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The mechanism of zolpidem and ramelteon to treat insomnia

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Abstract:

Insomnia, characterized by difficulty in getting or keeping sleep, has a serious impact on daytime performance and health. Zolpidem, a GABA-A receptor modulator, reduces sleep latency and increases sleep duration, making it suitable for short-term use. Ramelteon, a melatonin receptor agonist, regulates circadian rhythms and is effective for chronic insomnia, but is not addictive. The choice between zolpidem and ramelteon depends on the type of insomnia, and non-pharmacological treatments such as cognitive-behavioral therapy are recommended as a first choice. It is hoped that future treatments for insomnia will become safer and more personalized, combining medication with behavioral therapy to supplement treatment.

Keywords: Insomnia; Zolpidem; Ramelteon; GABA-A receptor; Melatonin

1. Introduction

Sleep is a natural and necessary physiological process that occurs in all mammals, including humans. The mechanism of sleep is complex and not fully understood. It involves the interaction of several body systems, including the brain and the endocrine system. During sleep, the brain produces different waves, such as slow and rapid eye movement (REM) sleep. During slow-wave sleep, the body repairs and regenerates tissues, and the immune system is strengthened. REM sleep is associated with dreaming and memory consolidation.

The functions of sleep are numerous. It helps to restore physical and mental energy, allowing the body and mind to recover from the day's activities. Good sleep also improves cognitive functions such as memory, attention, and problem-solving skills. It regulates the body's metabolism and hormone levels, affecting growth, appetite, and general health. Sleep also plays a vital role in maintaining emotional well-being and reducing stress.

Today, the sleep situation of human beings varies greatly. Many people struggle with getting enough quality sleep due to various factors. Stress from work, studies, and daily life often lead to insomnia or disrupted sleep patterns. The extensive use of electronic devices before bedtime also has a negative impact on sleep [1].

Insomnia is a common sleep disorder defined as persistent difficulty falling asleep, difficulty maintaining sleep, or non-restorative sleep, followed by impaired daytime functioning. Sleep disturbances in insomnia usually manifest as difficulty falling asleep, difficulty maintaining sleep (difficulty returning to sleep after waking during the night), or waking too early, regardless of whether adequate sleep conditions are present each night.

According to DSM-V criteria, the prevalence rate

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of insomnia in the general population is around 6%, but when daytime symptoms and sleep dissatisfaction associated with insomnia are taken into account, the prevalence can rise to 20%. Insomnia is more common in women, the elderly, people with chronic diseases, and those with high-life stress.

Long-term insomnia can have serious negative effects on physical and mental health. Physiologically, it can lead to weakened immunity and increase the risk of chronic diseases such as cardiovascular diseases, diabetes, and obesity. Psychologically, it can easily trigger emotional disorders such as anxiety and depression and affect cognitive functions, leading to decreased memory, lack of concentration, and slow response. In addition, it can cause troubles in daily life and work, reducing the quality of life and work efficiency [2].

2. Methods

2.1 Causes

Insomnia is a common sleep disorder with a variety of causes.

Psychological stress is one of the main factors leading to insomnia, including emotional problems such as anxiety, depression, mood swings or post-traumatic stress disorder (PTSD). Psychosocial factors such as work, school, family, or financial pressures are also common causes of insomnia.

Irregular work schedules, long daytime naps, excessive caffeine and alcohol consumption, and lack of exercise can all contribute to insomnia. The body's internal biological clock can be disrupted by traveling, night shifts, or irregular lifestyles, leading to insomnia [3].

Sleep in the human body can also be influenced by hormones such as melatonin and orexin.

Melatonin plays a crucial role in sleep regulation. It is produced by the body in response to darkness and signals to the brain that it's time to sleep. By increasing its secretion at night, melatonin reduces alertness, lowers body temperature and slows metabolism, promoting relaxation and drowsiness. Disruptions in the production or release of melatonin can lead to sleep disorders [4].

Orexin, also known as hypocretin, has a significant effect on sleep. It regulates wakefulness and promotes alertness. High levels of orexin keep us awake and active, while low levels allow the body to enter a sleep state. Imbalances in orexin levels can cause sleep disorders such as narcolepsy, where a lack of orexin leads to excessive daytime sleepiness and sudden sleep attacks [5].

2.2 Zolpidem to treat insomnia

Zolpidem is a sedative and hypnotic used in the short-term treatment of insomnia to improve sleep latency. In patients with insomnia, zolpidem improves sleep. It is used in patients who have difficulty falling asleep. In patients with transient insomnia, it shortens sleep duration, prolongs sleep and reduces the number of awakenings during sleep [6].

2.2.1 Structure & Discovery

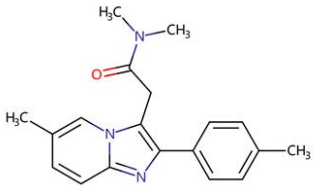

Figure 1. The chemical structural formula of zolpidem

The chemical structural formula of zolpidem is showed in Figure 1. With the discovery of the composition of GABA-A receptor subunits, the specific expression of receptor subtypes, and the development of short half-life compounds, researchers began to develop new sedative-hypnotic drugs to minimize side effects at the end of the 20th century. Zolpidem, developed by the French company Synthelabo, was launched in 1988 and quickly became an effective short-term treatment for insomnia. It was first on the market with FDA approval in 1992. As an imidazopyridine compound that binds selectively to benzodiazepine ω1 receptors, zolpidem has potent sedative-hypnotic properties with low tolerance and dependence [7].

2.2.2 Introduction to GABA and its receptors

Gamma-Aminobutyric Acid (GABA) is one of the most prominent inhibitory neurotransmitters in the central nervous system. This entity exerts a pivotal influence on the modulation of the nervous system's excitability, thereby facilitating relaxation and alleviating anxiety. GABA is a neurotransmitter found in the vertebrate brain. It reduces the frequency of neural activity by decreasing the excitability of neurons and helps to prevent neural overexcitation, which is important in sleep, stress response and anxiety control.

GABA receptors are a class of proteins found on the cell membrane of neurons that bind GABA. They are divided into two main groups: GABA-A receptor and GABA-B receptor. The rapid inhibitory effects of GABA are mediated primarily by the GABA-A receptor, which is widely recognized as an effective clinical drug target. So, we mainly talked about GABA-A receptor.

GABA-A receptors are ligand-gated ion channels, usually consisting of five subunits surrounding a central ion channel. When GABA binds to the GABA-A receptor, the channel opens, allowing chloride ions (Cl-) to flow into the cell, causing hyperpolarization of the neuron and thus inhibiting nerve signaling. The structure of GABA-A receptor and the binding sites for GABA and benzodiazepines is showed in Figure 2 [8].

Many drugs and toxins, including benzodiazepines, barbiturates, and some nonbenzodiazepines (e.g., zolpidem), potentiate the effects of GABA by binding to specific sites on the GABA-A receptor.

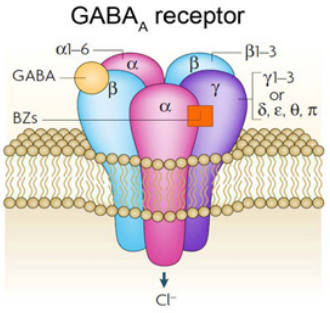

Figure 2. Schematic diagram of the composition of a GABA-A receptor, its structure and the binding sites for GABA and BZs (benzodiazepines). [9]

2.2.3 Mechanism of action

2.2.3 .1 Binding to the GABA-A receptor

Zolpidem binds specifically to the benzodiazepine receptor site on the GABA receptor complex. This binding triggers a series of physiological responses that greatly enhance the initial inhibitory effect of GABA. This is evidenced by a significant increase in the frequency of chloride channel opening. The influx of chloride ions into the neuron leads to hyperpolarization of the cell membrane, making it more difficult for the neuron to excite and transmit signals, effectively reducing the neuron's firing activity.

Through the above mechanism of action, zolpidem is able to exert an effective inhibitory effect on areas of the brain responsible for promoting arousal, such as the reticular activating system. This inhibitory process helps to reduce the level of excitation in the brain, so that the brain gradually transitions from wakefulness to a quiet, relaxed sleep state and is able to maintain a relatively stable sleep state, reducing the occurrence of sleep disturbances and arousals, thus achieving the effect of treating insomnia.

2.2.3 .2. Highly specific

Zolpidem and γ-aminobutyric acid receptor binding has a high degree of specificity, it only binds to the α1 subunit of the γ-aminobutyric acid receptor, and the effect on other structures is extremely small, so it will not produce obvious adverse reactions, and will not affect the synthesis and secretion of other central neurotransmitters, so there are few clinical adverse reactions, and will not produce obvious dependence [2].

2.2.3 .2. Pharmacokinetic properties

Zolpidem has a rapid onset of action, peaked within half an hour after ingestion, the drug utilization rate of up to 70% or more, with a rapid and strong sleep-promoting effect. Its duration of action is about 2-3 hours, the maintenance of deep sleep effect is limited, but due to the short duration of action, daytime side effects such as dizziness, headache, etc. are less, the safety is higher.

2.2.4 Different ways to take in zolpidem

2.2.4 .1. Oral zolpidem:

This is the most common way of taking it and usually comes in tablet form. Patients need to take it at bedtime and sometimes extra doses can be taken if they wake up in the middle of the night.

Oral zolpidem is absorbed in the gastrointestinal tract, then enters the bloodstream and finally reaches the brain to take effect. Absorption of the oral form can be affected by diet, and food can slow the absorption of the drug.

2.2.4 .2. Sublingual zolpidem:

This form of zolpidem is designed to dissolve quickly in the mouth and be absorbed directly into the bloodstream through the blood vessels under the tongue, allowing it to work more quickly.

Sublingual zolpidem is usually taken at a lower dose (e.g. 5 mg), which induces sleep more quickly than the oral form (usually 10 mg).

To take the tablet, the patient places it under the tongue and allows it to dissolve, avoiding swallowing until the medication is completely dissolved.

The sublingual form bypasses the gastrointestinal tract and reduces the first-pass effect (liver metabolism), potentially reducing the side effects of the drug and allowing a faster onset of action.

III Comparison of sublingual and oral zolpidem

A study was conducted to determine which of the 5 mg sublingual doses of zolpidem was better at inducing sleep than the traditional 10 mg oral dose.

Participants were randomly divided into two groups: an oral group (10 mg zolpidem and placebo sublingually before sleep and as needed) and a sublingual group (placebo and 5 mg zolpidem sublingually before sleep). Participants underwent physical examination, polysomnography

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(PSG) and psychomotor vigilance tests, and completed a questionnaire.

A total of 85 patients participated in the treatment, 67 of whom met criteria for insomnia (mean age 48 years, 79% female) and were randomized. Figure.3 compares the sleep data of the sublingual group and the oral group during the whole period. Both treatments reduced the number of nocturnal awakenings by an average of 3.1 days per week and increased total sleep time by 1.5 hours. A 5 mg sublingual dose of zolpidem induces sleep more quickly. The sublingual form may be a better choice for people who need to fall asleep quickly, as it is absorbed more quickly by the body and induces sleep better. However, the oral form may be more suitable for those who don't like the feel of the sublingual [10].

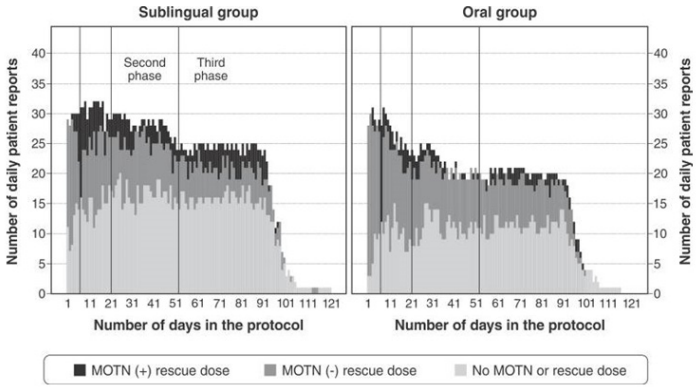

Figure 3. Histogram of sleep diary data: the number of daily reports during the treatment period broken down by middle-of-the-night awakenings (MOTN) with and without use of 'as needed' tablets. [10]

2.3 Ramelteon to treat insomnia

Ramelteon is a melatonin receptor agonist and the first in a new class of medicines that selectively binds to melatonin receptors in the suprachiasmatic nucleus (SCN). It is indicated for the treatment of insomnia, especially long-term insomnia. Ramelteon has no known potential for dependence or abuse [11].

2.3.1 Structure & Discovery

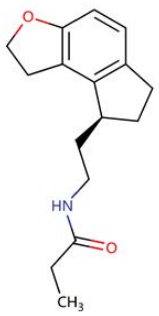

Figure 4. The chemical structural formula of ramelteon

The chemical structural formula of ramelteon is shown in Figure 4. Takeda's ramelteon was approved by the FDA in July 2005 and launched in the US in September 2005. Ramelteon is a melatonin 1 and 2 receptor agonist. Clinical trials have shown it to be effective in the treatment of chronic insomnia in adults and chronic primary insomnia in the elderly. It is the first non-addictive insomnia treatment that is not classified as a Schedule I drug and is used to treat insomnia and circadian rhythm disorders caused by difficulty falling asleep without significant adverse effects [7].

2.3.2 Introduction to melatonin and its receptors

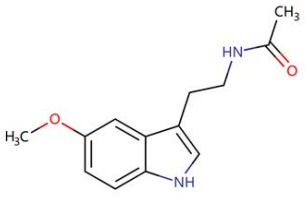

Figure 5. The chemical structural formula of melatonin

Melatonin is an endogenous hormone that is produced by the pineal gland. Its chemical structural formula is shown in Figure 5. It is mainly secreted at night to regulate the body's circadian rhythm and sleep cycle. Melatonin secretion is controlled by light, increasing at night when light is dimmed to promote sleep and decreasing during the day when light is brightened to maintain wakefulness. In addition to regulating sleep, melatonin has a variety of biological roles, including antioxidant, anti-inflammatory and immunomodulatory properties.

The action of melatonin is mainly mediated by its receptors, and there are three main types of melatonin receptor:
MT1 receptors are located mainly in SCN of the brain, which is the main region that regulates the body clock. Activation of the MT1 receptor can inhibit the production of cAMP, which in turn affects a variety of physiological processes.
MT2 receptors are also found in the SCN and are involved in the modulation of biological rhythms. Their activation inhibits the accrual of cAMP and is linked to the phase-shifting effect of melatonin.
MT3 receptors are the actual enzyme that binds to melatonin and has a different function from the MT1 & MT2 receptors, being mainly involved in antioxidant processes.
While MT1 & MT2 receptors are associated with the sleep-wake cycle, MT 3 has a completely different profile and is therefore unlikely to be involved in the sleep-wake cycle [9].
Melatonin receptor agonists are a class of drugs that activate these receptors and have been studied for the treatment of insomnia, modulation of biological rhythms and possible neuroprotective effects [12].

2.3.3 Mechanism of action

Sleep in humans begins with the perception of light/dark cycles in the environment by receptors in the retina, and this information is transmitted via the retino-hypothalamic pathway to neurons in the hypothalamus and the suprachiasmatic nucleus (SCN) in the hypothalamus, which acts as a rhythmic regulator of all physiological rhythmic activity, transmits physiological rhythms to the pineal gland, which in turn controls the release of melatonin, the endogenous neurohormone whose rhythmic release ultimately leads to the onset of sleep in humans. Ramelteon, when specifically bound to melatonin receptors in the hypothalamus, mimics the functions of melatonin in inducing sleep and regulating physiological rhythms, thereby improving sleep. Ramelteon has no significant affinity for the GABA receptor complex or receptors that bind neuropeptides, cytokines, serotonin, dopamine, norepinephrine, acetylcholine or opiates.
Unlike other hypnotics, ramelteon does not bind to neurotransmitter receptors, such as the GABA receptor complex, and does not interfere with the activity of most enzymes, avoiding the distraction, addiction and dependence associated with GABA drugs. Numerous clinical studies have shown that ramelteon is effective in shortening sleep latency and increasing total sleep time, with fewer next-day effects, and is safe and well tolerated.
However, it should be noted that ramelteon is contraindicated in patients with severe liver failure. And when using this drug, it is still necessary to follow the doctor's advice and watch out for possible adverse reactions. At the same time, ramelteon may interact with other drugs, e.g., with fluvoxamine, a strong CYP1A2 enzyme inhibitor, which will cause a significant increase in the Cmax and AUC of ramelteon [13].

3. Discussion

3.1 Comparison

3.1.1 Basic information comparison

Zolpidem is usually recommended to be taken at bedtime to reduce sleep latency. It can be taken orally or sublingually. Oral zolpidem may be affected by food and should be avoided immediately after eating. Long-term use of zolpidem can lead to dependence and should be used on an as-needed basis under medical supervision.
Ramelteon should be taken about 30 minutes before bedtime. Ramelteon is usually taken orally and should be swallowed with a drink of water. It should not be chewed or crushed. Ramelteon may cause photosensitivity and exposure to bright light should be avoided after taking this medicine. Ramelteon is not considered to be an addictive drug, but it should still be used as prescribed to avoid long-term abuse. Concomitant use of ramelteon with fluvoxamine is prohibited. Table 1 shows some basic information of zolpidem and ramelteon.

Table 1. Basic usage, dosage, main side effects and notes of Zolpidem & Ramelteon [14]

Drugs	Drug peaking Time (h)	Drug half-life(h)	Adult oral dose at bedtime(mg)	Side effects	Notes
Zolpidem	0.5~3.0	0.7~3.5	10	Dizziness, headaches, forgetfulness	Elderly 5mg
Ramelteon	0.75	1.0~2.6	8	Weakness, dizziness, nausea, vomiting, insomnia worsening, hallucinations.	Prohibited in combination with fluvoxamine

3.1.2 Comparison of zolpidem and ramelteon for the treatment of acute and long-term insomnia

In a report evaluating the acute and long-term effectiveness of drugs for treating insomnia in adults, zolpidem

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was more effective than placebo in acute treatment. In acute treatment, zolpidem had fewer treatment interruptions for any reason than ramelteon. In long-term treatment, ramelteon had fewer treatment interruptions for any reason compared to other drugs such as zolpidem. In terms of adverse events, drowsiness occurred more frequently with ramelteon than with other drugs, such as zolpidem.

According to the report, zolpidem is recommended for the treatment of acute insomnia, while ramelteon can be used for long-term treatment. However, the specific treatment needs to be more patient-specific, so please follow your doctor's instructions for the rational use of medicines. Figure.6 compares zolpidem and ramelteon in the treatment of long-term and short-term insomnia.

According to the report, zolpidem is recommended for the treatment of acute insomnia, while ramelteon can be used for long-term treatment. However, the specific treatment needs to be more patient-specific, so please follow your doctor's instructions for the rational use of medicines.

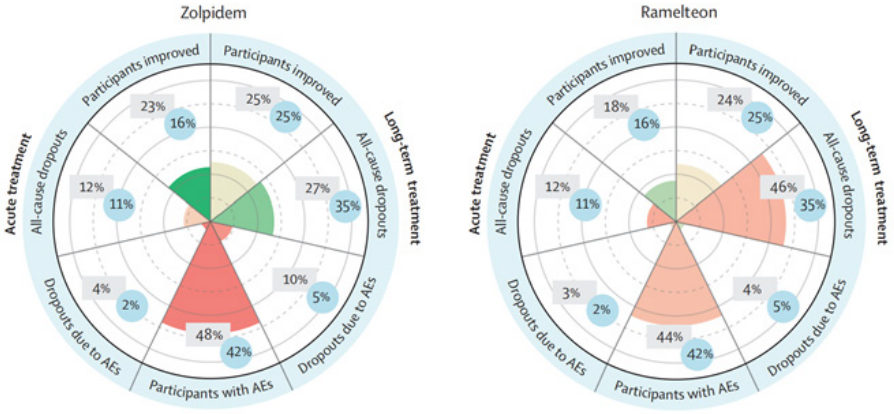

Figure 6. Vitruvian plot summary of the overall profile of zolpidem and ramelteon compared with placebo (Efficacy, acceptance and tolerability are shown for both acute and chronic treatment. Safety information (participators with AEs) is shown in the lower segment. The color indicates the relative efficacy of the intervention in question and the accuracy of the estimate compared to placebo: from green (better) to yellow (unclear) to red (worse). Estimated event rates are given as absolute percentages for active treatment (gray rectangles) and placebo (blue circles). AEs=adverse events.) [15].

3.2 Non-pharmacological treatments

Non-pharmacological treatments are recommended as the first choice in the treatment of insomnia. There are several types:

I Cognitive behavioral therapy (CBT-I):

CBT-I is the recommended first-choice non-pharmacological treatment for chronic insomnia in adults. It is a multi-component therapy that targets the behavioral, cognitive, and physiological factors contributing to insomnia, with the aim of changing maladaptive behaviors and misconceptions about sleep and insomnia. CBT-I can be used in a variety of forms, such as individual or individual group therapy or as a digital form of self-help.

II Phototherapy

Phototherapy is a non-pharmacological treatment for insomnia that uses light exposure to affect a person's biological clock and sleep patterns.

III Complementary and alternative therapies

These include acupuncture, massage, aromatherapy, reflexology, homeopathy, meditative movement therapy, moxibustion, music therapy and yoga.

Although nonpharmacological treatments are recommended as the first choice in the treatment of insomnia, they are not often used in practice because of their high cost or the workload they represent. As a result, patients suffering from insomnia are still often prescribed pharmacological drugs [16,17].

4. Conclusion

The path of insomnia medications has gone through a number of stages, from the early chloral hydrate and barbiturates to benzodiazepines, to modern non-benzodiazepines (zolpidem), melatonin receptor agonists (ramelteon) and orexin receptor antagonists. It is expected that as the mechanisms of insomnia are better understood and new drugs are developed, insomnia medications will evolve into safer, more effective, and more personalized treatments and that there will be a breakthrough in the safety

and tolerability of insomnia medications in the future. Medication can be combined with non-drug treatments, such as cognitive behavioral therapy and sleep hygiene education, to provide a more comprehensive treatment plan.

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