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SLEEP DISTURBANCES IN MAJOR DEPRESSIVE DISORDER: A COMPREHENSIVE NARRATIVE REVIEW

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ABSTRACT

Objectives: To review and synthesize current evidence on the characteristics, underlying mechanisms, and clinical significance of sleep disturbances in Major Depressive Disorder (MDD).
Methods: A narrative review of thirty peer-reviewed articles published between 2010 and 2025 was conducted. The included studies investigated sleep architecture, circadian rhythms, neurobiological mechanisms, and therapeutic interventions related to sleep disturbances in MDD using neuroimaging, electrophysiological, molecular, and clinical approaches.
Results: The reviewed literature indicates that sleep disturbances are a core feature of MDD. The most consistently reported abnormalities include shortened rapid eye movement (REM) latency, reduced slow-wave sleep, and circadian rhythm dysregulation. These alterations are associated with dysfunctions of monoaminergic neurotransmission, hyperactivity of the hypothalamic-pituitary-adrenal axis, and disruptions of circadian clock gene regulation. Sleep disturbances were also linked to impairments in emotional regulation, cognitive functioning, metabolic processes, and treatment response. Sleep-focused interventions, including cognitive-behavioral therapy for insomnia, chronotherapy, and light-based treatments, demonstrated antidepressant effects.
Conclusions: Sleep disturbances play a fundamental role in the pathophysiology and clinical course of MDD. Addressing sleep-related mechanisms may improve diagnostic accuracy, enhance treatment effectiveness, and contribute to better long-term outcomes in patients with depression.

KEYWORDS

Major Depressive Disorder, Sleep Disturbances, Insomnia, Hypersomnia, Circadian Rhythm, REM Sleep, Cognitive-Behavioral Therapy for Insomnia (CBT-I)

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Introduction

Major Depressive Disorder (MDD) is one of the most prevalent and disabling psychiatric conditions worldwide, characterized not only by persistent low mood but also by cognitive impairments, somatic symptoms, and prominent abnormalities of sleep [1, 2]. Sleep disturbances are reported in up to 90 percent of patients [3, 4], manifesting most commonly as difficulty initiating or maintaining sleep, early-morning awakenings, and non-restorative sleep [5]. Conversely, a smaller subset experiences hypersomnia and excessive daytime sleepiness [6, 7]. These sleep problems are diagnostically significant because they appear as both symptoms and potential predictors of depressive episodes. Longitudinal studies show that insomnia often precedes the onset of depression, suggesting a causal link [8, 9]. Moreover, residual sleep disturbances following apparent remission are strong indicators of relapse risk [10].

Sleep regulation and mood share overlapping neurochemical and anatomical substrates. Evidence from neurophysiological studies demonstrates that MDD is associated with characteristic alterations in sleep architecture—particularly shortened rapid eye movement (REM) latency, increased REM density, and decreased slow-wave sleep [11, 12]. Neuroimaging investigations and EEG power analyses have revealed changes in cortical connectivity and thalamocortical oscillations that underlie these phenomena [4, 10]. Such abnormalities persist even in euthymic individuals with a history of depression, implying trait-like dysfunction of sleep-related neural circuits [13]. Beyond architecture, melatonin rhythm disruption and diminished nocturnal secretion have been repeatedly observed [11, 14], indicating disturbance of temporal organization in biological systems.

Mechanistically, the pathophysiology linking depression and disturbed sleep involves dysregulation of the monoaminergic neurotransmitter systems—particularly serotonin and noradrenaline [15, 16]. Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis leads to excessive cortisol release

that interferes with slow-wave generation [17]. Inflammatory and oxidative processes further modulate this relationship by affecting synaptic plasticity and neurogenesis, especially within hippocampal and prefrontal regions [18]. Moreover, molecular chronobiology studies reveal altered expression of core clock genes (CLOCK, BMAL1, PER1/2, CRY1/2) in MDD, linking circadian misalignment to disrupted emotional and sleep regulation [3, 15, 19]. These mechanistic insights explain why depression is often accompanied by phase-shifted sleep patterns, morning fatigue, and mood variation across the day [20].

Clinically, abnormal sleep in depression has wide-ranging consequences. Disturbed sleep contributes to cognitive impairment, emotion dysregulation, reduced attention, and impaired quality of life [21, 22]. Actigraphy and polysomnography reveal that subjective reports of "poor sleep" often diverge from objective measurements [23], indicating altered perception and homeostatic dysregulation. In adolescents and young adults, excessive daytime sleepiness correlates with more severe depressive symptoms and higher exposure to pharmacotherapy [6]. Persistent insomnia is an independent risk factor for suicide in MDD [27], underscoring its prognostic importance. These findings together suggest that addressing sleep abnormalities is not ancillary but central to successful depression management.

Therapeutic research has advanced beyond viewing sleep changes as secondary phenomena. Pharmacological studies show that antidepressant classes vary in their impacts on sleep architecture: while some selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) can fragment sleep, others like agomelatine and certain sedating agents improve sleep continuity [13, 20, 21]. Non-pharmacological approaches have also gained prominence. Cognitive Behavioral Therapy for Insomnia (CBT-I), validated by multiple systematic reviews and randomized controlled trials, ameliorates both depressive and insomnia symptoms [14, 22, 23, 24]. Chronotherapy and light therapy demonstrate similar efficacy, particularly in patients with comorbid circadian misalignment [2, 15, 25, 26]. Combining these modalities with antidepressant pharmacotherapy significantly enhances remission stability and decreases relapse rates [27, 28]. Moreover, preventive trials indicate that treatment of insomnia in non-depressed populations lowers the incidence of future depressive episodes [26].

Despite this progress, notable gaps remain. The heterogeneity of circadian phenotypes, genetic predisposition, and environmental influences such as light exposure and lifestyle factors complicate the interpretation of existing data [29, 30]. A unified model integrating biological, psychological, and behavioral mechanisms is essential to translate laboratory findings into everyday clinical practice. Understanding sleep as both a symptom and a pathogenic pathway in MDD enables clinicians to move toward precision psychiatry—addressing individual circadian profiles, neurochemical imbalances, and behavioral patterns concurrently. This review therefore aims to synthesize current evidence on the neurobiological foundations, clinical correlates, and therapeutic implications of sleep disturbances in major depressive disorder, with the goal of highlighting actionable insights for future research and integrated treatment approaches.

Methods

This article was conceived as a narrative review integrating evidence on the prevalence, pathophysiology, clinical impact, and management of sleep disturbances in Major Depressive Disorder (MDD). The aim was to synthesize diverse research findings within a coherent conceptual framework rather than to quantitatively pool results, in order to provide a clinically oriented and mechanistically informative overview.

A comprehensive literature search was performed in PubMed/MEDLINE, Scopus, and PsycINFO, covering studies published between January 2010 and June 2025. The search strategy employed combinations of key terms and Medical Subject Headings (MeSH): "Major Depressive Disorder", "depression", "sleep disorders", "sleep disturbances", "insomnia", "hypersomnia", "circadian rhythm", "REM sleep", "sleep architecture", "melatonin", "cognitive-behavioral therapy for insomnia", and "chronotherapy". Boolean operators (AND, OR) were used to refine results. Manual searches of reference lists from key publications were also performed to capture additional eligible studies not identified through electronic databases. Inclusion criteria were defined a priori to ensure scientific rigor and relevance. Articles were considered eligible if they met the following conditions:

1. Original research (study or clinical trial) or systematic/narrative review published in a peer-reviewed medical journal.
2. Published in English within the specified time frame (2010–2025).
3. Focused primarily on sleep parameters, circadian mechanisms, or interventions related to MDD.
4. Included adult or adolescent populations diagnosed with MDD according to DSM-IV/5 or ICD-10/11 criteria.

5. Used subjective or objective measures of sleep, such as validated sleep questionnaires, actigraphy, EEG, or polysomnography.

Exclusion criteria were:

1. Case reports or small series (<5 participants).
2. Non-human or preclinical studies.
3. Papers where sleep was only a secondary outcome without substantial analysis.
4. Studies of primary sleep disorders unrelated to MDD (e.g., obstructive sleep apnea, narcolepsy).
5. Non-peer-reviewed material, abstracts, and conference proceedings.

Study Selection and Data Extraction

Titles and abstracts were reviewed first to exclude irrelevant material. Full texts were then examined for compliance with inclusion criteria. Ultimately, 30 studies matched all eligibility standards and were incorporated into the final synthesis. Data extracted from each publication included: [1] study type (observational, interventional, or review); [2] sample size and population demographics; [3] assessment methods for sleep and depressive symptoms; [4] primary findings; and [5] reported therapeutic implications.

Synthesis Approach

Given the heterogeneity of methods and outcomes across the included studies, qualitative integration rather than meta-analysis was used. Studies were thematically categorized into four analytic domains:

(1) pathophysiological mechanisms;
(2) circadian dysregulation;
(3) clinical manifestations and functional outcomes; and
(4) pharmacological and non-pharmacological treatments.

Narrative synthesis was structured to highlight consistency, divergence, and emerging trends across evidence domains. Key quantitative data were tabulated for clarity (see Table 1). The review was prepared in adherence with the SANRA (Scale for the Assessment of Narrative Review Articles) framework to ensure comprehensiveness, methodological transparency, and balance of interpretation.

Results

Pathophysiology of Sleep Disturbances in Major Depressive Disorder

Sleep regulation and mood are governed by complex neurobiological systems that interact at molecular, cellular, and network levels. In Major Depressive Disorder (MDD), these mechanisms become disrupted, producing characteristic abnormalities in sleep architecture and circadian timing [1–3].

Neurochemical mechanisms

The bidirectional association between depression and disturbed sleep reflects shared dysregulation of neurotransmitter systems. Altered serotonergic and noradrenergic signaling destabilizes both mood and non-rapid eye movement (NREM) sleep generation [4, 5]. Serotonin modulates SWS initiation, whereas noradrenaline influences REM latency; both are diminished in MDD [6]. Reduced γ-aminobutyric acid (GABA) activity and increased glutamatergic excitation further impair the homeostatic drive for restorative sleep [7, 8]. At the same time, dopaminergic dysregulation contributes to sleep fragmentation and early-morning awakening [9]. These neurochemical alterations collectively reflect shifts in the balance of inhibitory–excitatory neurotransmission within corticolimbic circuits.

Hypothalamic–pituitary–adrenal (HPA) axis and stress physiology

Chronic hyperactivation of the HPA axis is a hallmark of MDD, producing sustained cortisol elevation that interferes with normal sleep physiology [10]. High nocturnal cortisol suppresses SWS and shortens REM latency [11, 12]. This dysregulation results in a vicious circle: insufficient restorative sleep further amplifies stress reactivity, aggravating depressive symptomatology [13]. Neuroendocrine studies demonstrate that restoring sleep continuity through pharmacological or behavioral approaches can partially normalize cortisol rhythms [14].

Neuroinflammatory and neuroplastic processes

A growing body of evidence implicates immune–inflammatory pathways in mediating sleep–mood interactions. Elevated levels of cytokines such as interleukin-6 and TNF-α have been linked to reduced SWS and subjective insomnia in MDD [15]. Inflammation adversely affects hippocampal neurogenesis and synaptic plasticity, contributing simultaneously to cognitive dysfunction and altered sleep regulation [16, 17]. Sleep deprivation experiments show transient antidepressant effects, suggesting overlapping molecular substrates between sleep loss and antidepressant response [2]. The compensatory activation of plasticity-related signaling cascades, including BDNF upregulation, may transiently improve mood before rebound worsening occurs [18].

Circadian misalignment and clock-gene dysfunction

Circadian rhythm disturbance represents another pathophysiological foundation of sleep abnormalities in MDD [3, 19]. Under normal circumstances, the suprachiasmatic nucleus (SCN) synchronizes peripheral clocks through hormonal and neuronal cues. In depressed patients, desynchronization between central and peripheral oscillators leads to delayed sleep phase and diurnal mood variation [20, 21]. Altered expression of CLOCK, BMAL1, PER and CRY genes has been reported in neuroimaging and genomic studies [15, 22]. This circadian instability is mirrored by blunted melatonin rhythm and phase-delayed secretion profiles [11, 14]. Actigraphic findings highlight that correcting misalignment through chronotherapy or timed light exposure alleviates both insomnia and depressive mood [23, 24].

Neural circuit abnormalities

Functional neuroimaging confirms altered connectivity within prefrontal–limbic–thalamic networks responsible for emotional and sleep-wake regulation [25]. Reduced prefrontal cortex inhibition of the amygdala correlates with sleep fragmentation and nocturnal rumination. Electroencephalographic (EEG) studies demonstrate reduced delta power and elevated high-frequency activity during NREM sleep, reflecting cortical hyperarousal [10, 11, 26]. Such neural signatures persist as potential biomarkers distinguishing depressive from healthy sleepers [27]. Moreover, specific REM parameters—including increased REM density and shorter REM latency—consistently differentiate MDD from other psychiatric disorders [9, 28]. Together, these data suggest that malfunction within frontolimbic gating circuits mediates both affective instability and failure to achieve restorative sleep.

Integration of mechanisms

The convergence of monoaminergic depletion, HPA hyperactivity, inflammation, and circadian misalignment forms a systems-level model explaining why sleep disruption is intrinsic to depression rather than a secondary consequence [29]. Feedback loops among these subsystems sustain the disorder: circadian desynchrony increases stress reactivity, elevated cortisol enhances inflammatory signaling, and impaired neuroplasticity hinders adaptation [30]. This integrated perspective underscores that therapeutic strategies targeting sleep–wake restoration may simultaneously modulate mood, stress, and circadian pathways, offering multidimensional benefit beyond symptomatic relief.

Table 1. Summary of Selected Studies on Sleep Pathophysiology in Major Depressive Disorder (2010–2025)

Author (year)	Study type	Participants	Key focus	Main findings
Murphy & Peteron (2015) [1]	Narrative review	-	neurobiology of sleep in depression	Summarized neurochemical m echanisms; highlighted REM changes
Bovy et al. (2022) [4]	EEG study	MDD patients n = 72 vs controls	NREM sleep archit ecture	Reduced delta power; persiste nt anomalies after remission
Wescott et al. (2025) [3]	Systematic review	-	Circadian realignment and mood	Circadian misalignment drives mood dysregulation
Zhang et al. (2022) [18]	Meta-analysis	21 longitudinal tri als	Sleep and depressi on risk	Insomnia predicts MDD onset (BIDIRECTIONAL)
Cai et al. (2024) [10]	EEG study	MDD n=40	Sleep EEG and atte ntion	Decreased alpha power; associ ated with attention deficits
Wang et al. (2021) [11]	Clinical trial	MDD n = 33	Melatonin and EE G changes	Abnormal melatonin and EEG normalized after treatment
Arıkan et al. (2024) [9]	Meta-analysis	-	REM parameters	Shorter REM latency in drug-free MDD

Manosso et al. (2024) [15]	Review	-	Circadian rhythms	Clock-gene alterations underp in sleep/mood interaction
Bojarska et al. (2024) [2]	Review	-	Sleep deprivation a nd light therapy	Acute sleep deprivation and li ght exposure yield antidepress ant effect
Zhao et al. (2021) [16]	Observational	n = 184 MDD	Insomnia vs hypers omnia symptoms	Distinct clinical profiles based on sleep subtype
Solelhac et al. (2024) [5]	Cohort	n=6,000+	Sleep disturbances and incident MDD	Sleep complaints predict futur e MDD episodes

Discussion

Circadian Dysregulation and Chronobiological Aspects:

The circadian system and its interaction with mood

Circadian rhythms, generated by transcriptional–translational feedback loops of core clock genes, coordinate physiological processes such as sleep–wake cycles, hormonal secretion, and body temperature. In Major Depressive Disorder (MDD), these biological rhythms show consistent weakening, phase shifts, and internal desynchronization [3, 15, 18]. The central pacemaker in the suprachiasmatic nucleus (SCN) regulates peripheral oscillators through neural and humoral pathways linking the hypothalamus, pineal gland, and limbic structures [15]. When circadian signaling becomes misaligned with environmental light-dark cycles, the resulting desynchrony disrupts emotional homeostasis and sleep timing [3, 19].

Evidence of circadian misalignment in MDD:

Actigraphic and polysomnographic research has revealed characteristic circadian-sleep abnormalities among individuals with MDD [4, 11, 19]. Patients display delayed sleep phase, increased nocturnal wakefulness, and fragmented circadian rest–activity cycles [20]. Melatonin secretion rhythms are often dampened and phase-delayed [11, 14], while body-temperature minima occur later in the night [15]. These markers of circadian delay are associated with early-morning tiredness, low energy, and diurnal mood variation [21]. Neuroimaging findings complement these observations: reduced synchrony between SCN and prefrontal regions correlates with affective instability and disrupted REM architecture [22, 25].

Molecular evidence supports these physiological abnormalities. Post-mortem and peripheral-tissue analyses demonstrate reduced amplitude and phase instability in the expression of CLOCK, BMAL1, PER2, and CRY1 genes [15, 22]. Gene-expression rhythmicity normally confers temporal order to monoamine metabolism and synaptic plasticity; its disruption contributes to mood dysregulation [23]. Furthermore, abnormalities in melatonin receptors (MT1 and MT2) have been associated with diminished circadian entrainment and poorer antidepressant response [14, 20]. Taken together, these findings confirm that depression involves a state of partial circadian uncoupling between brain regions governing emotion and those controlling sleep propensity.

Chronotype, social rhythm, and depressive vulnerability:

Individual differences in circadian preference (chronotype) modulate susceptibility to depression. Evening-type individuals show higher rates of MDD and greater sleep onset delay than morning-type peers [5, 18]. Disruption of "social rhythms"—the timing of daily activities—can further destabilize internal clocks [24]. Stress, shift work, and increased exposure to artificial light at night exacerbate misalignment between social and biological timing [19, 25]. Population studies confirm that chronic irregular schedules predict both depressive onset and poorer treatment outcomes [5, 18]. Circadian regulation, therefore, constitutes both a trait vulnerability and a dynamic therapeutic target.

Chronotherapy and light-based interventions:

Recognition of circadian involvement in MDD has inspired interventions specifically targeting biological timing. Light therapy aims to resynchronize the circadian system by administering timed bright light exposure shortly after awakening. Numerous controlled trials demonstrate significant improvements in both mood and sleep among patients with seasonal and non-seasonal depression [2, 14, 25]. Dark therapy, conversely, restricts evening light exposure to enhance melatonin secretion and sleep quality [2, 15] Sleep phase advancement and wake therapy—temporary total or partial sleep deprivation followed by recovery sleep—produce rapid but often transient antidepressant effects [2, 18]. Combining these methods with

pharmacologic or cognitive-behavioral approaches helps sustain rhythm normalization and clinical improvement [24, 25]. Chronotherapeutic augmentation of antidepressant treatment has also been associated with normalized REM latency and improved daytime alertness [20, 22]. Collectively, such findings support the principle that realigning circadian function not only improves sleep but directly influences mood regulation.

Melatonergic and pharmacological modulation:

Pharmacotherapy can also be directed toward circadian mechanisms. Agomelatine, a melatonin receptor agonist with 5-HT_2C antagonist properties, exerts both antidepressant and sleep-restorative effects [13, 14, 20]. By resynchronizing circadian cycles, it increases sleep efficiency and reduces next-day fatigue without the sedative burden typical of traditional hypnotics. Adjunctive low-dose melatonin supplementation has been shown to improve both sleep initiation and overall mood stability [11, 14]. Such findings highlight that chemical or behavioral entrainment of internal rhythms constitutes a novel preventive strategy for relapse avoidance in MDD [3, 15, 19].

Future research directions in chronobiology:

Although existing evidence robustly links circadian dysregulation to MDD, several unresolved questions persist. First, it remains unclear whether circadian instability represents a trait marker or a state-dependent phenomenon. Second, differential susceptibility among chronotypes, including sex-specific and developmental variables, requires greater exploration [5, 6, 18]. Finally, technological advancements—such as continuous actigraphy, wearable light sensors, and genetic profiling—may provide objective tools for detecting early signs of circadian imbalance [29, 30]. Integration of these biomarkers into personalized therapeutic regimens could revolutionize prevention and maintenance strategies for MDD.

Clinical Manifestations and Consequences of Sleep Disturbances in Major Depressive Disorder.

Overview and prevalence

Sleep disturbances constitute one of the most pervasive clinical features of Major Depressive Disorder (MDD), occurring in up to 90 percent of patients [1, 3, 4]. They manifest as insomnia, hypersomnia, non-restorative sleep, fragmented rest–activity cycles, or misaligned circadian scheduling [5, 6]. The combination of disrupted nocturnal sleep and daytime fatigue uniquely characterizes depressive morbidity [7]. Large community-based cohorts demonstrate that chronic disturbances in sleep duration predict both incident and recurrent episodes of depression [5, 18]. This bidirectional association underscores sleep dysfunction as both a symptom and a mechanistic contributor to MDD [18, 29].

Subtypes of sleep disruption:

Insomnia—difficulty initiating or maintaining sleep or waking earlier than desired—is the most common presentation [21]. Insomnia subtypes in MDD include sleep-onset insomnia, middle insomnia, and terminal insomnia [1, 16]. Polysomnographic studies consistently reveal longer sleep-onset latency, reduced sleep efficiency, and increased REM density [4, 9, 11]. Subjectively, patients frequently report fragmented, light sleep accompanied by evening rumination [23]. These patterns correlate with reduced delta power on sleep EEG, signifying cortical hyperarousal [4, 10].

Hypersomnia affects 15–20 percent of depressive patients [6, 16]. It is more prevalent in atypical and seasonal subtypes, marked by prolonged total sleep time, difficulty waking, and persistent daytime sleepiness [16, 21]. Adolescent and young-adult populations display higher hypersomnia prevalence, which correlates with greater illness severity and antidepressant use [6]. Interestingly, patients with hypersomnia exhibit distinct metabolic and inflammatory profiles compared with insomniac subtypes [18]. This heterogeneity indicates diverse biological underpinnings within depressive phenotypes.

Circadian rhythm disorders also manifest clinically through delayed or advanced sleep phase, irregular patterns, and misalignment between sleep propensity and social obligations [3, 15, 19]. Patients often experience morning worsening of mood, diminished energy, and disrupted concentration [20, 21]. Actigraphic assessments reveal attenuated amplitude and phase delay in rest–activity cycles [19, 25], reinforcing the relationship between circadian instability and daily emotional fluctuation.

Subjective versus objective sleep perception

A notable feature of depressive sleep pathology is the discrepancy between subjective complaints and objective assessments. Although most patients rate their sleep as severely disturbed, actigraphy and polysomnography sometimes reveal relatively preserved structure [23]. Kung et al. [8] demonstrated considerable incongruence between self-reported and actigraphic sleep measures in MDD, suggesting an altered perception of sleep continuity and duration. This distortion may reflect attentional bias toward nocturnal wakefulness or cognitive exaggeration due to ruminative thought patterns [24]. Clinicians should therefore evaluate both objective and subjective data to form an accurate picture of the disorder.

Cognitive and emotional consequences

Disturbed sleep impairs cognitive performance, emotional processing, and stress regulation [12, 25, 26]. Sleep loss and REM abnormalities interfere with consolidation of positive memory traces and amplify the salience of negative stimuli [17]. These alterations accentuate hopelessness and anhedonia. Electrophysiological abnormalities, such as increased beta activity during NREM sleep, have been associated with cortical hyperarousal and emotional instability [10, 11]. Sustained deficits in attention and executive function correlate with diminished EEG alpha power [10], directly impeding psychomotor efficiency. Such findings align with the observation that effective antidepressant therapy is often accompanied by normalization of both sleep continuity and cognitive performance [11, 14].

Functional and physical health outcomes

Beyond emotional impairment, sleep abnormalities contribute to poorer occupational functioning, absenteeism, and diminished productivity [7, 27]. Insufficient sleep increases daytime fatigue, psychomotor slowing, and irritability [21, 22]. Metabolic and cardiovascular consequences have also been implicated: disrupted sleep architecture promotes insulin resistance, appetite dysregulation, and elevated cardiometabolic risk [12, 18]. Patients with persistent insomnia display higher inflammatory markers, which predict reduced response to antidepressant treatment [15, 16]. Therefore, the management of sleep is central not only to emotional recovery but also to physical well-being in depression.

Prognostic significance and therapeutic implications

Persistent sleep disturbance predicts unfavorable prognosis. Residual insomnia after partial mood remission increases the probability of relapse within 6–12 months [9, 27]. Longitudinal data demonstrate that insomnia symptom severity is linearly associated with depressive duration and recurrence [28, 30]. Conversely, therapeutic modulation of sleep—whether pharmacological or behavioral—correlates with improved mood stabilization and cognitive recovery [13, 14, 22]. Patients receiving Cognitive Behavioral Therapy for Insomnia (CBT-I) exhibit superior remission rates compared with those treated with antidepressants alone [22, 23, 25]. Chronotherapy and light therapy similarly accelerate response by synchronizing circadian timing [2, 15, 24]. Thus, accurate assessment and treatment of sleep disturbance should be regarded as a fundamental component of depression management rather than an ancillary concern.

Summary:

The clinical presentation of sleep disturbance in MDD is diverse and multifactorial, encompassing alterations in architecture, circadian patterns, and subjective perception. These abnormalities exert broad consequences across cognitive, emotional, and somatic domains, ultimately influencing treatment response and relapse prevention. Recognizing and addressing the multidimensional role of sleep is therefore essential to advancing personalized psychiatric care

Treatment Approaches for Sleep Disturbances in Major Depressive Disorder:

Pharmacological Management

Pharmacological strategies for managing sleep abnormalities in Major Depressive Disorder (MDD) focus on both depressive symptomatology and accompanying insomnia or hypersomnia. Traditional antidepressants influence sleep to varying degrees. Selective serotonin reuptake inhibitors (SSRIs) and serotonin–noradrenaline reuptake inhibitors (SNRIs) may initially fragment sleep and suppress REM phases [13, 20, 21]. Tricyclic antidepressants exhibit sedative effects and prolong total sleep time but often induce residual daytime fatigue [20]. By contrast, agomelatine, a melatonin receptor agonist and 5-HT_2C antagonist, restores both circadian synchronization and sleep efficiency while exerting antidepressant properties [13, 14, 20]. Clinical trials demonstrate that agomelatine improves sleep continuity, reduces wakefulness after sleep onset, and decreases next-day exhaustion [14].

Adjunctive hypnotic medications—z-drugs or benzodiazepines—may alleviate acute insomnia but are not recommended for long-term management due to tolerance and dependency risks [20, 21]. Meta-analyses indicate that melatonin receptor agonists and low-dose trazodone maintain efficacy while minimizing adverse effects [13, 14]. Pharmacological augmentation targeting the sleep–wake system, such as low-dose doxepin or gabapentinoids, can be appropriate for residual insomnia in partial responders [20]. Future drug development is increasingly directed toward agents selectively modulating circadian and neuroplastic pathways relevant to both sleep and mood [15, 19, 30].

In contrast, excessive daytime sleepiness and hypersomnia are less amenable to standard antidepressants. Management includes gradual sleep–wake regularization, behavioral activation, and, in certain refractory cases, wake-promoting agents or dopaminergic modulators under careful clinical

supervision [6, 16]. Overall, pharmacologic therapy should aim to optimize both nocturnal restoration and daytime alertness without inducing further circadian disruption.

Cognitive Behavioral Therapy for Insomnia (CBT-I)

Non-pharmacological approaches are recognized as first-line interventions for persistent insomnia during or following depressive episodes [14, 22, 23]. Cognitive Behavioral Therapy for Insomnia (CBT-I) addresses dysfunctional thoughts, maladaptive behaviors, and irregular sleep habits through techniques such as sleep restriction, stimulus control, relaxation, and cognitive restructuring [22]. Randomized controlled trials demonstrate that CBT-I yields clinically meaningful improvement in both insomnia and depressive symptom severity [22, 23, 24]. Manber et al. [22] showed that combining CBT-I with antidepressant pharmacotherapy doubles remission rates compared with antidepressant monotherapy. Systematic reviews underscore the durability of treatment effects, with sustained sleep improvement persisting for ≥ 12 months [22, 23].

CBT-I also confers preventive effects: patients achieving stabilized sleep architecture exhibit fewer mood fluctuations and lower relapse risk [23, 25]. Implementation is feasible in individual, group, or digital-health formats, including guided online programs [24, 25]. Such accessibility extends its reach among patients reluctant to use hypnotics. Given its efficacy, safety, and long-term benefits, CBT-I is now widely recommended as a core component of integrated depression management strategies [14, 22, 23].

Chronotherapy and Light-Based Interventions:

Chronotherapy encompasses techniques that manipulate biological timing to resynchronize circadian cycles. Methods include sleep deprivation therapy, sleep phase advancement, and bright light therapy [2, 14, 15]. Acute sleep deprivation exerts rapid yet transient antidepressant effects by modulating neuroplastic and monoaminergic pathways [2]. When combined with light exposure or pharmacological treatment, response durability improves [14, 15]. Light therapy administered in the early morning restores circadian amplitude and advances delayed sleep phase, thereby alleviating insomnia and diurnal mood variation [3, 25, 26]. Controlled trials report robust clinical benefits for both seasonal and non-seasonal MDD [2, 14]. In contrast, carefully timed dark therapy and blue-light restriction in the evening enhance melatonin secretion and improve subjective sleep quality [15, 19].

Chronotherapy's efficacy highlights the importance of synchronizing biological rhythms. Patients with delayed circadian phase (evening chronotype) often derive particular benefit [5, 18, 19]. Furthermore, coupling chronotherapeutic techniques with CBT-I or agomelatine pharmacotherapy optimizes clinical remission while minimizing relapse risk [13–15, 25]. By targeting both environmental and physiological timing cues, chronotherapy serves as an effective, mechanism-based complement to traditional psychosocial and pharmacologic strategies.

Integrative and Preventive Perspectives

Optimal management of depression-related sleep disturbance requires an integrative approach spanning biological, psychological, and behavioral domains [27, 28]. Combining pharmacotherapy with CBT-I and circadian-based interventions delivers synergistic outcomes on mood stabilization, sleep continuity, and cognitive recovery [14, 22–25]. Multicomponent programs—incorporating psychoeducation, social rhythm therapy, and digital monitoring—have shown promise in maintaining remission [24, 25, 27]. Addressing sleep early in the therapeutic process can prevent chronicity and improve overall prognosis [18, 19, 30]. Preventive public-health initiatives emphasizing sleep hygiene, consistent wake times, and light exposure patterns may reduce depression incidence in at-risk populations [5, 18].

Future research should clarify the optimal sequencing of multiple interventions and identify biomarkers predictive of individual treatment response. Incorporating wearable devices, actigraphy, and melatonin profiling may facilitate personalized rhythm-based care models. Ultimately, restoring restorative and rhythmic sleep represents a cornerstone of precision psychiatry for Major Depressive Disorder, with wide-ranging benefits for emotional and physical health

Future Directions and Research Gaps

Despite significant progress in understanding the interplay between sleep and depression, several conceptual and methodological limitations constrain current knowledge. Although consistent evidence supports a bidirectional association, the precise causal mechanisms linking sleep dysregulation with Major Depressive Disorder (MDD) remain unclear [3, 18, 19]. Future research should therefore move beyond cross-sectional correlations toward longitudinal, mechanistic studies capable of disentangling directionality and mediating factors.

Identifying causal pathways and biomarkers

Determining whether sleep dysfunction acts primarily as a precipitating factor, a consequence, or an epiphenomenon of depression is central to advancing prevention and treatment [18, 19, 30]. Prospective cohort studies with objective sleep tracking—integrating polysomnography, actigraphy, and melatonin profiling—could clarify temporal sequence and causal strength. Molecular biomarkers, such as gene-expression patterns of CLOCK, BMAL1, and PER genes [15, 22], and neuroimaging signatures within limbic–prefrontal networks [25], offer promising insights. However, replication and standardization across laboratories remain needed before these indicators can reliably guide clinical decision-making.

Personalization and chronotype-based interventions

Not all patients experience sleep dysfunction in the same form. Individual variability in chronotype, genetic background, and environmental exposure (e.g., light, stress, and social rhythm) modifies vulnerability [5, 18]. Future trials should stratify participants accordingly to test tailored interventions—such as morning light therapy for evening chronotypes or targeted CBT-I for high-arousal phenotypes [2, 14, 23]. Integration of genomic and phenotypic information could pave the way for precision chronopsychiatry, providing treatments synchronized to each patient's biological rhythms. Machine-learning algorithms may help predict which circadian or pharmacologic modalities yield optimal outcomes [29, 30]

Digital innovation and objective monitoring

Digital health technologies offer unprecedented opportunities to quantify sleep–mood interactions. Wearable devices capable of detecting rest–activity patterns, heart-rate variability, and ambient-light exposure can generate real-time circadian data [19, 25]. Mobile applications integrating CBT-I principles and ecological momentary assessment may enhance adherence and capture fluctuations in sleep and mood [24, 25]. However, validation of these tools against gold-standard laboratory techniques and addressing data-privacy issues are essential prerequisites. Combining digital metrics with neurobiological indicators may allow dynamic monitoring of treatment response and relapse prediction.

Translational implications and multidimensional models:

The convergence of neurochemical, hormonal, and circadian mechanisms highlights sleep disturbance as a core dimension of MDD pathophysiology [1, 15, 18]. Future translational studies should develop integrative models linking molecular cascades to clinical phenomena. Intervention trials comparing pharmacologic, behavioral, and chronotherapeutic regimens in multimodal designs would clarify synergistic effects [13–15, 22–25]. Cross-disciplinary collaboration between neuroscientists, chronobiologists, and clinicians will be crucial to move research from reductionist frameworks toward comprehensive pathophysiological mapping.

Taken together, the next decade should focus on personalization, objective tracking, and integration across biological and behavioral domains. Such progress will allow clinicians not only to treat insomnia within depression but also to pre-empt depressive onset through early stabilization of the sleep–wake cycle.

Digital and Social Dimensions of Sleep Research and Treatment in MDD

The increasing integration of technology into healthcare offers new ways to address sleep disturbances in Major Depressive Disorder (MDD). Digital tools such as smartphone-based sleep diaries, wearable devices, and telemedicine platforms allow continuous monitoring of sleep patterns and mood fluctuations, providing valuable data for early detection and personalized intervention.

Online versions of Cognitive Behavioral Therapy for Insomnia (CBT-I) and app-based chronotherapy programs have demonstrated comparable efficacy to face-to-face treatment, expanding access for patients in remote or resource-limited settings. These digital solutions also promote adherence, reduce costs, and support data-driven models of care.

From a social perspective, the widespread use of technology to track and manage sleep raises important questions about digital literacy, data privacy, and equitable access to telehealth services. Future research should explore how technology-enabled interventions can bridge psychosocial support and clinical care, fostering a more inclusive and community-based approach to improving sleep and mental health outcomes.

Limitations:

As a narrative review, this article is subject to certain limitations. Although every effort was made to comprehensively identify and synthesize relevant studies, potential selection bias and publication bias cannot be ruled out. The heterogeneity of study designs, assessment tools, and outcome measures precludes meta-analytic comparison. Consequently, the conclusions drawn should be interpreted as integrative and hypothesis-generating rather than definitive. Future systematic reviews and longitudinal studies are needed to validate and expand upon the mechanisms and therapeutic conclusions summarized here.

Implications for Clinical Practice and Research:

The recognition of sleep disturbance as a central feature of Major Depressive Disorder has direct implications for both clinical management and scientific investigation.

Clinicians should routinely assess sleep patterns, circadian timing, and chronotype as part of comprehensive depression evaluation, given their prognostic and therapeutic significance. Integrating evidence-based interventions such as Cognitive Behavioral Therapy for Insomnia, chronotherapy, and melatonergic agents into standard care can enhance remission stability, cognitive recovery, and overall quality of life.

From a research perspective, multidimensional approaches combining neurophysiology, molecular chronobiology, and digital monitoring are needed to clarify causal mechanisms and personalize treatments. By bridging biological and behavioral domains, future studies can establish sleep restoration not merely as symptom control but as a preventive and pathophysiological target in precision psychiatry.

Conclusions

Sleep disturbances are intrinsic to Major Depressive Disorder, bridging neurobiological, psychological, and environmental domains. Far from being epiphenomena, disruptions in sleep architecture and circadian timing exert direct influence on mood, cognition, and physiological health. Contemporary evidence demonstrates that interventions targeting the sleep–wake system—whether pharmacological, behavioral, or chronobiological—can markedly improve depressive outcomes.

While major strides have been made in characterizing the bidirectional relationship between sleep and mood, persistent research gaps underscore the need for longitudinal and mechanistic clarity. Personalized approaches based on chronotype, genetic markers, and lifestyle factors promise to redefine management strategies. Integrating digital technologies and objective biomarkers will further enhance diagnosis, monitoring, and prevention.

Ultimately, restoring restorative and rhythmic sleep represents a cornerstone of precision psychiatry. By harmonizing circadian physiology with emotional regulation, clinicians can achieve more sustainable remission, greater functional recovery, and improved quality of life for individuals living with Major Depressive Disorder.

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