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# Current status, mechanism and research progress of major sedative-hypnotic drugs for the treatment of insomnia

**Jiwu Wang**

School of Pharmacy, Chongqing Medical University, Chongqing, 400016, China
Email: wjw1009@stu.cqmu.edu.cn

**Abstract:**

Insomnia, a widespread condition in modern society, has seen a rise in its affected population in recent years. Prolonged insomnia not only causes anxiety and depression but also impairs individuals' work and study efficiency while posing a threat to their physical health. Drug therapy is the predominant treatment for insomnia, encompassing drugs such as barbiturates, benzodiazepines, novel non-benzodiazepines, melatonin receptor agonists, melatonin, and orexin receptor antagonists. However, concerns arise due to the significant side effects, ease of tolerance development, dependency issues, and rebound phenomena upon drug discontinuation for some of these medications. Hence, there's an urgent need for the research and development of novel hypnotic-sedative drugs that offer minimal toxic side effects, excellent tolerance, and reduced dependency. This paper presents a review of the mechanisms and research advancements of key sedative-hypnotic drugs in recent years. Furthermore, based on conformational relationships, we aim to predict the structure of these novel drugs, providing a valuable reference for drug research and development, while offering diverse drug options tailored to different patient needs.

**Keywords:** insomnia, sedative-hypnotics, barbiturates, benzodiazepines, novel nonbenzodiazepines, melatonin receptor agonists and melatonin analogs, orexin receptor antagonist analogs

## 1 Introduction

Sleep is a spontaneous and reversible resting state that occurs periodically in higher vertebrates and is characterized by a decrease in the body's responsiveness to external stimuli and an interruption of consciousness. Sleep consists of two alternating phases, one is non-rapid eye movement sleep (NREMS), also known as slow wave phase sleep, and the other is rapid eye movement sleep (REMS).The REMS phase is mainly used for restoring and improving brain power, while the NREMS phase is mainly used for restoring strength and repairing damage. Typically, the NREMS stage accounts for about 80% of the total sleep process, while the REMS stage accounts for about 20%. Once the ratio changes, insomnia is triggered. Insomnia specifically refers to a disordered physiological response in which the quality of sleep is chronically low. Insomniacs suffer from sleep deprivation due to the long-term inability to fall asleep or maintain a certain amount of sleep time, which often manifests itself in clinical symptoms such as lethargy, slow reaction time, headache and fatigue.[1] Chronic insomnia can induce anxiety and depression, affecting people's work and study efficiency.[2,3] An international epidemiological survey showed that: 24% of the respondents said that their sleep is poor, China's insomnia population up to 45.2%, and insomnia will increase the risk of coronary atherosclerotic heart disease, heart failure and stroke attack.[4,5]

Usually, the treatment for insomnia is medication. Drugs that cause sedation and near-physical sleep are called sedative-hypnotics. It is a class of drugs that depress the central nervous system, producing sedation, relieving agitation, eliminating restlessness and restoring quiet. Ideally, sedative hypnotics are capable of correcting various types of insomnia causing near-physiologic sleep as needed, without dependence or tolerance. Currently used sedative-hypnotics can be categorized as: benzodiazepines, barbiturates, newer non-benzodiazepines, anxiolytics, antidepressants, melatonin receptor agonists and melatonin, appetite hormone receptor antagonists, and other sedative-hypnotics. Dan its side effects are large, easy to produce tolerance and dependence, once the drug is stopped, it is very easy to rebound phenomenon. Therefore, the research and development of new hypnotic and sedative drugs with small toxic side effects, good tolerance and small dependence is a problem that needs to be solved urgently. In this paper, the mechanism and research progress

of the main sedative-hypnotic drugs in recent years are summarized to provide reference for the research and development of new drugs, as well as more choices of drugs for different patients.

## 2 Barbiturates

Barbiturates are the first generation of sedative-hypnotics and are all derivatives of barbituric acid (malonylurea) in their chemical structure. Barbiturates are a class of central depressants obtained by substituting H at the C5 position and O at the C2 position of barbituric acid. Because of the long substituent group at C5 position with branches and double bonds, the effect is strong but short, and the O at C2 position is replaced by S (such as thiopental), then the fat solubility increases, and the intravenous injection takes effect immediately, but the maintenance time is short.[6] According to the substitution of hydrocarbon groups, sedative-hypnotic effect of the length of time and the rapidity of onset of action, barbiturates can be divided into long, medium, short and ultra-short duration of action of the four types, commonly used more than a dozen kinds of representative of the drug has a long-acting drug phenobarbital drug than the long, medium-acting drug isoamylbarbital, short-acting drug Skoparbital, ultra-short-acting class of sodium thiopental. The classification and clinical application of the commonly used barbiturates are shown in Table 1.

**Table 1 Classification and clinical use of commonly used barbiturates**

| categorization | veterinary drug | Time to effect/h | Maintenance time/h | clinical application |
|---|---|---|---|---|
| Long-acting | Phenobarbital | 0.5~1.0 | 6.0~8.0 | Antiepileptic, treatment of jaundice |
| Medium-acting | Isopentylbarbital | 0.25~0.5 | 3.0~6.0 | Sedative-hypnotic,anticonvulsant |
| Short-acting | Secobarbital | 0.25 | 2.0~3.0 | Sedative-hypnotic, anticonvulsant |
| Ultra-short-acting | Thiopental | About0.05 | 0.25 | Pre-anesthesia |

**Mechanisms of action:** Gamma-aminobutyric acid is a central inhibitory neurotransmitter, and barbiturates agonize GABAA receptors and increase the timing of Cl-influx. Usually, in the absence of GABA, high concentrations of barbiturates also activate Cl- channels, increase Cl-influx, and produce inhibitory postsynaptic potentials, which act as feed-forward inhibition or feedback inhibition of postsynaptic neurons.[7]

**Adverse Reactions:**

1. Continuous administration of barbiturates leads to an addiction similar to that produced by paraldehyde and water and chloral.[8]
2. Hypnotic doses of barbiturates the next morning, sleepiness, dizziness, drowsiness and other after-effects; medium dose can be mild inhibition of the respiratory center, respiratory insufficiency (severe emphysema or asthma) significantly reduce the blood saturation per minute and arterial blood saturation.[7]
3. Abrupt discontinuation of the drug is prone to the phenomenon of "rebound".[7]

**Drug Conformation and Modification:**

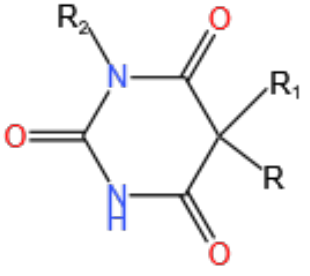


**Figure 1 Generalized formula for the structure of barbiturates**

Phenobarbital is a representative of the barbiturates. Structural modification of phenobarbital, such as the introduction of methyl group in the 1 position N of phenobarbital gives mephenobarbital, which has a longer duration of action than phenobarbital due to increased lipophilicity, and the change of ketone group in the 2 position of phenobarbital to hypomethyl group gives the C-2 deoxidized derivative pomidone, which can be used as an alternative to paracetamol for patients who are habituated to barbiturates. Primidone is a prodrug, which is metabolized in vivo by the liver to produce phenobarbital and exerts its effects.[9]

## 3 Benzodiazepines

Benzodiazepines are second generation sedative-hypnotics. Most benzodiazepines are derivatives of 1,4-benzodiazepine, whose basic structure contains a seven-atom heterocyclic ring and two benzene rings ,[10] and thousands of benzodiazepine derivatives can be obtained by modifying their side chains, due to their strong effects, small side effects, and no significant effect on liver and kidney function, bone marrow, and urinary routines, especially the second day of the drug, there is generally no abnormal drowsiness and dizziness. Therefore, it is widely used in clinical practice .[11] According to the duration of action of the drug, benzodiazepines can be divided into three categories, and the classification and clinical application of commonly used benzodiazepines are shown in Table 2.

**Table 2 Classification and clinical use of commonly used benzodiazepines**

| categorization | veterinary drug | Maintenance time/h | Half-life/h | clinical application |
|---|---|---|---|---|
| Long-acting | diazepam | >24.0 | 20.0~80.0 | Anxiolytic, sedative-hypnotic, antiepileptic, anticonvulsant and muscle relaxant |
| | flurazepam | | 40.0~100.0 | Sedative-hypnotic |
| Medium-acting | clonazepam | 6.0~24.0 | 24.0~48.0 | Anxiolytic, antiepileptic, anticonvulsant |
| | lorazepam | | 10.0~20.0 | Anxiolytic |
| | estazolam | | 10.0~24.0 | Anxiolytic, Sedative Hypnotic, Anti-Epileptic |
| | alprazolam | | 12.0~15.0 | Anxiolytic, Sedative Hypnotic |
| Short-acting | midazoalm | <6.0 | 1.5~2.5 | Sedative-hypnotic, pre-surgical |
| | triazolam | | 2.0~3.0 | Sedative-hypnotic |

Benzodiazepines sedative-hypnotics have an amide bond at the 1,2 position and an imide bond at the 4,5 position in their structure, both of which are susceptible to hydrolysis under acidic conditions (Fig. 2), generating benzodiazepines and the corresponding glycine compounds, and azolines are stable to hydrolysis due to the presence of a heterocyclic ring at the 1,2 positions in the concatenation.[9]

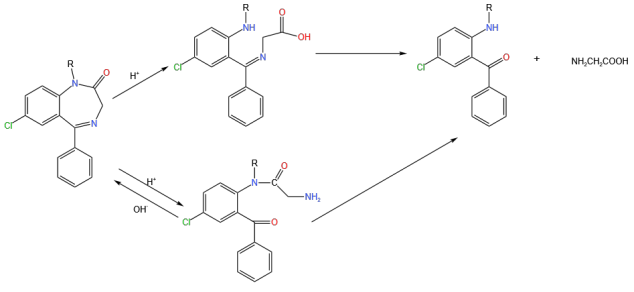

**Fig. 2 Hydrolysis of benzodiazepines for ring opening reactions**

**Mechanism of action:** Benzodiazepines enhance the binding effect of GABA to $GABA_A$ receptors, enhancing the transmission function and synaptic inhibitory effect of GABAergic nerves.[7] When GABA interacts with the receptor, it opens the chloride channel, inward flow of chloride ions, hyperpolarization of nerve cells and central inhibition.[9]

**Adverse reactions:**

1. Higher doses of benzodiazepines may be associated with varying degrees of dizziness, drowsiness, malaise, prolonged reaction time, uncoordinated motor mental and psychomotor disturbances, disorganized thoughts, confusion, dysarthria, retrograde memento mori, dry and bitter taste of the mouth, and even acute dyskinesia, slurred speech, myalgias, and even comatose suppression.[11]

2. weakness, headache, blurred vision, vertigo, nausea and vomiting, diarrhea unsuitable for the epigastrium, and in a few cases, arthralgia, chest pain and incontinence.[11]

3. Administration before labor can result in decreased muscle tone and mild respiratory depression in newborns.[12]

Long-term administration of this class of drugs is tolerated and dependent.[7]

**Drug Conformation and Modification:**

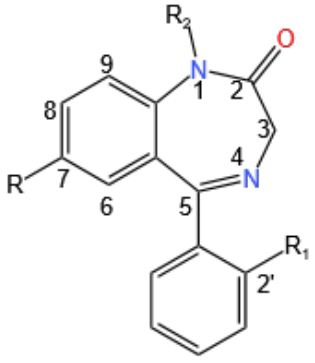

**Fig. 3 General formula of benzodiazepine drug structure**

Studies have shown that: benzodiazepine molecule in the seven-membered subglutacone for the bracket essential structure, in the molecule of the C-7 position and C-2 position (C-5 benzene ring substitution of the neighboring position) to introduce electron-withdrawing substituents, can significantly enhance the activity, that is thought to be related to the reduction of hydrolysis of the seven-membered ring between the 1,2 position, in the 1,2 position, benzodiazepine, and the five-membered nitrogen-containing heterocycles, such as imidazole and triazole ring, to obtain a series of strong action of zolium suffix for the zolium In the 1,2 position of benzodiazepine, the five-membered nitrogen-containing heterocycles such as imidazole and triazole are parallelized to obtain a series of benzazepines with strong effects with the suffix of zolan, and the drugs obtained are still suffixed with zolan when they are parallelized to the tetrahydroxazole ring at the 4,5 position.

# 4 Novel non-benzodiazepines

Most benzodiazepines are not selective in their action on receptors, which inevitably causes various neurological adverse effects. Newer non-benzodiazepine sedative-hypnotics do not have some of the adverse effects of benzodiazepines, which act selectively on receptors on the γ-aminobutyric acid-receptor complex.[13] Their primary structure is that of imidazopyridine or pyrazolopyrimidine analogs, which are mainly used for the short-term treatment of insomnia.[9] Since their introduction to the market, they appear to be a safe alternative to benzodiazepines with a rapidly growing global utilization, as they are considered to have a lower risk of abuse and dependence and better tolerability.[14] Common new non-benzodiazepine drugs include zaleplon, zolpidem, zopiclone, etc., which are referred to as "Z-drugs" because they usually begin with the letter "Z".

**Mechanism of action:**

Similar to benzodiazepines, Z analogs act on GABA receptors, binding to $GABA_A$ receptors to enhance GABA function and thus GABA neuron-mediated central inhibition, and thus are also known as GABAA-positive modulators of metabolism; however, there are differences in the pharmacokinetic profiles of the different Z analogs; for example, zolpidem, its controlled-release tablets, and zaleplon are believed to have a high selectivity for the α1 subunit of the GABA-A receptor's α1 subunit, whereas zopiclone and dexzopiclone bind to all four subunits of the $GABA_A$ receptor ($\alpha_1$, $\alpha_2$, $\alpha_3$, and $\alpha_5$), and thus it has been suggested that the receptor selectivity of zopiclone and dexzopiclone is intermediate between that of the low levels of benzodiazepines and that of the high levels of zolpidem and zaleplon.[15]The $\alpha_1$ subunit is known to be critical for producing sedative effects, while the $\alpha_2$ and $\alpha_3$ subunits may be associated with anxiolytic and muscle relaxant effects.

## 4.1 Zaleplon

The chemical name of zaleplon is {N-[3-3-cyanopyrazolo(1,5-a)pyrimidin-7-yl]
is-N-ethylacetamide}. The structural formula is shown in Figure 4. Zaleplon is a fast-acting sedative-hypnotic drug, which has no effect on the rapid eye sleep while maintaining normal sleep, not only shortens the sleep latency, increases the sleep time and improves the quality of sleep, but also has no obvious "sleep onset reaction", and there is a transient memory loss after taking the drug for about 1 hour. Dependence and withdrawal reactions are smaller than those of benzodiazepines.[7]

**Adverse effects:** headache, drowsiness, dizziness.

## 4.2 Zolpidem

The chemical name of zolpide isN,N,6-Trimethyl-2-p-tolylimidazo[1,2-a]pyridine-3-
Acetamide.The structural formula is shown in Figure 5.Zolpidem is a new type of non-benzodiazepine drug with a short half-life, no active metabolites, fast onset of action, strong hypnotic effect, no accumulation-level residual effects in the body at therapeutic doses, and low risk of drug dependence.[15]

**Adverse effects:** drowsiness, headache, dizziness, increased insomnia, paroxysmal amnesia, hallucinations, euphoria, nightmares, fatigue, diarrhea, nausea, vomiting, abdominal pain; state of confusion, irritability, diplopia, incontinence, etc. .[16]

## 4.3 Zopiclone

The chemical name of zopiclone is 4-Methyl-1-piperazinecarboxylic acid 6- (5-chloro-2-pyri -dinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl.The structural formula of zopiclone is shown in Figure 6.The pharmacological effects of zopiclone are similar to those of benzodiazepines, which can shorten the time of sleep onset, prolong the duration of sleep, reduce the number of awakenings, have no effect on normal sleep, have no hangover reaction on the next day, and do not affect memory. Oral absorption is rapid, peak time 1.5-2h, half-life of 5-6h, mainly in the liver metabolism, renal excretion, a small amount of fecal excretion, continuous multiple administrations of the drug does not have a cumulative effect.[17]

**Adverse reactions:** bitter mouth, nausea, stomach pain, drowsiness, headache, nightmares, anxiety, etc., and is contraindicated in patients with myasthenia gravis.[17]

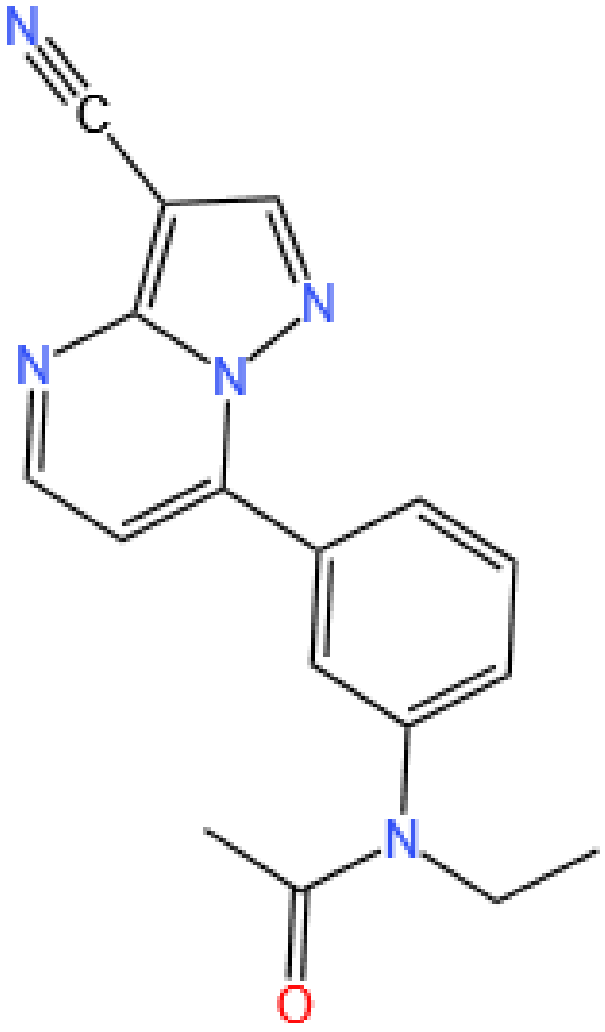

Figure 4 Zaleplon structural formula

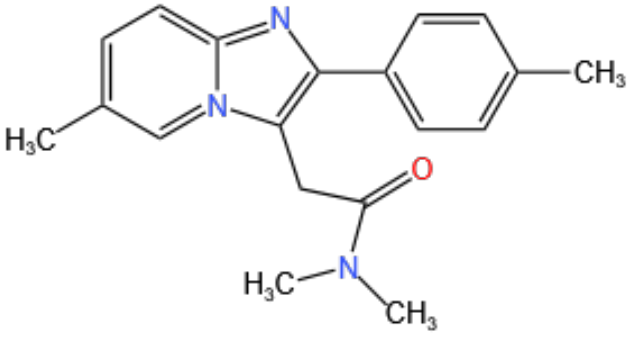

Figure 5 Zopiclone structural formula

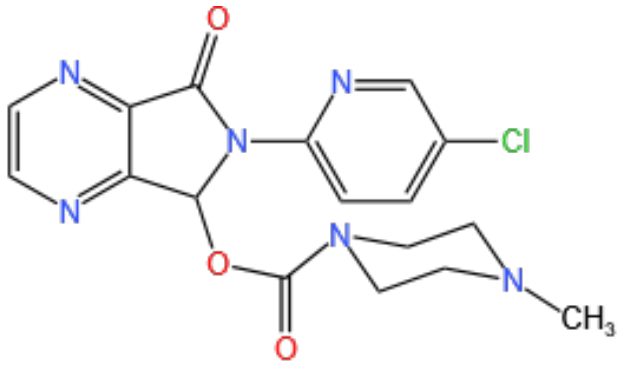

Figure 6 Zopiclone structural formula

## 5 Melatonin receptor agonists and melatonin

Melatonin (MT) is a neuroendocrine hormone produced by mammalian pineal gland, which has the functions of eliminating free radicals, antioxidant, and regulating immunity, and also has the functions of correcting the biological clock of human body, regulating and maintaining circadian rhythms, treating sleep rhythm disorders, and improving sleep, and therefore it is known as physiological hypnotic agent.[18,19] Melatonin receptor agonist drugs mainly exert sedative-hypnotic effects by agonizing MT1 and TM2 receptors, and by increasing exogenous melatonin to raise its concentration in the blood, good hypnotic effects can be achieved without drug residues and obvious side effects, but TM half-life is extremely short, which has a great limitation in the treatment of different symptoms of insomnia, and the selectivity to different biological targets is low,[20] therefore The development of novel TM drugs is a hotspot today, and the melatonin receptor agonists currently available on the market mainly include ramelteon, agomelatine, tasimelteon, and so on.

### 5.1 Ramelteon

The chemical name of ramelteon is N-[2-[(8S)-2,6,7,8-tetrahydro-1H-cyclopenta[e]
[1]benzofuran-8-yl]ethyl]propanamide.The structural formula is shown in Fig.7. Ramelteon has a strong first-pass effect after oral administration, and there are large individual differences in serum peak concentration and area under the drug-time curve. The half-life is longer than that of MT (0.8~1.93h), and it is mainly metabolized by the liver with minimal side effects.[21]Overseas studies have concluded that ramelteon is effective in reducing sleep onset and increasing total sleep time in patients with chronic insomnia.[22-24]

**Adverse effects:** headache, fatigue, drowsiness, vertigo.[25]

### 5.2 Agomelatine

The chemical name of Agomelatine is N-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide.

The structural formula is shown in Figure 8.Agomelatine is a novel melatonin analog, which has both high affinity for $MT_1/MT_2$ receptors and antagonistic effect with 5-$HT_2$c receptors,[21]thus it has dual antidepressant and hypnotic effects with good tolerability and safety, and it is expected to be the new hypnotic drug of choice, especially for depressive insomnia.[26]

**Adverse reactions:** dizziness, drowsiness, anxiety, nausea, diarrhea.

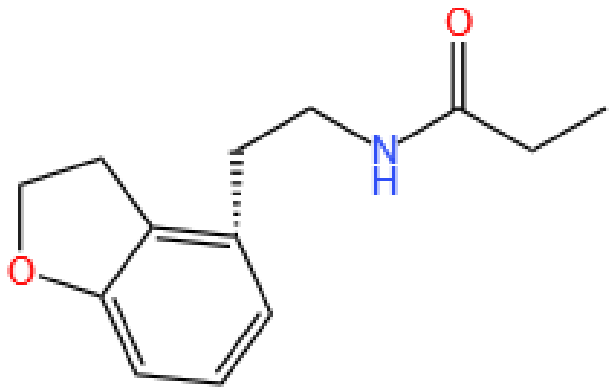


**Figure 7 Structural formula of ramelteon**

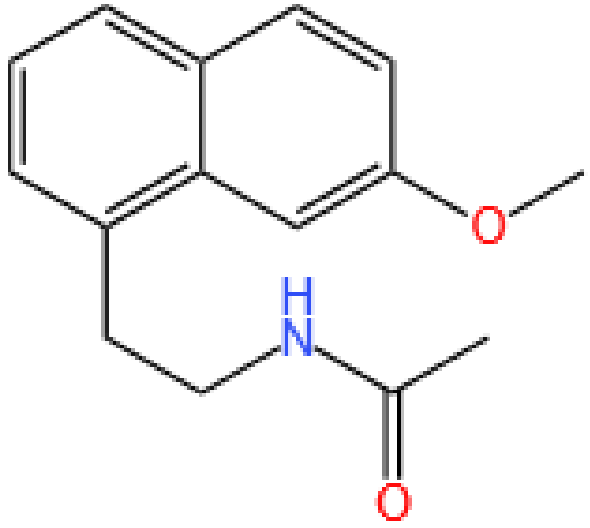


**Figure 8 Structural formula of agomelatine**

## 6 Appetite receptor antagonists

The orexin is secreted by the lateral hypothalamus, and orexin neurons project to a wide range of different regions of the brain, where they play a variety of roles. Over the past 20 years, dozens of compounds have been developed by national and international pharmaceutical companies targeting the orexin receptor, including selective orexin receptor-1 antagonists (1-SORAs), selective orexin receptor-2 antagonists (2-SORAs), and dual orexin receptor antagonists (DORAs). Among them, 1-SORAs have no significant improvement in insomnia,[27] some 2-SORAs only show potent hypnotic effects in animal studies, and further clinical studies are still needed,[28] and DORAs, because of their significant hypnotic effects and good safety, have become the main research and development direction for the treatment of insomnia with orexin receptor antagonists. Currently, there are three dual orexin receptor antagonists approved by the U.S. Food and Drug Administration (FDA) for the treatment of insomnia, namely Suvorexant, Lemborexant and Daridorexant.

### 6.1 Suvorexant

Suvorexant is the first dual orexin antagonist approved for the treatment of insomnia,[29]it can highly selectively block orexin A and orexin B as neurotransmitter peptide agonists to bind to orexin 1 receptor (OX1R) and orexin 2 receptor (OX2R) to inhibit wakefulness,[30] and it is well absorbed by the oral route and produces peak plasma concentrations in about 2h, with a plasma half-life is about 12h, and food does not interfere with drug absorption.[31]

**Adverse reactions:** drowsiness, diarrhea, dry mouth, upper respiratory tract infection, headache, dizziness, abnormal dreams and cough.[31-33]

### 6.2 Lemborexant

Lemborexant was approved by the U.S. Food and Drug Administration (FDA) on December 20, 2019, for the treatment of insomnia in adults to improve difficulty falling asleep or maintaining sleep,and by Japan on January 23,2020, for the treatment of insomnia.[34,35]It competitively binds to both OX1R and OX2R, thereby blocking the arousal effects of orexin, and is used to improve insomnia.[36]Lem is primarily metabolized by P4503A4 cytochrome enzyme(CYP3A4);therefore,CYP3A4 antagonists increase Lem blood levels and increase the risk of drug toxicity, and CYP3A4-inducing agents accelerate its metabolism.[37]

**Adverse effects:** drowsiness, sleepwalking, transient sleep paralysis.

### 6.3 Daridorexant

Daridorexant was approved by the FDA on January 10, 2022 for the treatment of adult patients with insomnia characterized by difficulty falling asleep or difficulty maintaining sleep. It is a is a potent and selective small molecule dual orexin receptor (OX1R and OX2R) inhibitor that inhibits OX1R and OX2R equivalently, blocks both OX1R and OX2R in the CNS simultaneously and equivalently, inhibits overactive arousal in the brain, and is rapidly absorbed and easily crosses the blood-brain barrier after oral administration, which is advantageous for the treatment of insomnia.[38]

**Adverse reactions:** headache, drowsiness, diarrhea or fa-

tigue.

## 7 Conclusion

Ideal sedative hypnotics are able to correct various types of insomnia causing near-physiologic sleep as needed, without dependence or tolerance. From the first-generation barbiturates, second-generation benzodiazepines to the current new non-benzodiazepines, melatonin receptor agonists and melatonin, orexin receptor antagonists and other new sedative-hypnotic drugs, the side effects are getting smaller and smaller, but there are still drowsiness, dizziness, fatigue, and other adverse reactions, so the research on sedative-hypnotic drugs with fewer side effects and less dependence is still an urgent problem to solve. Therefore, research on sedative-hypnotic drugs with fewer side effects and less dependence remains an urgent problem.

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