgenia.rozenblum@donders.ru.nl, or Martin Dresler, Ph.D., at martin.dresler@donders.ru.nl.

Received Feb 18, 2025; revised Jul 21, 2025; accepted Jul 29, 2025.

REFERENCES

1. American Psychiatric Association (2013): Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Association.
2. Ormel J, Kessler RC, Schoevers R (2019): Depression: More treatment but no drop in prevalence: How effective is treatment? And can we do better? Curr Opin Psychiatry 32:348–354.
3. Riemann D (2007): Insomnia and comorbid psychiatric disorders. Sleep Med 8(suppl 4):S15–S20.
4. Dolsen EA, Asarnow LD, Harvey AG (2014): Insomnia as a transdiagnostic process in psychiatric disorders. Curr Psychiatry Rep 16:471.
5. Geoffroy PA, Hoertel N, Etain B, Bellivier F, Delorme R, Limosin F, Peyre H (2018): Insomnia and hypersomnia in major depressive episode: Prevalence, sociodemographic characteristics and psychiatric comorbidity in a population-based study. J Affect Disord 226:132–141.
6. Seow LSE, Verma SK, Mok YM, Kumar S, Chang S, Satghare P, *et al.* (2018): Evaluating DSM-5 insomnia disorder and the treatment of sleep problems in a psychiatric population. J Clin Sleep Med 14:237–244.
7. Morin CM, Jarrin DC (2013): Epidemiology of insomnia. Sleep Med Clin 8:281–297.
8. Riemann D, Krone LB, Wulff K, Nissen C (2020): Sleep, insomnia, and depression. Neuropsychopharmacology 45:74–89.
9. Dolsen EA, Cheng P, Arnedt JT, Swanson L, Casement MD, Kim HS, *et al.* (2017): Neurophysiological correlates of suicidal ideation in major depressive disorder: Hyperarousal during sleep. J Affect Disord 212:160–166.

10. Wang X, Cheng S, Xu H (2019): Systematic review and meta-analysis of the relationship between sleep disorders and suicidal behaviour in patients with depression. BMC Psychiatry 19:303.
11. Johnson EO, Roth T, Breslau N (2006): The association of insomnia with anxiety disorders and depression: Exploration of the direction of risk. J Psychiatr Res 40:700–708.
12. Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, *et al.* (2011): Insomnia as a predictor of depression: A meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord 135:10–19.
13. Hill ED, Kashyap P, Raffanello E, Wang Y, Moffitt TE, Caspi A, *et al.* (2025): Prediction of mental health risk in adolescents. Nat Med 31:1840–1846.
14. Zhang M-M, Ma Y, Du L-T, Wang K, Li Z, Zhu W, *et al.* (2022): Sleep disorders and non-sleep circadian disorders predict depression: A systematic review and meta-analysis of longitudinal studies. Neurosci Biobehav Rev 134:104532.
15. Meerlo P, Havekes R, Steiger A (2015): Chronically restricted or disrupted sleep as a causal factor in the development of depression. Curr Top Behav Neurosci 25:459–481.
16. Boland EM, Goldschmied JR, Gehrman PR (2023): Does insomnia treatment prevent depression? Sleep 46:zsad104.
17. Gebara MA, Siripong N, DiNapoli EA, Maree RD, Germain A, Reynolds CF, *et al.* (2018): Effect of insomnia treatments on depression: A systematic review and meta-analysis. Depress Anxiety 35:717–731.
18. Hein M, Lanquart J-P, Loas G, Hubain P, Linkowski P (2019): Prevalence and risk factors of excessive daytime sleepiness in major depression: A study with 703 individuals referred for polysomnography. J Affect Disord 243:23–32.
19. Cheung MMS, Lam SP, Chau SWH, Chan NY, Li TMH, Wing YK, Chan JWY (2024): Hypersomnolence is associated with non-remission of major depressive disorder. Sleep Med 119:35–43.
20. Hawley CJ, Gale TM, Sivakumaran T, Paul S, Kondan VRG, Farag A, Shahzad J (2010): Excessive daytime sleepiness in psychiatric disorders: Prevalence, correlates and clinical significance. Psychiatry Res 175:138–141.
21. Fatani A, Al-Rouqi K, Al Towairky J, Ahmed AE, Al-Jahdali S, Ali Y, *et al.* (2015): Effect of age and gender in the prevalence of excessive daytime sleepiness among a sample of the Saudi population. J Epidemiol Glob Health 5:S59–S66.
22. Rye DB, Freeman AAH (2011): Dopaminergic substrates underlying hypersomnia, sleepiness, and REM sleep expression. In: Baumann CR, Bassetti CL, Scammell TE, editors. Narcolepsy. New York, NY: Springer, 61–71.
23. Rief W, Nestoriuc Y, Weiss S, Welzel E, Barsky AJ, Hofmann SG (2009): Meta-analysis of the placebo response in antidepressant trials. J Affect Disord 118:1–8.
24. Gupta MA, Simpson FC (2015): Obstructive sleep apnea and psychiatric disorders: A systematic review. J Clin Sleep Med 11:165–175.
25. Chinvararak C, Garcia-Borreguero D (2022): Comorbid major depressive disorder and obstructive sleep apnea. Case Rep Psychiatry 2022:2943059.
26. Yılbaş B, Öztürk Hİ (2022): Restless legs syndrome: Associated with major depressive disorder and anxiety disorder but not with antidepressant use. Psychiatry Clin Psychopharmacol 32:125–133.
27. Miyaguchi R, Masuda F, Sumi Y, Kadotani H, Ozeki Y, Banno M, Kuniyoshi Y (2024): Prevalence of depression or depressive state in patients with restless legs syndrome: A systematic review and meta-analysis. Sleep Med Rev 77:101975.
28. Wichniak A, Wierzbicka A, Walęcka M, Jernajczyk W (2017): Effects of antidepressants on sleep. Curr Psychiatry Rep 19:63.
29. Zou H, Zhou H, Yan R, Yao Z, Lu Q (2022): Chronotype, circadian rhythm, and psychiatric disorders: Recent evidence and potential mechanisms. Front Neurosci 16:811771.
30. Harris LM, Huang X, Linthicum KP, Bryen CP, Ribeiro JD (2020): Sleep disturbances as risk factors for suicidal thoughts and behaviours: A meta-analysis of longitudinal studies. Sci Rep 10:13888.
31. Pigeon WR, Hegel M, Unützer J, Fan M-Y, Sateia MJ, Lyness JM, *et al.* (2008): Is insomnia a perpetuating factor for late-life depression in the Impact cohort? Sleep 31:481–488.
32. Franzen PL, Buysse DJ (2008): Sleep disturbances and depression: Risk relationships for subsequent depression and therapeutic implications. Dial Clin Neurosci 10:473–481.
33. Palagini L, Bastien CH, Marazziti D, Ellis JG, Riemann D (2019): The key role of insomnia and sleep loss in the dysregulation of multiple systems involved in mood disorders: A proposed model. J Sleep Res 28:e12841.
34. Boland EM, Goldschmied JR, Wakschal E, Nusslock R, Gehrman PR (2020): An integrated sleep and reward processing model of major depressive disorder. Behav Ther 51:572–587.
35. Bao W, Jiang P, Xu P, Lin H, Xu J, Lai M, *et al.* (2025): Lower DTI-ALPS index in patients with major depressive disorder: Correlation with fatigue. Behav Brain Res 478:115323.
36. Gu S, Li Y, Jiang Y, Huang JH, Wang F (2022): Glymphatic dysfunction induced oxidative stress and neuro-inflammation in major depression disorders. Antioxidants (Basel) 11:2296.
37. van Hattem T, Verkaar L, Krugliakova E, Adelhöfer N, Zeising M, Drinkenburg WHIM, *et al.* (2025): Targeting sleep physiology to modulate glymphatic brain clearance. Physiology (Bethesda) 40:0.
38. Palagini L, Baglioni C, Ciapparelli A, Gemignani A, Riemann D (2013): REM sleep dysregulation in depression: State of the art. Sleep Med Rev 17:377–390.
39. Genzel L, Dresler M, Cornu M, Jäger E, Konrad B, Adamczyk M, *et al.* (2015): Medial prefrontal-hippocampal connectivity and motor memory consolidation in depression and schizophrenia. Biol Psychiatry 77:177–186.
40. Pillai V, Kalmbach DA, Ciesla JA (2011): A meta-analysis of electroencephalographic sleep in depression: Evidence for genetic biomarkers. Biol Psychiatry 70:912–919.
41. Baglioni C, Nanovska S, Regen W, Spiegelhalder K, Feige B, Nissen C, *et al.* (2016): Sleep and mental disorders: A meta-analysis of polysomnographic research. Psychol Bull 142:969–990.
42. Steiger A, Pawlowski M (2019): Depression and sleep. Int J Mol Sci 20:607.
43. Bruun CF, Arnbjerg CJ, Kessing LV (2021): Electroencephalographic parameters differentiating melancholic depression, non-melancholic depression, and healthy controls. A systematic review. Front Psychiatry 12:648713.
44. Solelhac G, Berger M, Strippoli MF, Marchi NA, Stephan A, Petit J-M, *et al.* (2023): Objective polysomnography-based sleep features and major depressive disorder subtypes in the general population. Psychiatry Res 324:115213.
45. Plante DT, Landsness EC, Peterson MJ, Goldstein MR, Riedner BA, Wanger T, *et al.* (2012): Sex-related differences in sleep slow wave activity in major depressive disorder: A high-density EEG investigation. BMC Psychiatry 12:146.
46. Ricciardiello A, McKinnon AC, Mowszowski L, LaMonica HM, Schrire ZM, Haroutonian C, *et al.* (2024): Assessing sleep architecture and cognition in older adults with depressive symptoms attending a memory clinic. J Affect Disord 348:35–43.
47. Arıkan MK, Uysal Ö, Gıca Ş, Orhan Ö, İlhan R, Esmeray MT, *et al.* (2024): REM parameters in drug-free major depressive disorder: A systematic review and meta-analysis. Sleep Med Rev 73:101876.
48. Riemann D, Dressle RJ, Benz F, Spiegelhalder K, Johann AF, Nissen C, *et al.* (2025): Chronic insomnia, REM sleep instability and emotional dysregulation: A pathway to anxiety and depression? J Sleep Res 34:e14252.
49. Benca RM, Obermeyer WH, Thisted RA, Gillin JC (1992): Sleep and psychiatric disorders. A meta-analysis. Arch Gen Psychiatry 49:651–668.
50. Murphy MJ, Peterson MJ (2015): Sleep disturbances in depression. Sleep Med Clin 10:17–23.
51. Claverie D, Becker C, Ghestem A, Coutan M, Bernard C, Trousselard M, *et al.* (2023): Sleep biomarkers for stress-induced vulnerability to depression. Sleep 46:zsad068.

52. Jiang J, Li Z, Li H, Yang J, Ma X, Yan B (2024): Sleep architecture and the incidence of depressive symptoms in middle-aged and older adults: A community-based study. J Affect Disord 352:222–228.
53. Plante DT, Cook JD, Goldstein MR (2017): Objective measures of sleep duration and continuity in major depressive disorder with comorbid hypersomnolence: A primary investigation with contiguous systematic review and meta-analysis. J Sleep Res 26:255–265.
54. Baena D, Toor B, Ray LB, Smith D, Kong P, Lopez J, *et al.* (2024): Sleep spindles in adolescents with major depressive disorder. J Affect Disord 344:535–545.
55. Vitiello MV, Prinz PN, Avery DH, Williams DE, Ries RK, Bokan JA, Khan A (1990): Sleep is undisturbed in elderly, depressed individuals who have not sought health care. Biol Psychiatry 27:431–440.
56. McCarthy MJ, Gottlieb JF, Gonzalez R, McClung CA, Alloy LB, Cain S, *et al.* (2022): Neurobiological and behavioral mechanisms of circadian rhythm disruption in bipolar disorder: A critical multi-disciplinary literature review and agenda for future research from the ISBD task force on chronobiology. Bipolar Disord 24:232–263.
57. Wamsley EJ, Tucker MA, Shinn AK, Ono KE, McKinley SK, Ely AV, *et al.* (2012): Reduced sleep spindles and spindle coherence in schizophrenia: Mechanisms of impaired memory consolidation? Biol Psychiatry 71:154–161.
58. Wu D, Tong M, Ji Y, Ruan L, Lou Z, Gao H, Yang Q (2021): REM sleep fragmentation in patients with short-term insomnia is associated with higher BDI scores. Front Psychiatry 12:733998.
59. Bernier V, Alsaleh G, Point C, Wacquier B, Lanquart J-P, Loas G, Hein M (2024): Low-grade inflammation associated with major depression subtypes: A cross-sectional study. Brain Sci 14:850.
60. Benca RM, Peterson MJ (2008): Insomnia and depression. Sleep Med 9(suppl 1):S3–S9.
61. Goldschmied JR, Cheng P, Hoffmann R, Boland EM, Deldin PJ, Armitage R (2019): Effects of slow-wave activity on mood disturbance in major depressive disorder. Psychol Med 49:639–645.
62. Sun H, Ye E, Paixao L, Ganglberger W, Chu CJ, Zhang C, *et al.* (2023): The sleep and wake electroencephalogram over the lifespan. Neurobiol Aging 124:60–70.
63. Nissen C, Feige B, Nofzinger EA, Voderholzer U, Berger M, Riemann D (2006): EEG slow wave activity regulation in major depression. Somnologie 10:36–42.
64. Cheng P, Goldschmied J, Casement M, Kim HS, Hoffmann R, Armitage R, Deldin P (2015): Reduction in delta activity predicted improved negative affect in major depressive disorder. Psychiatry Res 228:715–718.
65. Cheng P, Goldschmied J, Deldin P, Hoffmann R, Armitage R (2015): The role of fast and slow EEG activity during sleep in males and females with major depressive disorder. Psychophysiology 52:1375–1381.
66. Bovy L, Weber FD, Tendolkar I, Fernández G, Czisch M, Steiger A, *et al.* (2022): Non-REM sleep in major depressive disorder. Neuroimage Clin 36:103275.
67. Plante DT, Goldstein MR, Landsness EC, Peterson MJ, Riedner BA, Ferrarelli F, *et al.* (2013): Topographic and sex-related differences in sleep spindles in major depressive disorder: A high-density EEG investigation. J Affect Disord 146:120–125.
68. Pawlowski MA, Gazea M, Wollweber B, Dresler M, Holsboer F, Keck ME, *et al.* (2017): Heart rate variability and cordance in rapid eye movement sleep as biomarkers of depression and treatment response. J Psychiatr Res 92:64–73.
69. Mikoteit T, Spieker D, Steiger A, Hatzinger M, Zeising M (2020): P.733 Guidance of treatment with the biomarker prefrontal theta cordance in rapid eye movement sleep improved response rates in major depression. Eur Neuropsychopharmacol 40:S415–S416.
70. de Maertelaer V, Hoffman G, Lemaire M, Mendlewicz J (1987): Sleep spindle activity changes in patients with affective disorders. Sleep 10:443–451.
71. Ferrarelli F, Huber R, Peterson MJ, Massimini M, Murphy M, Riedner BA, *et al.* (2007): Reduced sleep spindle activity in schizophrenia patients. Am J Psychiatry 164:483–492.
72. Nishida M, Nakashima Y, Nishikawa T (2014): Topographical distribution of fast and slow sleep spindles in medicated depressive patients. J Clin Neurophysiol 31:402–408.
73. Steiger A, Holsboer F (1997): Nocturnal secretion of prolactin and cortisol and the sleep EEG in patients with major endogenous depression during an acute episode and after full remission. Psychiatry Res 72:81–88.
74. Tekell JL, Hoffmann R, Hendrickse W, Greene RW, Rush AJ, Armitage R (2005): High frequency EEG activity during sleep: Characteristics in schizophrenia and depression. Clin EEG Neurosci 36:25–35.
75. Armitage R (2007): Sleep and circadian rhythms in mood disorders. Acta Psychiatr Scand Suppl 115:104–115.
76. Bódizs R, Schneider B, Ujma PP, Horváth CG, Dresler M, Rosenblum Y (2024): Fundamentals of sleep regulation: Model and benchmark values for fractal and oscillatory neurodynamics. Prog Neurobiol 234:102589.
77. Rosenblum Y, Bovy L, Weber FD, Steiger A, Zeising M, Dresler M (2023): Increased aperiodic neural activity during sleep in major depressive disorder. Biol Psychiatry Glob Open Sci 3:1021–1029.
78. Gao R, Peterson EJ, Voytek B (2017): Inferring synaptic excitation/inhibition balance from field potentials. Neuroimage 158:70–78.
79. Gerster M, Waterstraat G, Litvak V, Lehnertz K, Schnitzler A, Florin E, *et al.* (2022): Separating neural oscillations from aperiodic 1/f activity: Challenges and recommendations. Neuroinformatics 20:991–1012.
80. Wichniak A, Wierzbicka A, Jernajczyk W (2012): Sleep and antidepressant treatment. Curr Pharm Des 18:5802–5817.
81. Rosenblum Y, Jafarzadeh Esfahani M, Adelhöfer N, Zerr P, Furrer M, Huber R, *et al.* (2025): Fractal cycles of sleep, a new aperiodic activity-based definition of sleep cycles. eLife 13:RP96784.
82. Hu P, Vinturache A, Chen Y, Ding G, Zhang Y (2024): Joint association of sleep onset time and sleep duration with cardiometabolic health outcome. J Am Heart Assoc 13:e034165.
83. Nôga DA, e Meth EMES, Pacheco AP, Tan X, Cedernaes J, Van Egmond LT, *et al.* (2024): Habitual short sleep duration, diet, and development of type 2 diabetes in adults. JAMA Netw Open 7:e241147.
84. Costemale-Lacoste J-F, Asmar KE, Rigal A, Martin S, Kader Ait Tayeb AE, Colle R, *et al.* (2020): Severe insomnia is associated with metabolic syndrome in women over 50 years with major depression treated in psychiatry settings: A METADAP report. J Affect Disord 264:513–518.
85. Sgoifo A, Carnevali L, de los Alfonso M, Amore M (2015): Autonomic dysfunction and heart rate variability in depression. Stress 18:343–352.
86. Koch C, Wilhelm M, Salzmann S, Rief W, Euteneuer F (2019): A meta-analysis of heart rate variability in major depression. Psychol Med 49:1948–1957.
87. Kwon HB, Yoon H, Choi SH, Choi J-W, Lee YJ, Park KS (2019): Heart rate variability changes in major depressive disorder during sleep: Fractal index correlates with BDI score during REM sleep. Psychiatry Res 271:291–298.
88. Saad M, Ray LB, Bradley-Garcia M, Palamarchuk IS, Gholamrezaei A, Douglass A, *et al.* (2020): Autonomic modulation of cardiac activity across levels of sleep depth in individuals with depression and sleep complaints. Psychosom Med 82:172–180.
89. Shaffer F, Ginsberg JP (2017): An overview of heart rate variability metrics and norms. Front Public Health 5:258.
90. da Estrela C, McGrath J, Booij L, Gouin J-P (2021): Heart rate variability, sleep quality, and depression in the context of chronic stress. Ann Behav Med 55:155–164.
91. Argyropoulos SV, Wilson SJ (2005): Sleep disturbances in depression and the effects of antidepressants. Int Rev Psychiatry 17:237–245.
92. Pesonen A-K, Koskinen M-K, Vuorenhela N, Halonen R, Mäkituuri S, Selin M, *et al.* (2024): The effect of REM-sleep disruption on affective processing: A systematic review of human and animal experimental studies. Neurosci Biobehav Rev 162:105714.
93. Landolt HP, Raimo EB, Schnierow BJ, Kelsoe JR, Rapaport MH, Gillin JC (2001): Sleep and sleep electroencephalogram in depressed patients treated with phenelzine. Arch Gen Psychiatry 58:268–276.

94. Feige B, Voderholzer U, Riemann D, Dittmann R, Hohagen F, Berger M (2002): Fluoxetine and sleep EEG: Effects of a single dose, subchronic treatment, and discontinuation in healthy subjects. Neuropsychopharmacology 26:246–258.
95. Dhuna NA, Malkani RG (2020): Antidepressants and their impact on sleep. Curr Sleep Medicine Rep 6:216–225.
96. Hutka P, Krivosova M, Muchova Z, Tonhajzerova I, Hamrakova A, Mlyncekova Z, *et al.* (2021): Association of sleep architecture and physiology with depressive disorder and antidepressants treatment. Int J Mol Sci 22:1333.
97. DeMartinis NA, Winokur A (2007): Effects of psychiatric medications on sleep and sleep disorders. CNS Neurol Disord Drug Targets 6:17–29.
98. Winokur A, DeMartinis NA, McNally DP, Gary EM, Cormier JL, Gary KA (2003): Comparative effects of mirtazapine and fluoxetine on sleep physiology measures in patients with major depression and insomnia. J Clin Psychiatry 64:1224–1229.
99. Schmid DA, Wichniak A, Uhr M, Ising M, Brunner H, Held K, *et al.* (2006): Changes of sleep architecture, spectral composition of sleep EEG, the nocturnal secretion of cortisol, ACTH, GH, prolactin, melatonin, ghrelin, and leptin, and the DEX-CRH test in depressed patients during treatment with mirtazapine. Neuropsychopharmacology 31:832–844.
100. Sonntag A, Rothe B, Guldner J, Yassouridis A, Holsboer F, Steiger A (1996): Trimipramine and imipramine exert different effects on the sleep EEG and on nocturnal hormone secretion during treatment of major depression. Depression 4:1–13.
101. Wang Y-Q, Li R, Zhang M-Q, Zhang Z, Qu W-M, Huang Z-L (2015): The neurobiological mechanisms and treatments of REM sleep disturbances in depression. Curr Neuropharmacol 13:543–553.
102. Zheng Y, Lv T, Wu J, Lyu Y (2022): Trazodone changed the polysomnographic sleep architecture in insomnia disorder: A systematic review and meta-analysis. Sci Rep 12:14453.
103. Quera-Salva MA, Lemoine P, Guilleminault C (2010): Impact of the novel antidepressant agomelatine on disturbed sleep–wake cycles in depressed patients. Hum Psychopharmacol 25:222–229.
104. Quera-Salva M-A, Hajak G, Philip P, Montplaisir J, Keufer-Le Gall S, Laredo J, Guilleminault C (2011): Comparison of agomelatine and escitalopram on nighttime sleep and daytime condition and efficacy in major depressive disorder patients. Int Clin Psychopharmacol 26:252–262.
105. Boland EM, Rao H, Dinges DF, Smith RV, Goel N, Detre JA, *et al.* (2017): Meta-analysis of the antidepressant effects of acute sleep deprivation. J Clin Psychiatry 78:e1020–e1034.
106. Bunney BG, Bunney WE (2013): Mechanisms of rapid antidepressant effects of sleep deprivation therapy: Clock genes and circadian rhythms. Biol Psychiatry 73:1164–1171.
107. Chai Y, Gehrman P, Yu M, Mao T, Deng Y, Rao J, *et al.* (2023): Enhanced amygdala–cingulate connectivity associates with better mood in both healthy and depressive individuals after sleep deprivation. Proc Natl Acad Sci U S A 120:e2214505120.
108. Harrington MO, Johnson JM, Croom HE, Pennington K, Durrant SJ (2018): The influence of REM sleep and SWS on emotional memory consolidation in participants reporting depressive symptoms. Cortex 99:281–295.
109. Nissen C, Feige B, König A, Voderholzer U, Berger M, Riemann D (2001): Delta sleep ratio as a predictor of sleep deprivation response in major depression. J Psychiatr Res 35:155–163.
110. Riemann D, Wiegand M, Berger M (1991): Are there predictors for sleep deprivation response in depressed patients? Biol Psychiatry 29:707–710.
111. Hemmeter U, Rothe B, Guldner J, Holsboer F, Steiger A (1998): Effects of thyrotropin-releasing hormone on the sleep EEG and nocturnal hormone secretion in male volunteers. Neuropsychobiology 38:25–31.
112. Landsness EC, Goldstein MR, Peterson MJ, Tononi G, Benca RM (2011): Antidepressant effects of selective slow wave sleep deprivation in major depression: A high-density EEG investigation. J Psychiatr Res 45:1019–1026.
113. Crişan CA, Milhem Z, Stretea R, Ţaţa I-M, Chereches RM, Micluţia IV (2023): A narrative review on REM sleep deprivation: A promising non-pharmaceutical alternative for treating endogenous depression. J Pers Med 13:306.
114. Hu B, Liu C, Mou T, Luo F, Lv T, Qian C, *et al.* (2021): Meta-analysis of sleep deprivation effects on patients with depression. Front Psychiatry 12:783091.
115. Mitter P, De Crescenzo F, Loo Yong Kee K, Xia J, Roberts S, Chi W, *et al.* (2022): Sleep deprivation as a treatment for major depressive episodes: A systematic review and meta-analysis. Sleep Med Rev 64:101647.
116. Harrington MO, Pennington K, Durrant SJ (2017): The 'affect tagging and consolidation' (ATaC) model of depression vulnerability. Neurobiol Learn Mem 140:43–51.
117. Harrington MO, Reeve S, Bower JL, Renoult L (2023): How do the sleep features that characterise depression impact memory? Emerg Top Life Sci 7:499–512.
118. Harrington MO, Nedberge KM, Durrant SJ (2018): The effect of sleep deprivation on emotional memory consolidation in participants reporting depressive symptoms. Neurobiol Learn Mem 152:10–19.
119. Dresler M, Kluge M, Genzel L, Schüssler P, Steiger A (2010): Impaired off-line memory consolidation in depression. Eur Neuropsychopharmacol 20:553–561.
120. Dresler M, Kluge M, Pawlowski M, Schüssler P, Steiger A, Genzel L (2011): A double dissociation of memory impairments in major depression. J Psychiatr Res 45:1593–1599.
121. Taitz I (2011): Learning lucid dreaming and its effect on depression in undergraduates. Int J Dream Res 4:2.
122. Gott J, Rak M, Bovy L, Peters E, van Hooijdonk CFM, Mangiaruga A, *et al.* (2020): Sleep fragmentation and lucid dreaming. Conscious Cogn 84:102988.
123. Tzioridou S, Campillo-Ferrer T, Cañas-Martín J, Schlüter L, Torres-Platas SG, Gott JA, *et al.* (2025): The clinical neuroscience of lucid dreaming. Neurosci Biobehav Rev 169:106011.
124. Carr M, Youngren W, Seehuus M, Semin R, Angle E, Pigeon WR (2025): The effects of lucid dreaming and nightmares on sleep quality and mental health outcomes. Behav Sleep Med 23:133–140.
125. Gieselmann A, Ait Aoudia M, Carr M, Germain A, Gorzka R, Holzinger B, *et al.* (2019): Aetiology and treatment of nightmare disorder: State of the art and future perspectives. J Sleep Res 28: e12820.
126. Sackwild L, Stumbrys T (2021): The healing and transformative potential of lucid dreaming for treating clinical depression. Int J Dream Res 14:307–319.
127. Ellis JG, De Koninck J, Bastien CH (2021): Managing insomnia using lucid dreaming training: A pilot study. Behav Sleep Med 19:273–283.
128. Zhou Q, Yu C, Yu H, Zhang Y, Liu Z, Hu Z, *et al.* (2020): The effects of repeated transcranial direct current stimulation on sleep quality and depression symptoms in patients with major depression and insomnia. Sleep Med 70:17–26.
129. Collins AR, Cheung J, Croarkin PE, Kolla BP, Kung S (2022): Effects of transcranial magnetic stimulation on sleep quality and mood in patients with major depressive disorder. J Clin Sleep Med 18:1297–1305.
130. Pu Z, Hou Q, Yan H, Lin Y, Guo Z (2023): Efficacy of repetitive transcranial magnetic stimulation and agomelatine on sleep quality and biomarkers of adult patients with mild to moderate depressive disorder. J Affect Disord 323:55–61.
131. Pellicciari MC, Cordone S, Marzano C, Bignotti S, Gazzoli A, Miniussi C, De Gennaro L (2013): Dorsolateral prefrontal transcranial magnetic stimulation in patients with major depression locally affects alpha power of REM sleep. Front Hum Neurosci 7:433.
132. Esfahani MJ, Farboud S, Ngo HVV, Schneider J, Weber FD, Talamini LM, Dresler M (2023): Closed-loop auditory stimulation of

sleep slow oscillations: Basic principles and best practices. Neurosci Biobehav Rev 153:105379.
133. Danilenko K, Kobelev E, Yarosh SV, Khazankin GR, Aftanas LI (2019): Effectiveness of auditory closed-loop stimulation during sleep on depression. Eur Neuropsychopharmacol 29:S69–S70.
134. Segal A, Tiego J, Parkes L, Holmes AJ, Marquand AF, Fornito A (2025): Embracing variability in the search for biological mechanisms of psychiatric illness. Trends Cogn Sci 29:85–99.
135. Farías Venegas C, Varela Espinoza LF, Ramírez Matta C, Barra Cañas B, Araneda Maldonado M, Sánchez Oñate A (2025): New developments in psychiatric classification: A transdiagnostic approach. Cureus 17:e84580.
136. Fried EI (2022): Studying mental health problems as systems, not syndromes. Curr Dir Psychol Sci 31:500–508.
137. Simor P, van der Wijk G, Nobili L, Peigneux P (2020): The microstructure of REM sleep: Why phasic and tonic? Sleep Med Rev 52: 101305.
138. Rosenblum Y, Bogdány T, Nádasy LB, Chen X, Kovács I, Gombos F, *et al.* (2025): Aperiodic neural activity distinguishes between phasic and tonic REM sleep. J Sleep Res 34:e14439.
139. Ioannides AA, Orphanides GA, Liu L (2022): Rhythmicity in heart rate and its surges usher a special period of sleep, a likely home for PGO waves. Curr Res Physiol 5:118–141.
140. Bernardi G, Betta M, Ricciardi E, Pietrini P, Tononi G, Siclari F (2019): Regional delta waves in human rapid eye movement sleep. J Neurosci 39:2686–2697.
141. Zerr P, Adelhöfer N, Dresler M (2024): The neuroscience of lucid dreaming: Past, present, future. Neuron 112:1040–1044.
142. Fischer D, Klerman EB, Phillips AJK (2021): Measuring sleep regularity: Theoretical properties and practical usage of existing metrics. Sleep 44:zsab103.
143. Windred DP, Jones SE, Russell A, Burns AC, Chan P, Weedon MN, *et al.* (2021): Objective assessment of sleep regularity in 60 000 UK Biobank participants using an open-source package. Sleep 44:zsab254.
144. Pye J, Phillips AJ, Cain SW, Montazerolghaem M, Mowszowski L, Duffy S, *et al.* (2021): Irregular sleep-wake patterns in older adults with current or remitted depression. J Affect Disord 281:431–437.
145. Walsh RFL, Maddox MA, Smith LT, Olino T, Zee PC, Nusslock R, Alloy LB (2025): Sleep regularity in adolescents: Associations with sleep, rest–activity indices, and prospective substance use and depression. J Sleep Res :e14468.
146. Jafarzadeh Esfahani M, Sikder N, ter Horst R, Daraie AH, Appel K, Weber FD, *et al.* (2024): Citizen neuroscience: Wearable technology and open software to study the human brain in its natural habitat. Eur J Neurosci 59:948–965.
147. Yirmiya R (2024): The inflammatory underpinning of depression: An historical perspective. Brain Behav Immun 122:433–443.
148. Miller AH, Felger JC, Haroon E (2025): Designing clinical trials for an inflammatory subtype of major depressive disorder. [published online Apr 10]. Biol Psychiatry.
149. Besedovsky L, Lange T, Haack M (2019): The sleep-immune crosstalk in health and disease. Physiol Rev 99:1325–1380.
150. Fultz NE, Bonmassar G, Setsompop K, Stickgold RA, Rosen BR, Polimeni JR, Lewis LD (2019): Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. Science 366:628–631.
151. Ilvesmäki M, Moradi S, Paunonen J, Huuskonen U, Kallio M, Kiviniemi V, *et al.* (2024): Spectral entropy of cerebral fluids during human sleep measured by wearable fNIRS device. In: Tuchin VV, Leahy MJ, Wang RK, editors. Dynamics and Fluctuations in Biomedical Photonics XXI. Bellingham, WA: SPIE, 26.
152. Kohtala S, Alitalo O, Rosenholm M, Rozov S, Rantamäki T (2021): Time is of the essence: Coupling sleep-wake and circadian neurobiology to the antidepressant effects of ketamine. Pharmacol Ther 221:107741.
153. Sato S, Bunney B, Mendoza-Viveros L, Bunney W, Borrelli E, Sassone-Corsi P, Orozco-Solis R (2022): Rapid-acting antidepressants and the circadian clock. Neuropsychopharmacology 47:805–816.
154. Duncan WC, Slonena E, Hejazi NS, Brutsche N, Yu KC, Park L, *et al.* (2017): Motor-activity markers of circadian timekeeping are related to ketamine's rapid antidepressant properties. Biol Psychiatry 82:361–369.
155. Orozco-Solis R, Montellier E, Aguilar-Arnal L, Sato S, Vawter MP, Bunney BG, *et al.* (2017): A circadian genomic signature common to ketamine and sleep deprivation in the anterior cingulate cortex. Biol Psychiatry 82:351–360.
156. Ballard ED, Greenstein D, Reiss PT, Crainiceanu CM, Cui E, Duncan WC, *et al.* (2024): Functional changes in sleep-related arousal after ketamine administration in individuals with treatment-resistant depression. Transl Psychiatry 14:238.
157. Hemmeter U, Bischof R, Hatzinger M, Seifritz E, Holsboer-Trachsler E (1998): Microsleep during partial sleep deprivation in depression. Biol Psychiatry 43:829–839.
158. Zhang GF, Wang J, Han JF, Guo J, Xie ZM, Pan W, *et al.* (2016): Acute single dose of ketamine relieves mechanical allodynia and consequent depression-like behaviors in a rat model. Neurosci Lett 631:7–12.
159. Yang Y, Cui Y, Sang K, Dong Y, Ni Z, Ma S, Hu H (2018): Ketamine blocks bursting in the lateral habenula to rapidly relieve depression. Nature 554:317–322.