

# Melatonin Receptor Agonists in Sleep Disorders: An Evidence-Based Review of Circadian Biology, MT1 and MT2 Receptor Pharmacology, Clinical Effectiveness, and Future Therapeutic Directions

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**Abstract**—Sleep disorders are prevalent conditions associated with impaired daytime functioning, cognitive disturbances, mood alterations, and reduced quality of life. The regulation of sleep is closely associated with the circadian timing system, in which melatonin acts as an important endogenous signal of darkness. The physiological effects of melatonin are primarily mediated through two G-protein-coupled receptors, MT1 and MT2. Pharmacological agents that activate these receptors have therefore emerged as therapeutic options for insomnia and circadian rhythm sleep–wake disorders. This review discusses the physiological role of melatonin, the molecular mechanisms associated with MT1 and MT2 receptor activation, and the pharmacological characteristics of major melatonergic agents, including melatonin, ramelteon, tasimelteon, and agomelatine. Their clinical applications in insomnia disorder, delayed sleep–wake phase disorder, Non-24-Hour Sleep–Wake Disorder, jet lag, and sleep disturbances associated with psychiatric conditions are reviewed. Although these agents share a common melatonergic mechanism, they differ in receptor affinity, pharmacokinetic properties, clinical indications, and therapeutic effects. Melatonin is particularly important as a chronobiotic agent, whereas ramelteon is primarily associated with sleep-onset insomnia. Tasimelteon has a specific role in circadian entrainment, particularly in Non-24-Hour Sleep–Wake Disorder. Agomelatine is pharmacologically distinctive because it combines MT1/MT2 receptor agonism with 5-HT<sub>2C</sub> receptor antagonism and may be useful in patients with depressive illness accompanied by sleep disturbance. Overall, melatonin receptor agonists provide a pharmacologically targeted approach to sleep and circadian disorders with generally favorable tolerability and low abuse potential compared with conventional hypnotics. However, their efficacy is influenced by the underlying sleep disorder, dose, formulation, administration timing, and patient characteristics. Future research should focus on personalized chronotherapy, circadian biomarkers, receptor-selective ligands, and individualized treatment strategies.

**Index Terms**—Melatonin, MT1 receptor, MT2 receptor, ramelteon, tasimelteon, agomelatine, insomnia, circadian rhythm sleep–wake disorders, chronobiotic agents

## I. Introduction

Sleep is an essential biological process involved in the maintenance of neurological, metabolic, endocrine, immune, and psychological homeostasis. Sleep disorders include insomnia disorder, circadian rhythm sleep–wake disorders, parasomnias, and sleep disturbances secondary to medical and psychiatric conditions. Insomnia and circadian rhythm sleep–wake disorders are particularly important because they

can produce substantial impairment in daytime functioning and quality of life.

Conventional pharmacological treatment of insomnia has traditionally involved drugs that produce central nervous system depression or enhance inhibitory neurotransmission. Although benzodiazepines and non-benzodiazepine hypnotics may be effective in the short term, their use may be associated with tolerance, dependence, withdrawal symptoms, cognitive impairment, and psychomotor adverse effects. These limitations have stimulated interest in pharmacological approaches that target physiological mechanisms involved in sleep regulation.

Melatonin is an endogenous hormone synthesized primarily by the pineal gland and released predominantly during the dark phase of the light–dark cycle. It functions as an important endocrine signal of darkness and contributes to the synchronization of circadian rhythms. Melatonin does not simply act as a nonspecific sedative; rather, it provides temporal information to the biological clock and influences the timing of sleep and other circadian physiological processes <sup>[1,2]</sup>.

The discovery and characterization of the MT1 and MT2 melatonin receptors led to the development of selective and non-selective melatonergic agents. These drugs may influence sleep initiation, circadian phase, and synchronization of biological rhythms. Major clinically relevant agents include melatonin, ramelteon, tasimelteon, and agomelatine. Although these compounds share activity within the melatonergic system, they differ in receptor selectivity, pharmacokinetics, clinical indications, and therapeutic effects <sup>[2-4]</sup>.

The present review summarizes the mechanisms of melatonin receptor agonists and evaluates the clinical evidence supporting their use in sleep and circadian rhythm disorders.

## **II. Melatonin and the Circadian Sleep–Wake System**

### **● Biosynthesis of melatonin**

Melatonin is synthesized from tryptophan through a series of enzymatic reactions: Tryptophan → 5-Hydroxytryptophan → Serotonin → N-Acetylserotonin → Melatonin

The final two steps are catalyzed by:

Arylalkylamine N-acetyltransferase (AANAT), which converts serotonin into N-acetylserotonin.

Acetylserotonin O-methyltransferase (ASMT), also known as hydroxyindole-O-methyltransferase, which converts N-acetylserotonin into melatonin.

Melatonin synthesis exhibits a strong circadian rhythm and is stimulated during darkness. Light exposure, particularly during the biological night, suppresses melatonin secretion through neural pathways connecting the retina with the suprachiasmatic nucleus and pineal gland <sup>[5-7]</sup>.

### **● The suprachiasmatic nucleus and circadian regulation**

The suprachiasmatic nucleus (SCN) of the hypothalamus is the principal circadian pacemaker in mammals. SCN neurons generate approximately 24-hour rhythms through molecular transcriptional–translational feedback loops involving clock genes such as CLOCK, BMAL1, PER, and

CRY.

Light detected by the retina is transmitted through the retinohypothalamic tract to the SCN. The SCN subsequently regulates autonomic pathways controlling pineal melatonin secretion. Melatonin therefore acts as an endocrine signal that communicates information about the environmental light–dark cycle to the organism. Disruption of the circadian system may occur due to:

- Irregular sleep schedules
- Night-shift work
- Rapid travel across time zones
- Exposure to artificial light during the biological night
- Aging
- Blindness
- Neurological disorders
- Psychiatric disorders

Melatonin receptor agonists may therefore be useful not only for promoting sleep but also for correcting abnormal circadian timing <sup>[1,8]</sup>.

### III. Melatonin Receptors and Molecular Mechanisms

- MT1 and MT2 receptors

Melatonin exerts its primary physiological effects through two high-affinity G-protein-coupled receptors: MT1 receptor (MTNR1A) MT2 receptor

(MTNR1B)

Both receptors are predominantly coupled to inhibitory Gi/o proteins and can reduce intracellular cyclic adenosine monophosphate (cAMP) signaling.

The two receptor subtypes have overlapping but distinct physiological functions. MT1 receptor

MT1 receptor activation is associated primarily with Suppression of SCN neuronal activity, Facilitation of sleep initiation, Regulation of circadian output & Modulation of neuronal excitability

MT2 receptor

MT2 receptor activation is particularly associated with Circadian phase shifting, Synchronization of biological rhythms, Regulation of circadian phase & Modulation of sleep timing

However, the functions of MT1 and MT2 receptors are not completely independent. Both receptor subtypes may contribute to sleep regulation and circadian control <sup>[2,3,9]</sup>.

- **Intracellular signaling pathways**

Following activation of melatonin receptors, the receptor–G protein complex influences several intracellular signaling pathways.

Melatonin receptor activation

↓

Gi/o protein coupling

↓

Inhibition of adenylyl cyclase

↓

Reduction in intracellular cAMP

↓

Modulation of protein kinase and downstream signaling pathways

↓

Alteration of neuronal activity and circadian signaling

Melatonin receptor activation may also influence:

- Protein kinase C
- Mitogen-activated protein kinase pathways
- Ion channel activity
- Intracellular calcium signaling
- Transcriptional mechanisms involved in circadian regulation

The final physiological effect depends on the receptor subtype, anatomical location, ligand concentration, circadian phase, and timing of administration <sup>[2,3,9]</sup>.

#### **IV. Chronobiotic and Sleep-Promoting Actions**

A major pharmacological concept in melatonergic therapy is the distinction between chronobiotic and sleep-promoting actions.

- **Chronobiotic action**

A chronobiotic agent modifies the timing of the circadian system. It may: Advance or delay the circadian phase, Synchronize the biological clock, Correct circadian misalignment & Improve the timing of sleep and awakening.

This action is particularly important in: Delayed Sleep–Wake Phase Disorder, Non-24-Hour Sleep–Wake Disorder, Jet lag & Shift-work-related circadian disruption

- **Sleep-promoting action**

Melatonergic activation may facilitate sleep initiation and, in selected patients, improve sleep-related parameters. The magnitude of this effect depends on:

Circadian phase, Endogenous melatonin secretion, Dose, Formulation, Pharmacokinetic profile, Receptor selectivity, Age, Underlying sleep disorder Consequently, melatonin receptor agonists should not be considered pharmacologically identical to conventional sedative-hypnotics <sup>[1,4,10]</sup>.

## V. Major Melatonin Receptor Agonists

### ● Melatonin

Melatonin is the endogenous ligand of MT1 and MT2 receptors. Exogenous melatonin is used to provide a melatonergic signal when endogenous secretion is insufficient, mistimed, or unable to adequately synchronize the circadian system.

#### Pharmacological characteristics of Melatonin:

It Activates MT1 and MT2 receptors and has a relatively short half-life which Undergoes rapid metabolism with variable oral bioavailability It Produces effects strongly influenced by administration timing “The therapeutic effects of melatonin may therefore differ according to formulation, pharmacokinetic properties, and administration timing.” <sup>[1,10]</sup>.

## VI. Clinical applications

Melatonin has been studied in:

- Circadian rhythm sleep–wake disorders
- Delayed sleep–wake phase disorder
- Jet lag
- Sleep disturbances in older adults
- Insomnia
- Sleep disturbances associated with neurological disorders

Evidence for chronic primary insomnia is more variable than evidence for circadian rhythm disorders. A systematic review and meta-analysis found that the effects of melatonin depend on factors including treatment duration, patient characteristics, formulation, and clinical outcome assessed <sup>[11]</sup>.

### ● Ramelteon

Ramelteon is a synthetic melatonin receptor agonist with high affinity for both MT1 and MT2 receptors. It is not a benzodiazepine receptor agonist and does not produce sleep primarily through nonspecific

GABAergic central nervous system depression.

Ramelteon exhibits approximately ten-fold greater affinity for MT1 than MT2 receptors. This pharmacological profile is considered particularly relevant to the regulation of sleep initiation <sup>[2,12]</sup>.

### **Mechanism of action**

MT1/MT2 receptor agonism

↓

Modulation of SCN neuronal activity

↓

Reduction of circadian arousal

↓

Facilitation of sleep initiation

### **Clinical evidence:**

Ramelteon has been investigated extensively in chronic insomnia. The American Academy of Sleep Medicine suggests ramelteon for sleep-onset insomnia in adults, although the recommendation is weak because the overall quality of evidence is limited and the magnitude of benefit is modest <sup>[13]</sup>.

A systematic review and meta-analysis of melatonin and ramelteon reported that the efficacy of these agents varies according to treatment duration, population, and outcome measure <sup>[10,14]</sup>.

### **Advantages**

- ◆ Low potential for abuse and dependence
- ◆ No classical benzodiazepine mechanism
- ◆ Useful for sleep-onset difficulty
- ◆ Generally favorable tolerability

### **Limitations**

- ◆ Modest improvement in objective sleep parameters
- ◆ Variable individual response
- ◆ Potential for drug interactions through hepatic metabolism

### **● Tasimelteon**

Tasimelteon is a synthetic melatonin receptor agonist that acts at both MT1 and MT2 receptors. <sup>[2,3,15]</sup>.

## Clinical application

Tasimelteon has particular importance in:

- Non-24-Hour Sleep–Wake Disorder
- Selected circadian rhythm sleep–wake disorders
- Non-24-Hour Sleep–Wake Disorder is characterized by a circadian rhythm that fails to remain synchronized with the 24-hour environmental cycle. It occurs particularly in individuals who are totally blind and lack adequate photic input to the circadian system.

Clinical trials have demonstrated that tasimelteon can promote circadian entrainment and improve the alignment of sleep–wake timing in appropriate patients <sup>[15]</sup>.

The clinical importance of tasimelteon illustrates that melatonin receptor agonists may be used not only to induce sleep but also to correct abnormal circadian timing.

### ● Agomelatine

Agomelatine is pharmacologically distinctive because it combines:

MT1 receptor agonism, MT2 receptor agonism & 5-HT<sub>2C</sub> receptor antagonism.<sup>[19]</sup> The melatonergic activity contributes to circadian regulation, whereas 5-HT<sub>2C</sub> receptor antagonism contributes to its effects on monoaminergic neurotransmission.

Agomelatine may influence:

- Sleep timing
- Circadian rhythms
- Serotonergic signaling
- Noradrenergic transmission
- Dopaminergic transmission

Because of this combined mechanism, agomelatine has been studied particularly in patients with depression accompanied by sleep disturbances.

However, hepatotoxicity is an important clinical consideration, and appropriate liver function monitoring is required during treatment.<sup>[19,20]</sup>

## VII. Comparative Pharmacology of Major Melatonergic Agents

| Agent              | Principal receptor activity                      | Main pharmacological role        | Important clinical application                               | Major limitation                                       |
|--------------------|--------------------------------------------------|----------------------------------|--------------------------------------------------------------|--------------------------------------------------------|
| <b>Melatonin</b>   | MT1/MT2 agonist                                  | Chronobiotic and sleep-promoting | Circadian rhythm disorders and selected insomnia populations | Variable bioavailability and timing-dependent efficacy |
| <b>Ramelteon</b>   | MT1/MT2 agonist; greater MT1 affinity            | Sleep initiation                 | Sleep-onset insomnia                                         | Modest clinical effects                                |
| <b>Tasimelteon</b> | MT1/MT2 agonist; relatively greater MT2 affinity | Circadian entrainment            | Non-24-Hour Sleep–Wake Disorder                              | More limited, indication-specific use                  |
| <b>Agomelatine</b> | MT1/MT2 agonist + 5-HT <sub>2C</sub> antagonist  | Circadian and mood regulation    | Depression with sleep disturbance                            | Hepatic safety concerns                                |

The pharmacological differences between these agents demonstrate that melatonin receptor agonists should not be regarded as interchangeable drugs. Differences in receptor affinity, active metabolites, half-life, and pharmacokinetics may influence their clinical effects [2-4,12,19].

## VIII. Clinical Evidence in Sleep Disorders

### • Insomnia disorder

Insomnia is characterized by difficulty initiating sleep, difficulty maintaining sleep, early morning awakening, or non-restorative sleep despite adequate opportunity for sleep.

Melatonergic agents may be particularly useful when insomnia is associated with:

- ☐ Circadian misalignment
- ☐ Advanced age
- ☐ Reduced endogenous melatonin secretion
- ☐ Sleep-onset difficulty
- ☐ Melatonin

The clinical evidence for melatonin in chronic insomnia is heterogeneous. Differences in dose, formulation, timing of administration, age, and diagnostic criteria contribute to variability among studies. Melatonin may be more beneficial when the underlying problem includes circadian misalignment rather than isolated physiological or psychological hyperarousal <sup>[10,11]</sup>.

Ramelteon:

Ramelteon has demonstrated its most consistent benefit in sleep-onset insomnia. The AASM guideline suggests ramelteon for sleep-onset insomnia, although the strength of recommendation is weak because improvements in objective sleep measures are relatively modest <sup>[13-14]</sup>.

Agomelatine:

Agomelatine may be particularly relevant when sleep disturbance occurs in association with depression. Its combined melatonergic and serotonergic pharmacology may produce benefits in both sleep and mood-related symptoms. <sup>[19,20]</sup>.

### **Delayed Sleep–Wake Phase Disorder**

Delayed Sleep–Wake Phase Disorder is characterized by a persistent delay in the timing of sleep and awakening relative to the desired or socially required schedule.

Affected individuals may fall asleep considerably later than desired and Experience difficulty awakening at conventional times also have relatively normal sleep quality when allowed to follow their preferred schedule.

Melatonin may be useful as a chronobiotic intervention when administered at an appropriate circadian time. <sup>[8,16]</sup>.

Treatment may be combined with:

- ✓ Consistent wake times
- ✓ Morning bright-light exposure
- ✓ Reduction of evening light exposure
- ✓ Behavioral sleep scheduling

The timing of melatonin administration is often more important than simply increasing the dose.

### **Non-24-Hour Sleep–Wake Disorder**

Non-24-Hour Sleep–Wake Disorder occurs when the endogenous circadian rhythm fails to remain synchronized with the 24-hour environmental cycle.

The condition is particularly important in totally blind individuals without adequate photic input.

Tasimelteon is a particularly important treatment in this condition because it can act as a melatonin receptor agonist capable of promoting circadian entrainment. Clinical studies have demonstrated its ability to improve circadian synchronization in appropriately selected patients [8,15].

### **Jet lag disorder**

Jet lag results from a temporary mismatch between the endogenous circadian rhythm and the external light–dark cycle after rapid travel across time zones.

The effectiveness of melatonin in jet lag depends on: Direction of travel, Number of time zones crossed, Timing of administration and Individual circadian phase.

The pharmacological objective is to facilitate adaptation of the circadian clock to the new environmental schedule.

### **Shift-work-related sleep disturbance**

Night-shift work creates a mismatch between the endogenous circadian system and the required sleep–wake schedule.

Melatonin may assist daytime sleep following night work, although effectiveness depends on: Administration timing, Light exposure, Duration of treatment and Degree of circadian adaptation.<sup>[18]</sup>

Melatonergic treatment may be particularly useful when combined with appropriate light-management strategies.

### **Sleep disturbances associated with psychiatric disorders**

Sleep disturbances commonly occur in: Major depressive disorder, Bipolar disorder Anxiety disorders and Schizophrenia.

Agomelatine has attracted interest because it combines melatonergic receptor agonism with 5-HT<sub>2C</sub> receptor antagonism.<sup>[19,20]</sup>

This dual pharmacological mechanism may theoretically address: Circadian dysregulation & Mood-related neurotransmitter abnormalities. However, its hepatic safety profile must be considered during clinical use.

### **Pharmacokinetic Considerations**

The clinical efficacy of melatonergic agents is strongly influenced by their pharmacokinetic properties. Important factors include:

- Absorption
- Oral bioavailability
- Distribution

- Hepatic metabolism
- Half-life
- Active metabolites
- Timing of administration

Melatonin has a relatively short half-life and variable oral bioavailability. These properties may limit prolonged receptor stimulation.

Ramelteon undergoes hepatic metabolism to an active metabolite, M-II, which contributes to its overall pharmacological profile.

Tasimelteon undergoes hepatic metabolism and has pharmacokinetic properties compatible with its chronobiotic activity.

Agomelatine is extensively metabolized in the liver, making hepatic metabolism and potential drug interactions clinically important.

Comparative pharmacological reviews have demonstrated substantial differences in receptor affinity and pharmacokinetic characteristics among approved melatonin agonists [2-4].

## **IX. Safety and Tolerability**

Melatonin receptor agonists generally have a favorable tolerability profile compared with several conventional hypnotic drugs.

The Commonly reported adverse effects may include:

- Headache
- Dizziness
- Somnolence
- Fatigue
- Nausea

Melatonin- Potential concerns include:

- Daytime sleepiness
- Drug interactions

- Variable product quality
- Timing-related effects Ramelteon

Potential adverse effects include:

- Somnolence
- Dizziness
- Fatigue Tasimelteon

Potential adverse effects may include:

- Headache
- Somnolence
- Abnormal dreams
- Liver enzyme abnormalities in some patients Agomelatine
- The most important safety concern is potential hepatotoxicity.
- Liver function monitoring is therefore an important aspect of clinical management.

Although melatonergic agents generally have favorable tolerability, differences in hepatic metabolism, receptor pharmacology, and clinical indications must be considered <sup>[10]</sup>.

## **X. Limitations of Current Clinical Evidence**

### **Heterogeneity of clinical trials**

Clinical studies differ considerably in: Patient populations, Diagnostic criteria, Dose Formulation, Treatment duration, Outcome measures

This makes direct comparison between studies difficult.

### **Importance of administration timing**

The clinical response to melatonergic agents depends substantially on the circadian phase at which the drug is administered.

Administration at an inappropriate circadian time may: Produce limited benefit, Fail to correct circadian misalignment and Produce an undesired phase shift.

### **Differences between sleep disorders**

An agent effective for circadian entrainment may not be equally effective for primary insomnia. Similarly, an agent that improves sleep initiation may not adequately correct a circadian rhythm disorder.

## **XI. Limited long-term evidence**

Additional research is required to establish: Long-term effectiveness, Effects on sleep architecture, Effects in vulnerable populations, Long-term safety during polypharmacy and Effects on cognition and daytime functioning.<sup>[10-11]</sup>.

## **XII. Future Perspectives**

### **Receptor-selective ligands**

More selective MT1 or MT2 receptor agonists may help separate: Sleep-promoting effects and Circadian phase-shifting effects.<sup>[2,3,9]</sup>.

### **Personalized chronotherapy**

Individual treatment may be guided by:

Dim-light melatonin onset, Actigraphy, Sleep diaries, Circadian biomarkers and Genetic variation in circadian clock genes.

### **Combination with light therapy**

The combination of pharmacological melatonergic signaling and controlled light exposure may provide a more effective strategy for correcting circadian misalignment.

### **Precision medicine**

Future research may identify patients most likely to respond to particular melatonergic agents based on:

- Age
- Circadian phenotype
- Receptor polymorphisms
- Endogenous melatonin profile
- Sleep disorder subtype
- 

### **Novel pharmacological targets**

Interactions between the melatonergic system and other sleep-regulating systems, including:

- GABAergic pathways
- Serotonergic pathways
- Dopaminergic pathways
- Noradrenergic pathways
- Orexinergic pathways

### XIII. Conclusion

Melatonin receptor agonists represent an important pharmacological approach to the management of sleep and circadian rhythm disorders. Their therapeutic significance arises from their ability to act on physiological mechanisms involved in the regulation of sleep timing and circadian synchronization.

Melatonin primarily functions as an endogenous chronobiotic signal, although its clinical efficacy in insomnia varies according to formulation, dose, timing, and patient characteristics. Ramelteon provides a selective melatonergic approach for sleep-onset insomnia and has a generally favorable safety profile with low abuse potential. Tasimelteon has particular importance in circadian entrainment, especially in Non-24-Hour Sleep–Wake Disorder. Agomelatine is pharmacologically distinctive because it combines MT1/MT2 receptor agonism with 5-HT<sub>2C</sub> receptor antagonism and may be particularly useful when sleep disturbance is associated with depressive illness.

The available evidence indicates that melatonin receptor agonists should not be viewed as a single therapeutically interchangeable class. Their effects depend on receptor pharmacology, pharmacokinetics, circadian timing, and the specific sleep disorder being treated. Although their efficacy is often modest and heterogeneous, their physiological mechanism of action and generally favorable tolerability make them valuable therapeutic options in selected patients.

**Table 1. Pharmacological comparison of major melatonergic agents**

| Parameter               | Melatonin          | Ramelteon         | Tasimelteon       | Agomelatine                   |
|-------------------------|--------------------|-------------------|-------------------|-------------------------------|
| Origin                  | Endogenous hormone | Synthetic agonist | Synthetic agonist | Synthetic analogue            |
| MT1 activity            | Yes                | Yes               | Yes               | Yes                           |
| MT2 activity            | Yes                | Yes               | Yes               | Yes                           |
| Additional major target | None               | None              | None              | 5-HT <sub>2C</sub> antagonist |

| Main therapeutic role   | Chronobiotic and sleep regulation            | Sleep initiation     | Circadian entrainment           | Sleep and mood regulation         |
|-------------------------|----------------------------------------------|----------------------|---------------------------------|-----------------------------------|
| Important clinical area | Circadian disorders; selected insomnia       | Sleep-onset insomnia | Non-24-Hour Sleep–Wake Disorder | Depression with sleep disturbance |
| Major limitation        | Variable bioavailability and short half-life | Modest efficacy      | More limited indication         | Hepatic safety                    |

**Table 2. Major sleep disorders and potential role of melatonergic agents**

| Sleep Disorder                       | Principal Pharmacological Objective         | Potentially Relevant Agent |
|--------------------------------------|---------------------------------------------|----------------------------|
| Sleep-onset insomnia                 | Facilitation of sleep initiation            | Ramelteon; Melatonin       |
| Delayed Sleep–Wake Phase Disorder    | Circadian phase adjustment                  | Melatonin                  |
| Non-24-Hour Sleep–Wake Disorder      | Circadian entrainment                       | Tasimelteon                |
| Jet lag disorder                     | Adaptation to new time zone                 | Melatonin                  |
| Shift-work-related sleep disturbance | Support of sleep during an altered schedule | Melatonin                  |
| Depression with sleep disturbance    | Circadian and mood modulation               | Agomelatine                |

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