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Review Article

Harnessing Melatonergic Agonists and Antagonists: A Dual Approach to Alleviating Depression and Depression-associated Insomnia

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ABSTRACT

Depression exists in different aspects, involving Major Depressive Disorder (MDD) and bipolar disorder, each identified by neurobiological manifestations that affect both therapeutic approaches and prognostic conclusions. The etiology of this mental disorder is composite, encompassing genetic predispositions, environmental processes, psychological factors, and behavioral models. Sleep disturbances, especially insomnia, are the frequent symptoms of depression. This state is usually investigated by the scale of Hamilton Depression Rating. Polysomnographic studies have detected variations in both types of sleep; slow-wave and rapid eye movement among people suffering from depression, which has grabbed attention in circadian rhythm-based curative interventions. Melatonin, a hormone closely linked to circadian rhythms, is synthesized from tryptophan via the serotonin pathway and regulated by the suprachiasmatic nucleus. Additionally, it influences the expression of clock genes by directly inhibiting proteasome activity. Exogenous administration of melatonin has been revealed to proceed or reset circadian phases, making it a candidate for treating sleep disorders and reducing insomnia linked with depression. This article aimed to examine the preclinical and therapeutic impacts of agonists of melatonin receptors, like agomelatine and ramelteon, on depression. The detected reduction in melatonin production in patients with depression underscores the potential relevance of these treatments. Clinical studies have shown the antidepressant effects of melatonin, with affirmation from both animal models and human MDD patients. Despite that, the complex role of melatonin in depression needs further investigation. In addition, melatonin interacts with the neurotransmitters norepinephrine and serotonin, affecting norepinephrine accessibility. Studies have shown that melatonin can inhibit norepinephrine release. Appealingly, high melatonin levels manifested in some patients with depression have led to the exploration of melatonin abatement strategies, including the use of antagonists such as Luzindole, 4-phenyl-2-propionamidotetraline, and 4-phenyl-2-acetamidotetraline, which may hold potential as novel antidepressants.

Keywords: *Depression; Insomnia; Circadian Rhythm; Melatonin; Hypersomnia; Sleep architecture.*

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1. Introduction

Depression is a significant medical disorder that influences humans mentally and functionally **[1]**. There are several types of depression, mainly major depressive disorder (MDD) and bipolar depression (BD). MDD is the most frequent type of primary mood disorder, and its depressive episodes can be single or recurrent; however, they frequently occur as discrete episodes with distinct remission periods. Depression is categorized into three levels-mild, moderate, and severe-based on the number and intensity of

symptoms, as well as their impact on occupational functioning. Patients with BD experience symptoms for longer periods, showing swinging moods between depression and mania **[3]**. The etiology of depression is unknown. Different factors may be included, like biological variations, brain chemistry, hormonal factors, and inherited characters. People with depression show physical changes in their brains. The overall effects, which have been accurately termed "neuroprogression," include loss of personal independence, decline in autonomy, and role-functioning impairment. Because of the disruption of the homeostatic balance brought on by elevated "allostatic load," this load's phases of mood disturbances are characterized by remarkable challenges, with gradual harm to different systems of the body **[3]**. Recent studies manifested those alterations in the function and influence of these neurotransmitters, especially serotonin and norepinephrine, and their interactions with neurocircuits linked with maintaining mood stability may show a noticeable position in the pathogenesis of depression, as well as depression treatment **[2]**.

Unipolar depression is called so due to consistently low levels of serotonin, and norepinephrine, dopamine deficiency may be involved as well. MDD can thus be managed by antidepressants. On the other hand, BD is specified by swinging between high and low levels of the mentioned neurotransmitters, and it can be managed by mood stabilizers. In contrast, there is a lack of knowledge on the neurobiology of mood disorders, and current therapies are more palliative than curative **[3]**.

An estimated 3.8% of the global population has depression, with 5% of adults affected (4% between men and 6% between women), and this rises to 5.7% for those over 60. Around 280 million people worldwide suffer from depression **[4]**. It is impressively about 50% more prevalent in women than in men, and over 10% of pregnant women and new mothers also experience depressive symptoms **[5]**. Annually, more than 700,000 people commit suicide, making it the fourth main trigger of death among 15 to 29-year-olds. Despite the availability of effective treatments for mental disorders, more than 75% of individuals in low- and middle-income countries do not receive care **[6]**. Key barriers to effective treatment include insufficient investment in mental health services, a shortage of trained healthcare professionals, and the social stigma bordering on mental health issues.

2. Depression-associated Symptoms

Unipolar depression (MDD) symptoms can be classified, according to their severity, as mild or severe. These include persistent feelings of sadness, anhedonia, insomnia (most common) or hypersomnia, increased fatigue, suicidal thoughts, low self-esteem, cognitive impairment such as difficulty thinking, concentrating, indecisiveness, weight loss or gain unconnected to dieting, increase in meaningless physical activity (such as handwringing), and psychomotor retardation **[1, 2]**. To diagnose a depression case, the person should have not less than five of these symptoms persistent every day for more than two weeks, along with decreased social or occupational functioning, and symptoms unrelated to other medical cases (stroke, Parkinson's disease, thyroid problems, Alzheimer's disease, brain tumor, drug abuse, or vitamin deficiency) that can imitate symptoms of depression. Symptoms of depression may differ among persons. Patients may manifest their mood changes in the form of biological symptoms, such as chronic pain, fatigue, loss of libido, disturbed sleep, and appetite. However, these physical symptoms are validated as depressive symptoms only after the exclusion of any related medical conditions or drug therapy **[1]**. Symptoms vary according to age. Although depression may

happen only once in a person's lifetime, some people typically experience recurring episodes. During these episodes, a person experiences significant difficulty in personal, social, educational, occupational, and/or other crucial areas of functioning **[1, 7-8]** (**Fig. 1**).

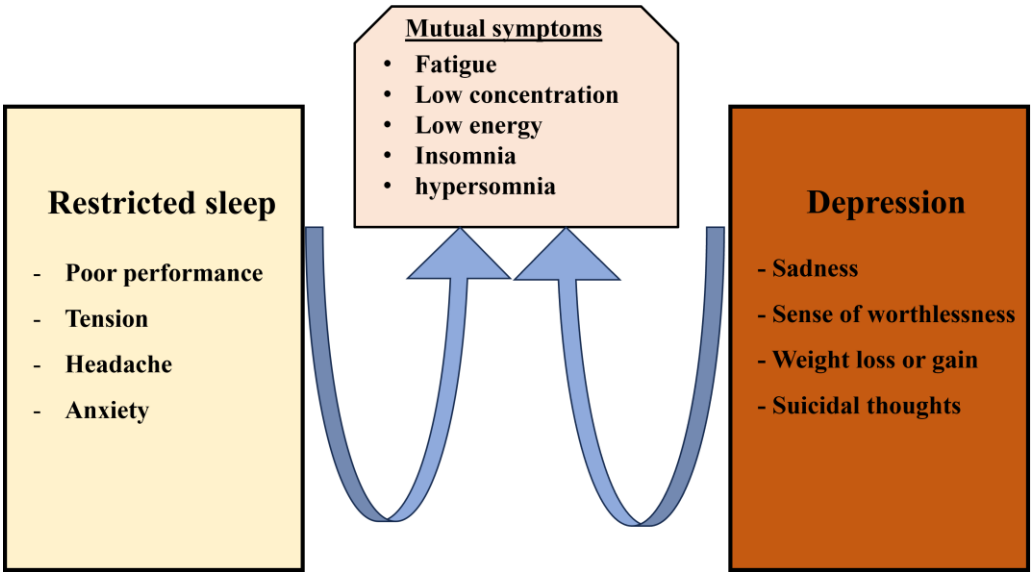

Fig. 1. Symptoms of restricted sleep, depression symptoms, and mutual symptoms between them (Gradisar et al., 2022).

3. Assessment of depression

Major depression is identified by the Diagnostic and Statistical Manual of Mental Disorders (DSM) as the presence of five or more depressive symptoms over two weeks, as determined by a primary healthcare provider. Patients who appear to be symptomatic but do not meet the criteria may have sub-syndromal depression, such as minor depression or dysthymic disorder **[10]**.

Multiple scoring systems have been established specifically to determine the severity of depression, such as the Beck Depression Inventory (BDI), which is more commonly used in the USA, and the Hamilton Depression Rating Scale (HDRS), being more reliably used due to frequent updating. Scoring systems are important as they reflect the patient's status before, during, and after treatment **[11]**.

Regarding the diagnostic aspects of major depressive episodes (MDE), current nosological classifications do not distinguish between these disorders. However, the prevailing theory suggests that MDD and BD have distinct neurobiological differences, which carry important therapeutic and prognostic implications **[3, 10]**. In light of that fact, HDRS is one of the commonly used clinician-administered depression assessment scales. HDRS17 consists of 17 items concerning symptoms of depression indicated over the previous week. It involves a multi-item questionnaire designed to assess depression. Various versions of the questionnaire differ in length, including HDRS8, HDRS17, HDRS21, HDRS24, HDRS29, HDRS6, and HDRS7 **[12]**.

HDRS focuses on depressed mood, guilt sentiments, suicidal thoughts, somatic anxiety, work and activities, genital symptoms, hypochondriasis, retardation, weight loss, patient insights, and insomnia. There are several versions

with varying lengths including the HDRS17, HDRS21, HDRS29, HDRS8, HDRS6, HDRS24, and HDRS7 **[12]**. According to The National Institute for Health & Clinical Excellence, levels of depression have been established about the 17-item HRDS. Scores of 0-7 are acknowledged to be within the normal range, the scores of 8-13 indicate mild depression, while 14-18 hint at a moderate state. Scores within 19-22 and >23 points to a severe and very severe melancholy **[12]**. HDRS has been questioned by a few associations for its therapeutic use since it emphasizes insomnia above hopelessness, self-destructive thoughts, and suicidal cognitions and behaviors **[12]**.

Consequently, depression is distinct from bereavement. Since various elements, including biological and psychosocial changes, are taken into consideration, the triggers of depression are not yet fully covered. The most typical form of depressive disorder is MDD, and it frequently comes with insomnia. To diagnose MDD or BD, the clinician-administered assessment scale HDRS is frequently employed, and nowadays treatments are more palliative rather than curative.

4. Pathophysiology of depression

It has been difficult to explore the exact pathophysiology of depression because of the clinical and etiological diversity of depressive disorder.

4.1. Genetic factors

Studies provide solid proof that MDD is a familial condition and that genetic factors are primarily involved. The mentioned studies point out that the impact of genetic factors is about 30-40%, having the non-genetic factors involving 60-70%. These results suggest that psychotherapy can be very beneficial in the prevention of MDD. Genome-wide association studies have demonstrated the involvement of numerous small-effect genes in complicated psychological disorders, which makes it more challenging to identify these genes. Yet, there have been ongoing studies on the potential risk genes; for example, it has been proposed that the etiology of depression involves an interaction between a unique genetic variant in the promoter area of the serotonin transporter and stress conditions. Despite the limited success of genetic studies on depression, a patient's family history remains the most reliable source of information for uncovering the genetic risks associated with MDD **[13]**.

4.2. Effect of cytokines on stress hormones

The role of the hypothalamic-pituitary-adrenal (HPA) axis in the pathogenesis of MDD remains a topic of debate. This axis is regulated by two receptor systems: mineralocorticoid (MR) and glucocorticoid (GR) receptors. In response to stress perceived by the cortical region, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the adrenal glands to secrete cortisol into the bloodstream. It is known that physiological stress response varies by gender: females show higher responsiveness to stress than males, which is in line with women experiencing major depression at a higher rate. Although there is no sufficient evidence that depressed subjects suffer from a dysfunction in the HPA axis, some do show abnormalities in that axis with altered stress hormone secretion but only in certain types of depression. The epigenetic maintenance of GR receptors has been linked with childhood trauma, leading to an imbalance in the MR/GR ratio in stress-linked situations. The impact of environmental programming on gene expression is a likely mechanism connecting early life stress to dysregulation of the HPA axis and increased susceptibility to MDD in adulthood. Clinical evidence further indicates that cytokines may play a role in the pathophysiology of a subset of

depressive patients, particularly those with coexisting physical health conditions. Around 30% of recombinant interferon recipients report depression as a side effect. Animals experience similar effects to antidepressants when pro-inflammatory cytokine-mediated signaling is blocked. The utilization of certain psychotherapies in treating depressed individuals with early life trauma is suggested by the connection between childhood trauma and a continuously changed physiological stress system, with the most compelling evidence for the involvement of serotonin- 1A receptor, which controls serotonin activity. Multiple brain regions of people with MDD have reduced availability of the receptor **[13]**.

The pathophysiology of MDD is thought to involve disruptions in the central noradrenergic system. Evidence for this includes findings of reduced norepinephrine metabolism, heightened tyrosine hydroxylase activity, and a lower expression of norepinephrine transporters in the locus coeruleus among individuals with depression. Additionally, post-mortem studies of depressed suicide victims revealed an increased density of alpha-2 adrenergic receptors alongside a reduced density of alpha-1 adrenergic receptors **[13-15]**.

4.3. Mediating role of monoamines

Norepinephrine, dopamine, and serotonergic receptors are in the brainstem and midbrain, projecting to different brain regions. The anatomical examination of the brain explains the involvement of these neurotransmitters in controlling different mental activities, such as mood, appetite, attention, sleep, cognition, and reward processing. This explains how any compound that increases the levels of these neurotransmitters successfully acts as an antidepressant. These observations contributed to the development of the pharmacological depression theory, known as the monoamine-deficiency hypothesis. Serotonin has been the most extensively studied neurotransmitter in depression, largely due to the common depletion of tryptophan, which reduces serotonin synthesis and results in symptoms similar to those of depression. Additionally, there is proof that serotonin receptor defects are linked to depression **[13]**.

While serotonin and norepinephrine were the primary focus of the conventional ideas of the neurobiology of depression, dopamine is now receiving more attention. In placebo-controlled investigations of MDD, dopamine reuptake inhibitors and dopamine receptor agonists, such as nomifensine and pramipexole-respectively-, demonstrated antidepressant effects. Depression was consistently associated with decreased levels of dopamine metabolites in the cerebrospinal fluid and jugular vein plasma, referring to slowed dopamine turnover. This explains why Parkinson's disease was linked to a significant depressive disorder in about 50 % of cases, since the degeneration of dopamine projections to the striatum **[13]**.

4.4. Brain-gut microbiota axis

As technology has proceeded, attention has been grabbed toward investigating the intestinal microbiome as a therapeutic goal for different illnesses. Late research brings about the gut microbiota's promising therapeutic capability in diseases like gastrointestinal cancer, type II diabetes, autistic spectrum disorder, Alzheimer's disease, and Parkinson's disease **[16-20]**. Concerning mental disorders, several studies have detected a strong relationship between mental health problems and gut microbiota, especially in depression. New investigations indicate that patients with depression generally show gut microbiota disturbances, often related to irritable bowel syndrome **[21]**. High-throughput sequencing of fecal samples from both patients having depression and healthy

candidates has manifested significant variations in the microbial constitution of those with depression **[22]**. In addition, fecal microbiota transplantation has revealed that modifying gut microbiota can either activate or alleviate depression manifestations **[23]**. This two-way interplay between the gut microbiota and the central nervous system in depression proposes that selecting the gut microbiota may be an encouraging perspective for handling depression **[23-25]**. Accordingly, the participation of gut microbes in depression therapy has become well-accepted, leading to an increasing concentration on their powerful role in carrying depression therapy.

4.5. The kynurenine pathway and effects of immune activation

An elevating body of research indicates a relation between inflammatory markers and mood variations **[26, 27]**. Notably, patients with a history of MDD often show high levels of interleukin-6 (IL-6), even when comorbidities exist[28] other inflammatory markers, like tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), may also correspond with depressive symptoms **[29]**. One probable mechanism through which these cytokines may participate in depression is the kynurenine pathway **[30-32]**. The kynurenine (KYN) pathway includes the breakdown of tryptophan into KYN metabolites, causing the formation of nicotinamide adenine dinucleotide. Tryptophan represents a precursor for serotonin. Serotonin is a pivotal regulator of mood and represents a target for many antidepressant medications. The KYN pathway accounts for 95% of TRP metabolism **[33]** and produces metabolites known as kynurenines, which have been associated with different psychiatric and neurodegenerative problems **[34, 35]**. Abnormal levels of kynurenines have been linked with MDD, as well as conditions like cancer, diabetes, cardiovascular disease, autoimmune disorders, and neurodegenerative diseases like Alzheimer's, Parkinson's disease, and amyotrophic lateral sclerosis **[34]**.

4.6. Blood-brain barrier dysfunction

MDD is linked to disturbances in the blood-brain barrier, which disturb brain homeostasis and cause negative health consequences **[36]**. Besides depression, BBB dysfunction is involved in different neurological problems, like Alzheimer's disease and Parkinson's disease **[37]**. This suggests that these conditions might have common mechanisms of BBB disruption, like neuroinflammation, or that the regulation of the BBB differs between different conditions. In the context of depression, there is growing evidence indicating disturbed BBB integrity. The functionality of endothelial cells in MDD patients can be evaluated by the relative uptake ratio of blood flow in the brachial artery following a hyperemic challenge, using dynamic nuclear imaging. A lower RUR is indicative of poorer endothelial function, and studies show that MDD patients have low RUR values **[38]**. Additionally, the serum of individuals with MDD has been detected to enhance apoptosis in endothelial cells in vitro compared to serum from non-depressed individuals **[39]**. Moreover, MDD patients show decreased levels of Claudin-5 mRNA in the nucleus accumbens **[40]** highlighting the significant bidirectional relationship between MDD and the development of vascular endothelial pathologies **[41]**.

5. Pharmacotherapy

5.1. Overview

Patients suffering from mild to moderate depression generally respond well to the initiation of antidepressant medications. Combination medication management with psychotherapy showed no short-term advantage in patients with mild and moderate levels of depression, patient preference should guide the

initial course of treatment. However, combination therapy is strongly recommended for patients having severe or chronic depression. Whatever the chosen treatment may be, follow-up is essential.

All first-class antidepressants increase the activity of serotonin, norepinephrine, and dopamine receptor activity. Symptom profiles may be beneficial in some cases to determine the appropriate class. For example, Bupropion, a dopamine reuptake inhibitor, may help obese subjects with fatigue. On the other hand, the sedating and appetite-stimulating effects of the alpha-2 receptor blocker Mirtazapine may be advantageous for depressed patients who suffer from significant weight loss and insomnia. Second-line therapy involves tricyclic antidepressants (TCAs), which are not preferably used due to decreased receptor selectivity and the adverse effects profile. Monoamine oxidase inhibitors (MAOIs) are also on the list but used infrequently because of the long list of dietary restrictions, and the potential risk of hypertensive crisis and serotonin syndrome if taken with any serotonergic drug. However, MAOIs may be employed as a first line in patients with atypical depression presenting with hypersomnia, rejection sensitivity, and hyperphagia **[42]**.

5.2. Medication side effects

More than 60% of patients on antidepressants experience one more side effect. The most reported side effects from patients on SSRIs and SNRIs include agitation, constipation, insomnia, dizziness, headaches, and loss of libido. TCAs cause dry mouth, constipation, urination difficulty, dizziness, weight gain, hyperhidrosis, tachycardias, and arrhythmias. Additional potential health risks include serotonin syndrome, which is uncommon but serious. It occurs by combining an SSRI or SNRI with a medication that also increases brain levels of serotonin. Symptoms include agitation, confusion, muscle twitching, perspiration, and diarrhea. Other risks of antidepressant medications involve hyponatremia, diabetes, and suicidal thoughts in fewer cases **[43]**.

6. Sleep and depression "A bidirectional relationship"

Sleep is one of the essential physiologic activities for survival **[44]**. Sleep is not just for physical and mental rest but also there is a scientifically proven function of sleep in learning, memory consolidation **[45],** and metabolic homeostasis **[46]**. Sleep at the electrophysiological level is made up of a set of cycles. Each cycle consists of five stages. Four stages are named non-rapid eye movement (non-REM) and one rapid eye movement stage. One cycle goes in the order: of N1, N2, N3, N4, N2, REM. Stages 3 and 4 (slow wave sleep) of the non-REM are with the least brain excitability and absolute glucose metabolism as the delta waves are predominant. REM, associated with dreaming, is more active. Beta waves are the predominant during REM sleep **[47-50]**.

About 80% of depressed patients complain about the amount and quality of sleep they have **[51]**. Sleep disturbances are a major symptom of depression and used as a diagnostic marker by physicians since ancient Greek physicians **[52]**. Even some researchers have suggested that the diagnosis of depression in the absence of sleep complaints should be performed with caution **[47]**. Besides, sleep disturbances for non-depressed people are a risk factor for depression. In a meta-analytical evaluation, considered 21 studies, it was found that that those with insomnia who are not depressed are twice as likely to become depressed as those who do not have sleep issues **[53]**. These findings made it clear that the depression-sleep disturbances relationship is a bidirectional relation, involved in a vicious cycle.

The World Health Organization (WHO) categorized sleep disorders, in their latest version of the International Classification of Diseases (ICD-11), into seven main disorders. Each disorder is categorized further into more specific disorders. The seven main disorders are insomnia, hypersomnia, parasomnia, sleep apnea, circadian rhythm sleep-wake disorders, and sleep-related movement problems **[54]**. Insomnia appears in three forms: early morning awakening, difficulty maintaining sleep, and difficulty falling asleep. A 2009 study examining the impact of insomnia on well-being found that 24.4% of depressed patients experienced difficulty maintaining sleep. Additionally, approximately 23% of patients reported issues with falling asleep and early morning awakening **[55]**. A study conducted by Johns Hopkins University revealed that 75% of individuals with depression struggle with either falling asleep or staying asleep. According to Patrick H. Finan, Ph.D., a sleep researcher at Johns Hopkins, either issue can be the initial factor. This finding reinforces the evidence that cognitive behavioral therapy for insomnia (CBT-I) can improve sleep and enhance the chances of remission for those with depression.

While insomnia is the highest encountered sleep disorder occurring in patients suffering depression there are comorbid primary sleep disorders other than insomnia **[57]**. About 15% of depressed patients encounter hypersomnia. Hypersomnia can be a symptom associated with seasonal depression **[58]**. With Obstructive sleep apnea occurs frequently in depression. 26% of patients with unipolar depression show restless leg syndrome symptoms **[59, 60]**. The previous findings support the statement that diagnosis of depression in the absence of sleep disturbances should be made with caution.

Depressed patients show changes in sleep structure that might be the reason for the previously discussed sleep disorders. Polysomnograms of patients with depression showed increased wakefulness regarding period and frequency, elevated sleep onset latency, declined total sleeping time, SWS reduction, and REM disturbances. REM disturbances appear as: shortened REM latency, increased REM sleep, and increased REM density (the frequency of rapid eye movements) **[61, 62]**.

Consequently, antidepressants that influence sleep and circadian rhythms-such as bright light therapy, sleep deprivation, social rhythm therapies **[62]**, and melatonin-have emerged as promising options. Melatonin, often referred to as the "sleep hormone," facilitates sleep and induces feelings of drowsiness. The suprachiasmatic nucleus (SCN), the primary regulator of circadian rhythms **[65]**, controls the synthesis of melatonin **[68]**. Additionally, melatonin has a chronobiotic effect, meaning it can synchronize and reset biological rhythms **[65]**.

7. Melatonin

7.1. Background

Melatonin, N-acetyl-5-methyoxytrptamine, is an indolamine released from the pineal gland and directly transferred to the blood. Melatonin's amphiphilic characteristics allow it to be present in all organism's compartments **[63]**.

Melatonin synthesis is stimulated by norepinephrine while serotonin acts as a precursor **[64]**. After the release of norepinephrine, it interacts with beta and alpha noradrenergic receptors in the pinacocytes, which stimulates PLC-Ca^{++}-PKC and cAMP-PKA-CREB axes to activate melatonin synthesis.

Tryptophan is converted into melatonin through the serotonin pathway. The process begins with tryptophan, which is first converted into 5-hydroxytryptophan by tryptophan hydroxylase. This compound is then transformed into serotonin. Subsequently, serotonin

undergoes acetylation to form N-acetylserotonin, which is finally converted into melatonin by acetylserotonin O-methyltransferase, formerly known as hydroxy-indole-O-methyltransferase **[65]**. In the bloodstream, melatonin binds to albumin and is then conjugated to 6-sulfatoxymelatonin in the liver, which is subsequently excreted in the urine **[63]**.

Melatonin synthesis is controlled via the suprachiasmatic nuclei (SCN). The suprachiasmatic nuclei (SCN) times melatonin production daily in harmony with the light/dark cycle. Darkness at night stimulates a polysynaptic pathway beginning with the retinohypothalamic tract and ending with the suprachiasmatic nuclei (SCN) and promotes melatonin production at the pineal gland **[33]**. By contrast, light suppresses the production of melatonin also through the retinohypothalamic pathway. Accordingly, melatonin transduces light-dark information to the whole body, coordinating physiological functions and behaviors. However, there are other factors affecting melatonin synthesis **[66, 67] (Fig. 2)**.

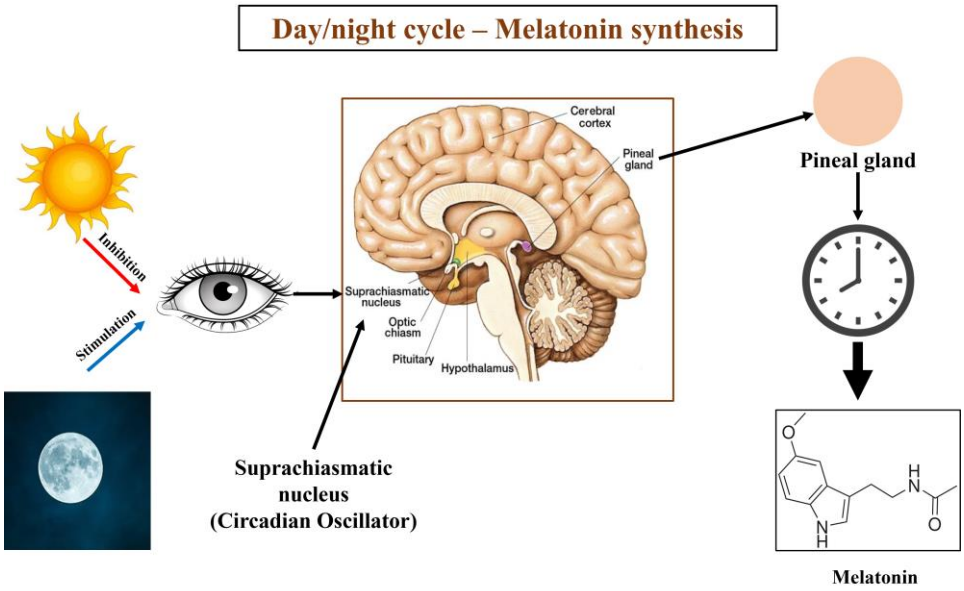

Fig. 2. Synthesis of melatonin and the effect of day/night cycles on melatonin level.

7.2. Melatonin mechanisms of action

Melatonin operates through two distinct mechanisms: receptor-mediated action, where it interacts with both membrane-bound and nuclear receptors, and non-receptor-mediated action, where it crosses cellular, organellar, and nuclear membranes to interact with intracellular molecules **[68]**.

7.3. Non-receptor mediated actions

This mechanism of action involves the direct interplay between melatonin and other proteins. Melatonin's antioxidant action is an example of non-receptor-mediated actions, as it's a proficient direct free radical scavenger and an activator of free radicals' scavenging mechanisms. Besides, being highly concentrated in the mitochondria, melatonin protects lipids, DNA, and proteins from oxidative damage **[68]**. Melatonin is significantly present in the mitochondria and plays a critical role in mitochondrial functions. For instance, it was recently revealed that melatonin is formed in mice brain mitochondria preventing cytochrome c leakage and subsequent apoptosis by acting through the mitochondrial

external membrane MT1 **[69]**.

Another melatonin role done via the non-receptor-mediated actions is the manipulation of the ubiquitin-proteasome system that regulates protein degradation **[68, 70]**. Furthermore, melatonin affects clock gene expression by working as a direct proteasome inhibitor. Melatonin's direct influence on the clock gene expression is demonstrated in its prospective effects **[68, 71]**.

All the previously mentioned fundamental roles of melatonin are done through its direct interaction with the intracellular molecules of the cells without the involvement of receptors.

7.4. Receptor-mediated actions

Melatonin, like any hormone, acts through particular receptors to perform its functions. Melatonin has 2 types of receptors in mammals, MT1 and MT2. Both receptors are heterotrimeric G-protein-coupled receptors (GPCRs) that are located at the periphery and in the central nervous system **[68]**. MT-receptor-mediated actions require secondary messengers to keep melatonin sites functional and with respective selectivity. The second messenger's immediate responses influence the cAMP, cGMP, and IP3 by production either increasing or decreasing their depending on the context **[63]**. Besides its action through MT1 and MT2 receptors, melatonin may also interact with ROR/RZR (retinoid orphan receptors/retinoid Z receptors) nuclear receptors **[72]**.

7.4.1. Melatonin receptors and their roles

Melatonin adjusts various physiological roles through activating its receptors, MT1 and MT2. MT1 and MT2 receptors are present in the SCN and cardiac vasculature **[63, 73]**.

The MT1 receptor is coupled with Gαi2, Gαi3, and Gq/11 G proteins and is encoded by the melatonin receptor 1A gene located on chromosome 4q35.1. MT1 plays a key role in regulating the rhythmic expression of clock genes such as Bmal1, Cry1, Per1, and Per2 **[74, 75]**. It also has other various physiological functions such as its anti-inflammatory, antiapoptotic, and antioxidative effects **[43]**. Additionally, the MT2 receptor is coupled with Gi/o-type proteins and is encoded by the melatonin receptor 1B gene on chromosome 11q21-q22. It has two primary effects: it inhibits the formation of cyclic guanine monophosphate and reduces calcium-dependent dopamine release in the retina. Furthermore, melatonin is believed to have additional, yet-to-be-discovered neurogenic effects through MT2 receptors **[75]**.

Both MT1 and MT2 receptors primarily function by activating protein kinase C in the SCN and enhancing the phosphorylation of extracellular signal-regulated kinase. This process regulates the transcription of clock genes and inhibits the production of cyclic adenosine monophosphate (cAMP) stimulated by forskolin. Recent research assessing their pharmacology and functions has utilized mice with genetic deletions of either the MT1 or MT2 receptors, as well as prototype competitive melatonin receptor antagonists like luzindole **[77]**. For example, a recent study involving electrophysiological recordings in MT1 receptor knockout mice yielded significant findings. The study detected reduced impulse activity in locus coeruleus NE neurons throughout the dark phase, as well as the elimination of circadian variations in the spontaneous impulse activity of both NE and 5-HT neurons in the dorsal suture. These results suggest that the MT1 receptor could play a role in alleviating melancholic depression and may serve as a promising pharmacological target for this mental condition **[74, 75]**.

MT receptors MT1 and MT2 also form heterodimers with serotonin (5-HT_2C) receptors. However, the formation of MT2/5-HT_2C

heterodimers is more efficient than that of MT1/5-HT_2C heterodimers. The MT2/5-HT_2C heterodimer exhibits an inhibition of forskolin-stimulated cAMP production as a signaling response to melatonin. Therefore, melatonin receptor heterodimerization with the 5-HT_2C receptor conducts additional signaling responses with therapeutic potentials for attenuating sleep disorders and depressive symptoms **[75]**. In sum, such findings motivate for further development of MT1 and MT2 receptors as targets for neuropharmacology drug design.

7.5. Melatonin and insomnia

Benzodiazepine drugs are commonly employed for treating insomnia. However, it is not appropriate for long-term treatment due to side effects like next-day hangover, addiction, and memory decline. MT has been employed to improve sleep in insomniacs. This is because it does not induce hangovers and does not exhibit addictive potential. However, its therapeutic value is inconsistent (partly due to its short half-life and low dose of melatonin used) **[78]**.

When administered as a drug, exogenous melatonin affects numerous physiological systems and can have significant drug interactions. Regarding its effectiveness in treating sleep disorders, melatonin can help initiate sleep, but its impact is generally modest and varies among individuals. In children with neurodevelopmental disabilities, melatonin is particularly effective in promoting sleep onset, though it has a minimal effect on overall sleep quality **[79]**. A European consensus conference was held in Rome on 4th October 2014 to discuss several issues including appropriate medication, timing of administration, and duration of treatment in infants, children, and adolescents. This conference suggested that exogenous MT supplementation is well endured and has no obvious short- or long-term adverse effects. A dosage of 1-3 mg of melatonin should be administered 30 minutes before bedtime. If no improvement is observed, the dose can be gradually elevated to up to 5 mg per night [80].

Twelve meta-analyses have been conducted based on clinical trial data. Among these, four focused exclusively on children, three on adults, and five included both children and adults. The children-only meta-analyses addressed insomnia, autistic spectrum disorder, and general neurodevelopmental disorders. All three adult meta-analyses were related to sleep disorders. The meta-analyses covering both children and adults included studies on insomnia, delayed sleep phase disorder (DSPD), intellectual disabilities (ID), and general sleep disorders. The main results are summarized in **Table 1**.

An analysis employed information from 17 various research (including 284 subjects) that met the inclusion criteria. Sleep onset latency, total sleep time, and sleep effectiveness were chosen as the result variables. Study effect sizes were detected as differences between the reaction to placebo and the mean response to MT for every endpoint assessed. Administration of MT remarkably diminished sleep onset latency by 4.0 min (95% CI 2.5, 5.4); sleep effectiveness increased by 2.2% (95% CI 0.2, 4.2), and total sleep duration increased by 12.8 min (95% CI 2.9, 22.8). Since 15 of the 17 studies included healthy participants or people with no associated medical conditions other than insomnia, the analysis was also conducted encompassing only these 15 studies. The sleep onset results were modified to 3.9 min (95% CI (2.5, 5.4)); sleep effectiveness increased to 3.1% (95% CI (0.7, 5.5)); sleep duration was elevated to 13.7 min (95% CI (3.1, 24.3)) **[91]**.

Following clinical practice guidelines for the treatment of intrinsic circadian rhythm sleep-wake disorders **[93]** encouraged by the American Academy of Sleep Medicine in its 2015 update, which gave MT a second level of confidence for

the treatment of intrinsic circadian rhythm sleep-wake problems, melatonin given from outside the body is considered an effective treatment in cases suffering sleep disorders due to its low side effects and tolerability.

Table 1. Findings from a published meta-analysis on the effectiveness of melatonin in improving sleep parameters and/or its tolerability in individuals with sleep disorders or psychiatric problems [59]

Age Group	Disorder	Main Findings
Adults	Sleep disorders	Melatonin was detected to exert a potential effect on the quality of sleep when compared to placebo for adult candidates having sleep disturbances **[81]**.
All Ages	Insomnia	Melatonin remarkably ameliorated sleep-onset latency for insomnia, in both age categories, either children or adults **[82]**.
Kids and teenagers	Insomnia	Melatonin significantly improves the time children take to fall asleep **[83]**.
Adults	Sleep disorders	Melatonin significantly improves total sleep time and reduces sleep onset latency for adults with sleep disorders **[84]**.
Children and adolescents	Neurodevelopmental disorders	Melatonin noticeably ameliorated total sleep time and diminished sleep onset latency for children suffering from neurodevelopmental problems **[85]**.
Kids and teenagers	Neurodevelopmental disorders	Melatonin remarkably ameliorated total sleep time and decreased sleep onset latency. No noticeable difference in the frequency of nocturnal awakenings for children having neurodevelopmental problems **[86]**.
All Ages	Sleep disorders	Melatonin remarkably ameliorated whole sleep time and reduced sleep onset latency for both kids and adults with sleep problems **[87]**.
Kids and teenagers	Autism spectrum disorder	Melatonin significantly ameliorated whole sleep duration and diminished sleep onset latency. No remarkable difference was noticed in the frequency of nighttime awakenings for children with autism spectrum disorder **[88]**.
Kids and teenagers	Intellectual disabilities	Melatonin ameliorated whole sleep time, reduced sleep onset latency, and decreased the frequency of nighttime awakenings for both kids and adults with intellectual problems **[89]**.
All Ages	Sleep disorders	Melatonin had no remarkable impact on sleep factors for both kids and adults with sleep problems **[90]**.
Adults	Sleep disorders	Melatonin significantly ameliorated total sleep time and reduced sleep onset latency for adults with sleep disorders **[91]**.

7.6. Melatonin agonists

Several MT receptor agonists have been accessible for treating sleep problems: ramelteon for treating insomnia described by struggles with the beginning of sleep, agomelatine for depression handling and linked sleep problems, and tasimelteon for the management of non-24-hour sleep-wake problems in the blind. This review provides an overview of the latest evidence on the effectiveness and safety of melatonin receptor agonists for treating the identified sleep problems.

7.6.1. Agomelatine

Synthesis of the naphthalene scaffold can alternatively be seen as the creation of a biomolecule with great potency and affinity for the melatonin system. The crucial intermediate in this synthesis is 2-(7-methoxy-1-naphthyl) ethanol (31). N-[2-(7-methoxy-1-naphthylethyl] acetamide (32), also known as agaomelatine, has recently received medical use approval in Australia and Europe **[94]**.

7.6.1.1. Mechanism of action

Agomelatine differs from other antidepressants in terms of its pharmacological activity, and its antidepressant effectiveness has been compared to that of other antidepressants from other classes. Agomelatine enhances sleep without daytime sedation. Agomelatine exhibits serotonin 5-HT2C antagonistic and melatonin agonistic effects, it also sounds to be well tolerated. For its melatonin agonistic properties, agomelatine binds to melatonin receptors (MT1, MT2), inhibits cAMP synthesis, and has the same effects as melatonin, including dose-dependent inhibition of SCN neuron firing rate. Agomelatine's 5-HT2C antagonist characteristics needed to be discovered. Understanding the discrepancy between its high affinities for MT1 and MT2 locations and its reduced affinity for 5-HT2C receptors was critical. It was revealed that agomelatine impeded cerebral populations of 5-HT2C receptors. It was not yet clear, nevertheless, whether agomelatine's antidepressant impacts resulted from its agonistic property with melatonin or its antagonistic property with 5-HT2C. Therefore, the effects of agomelatine were compared to those of both melatonin and 5-HT2C antagonists **[95]**. The existence of MT1 and/or MT2 receptors in the hippocampus, nucleus accumbens, and frontal brain, where they are believed to play a function in the regulation of mood, supports the idea that melatonergic pathways contribute to agomelatine's antidepressant effects. In contrast, 5-HT2C receptor antagonists simulated agomelatine's enhancement of frontal cortical dopaminergic and adrenergic input and its reducing hyperactivity in rats with olfactory bulbectomy, a model of depression-linked agitation. It was resolved that agomelatine's combined actions at melatonergic and 5-HT2C sites were necessary for its effectiveness. Following this notion, while 5-HT2C antagonists replicate agomelatine’s ability to promote cellular growth in the hippocampus, they do not replicate its effects on enhancing cell survival or increasing brain-derived neurotrophic factor (BDNF) levels, which melatonin only moderately elevates **[95]**.

7.6.1.2. Advantages and limitations

Due to its unique pharmacological mechanism and good tolerability, agomelatine's apparent acute efficacy is of particular interest. Given its lower likelihood of sexual desire side effects, insomnia, and withdrawal symptoms, it is no less effective than other antidepressants in comparison (which are generally notified with serotonergic antidepressants). In other words, it is a suitable alternative for the longer established antidepressants **[95]**. Drawbacks include low absorption when taken orally and a tendency to increase liver enzymes **[96]**. Agomelatine is

given orally, undergoes first-pass metabolism, and therefore has a low bioavailability. It has a 2.3-hour half-life and is 95% substantially protein-bound. 90% of its metabolism is carried out by CYP1A2, and the remaining 10% by CYP2C9. It is eliminated in urine and does not produce active metabolites **[96]**.

7.6.1.3. Clinical Trials

The clinical trials of agomelatine can be classified into short-term and long-term experiments **[96]**.

7.6.1.3.1. Short-term trials

The short-term trials, exceptionally the one that is a dose-finding study, are primarily intended to assess efficacy and safety. Hamilton Depression Score is used in all of these experiments to evaluate success. Agomelatine was studied at several dosing regimens (1, 5, and 25 mg), and the dose-finding trial, which had 711 individuals with major depression or bipolar II depression, revealed that 25 mg was the most beneficial dose. Agomelatine's effectiveness was assessed in two 6-week trials each using a double-blind, placebo-controlled design. They each had 212 and 238 patients who had major depression. In each of these studies, the dosage was first 25 mg and then elevated to 50 mg if no improvements were seen after two weeks. Agomelatine (two doses combined) significantly improved in both studies when compared to placebo. On the other hand, there are three short-term, where Agomelatine was in comparison with a placebo and an active comparator in each of these trials (fluoxetine or paroxetine). According to these studies, Agomelatine is not substantially more efficacious than a placebo.

7.6.1.3.2. Long-term trials

A long-term trial involving 492 patients with major depression found that agomelatine had a significantly lower total relapse rate after following the participants for up to 24 weeks. A 12-week trial compared agomelatine to venlafaxine, and the findings indicated that the rate of remission was comparable to venlafaxine.

7.6.1.4. Efficacy and Safety

In clinical investigations, agomelatine has great tolerance and safety. When in comparison with a placebo, a double-blind, placebo-controlled experiment found that agomelatine treatment at doses of 25-50 mg significantly ameliorated patients' clinical conditions. Another 12-week, double-blind, placebo-controlled research found that agomelatine was very well tolerated in patients with generalized anxiety disorder **[97]**.

7.6.2. Ramelteon

Ramelteon is synthesized from N-{2-[(8S)-1,6,7,8-tetrahydro-2H indeno[5,4-b] furan- 8 yl] ethyl] propanamide with the use of dibenzoyl-L-tartaric acid as an acid to form the salt at the end of hydrogenation and as the resolution agent along with **[94]**.

7.6.2.1. Mechanism of action

Ramelteon exhibits a high preference for the MT1 and MT2 receptors located in the suprachiasmatic nucleus (SCN). Ramelteon has no considerable tendency for the γ-aminobutyric acid (GABA) receptor complex nor for any other receptor that binds norepinephrine, dopamine, acetylcholine, opiates, or neuropeptides. Furthermore, ramelteon has a very low affinity for the serotonin receptor 5-HT1A. The drug does not reach high concentration which may cause interferences, ruling out any possible interactions between ramelteon and the serotonergic system at clinically useful doses. It's thought that ramelteon may be more efficient for insomnia described by problems falling asleep as its selectivity for the MT1 receptor is 1000-fold higher for the MT2 receptor when compared with melatonin **[98]**.

7.6.2.2. Advantages and limitations

Lack of potential for addiction, non-scheduled DEA status, absence of cognitive and psychomotor problems, low risk of drug interactions, and unique mode of action. Ramelteon has been proven to be safe and effective in both adult and senior individuals. However, its primary benefit is in improving sleep onset, with limited effects on sleep maintenance, which is a notable limitation **[99]**.

7.6.2.3. Clinical studies

It was detected that Ramelteon reduced the latency of persistent sleep in elderly people with chronic insomnia by 40 min. (56%) as compared to 30 minutes (43%) in placebo-controlled subjects after 6 months. In 2005, the FDA approved 8 mg tablets for the treatment of insomnia described by problems in falling asleep. It is not regarded as a scheduled hypnotic in the US, as it lacks the adverse effects on motor and cognition, and the potential for abuse. Studies show no evidence of euphoric effects **[98]**. A Clinical study published in 2019 investigated the effect and safety of Ramelteon in the treatment of insomnia with outpatients aged 20 to<65 years with sleep-onset insomnia and major depressive disorder **[98]**; They had been taking 8 mg/day Ramelteon for 8 weeks plus their usual antidepressants. HAM-D17 total scores improved at the end of treatment.

7.6.2.4. Efficacy and Safety

Ramelteon was noticeably associated with decreased perceived time to fall asleep and enhanced sleep quality, without being related to an elevation in total subjective sleep time, according to analyses of trials on individuals with insomnia or insomnia symptoms. The only significant side effect of ramelteon was somnolence. Ramelteon considerably reduces subjective sleep latency and overall sleep time, according to long-term safety and efficacy studies done on individuals with chronic insomnia. There were no indications of dependence, rebound sleeplessness, next-day residual impact, or withdrawal symptoms, which are typically seen with benzodiazepine or Z-drug use.

Ramelteon should be co-administered with CYP3A4 inhibitors like fluconazole, fluvoxamine, and ketoconazole with caution since it has been demonstrated to prolong ramelteon's half-life and serum concentration **[64]**.

7.6.3. Tasimelteaon

7.6.3.1. Mechanism of action

An MT1 and MT2 melatonin receptor agonist is tasimelteon. Tasimelteon can be used to modify circadian rhythms in Non-24 sleep-wake disorder because it has affinities for both receptors but has a larger MT2 affinity. Ramelteon has been authorized for treating insomnia, although tasimelteon is more commonly used to change sleep-wake patterns. In those with Non-24 sleep-wake disorder, it has been shown to have a noticeable positive influence on quality of life and entrainment of the circadian rhythm clock **[103]**. Tasimelteon has been shown to relieve insomnia and daytime sleepiness while entraining circadian rhythms to run on a 24-hour cycle. Additionally, tasimelteon-treated patients reportedly displayed increases in overall functioning. The exact mechanism by which tasimeton provides therapeutic benefits for people with non-24 sleep-wake disorder is yet not fully understood **[100]**.

7.6.3.2. Advantages

Tasimelteon was found to be well tolerated by the liver in numerous clinical investigations. Clinically obvious liver damage was not documented in any cases **[106]**.

7.6.3.3. Clinical trials

Studies in phases II and III have been done on temporary insomnia brought on by changed sleep and wake times. Tasimelteon improved sleep efficiency in the phase II study when compared to placebo, decreased sleep latency, and dose-dependently advanced plasma melatonin rhythm. Tasimelteon increased sleep latency, sleep efficiency, and wakefulness following the start of sleep in the phase III research. The frequency of side effects in both studies was similar to placebo **[100]**. A meta-analysis showed that tasimelteon 20 mg for 8 weeks had improved symptoms of depression in African American patients with MDD **[104]**.

7.6.3.4. Efficacy and Safety

Tasimelteon exposure is about twice in elderly subjects, according to studies in specific groups, and is approximately 20-30% higher in women than in men. Smokers' exposure is reduced by roughly 40% as a result of CYP1A2 induction. People with renal impairment do not require a dosage adjustment. Correspondingly, no dose adjustment is required for people with mild to severe hepatic problems, even though their exposure is almost doubled. Patients with severe hepatic impairment are not advised to take it because it has not been tested **[105]**.

According to Vanda, tasimelteon was well tolerated and considered safe during the clinical trials. The clinical trials did not reveal any measurable next-day residual effects. Headache (17%), alanine aminotransferase increase (10%), nightmares or strange dreams (7%), and upper respiratory (7%) or urinary tract infections (7%) were the adverse effects documented in the clinical experiments that happened with an occurrence higher than 5% and were at least twice as common when compared to placebo. **[105]**.

7.7. Extended-Release Melatonin

It is challenging to offer coverage for a whole sleep cycle using immediate-release formulations since they are quickly absorbed and eliminated from the body. Extended-release melatonin formulations can more closely resemble the melatonin profile found in the body and improve effectiveness as extended-release preparation releases melatonin into the bloodstream throughout the course of the next 8–10 hours. **[107]**.

7.7.1. Circadin

Prolonged-release melatonin is used for treating primary insomnia in patients 55 years or older. In patients aged 55 years and having bad sleep quality; melatonin formation is even smaller than in healthy elderly persons without such problems due to an age-related reduction in the functionality of the biological clock and melatonin formation, and thus the brain is deprived of a critical sleep adjustor **[100]**.

According to Good Clinical Practice (GCP) guidelines, Circadin and a placebo were tested for their effectiveness in treating primary insomnia in patients under the age of 55 in three randomized, double-blind trials with comparable designs. These trials had the same main design involving a 1-2-week run-in period of single-blind placebo followed by 3 weeks of randomized, double-blind experiment. Patients were advised to take either an active drug (Circadin 2 mg) or a placebo tablet daily, 2 h before bedtime. Efficacy parameters were assessed at the baseline and the termination of the 3-week double-blind period. Sleep beginning latency declined with Circadin to 50% from pretreatment values, which was 9 min. Longer than with placebo ($p= 0.011$). The amount of time spent awake before falling asleep was reduced by 50% ($p= 0.011$), without significantly influencing the structure and pattern of sleep **[108]**. Using Circadian significantly improved sleep quality at home for 50% of the patients compared to 15% with a placebo ($p= 0.018$). No

withdrawal or rebound effects were noted for any of the documented variables 1 day or 3 weeks after discontinuing the dose in both groups **[108]**.

7.7.1.1. Efficacy and Safety

There have been no clinically significant side effects, and both the immediate and sustained release formulations are well tolerated. For both formulations, safety parameters remained within the accepted clinical range **[109]**.

7.8. Melatonin agonists under clinical trial

In addition to being effective in treating insomnia, melatonin and melatonergic medications have also been shown to be effective in treating parasomnia, circadian rhythm problems, night eating disturbances, and depression. The potential for widespread usage of the recently created melatonin and melatonergic medications in numerous clinical settings is great. However, extensive clinical trials are recommended to clarify the effectiveness and safety of these recently produced melatonergic medications **[97]**.

7.8.1. TIK-301

TIK-301, N-[(2R)-2-(6-chloro-5-methoxy-1H-indol-3-yl) propyl] acetamide, a chlorinated high-affinity, and orally active melatonin MT1 and MT2 receptor agonist (Kis: 0.081 nM and 0.042 nM, respectively). It is more selective for MT2 than MT1 as a typical feature of 6-chlorinated melatonin derivatives. In addition, 5-HT2B/5-HT2C receptor antagonists with antidepressant properties. According to reports, TIK-301 has a half-life of around one hour. Due to its chlorine atom at position 6 of the indolic moiety, it precludes 6-hydroxylation (i.e., degradation) via the main catabolic pathway of MLT, the action is only somewhat prolonged **[105]**.

7.9. Melatonin antagonists

The etiology of MDD is complex and multifaceted, with emerging evidence implicating the dysregulation of monoaminergic neurotransmitters as a significant contributor to its pathophysiology. Notably, monoamines such as noradrenaline, serotonin, and dopamine play roles in the maintenance of different brain roles, encompassing mood, cognition, memory, sleep, and appetite. These monoaminergic neurotransmitter systems, predominantly situated within the midbrain and brainstem nuclei, project widely throughout the brain, hinting at their involvement in a diverse array of neurological processes **[110]**.

Extensive research has shown that pharmacological compounds that inhibit the reuptake of monoamines, thereby elevating their concentration within the synaptic cleft, exhibit clinical efficacy as antidepressants. Notably, interventions targeting serotonergic, noradrenergic, and dopaminergic reuptake mechanisms have shown promise in alleviating depressive symptoms. Such interventions are believed to restore monoamine balance, which is perturbed in MDD, potentially contributing to the amelioration of mood disturbances **[111]**.

Another relevant approach involves the inhibition of the enzyme monoamine oxidase, responsible for the breakdown of monoamines within presynaptic neurons. This inhibition leads to increased availability of monoamines in the synaptic terminals, facilitating enhanced neurotransmission and potential therapeutic benefits for MDD. Notably, these observations collectively support the monoamine-deficiency hypothesis, a prevailing pharmacological theory positing that the depletion of monoaminergic neurotransmitters underlies the manifestation of depression **[110]**.

The relationship between melatonin, norepinephrine, and serotonin has been a subject of theoretical interest, suggesting that changes in melatonin secretion may reflect underlying

disease states, given that Melatonin synthesis is stimulated by norepinephrine while serotonin acts as a precursor **[112]**.

Moreover, in research investigating the presynaptic impacts of melatonin on norepinephrine release and uptake in rats, it was observed that during maximal melatonin secretion, melatonin exerts an inhibitory effect on norepinephrine availability at pineal sympathetic synapses. This inhibition was demonstrated by a reduction in norepinephrine turnover *in vivo* and impaired norepinephrine release *in vitro [113]*.

Additionally, in a separate study, researchers administered a single intraperitoneal injection of melatonin to three avian species (bulbul, babbler, and pigeon). The study results indicated that lower doses of melatonin caused a significant decrease in norepinephrine content in bulbul (42%), babbler (52%), and pigeon (39%) species. At a higher dose, a decrease in norepinephrine content was observed only in the bulbul (51%) species, 30 min. after treatment **[114]**.

These findings, in conjunction with the significant observation of elevated serum melatonin levels in individuals afflicted with endogenous depression **[82]**, have raised interest in investigating the possibility of reducing melatonin levels in depressed patients **[116]**. This can be achieved by using melatonin antagonists. Here we will discuss three melatonin antagonists that can be promising in the role of antidepressants.

7.9.1. Luzindole

7.9.1.1. Mechanism of action

Luzindole (N-0774), also designated as N-acetyl-2-benzyltryptamine, is a drug that has been employed in scientific studies to investigate the function of melatonin in the human body. Luzindole is a selective melatonin receptor antagonist, with an affinity for the MT2 receptor that is 11 to 25 times larger than the MT1 receptor. It blocks melatonin receptors at target positions within the central nervous system and may thus mimic the influences of pinealectomy or suppression of melatonin formation. It has been shown in animal experiments to alter the circadian rhythm as well as have antidepressant impacts **[117]**.

7.9.2. 4-P-PDOT

7.9.2.1. Mechanism of action

The melatonin receptor antagonist 4-P-PDOT, or cis-4-Phenyl-2-propionamidotetralin, is >300-fold more selective for the MT2 subtype than the MT1 subtype. 4P-PDOT acts as a partial agonist in the rat peripheral microcirculation, in that it directly inhibits leukocyte rolling and in human MT2 melatonin receptors expressed in mammalian cells, where it inhibits stimulated cAMP formation **[118, 119]**.

7.9.3. 4P-ADOT

7.9.3.1. Mechanism of action

4-phenyl-2-acetamidotetraline is a potent MT2 antagonist, and it's considered a congener to 4-P-PDOT **[108]**. It is characterized by the powerful selective ability to bind to MT2 receptors in very small doses. A wide variation of experimental tests that try to investigate the ambiguous role of MT2 receptors are beginning to favorably adopt 4P-ADOT; as many studies have supported the propositions of its ability to significantly reduce the phase-shifting impact of 0.9 and 3 mg melatonin **[120]**.

Conclusion

Depression is a mental disorder and one of the main causes of morbidity. MDD and BD are two of the most common types of primary mood disorders, they differ fundamentally from one another from a neurobiological perspective, with implications for treatment and prognosis. Depression can develop for a variety of reasons, including genetic, environmental, psychological,

and behavioral ones. One of the most prominent depression assessment scales is the Hamilton Depression Rating Scale, as depression levels have been assessed following the 17-item HRDS.

Most patients diagnosed with depression have subjective and objective sleep disorders. Insomnia is the most recurrent comorbid primary sleep disorder in depression. Polysomnography findings in depressed patients showed SWS and REM sleep disturbances. Such findings made the way to new treatment options acting on circadian rhythms. Melatonin is related to circadian rhythms in many ways. First, its synthesis from tryptophan via the serotonin pathway that is controlled by the suprachiasmatic nucleus (master clock). Then, melatonin affects clock gene expression by working as a direct proteasome inhibitor as a non-receptor action. Finally, when used exogenously through receptor-mediated actions it may cause phase advance or phase relay of the circadian system. Thus, melatonin was effective in cases suffering sleep disorders and depression symptoms such as insomnia.

This article reviews the preclinical and therapeutic effects of the melatonin receptor agonists agomelatine, ramelteon, circadian, and tasimelteon on depression. Most clinical research confirms impaired melatonin production in depressed patients. Melatonin receptor agonists, which treat insomnia, are also extremely important for the pharmacological treatment of depression, as clinical studies showed that exogenous melatonin exhibited antidepressant effects in mice with depression-like phenotypes, which was supported by the outcomes of the trials conducted on human participants diagnosed with MDD. However, given that studies have connected MT to depression, there are still several important aspects to take into account, and more research is required. Since melatonin plays a role in depression, nocturnal light has a varied effect on melatonin secretion. MT antagonists, on the other hand, proved to be promising in countering the MT-mediated inhibitory effect on norepinephrine secretion in some patients. They also had an important role in discovering more about the implication of MT receptors in regulating phase shifting of circadian activity rhythms and more selective antagonists are being developed to further understand the various complex functions of melatonergic receptors and their potential for being a valuable option as an antidepressant in indicated patients.

List of abbreviations

5-HT, serotonin; BD, Bipolar disorder; BDI, Beck Depression Inventory; CBT-I, cognitive behavioral therapy for insomnia; CRH, Corticotropin-releasing hormone; GPCRs, G-protein-coupled receptors; GR, glucocorticoid; HDRS, Hamilton Depression Rating Scale; HPA, hypothalamic-pituitary-adrenal axis; ICD, International Classification of Diseases; MAOIs, monoamine oxidase inhibitors; MDD, Major Depressive Disorder; MDE, major depressive episodes; MR, mineralocorticoid; MT, melatonin; REM, rapid eye movement; ROR/RZR, retinoid orphan receptors/retinoid Z receptors; SCN, superchiasmatic nuclei; SWS, slow-wave sleep; TCAs, tricyclic antidepressants; WHO, The World Health Organization.

Declarations

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Not applicable.

Consent to publish

Not applicable.

Availability of data and material

Data will be made available on reasonable request.

Competing interests

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