International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 21s, 2025
https://theaspd.com/index.php

The Role Of Serotonin In Sleep And Mood Regulation: A Comparative Physiological Review Of Healthy And Depressed Populations

Talib Saddam Mohsin[1], Ghassaq Jewad Kadhem[2], Shaima Jassem Hussen Idrees[3], Hind Alrubaye[4]
[1]Physiologist, Department of Anesthesia Techniques, college of health and medical techniques, University of Kut, Wasit, IRAQ, talib.saddam@alkutcollege.edu.iq
[2]Wasit health director ghassaq1985@gmail.com
[3]Biologist, department of anesthesia, college of health and medical techniques , university of Kut
[4]Lake Erie College of osteopathic . Medicine, USA

Abstract
Serotonin (5-hydroxytryptamine, 5-HT) plays a critical role in synchronizing sleep architecture and emotional regulation. Although its influence on mood and sleep has been extensively studied individually, their integrated physiological regulation,and how its disruption contributes to depression,remains insufficiently explored. This review presents a comparative physiological analysis of serotonergic function in healthy versus depressed individ- uals, emphasizing how serotonin rhythms, receptor dynamics, and neural circuits coordinate sleep-wake cycles and mood stability.
In healthy individuals, serotonin follows a distinct circadian rhythm. Daytime increases support arousal and emotional resilience, while nighttime declines facilitate sleep onset and progression through sleep stages. In depression, these rhythms become flattened. Serotonin synthesis decreases, receptor sensitivity changes, and neural circuits lose coherence. These alterations contribute to fragmented sleep, shortened REM latency, and persistent mood instability.
Synthesizing evidence from neuroanatomy, receptor pharmacology, and circadian physiology, this review pro- poses the Serotonergic Synchronization Failure Model, conceptualizing depression as a breakdown in serotoner- gic integration across sleep and mood systems. This perspective reframes depressive symptoms not as isolated dysfunctions but as interconnected failures of physiological synchrony. The analysis underscores the need for therapeutic interventions,pharmacological, behavioral, and circadian-based,that restore serotonergic coher- ence to improve both sleep and mood regulation.
Keywords: *Serotonin, Sleep Regulation ; Mood Disorders; Circadian Rhythms; Depression; Neurophysiology*

1 INTRODUCTION

Serotonin is a fundamental neuromodulator that orchestrates key physiological processes, including emotional reg- ulation and the sleep-wake cycle. While extensive research has clarified serotonin's individual role in either mood disorders or sleep regulation, far fewer studies have examined its integrative function across these interconnected domains. In reality, mood and sleep share overlapping serotonergic pathways, receptor mechanisms, and neural circuits, suggesting that these systems do not operate in isolation but are tightly coupled through physiological synchrony.

The serotonergic system originates in the brainstem's dorsal and median raphe nuclei, projecting widely to cortical, limbic, and hypothalamic regions (Hornung, 2010). These pathways regulate arousal, circadian entrainment, and emotional processing. Under typical physiological conditions, serotonin levels follow a circadian pattern: daytime elevations sustain wakefulness and emotional resilience, while nighttime declines permit the initiation of non- REM and REM sleep stages (Mistlberger & Skene, 2011). This dynamic modulation aligns behavioral states with environmental light-dark cycles, ensuring homeostasis across sleep and emotional systems.

However, depression disrupts this physiological synchrony. Individuals with depression frequently exhibit flat- tened serotonin rhythms, altered receptor sensitivity, and impaired neural circuit coherence (Meyer et al., 2004). Clinically, these disruptions manifest as fragmented sleep, shortened REM latency, diminished slow-wave sleep, and persistent emotional instability (Riemann et al., 2017; Steiger, 2007). While these disturbances are often stud- ied separately as insomnia or mood instability, they may actually reflect a systemic breakdown in serotonergic regulation.

Prior models of depression, such as the monoamine hypothesis (Blier & El Mansari, 2013) and the neuroplasticity hypothesis (Duman, 2014), focused on serotonin's role in neurotransmission and synaptic

plasticity but offered little insight into its circadian and sleep-related functions. More recent perspectives (McClung, 2013; Dollish et al., 2024) have highlighted the importance of circadian misalignment in mood disorders, yet they typically address circadian rhythms, mood, and sleep as distinct processes rather than parts of an integrated system. Furthermore, the functional roles of specific serotonin receptors,such as 5-HT_7 in circadian entrainment and 5-HT_2A in REM regulation,remain incompletely synthesized into a unified model of depressive physiology.

This article addresses these intervals by presenting comparative physical analysis of serotonargic regulation in healthy and depressed individuals. Drawing from neuronatomy, receptor pharmacology, 24 -hour physiology and clinical sleep studies, it proposes a new conceptual structure: Serotonergic synchronization failure models. This model does not make depression as a failure of isolated neurotransmitter deficit disorders, but as a failure of physical intelligence, a fracture in the 24-hour cycle as an integrator of sleep-vegetable and mood stability in the role of serotonin as an integral stability.

This integrated perspective suggests that the restoration of serotonary rhythm and consistently can improve continuity and emotional regulation of sleep together. In this way, it offers a new theoretical lens, through the understanding of depressed disorders and informs the approach to treatment that both addresses the domain, which addressed the domains in general instead of symptoms.

2 Neurophysiological Basis of Serotonin Regulation

2.1 Serotonergic System Architecture

The serotonorous system is mainly produced in the Dorsal Rafe core (DRN) and the Madhyika Rafa core (MRN) in the brain stem, which gives rise to serotonurgic projections throughout the central nervous system (Hornung, 2010). These routes are spread to important areas included in sleep-waking regulation, mood modulation and 24-hour control, including the hypothalamus, thalamus, limbic system and prefrontal cortex (Gaspar et al., 2003; Hornung, 2003).

The hypothalamus, especially superciamatic core (SCN), coordinates the rhythm and is an important place for serotonorgic modulation. Through estimates of SCN and other hypothalamic structures, serotonin adjusts physiological processes with environmental light dark cycle (Saper et al., 2005). Parallel to Serotonorgian input to the limbic system (eg Amigdala and Hippocampus) the emotional response, while the estimates

The prefrontal cortex provides executive control plants on effective states (Cowen and Browning, 2015; Jacobs and Azmitia, 1992).

This widespread anatomical distribution allows serotonin to function as an integrator of physiological states, co- ordinating transitions between wakefulness and sleep, emotional stability and vulnerability, and circadian align- ment with environmental cues. Importantly, the serotonergic system interacts with other neuromodulatory cir- cuits,including dopaminergic and noradrenergic pathways,further integrating behavioral and physiological states (Robbins & Arnsten, 2009).

However, this integrative role is context-dependent and receptor-specific. The precise influence of serotonin on sleep and mood varies according to brain region, receptor subtype, and circadian phase, underscoring the need for a nuanced understanding of serotonergic regulation rather than simplistic models of global serotonin “deficiency.”

The neuroanatomical architecture of these pathways is summarized in Figure 1, illustrating serotonergic projections to sleep and mood regulatory centers and highlighting the receptor subtypes mediating these effects.

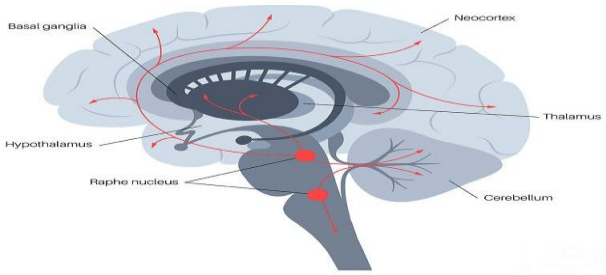

Figure 1: Serotonergic pathways originating from the raphe nuclei project to key regions regulating sleep and mood, including the hypothalamus, thalamus, and limbic cortex. Receptor subtypes (5-HT1A, 5-

HT2A/2C, and 5-HT7)mediate sleep-wake and emotional processes.

2.2 Receptor Mechanisms and Functional Roles

Serotonin mediates its diverse physiological effects through a complex family of 14 receptor subtypes, broadly clas- sified into seven families (5-HT_1 to 5-HT_7) (Nichols & Nichols, 2008). Among these, the 5-HT_1A, 5-HT_2A/2C, and 5-HT_7 receptors play particularly important roles in regulating sleep and mood states.

5-HT_1A Receptors

The 5-HT_1A receptor, expressed abundantly in the prefrontal cortex, hippocampus, and amygdala, functions both as an autoreceptor in the raphe nuclei and as a postsynaptic receptor in limbic circuits (Savitz et al., 2009). Ac- tivation of 5-HT_1A receptors inhibits serotonergic firing and dampens neural excitability, stabilizing mood and facilitating non-REM sleep through cortical inhibition (Monti, 2011). Reduced 5-HT_1A sensitivity in depression is associated with emotional dysregulation and impaired sleep onset (Cowen & Browning, 2015).

5-HT_2A and 5-HT_2C Receptors

The 5-HT_2A and 5-HT_2C receptors are primarily involved in arousal regulation and REM sleep modulation. Ac- tivation of these receptors increases cortical excitability, promotes sensory processing, and suppresses slow-wave sleep (SWS) (Millan, 2006). Dysregulation of 5-HT_2A activity has been implicated in hyperarousal and premature REM sleep onset in depression (Steiger, 2007). In particular, while some studies emphasize the 5-HT2A antagonist in stabilizing sleep, other mixed results report on its role in REM regulation, further clarification requirements (Carhart-Harris & Nutt, 2017) suggest.

5-HT_7 Receptors

The high-expression 5-HT_7 receptor in the Thalamus and Hypothalamus plays an important role in the 5-HT_7 receptor, sarcadica rhythm and sleep road crossing (headed, 2009). Activation of 5-HT_7 receptors promotes synchronism of practical conditions with environmental light signals, supports sleep initiation and daily vigilance (Oicomono et al., 2019). However, recent evidence (Dolish et al., 2024) suggests interindividual variability in 5-by 7-madhya Pradesh 24-hour regulation, and postpone this receptor as a possible therapeutic target, but a complex, one with reference-dependent effects.

Integrative Receptor Dynamics

These receptor systems work instead of insulation.During the daytime, serotonergic activation of 5-HT_1A and 5-HT_7 receptors supports wakefulness and emotional resilience. At night, reduced serotonergic tone allows for sleep initiation, while 5-HT_2A/2C activity modulates REM transitions. Disruption of this receptor network in depression leads to a loss of physiological balance, producing unstable mood, fragmented sleep, and circadian misalignment.

Critically, the functional roles of these receptors are modulated by circadian phase, stress exposure, and pharma- cological intervention. SSRIs, for example, globally increase serotonin availability but may produce mixed effects on sleep depending on receptor-specific actions (Wilson & Argyropoulos, 2005).

3 Circadian Dynamics of Serotonin Activity

Serotonin's influence on behavioral states is not static; rather, it fluctuates across the 24-hour day according to circadian rhythms. These rhythms align behavioral states,wakefulness, sleep, and mood,with environmental light-dark cycles, ensuring physiological coherence across neural systems. The suprachiasmatic nucleus (SCN) of the hypothalamus functions as the body's master circadian pacemaker and plays a pivotal role in modulating serotonergic activity (Saper et al., 2005).

In healthy individuals, serotonin levels demonstrate a robust circadian oscillation. During daylight hours, seroton- ergic tone increases, supporting wakefulness, cognitive flexibility, and emotional stability. This elevation facilitates prefrontal control over limbic circuits, enhancing emotional resilience and attentional stability (McClung, 2013). As evening approaches, serotonin levels decline, reducing cortical excitability and permitting the initiation of non- REM sleep, followed by the transition to REM sleep later in the night (Monti, 2011).

This rhythmic serotonergic modulation does not operate in isolation. It interacts with melatonin secretion from the pineal gland, cortisol rhythms, and environmental cues such as light exposure and social

interaction. Together, these factors align behavioral rhythms with the external environment, maintaining homeostasis.

3.1 Circadian Flattening in Depression

In contrast, individuals with depression exhibit a profound flattening of this serotonergic rhythm (Meyer et al., 2004). Daytime serotonin levels are insufficient to sustain mood and cognitive stability, while nighttime declines are inadequate to properly initiate and maintain restorative sleep (Riemann et al., 2017). The consequences are evident in clinical polysomnography:

- Delayed sleep onset,
- Reduced slow-wave sleep,
- Shortened REM latency,
- Increased sleep fragmentation.

This flattening of serotonergic rhythms contributes to daytime mood lability and nighttime sleep instability, cre- ating a bidirectional disruption of circadian alignment. Moreover, depressive individuals often experience social rhythm disruption (irregular meal times, inconsistent sleep-wake schedules) and reduced light exposure,factors that further impair circadian entrainment (Dollish et al., 2024).

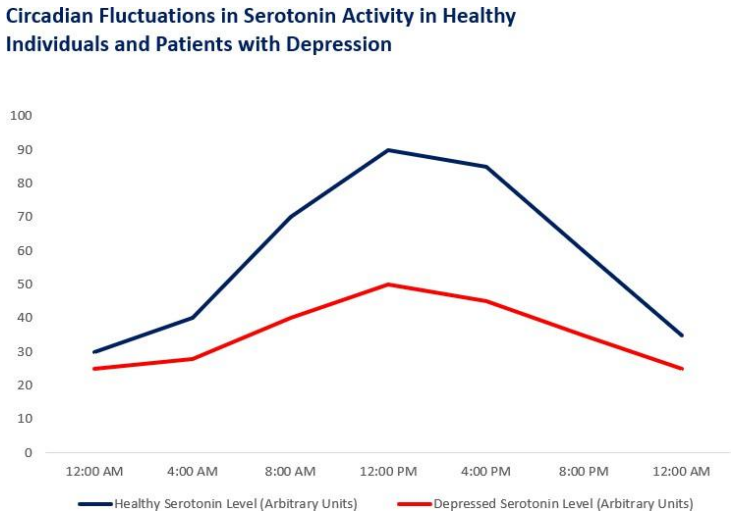

Figure 2: Circadian serotonin activity in healthy and depressed individuals. Healthy physiology shows distinct daily peaks and nighttime declines, while depression flattens these rhythms, disrupting sleep-wake cycles and mood stability. Data synthesized from Gaspar et al. (2003), Meyer et al. (2004), and Mistlberger & Skene (2011).

3.2 Complex Role of the 5-HT_7 Receptor in Circadian Alignment

The 5-HT_7 receptor plays a particularly critical role in mediating serotonin's circadian effects (Hedlund, 2009). Experimental models show that 5-HT_7 activation promotes sleep-wake transitions and stabilizes phase alignment with environmental cues. Recent human neuroimaging and genetic studies (Oikonomou et al., 2019; Dollish et al., 2024) suggest that inter-individual differences in 5-HT_7 receptor sensitivity may explain why some patients with depression show more severe circadian disruption than others.

These findings challenge older models that viewed circadian rhythm abnormalities in depression as purely down- stream consequences of mood symptoms. Instead, they suggest that serotonin receptor dysregulation,particularly involving 5-HT_7,may drive both mood instability and circadian misalignment.

3.3 Environmental and Epigenetic Influences

Environmental factors also modulate circadian serotonin rhythms. Reduced daylight exposure, a common feature of modern indoor lifestyles, dampens serotonin synthesis via decreased SCN stimulation (Mistlberger & Skene, 2011). Chronic stress, social isolation and irregular social rhythm further reduce serotonorgic 24 -hour regulation (Ciarlegio et al., 2011). Emerging evidence from epigezenatic studies suggests that sarcadician gene expression in serotonergic neurons are sensitive to environmental and development signals (Fernstrom, 2016; Calabury et al., 2009), which highlights an epigenetic vulnerability in depression.Summary: Contrasting Rhythms in Health and Depression

These contrasting serotonergic patterns are summarized in Figure 2, illustrating the distinct circadian profiles of healthy individuals and those with depression. In health, serotonin shows sharp daytime peaks and nighttime declines, aligning behavioral states with environmental cycles. In depression, these rhythms are flattened and willing, which contributes to simultaneous losses in sleep-chase regulation and mood stability.

4 Comparative Physiological Patterns in Health and Depression

Understanding physical distinctions between healthy and depressed individuals requires an integrated approach to how serotonin controls both sleep architecture and mood regulation. Instead of looking at sleep and mood in parallel, but as separate domains, this analysis affects them as mutually dependent physiological systems, which are coordinated by serotonorgic rhythm. The following segments examine these comparative patterns during sleep, emotional regulation and their integrated synchronization.

4.1 Sleep Architecture

Healthy Sleep Patterns

In healthy individuals, sleep follows a predictable architecture, cycling through non-rapid eye movement (non- REM) and rapid eye movement (REM) stages. Serotonin plays a crucial role in stabilizing these cycles:

- During non-REM sleep, serotonin promotes cortical inhibition and sensory disengagement, facilitating phys- ical restoration and memory consolidation.
- Toward REM onset, serotonergic tone declines, allowing for cholinergic activation and REM sleep induction (Monti, 2011).
- These dynamic transitions minimize awakenings, ensuring sleep continuity and restorative function.

Healthy sleep architecture is characterized by:

- Adequate slow-wave sleep (SWS) in early night phases.
- Delayed but stable REM onset.
- Smooth transitions between sleep stages.

Sleep in Depression

In contrast, depressive physiology presents a fragmented sleep structure. Polysomnographic studies consistently report:

- Reduced slow-wave sleep, reflecting impaired serotonergic-mediated cortical inhibition.
- Shortened REM latency, where REM sleep begins prematurely, reflecting serotonergic-cholinergic imbal- ance (Steiger, 2007).
- Increased REM density and sleep fragmentation, disrupting restorative sleep cycles (Riemann et al., 2017).

These abnormalities stem from the blunted serotonin rhythms and receptor dysfunction described earlier. The result is non-restorative sleep, contributing to the fatigue, irritability, and cognitive slowing often observed in depression.

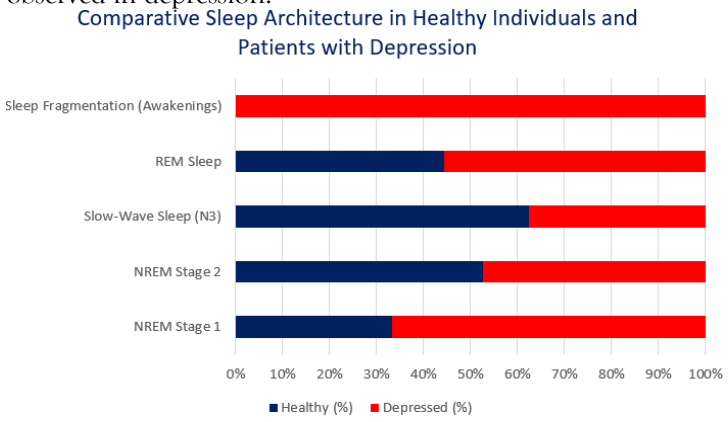

Figure 3: Comparative sleep architecture in health and depression. Depression is characterized by reduced slow-wave sleep, increased REM sleep, and greater sleep fragmentation compared to stable sleep stages in

healthy individuals. Adapted from Riemann et al. (2017) and Steiger (2007).

4.2 Mood Regulation

Emotional Stability in Health

In healthy physiology, serotonin modulates emotional reactivity by regulating prefrontal-limbic interactions:

- Prefrontal cortex projections maintain top-down control over the amygdala and hippocampus, dampening excessive emotional responses.
- 5-HT_1A receptor activation promotes emotional resilience, reduces anxiety, and stabilizes affective tone throughout the waking day (Savitz et al., 2009).
- Serotonergic tone during daytime supports cognitive flexibility and adaptive coping with stressors, while nocturnal declines allow for emotional processing during REM sleep.

Mood Instability in Depression

Depression disrupts this regulatory system:

- Serotonergic transmission in prefrontal-limbic pathways is reduced.
- 5-HT_1A receptor desensitization weakens inhibitory control over limbic circuits, resulting in heightened emotional reactivity (Cowen & Browning, 2015).
- Circadian serotonin modulation is flattened, leading to mood instability that lacks the rhythmic stabilizing influence seen in healthy individuals (Meyer et al., 2004).

This breakdown manifests clinically as persistent negative mood, impaired stress coping, and emotional lability. Importantly, these mood disturbances are bidirectionally linked to sleep dysfunction: poor sleep further destabilizes mood regulation, while emotional instability impairs sleep initiation and continuity.

4.3 Integrative Physiological Model

The physiological evidence from both sleep and mood domains highlights serotonin as a unifying synchronizer, coordinating these behavioral states across circadian cycles. In health, serotonergic systems maintain:

- Stable sleep-wake transitions.
- Balanced emotional responses.
- Circadian alignment with environmental signals.This coordination is the result of serotonorous tone, receptor -specific activity and dynamic modulation of nervous network control. In this context, serotonin is not only a neurotransmitter, but a physical integrator, which ensures consistency between behavioral states.

Depression as Desynchronization

In contrast, depression fails in the serotonergic synchronization:

- Blunted serotonin rhythms disrupt both sleep and mood regulation.
- The receptor Dysfunction Destabilizes nerve stimulation in sleep stays and emotional cycle.
- Circadian misleading improves this relaxation and causes a self -righteous cycle of physical desynchronization.

This perspective makes the original Serotonergic Synchronization Failure Model, which concepts them as a disorders of physical decryonization instead of different neurotransmitters deficiency or neuro -raplastyity loss. According to this model, the disorders of sleep and mood are not parallel symptoms, but there are mutually associated manifestations of impaired serotonurgic regulation.

This conceptual structure produces the area by integrating the integrated explanation of receptor pharmacology, 24 -hour physiology and neural cycles in the integrated explanation of depressed pathology. This suggests that effective treatment should restore serotonorgic texture in both domains, not just mood or sleep symptoms isolated. Physical evidence from both sleep and mood regulation exposes serotonin as an integrated renovation that maintains behavioral interaction in daily rhythm. Instead of acting as different routes, Serotonorgian circuit sarcadians coordinate these processes through the shared mechanisms of receptor-media-rich modulation and nervous network regulation.

In healthy people, in this coordination:

- Stantic Sleep-wake transitions, non-strap start with serotonin and the system of REM sleep progression

at the right time;
- Balanced emotional response, where serotonargic tone controls the interaction between cortical and limbic areas;
- Circadian alignment and ensures that these processes follow environmental signs for optimal physical performance.

These dynamic interactions reflect the role of the serotonin as a physiological synchroniser, not just a neurotransmitter for isolated systems.
In contrast, depression represents the breach of this interaction. The reenal serotonin rhythm, decreased receptor signaling and interrupted neurocutorically led to simultaneous disturbances in sleep and mood. This dysfunction produces fragmented sleep, remodeled RAM delays, low-wave sleep and mood labels, all arising from a regular failure in all serotonurgic modulation (Mayor et al., 2004; Stegar, 2007).
This conceptual structure, described as the best serotonargic synchronization failure model, suggests that the de-sensor is a basic disruption of physical will. Instead of looking at insomnia and mood volatility in the form of parallel symptoms, this model affects them as mutual consequences of disturbed serotonin medieval regulation.
Understanding depression through these integrated lenses reveals the importance of restoring Serotonorgic Sin-Cron to restore both sleep and mood stability. This symptom changes the targets of treatment from specific relief to broader physical reality.
Therapeutic Implications
Serotonargic synchronization failure models Depression as a disorder of dysincronized physiology-cala-rhythm, rather than just a neurotransmitter deficiency. From this point of view, remedies should not only aim to increase the availability of serotonin, but to restore their rhythmic modulation in sleep and mood control systems. This calls for integrative therapeutic strategies that address:
Neurotransmitter dynamics, Circadian alignment, Receptor-specific function,
Behavioral rhythm stabilization.

4.4 Pharmacological Interventions

Current Treatments: SSRIs and Their Limitations

Selective serotonin reuptake inhibitors (SSRIs) remain the cornerstone of depression treatment, enhancing synaptic serotonin availability. While SSRIs improve mood symptoms in many patients, their effects on sleep are variable and often problematic:
- Some patients experience insomnia or REM sleep disturbances, particularly during the early phases of treat- ment (Wilson Argyropoulos, 2005).
- SSRIs increase global serotonin levels without addressing the receptor-specific roles of 5-HT_1A, 5-HT_2A/2C, and 5-HT_7 in sleep-wake regulation and circadian alignment.

This mismatch between serotonin enhancement and receptor-specific physiological roles explains why mood may improve while sleep remains fragmented, or vice versa.

Receptor-Targeted Therapies

Emerging pharmacological approaches offer greater specificity:
- 5-HT_1A receptor agonists (e.g., buspirone) promote non-REM sleep and reduce anxiety by enhancing cor- tical inhibition (Savitz et al., 2009).
- 5-HT_2A/2C receptor antagonists stabilize REM sleep and reduce cortical hyperarousal, potentially improv- ing both sleep architecture and emotional reactivity (Millan, 2006).
- 5-HT_7 receptor modulators, though still experimental, show promise in restoring circadian synchronization and stabilizing sleep-wake transitions (Hedlund, 2009; Oikonomou et al., 2019).

Future pharmacotherapy should move beyond boosting serotonin levels indiscriminately, toward modulating receptor- specific circuits to reestablish physiological synchrony.

Novel Pharmacological Directions

Recent studies (Dollish et al., 2024) also suggest the potential of melatonin receptor agonists, serotonergic psychedelics (e.g., psilocybin), and other neuromodulators that influence both serotonin and circadian

rhythms. While experi- mental, these approaches highlight the potential of targeting system-level synchrony rather than individual symp- toms.

Selective serotonin reuptake inhibitors (SSRIs) are the cornerstone of depression treatment, enhancing synaptic serotonin availability. However, while SSRIs improve mood symptoms, their effects on sleep are variable. Some patients experience insomnia or REM sleep disruption during early treatment phases, reflecting serotonin's com- plex role in sleep-wake regulation (Wilson & Argyropoulos, 2005).

Receptor-specific therapies offer a more targeted approach. 5-HT_1A receptor agonists reduce anxiety and promote non-REM sleep by enhancing cortical inhibition (Savitz et al., 2009). 5-HT_2A/2C receptor antagonists help stabilize REM sleep and reduce cortical hyperarousal, while emerging interest in 5-HT_7 receptor modulators points to potential benefits in restoring circadian alignment (Hedlund, 2009). Future pharmacological strategies should prioritize balancing serotonin's role across both sleep and mood domains, rather than enhancing global serotonergic tone alone.

4.5 Chronotherapeutic and Behavioral Interventions

Pharmacotherapy alone is insufficient to restore physiological synchrony, particularly when environmental and behavioral rhythms remain disrupted.

Chronotherapeutic Interventions

- Bright light therapy realigns the circadian system by enhancing SCN stimulation and increasing daytime serotonin synthesis (McClung, 2013).
- Social rhythm therapy stabilizes daily routines (e.g., wake times, meal schedules), reducing circadian mis- alignment.
- Controlled sleep phase shifting adjusts the sleep-wake schedule to synchronize internal rhythms with exter- nal light cycles.

These interventions directly influence the serotonergic-circadian axis, supporting improvements in both mood and sleep regulation.

Behavioral Interventions

Behavioral approaches remain critical adjuncts:

- Cognitive Behavioral Therapy for Insomnia (CBT-I) improves sleep continuity and reduces hyperarousal, indirectly stabilizing serotonergic rhythms (Baglioni et al., 2010).
- Mindfulness-based therapies may attenuate limbic hyperactivity, reducing emotional volatility and support- ing mood stability.
- Structured exercise programs have been shown to enhance circadian entrainment and increase serotonin synthesis (Young, 2007).

Together, these strategies target not only neurotransmission but also behavioral rhythms, helping to restore the synchrony between environmental cycles, sleep architecture, and mood regulation.

4.6 Toward Integrative Treatment Models

The complexity of serotonergic dysfunction in depression calls for multimodal treatment models:

- Pharmacological approaches targeting receptor-specific dysfunction,
- Chronotherapeutic strategies re-aligning circadian rhythms,
- Behavioral interventions stabilizing lifestyle factors.

Personalized treatment,tailored to individual circadian phenotypes, receptor sensitivity profiles, and environmen- tal exposures,may optimize outcomes. For example, an evening chronotype patient with 5-HT_7 receptor dys- function may benefit more from morning light therapy and 5-HT_7 agonists, whereas a stress-induced depressive state may respond to 5-HT_1A targeting and CBT-I.

Future research should explore combined interventions, such as pairing 5-HT_7 receptor modulators with light therapy, to synergistically restore serotonergic and circadian coherence.

5 DISCUSSION

This comparative physiological analysis reinforces the view that serotonin plays a central synchronizing role, coordinating sleep-wake architecture and emotional regulation. Unlike earlier models that

considered serotonin's influence on mood and sleep as parallel but independent, this review positions serotonin as a dynamic integrator, modulating both systems through receptor-specific actions, circadian rhythms, and neural circuitry interactions.

5.1 Reframing Depression as Desynchronization

The proposed Serotonergic Synchronization Failure Model reframes depression as a disorder of physiological desynchronization. Instead of interpreting sleep disturbances and mood instability as separate symptoms, this model conceptualizes them as interdependent manifestations of disrupted serotonergic rhythms. Flattened sero- tonin oscillations, impaired receptor sensitivity, and dysfunctional neural circuits lead to fragmented sleep and emotional dysregulation, perpetuating a cycle of physiological instability.

This model advances beyond prior frameworks:

- The monoamine hypothesis emphasized serotonin deficits but did not integrate circadian or receptor-specific physiology (Blier & El Mansari, 2013).
- Neuroplasticity models focused on synaptic remodeling without addressing rhythmic modulation (Duman, 2014).
- Recent circadian models highlighted light entrainment but overlooked receptor-level serotonergic dynamics (McClung, 2013; Dollish et al., 2024).

By integrating these domains, the Serotonergic Synchronization Failure Model offers a more comprehensive un- derstanding of how depression emerges from the breakdown of biological coherence.

5.2 Clinical Implications

This integrative perspective suggests that treating either sleep or mood in isolation is unlikely to fully restore physiological stability. While SSRIs and cognitive therapies improve mood symptoms, they often leave circadian misalignment and sleep fragmentation unresolved. Conversely, sleep-focused therapies (e.g., CBT-I) may improve sleep continuity without correcting underlying mood instability.

Effective treatment likely requires a multimodal approach:

- Pharmacological agents that balance receptor-specific serotonergic modulation,
- Chronotherapeutic interventions (e.g., light therapy) that realign circadian rhythms,
- Behavioral therapies that stabilize daily routines and reduce environmental stressors.

Personalized treatment approaches, considering individual differences in circadian phenotype, receptor sensitivity, and environmental exposures, may optimize outcomes.

5.3 Limitations of Current Evidence

Despite the conceptual advances proposed, several limitations must be acknowledged:

- Much of the physiological evidence is derived from animal studies, and direct measures of serotonergic circadian dynamics in humans remain limited (Oikonomou et al., 2019).
- Inter-individual differences, such as genetic polymorphisms (e.g., 5-HTTLPR variants) and receptor expres- sion profiles, complicate generalizations.
- Environmental influences, such as light exposure, stress, and social rhythms, interact in complex ways with serotonergic function but are often poorly controlled in clinical studies.
- The causal direction between serotonergic dysregulation and depressive symptoms remains debated: whether serotonin rhythm disruption precedes depression or results from it is not fully resolved.

5.4 Future Research Directions

Addressing these gaps will require multimodal longitudinal studies combining:

- MNeuroimaging of serotonergic circuits (e.g., PET imaging of serotonin transporter dynamics),
- Polysomnographic sleep assessments across circadian phases,
- Actigraphy and melatonin profiling to map circadian alignment,
- Genetic and epigenetic profiling of serotonergic pathways,
- Studies of environmental modulators such as light therapy, social rhythms, and stress exposure.

Particularly, future work should examine whether restoring serotonergic rhythms via targeted pharmacological or chronotherapeutic interventions can normalize both sleep and mood parameters.

5.5 Broader Implications

Beyond depression, the Serotonergic Synchronization Failure Model may apply to other disorders marked by serotonergic and circadian dysfunction:

- Bipolar disorder, characterized by circadian and mood instability (Harvey, 2008),
- Generalized anxiety disorder, which shows serotonergic dysregulation and sleep disturbances,
- Neurodegenerative diseases (e.g., Parkinson's disease), where sleep and mood disruption are early symptoms of serotonergic degeneration.
- Genetic and epigenetic profiling of serotonergic pathways,
- Studies of environmental modulators such as light therapy, social rhythms, and stress exposure.

Exploring serotonin's synchronizing role across these conditions could broaden the model's clinical relevance and support integrative treatment paradigms.

6 CONCLUSION

Serotonin is not merely a neurotransmitter influencing mood and sleep in parallel; it is a central synchronizer of physiological rhythms, aligning behavioral states with environmental and circadian cues. In healthy individuals, serotonergic activity follows a robust daily cycle that supports emotional resilience during wakefulness and facil- itates restorative sleep during the night. This synchronization ensures optimal cognitive and affective functioning across the 24-hour cycle.

In depression, this integrative role is disrupted. Blunted serotonin rhythms, impaired receptor signaling, and desyn- chronized neural circuits lead to parallel disturbances in sleep architecture and emotional regulation. Clinically, these disruptions manifest as fragmented sleep, altered REM dynamics, and mood instability,symptoms that reflect a common breakdown in serotonergic homeostasis, rather than isolated dysfunctions.

Synthesizing evidence from neuroanatomy, receptor pharmacology, circadian physiology, and clinical studies, this review proposes the Serotonergic Synchronization Failure Model, reframing depression as a disorder of physio- logical desynchronization. This framework highlights the importance of restoring serotonergic rhythmicity and coherence across sleep and mood systems, rather than addressing each symptom domain in isolation.

Therapeutic strategies should therefore move beyond increasing global serotonin availability. Instead, they must balance receptor-specific modulation, promote circadian alignment, and stabilize behavioral rhythms. Pharmaco- logical therapies, chronotherapeutic interventions, and behavioral strategies must work synergistically to restore the coherence of serotonergic regulation across domains.

Future research should continue to clarify serotonin's synchronizing role across behavioral states and develop integrative treatments that target this physiological function. Longitudinal, multimodal studies combining neu-
roimaging, sleep assessment, and circadian profiling will be essential to validate the Serotonergic Synchronization Failure Model and guide the development of personalized therapies.

Ultimately, addressing serotonergic desynchronization holistically may lead to more effective and lasting solutions for depression and potentially for other disorders characterized by sleep-mood-circadian dysregulation.

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