

Classification of drugs for the treatment of circadian rhythm disorders

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Abstract. Survey studies found that more than 3% of adults have CRSD, and about 16% of teenagers may have CRSD. Although it may be self-limiting, others will cause burden consequences. Many existing papers on drug classification focus on the classification method, or discuss some drug characteristics, but because the target range of drugs is too large, there is no way to expand each drug mentioned, and make their characteristics more detailed and clear. With the development of sleep drug research, there are a lot of reviews on the regulation of circadian rhythm, especially on the circadian rhythm disturbance, but most of them are very detailed studies on a specific drug, such as melatonin or amphetamine. The drugs used to treat circadian disorders can be classed as sedative hypnotics, stimulant stimulants, chronotropic drugs, and gives a cursory mention of other drugs that do not fall into the first three categories. Among the sedatives and hypnotics, barbiturates, benzodiazepines and other drugs include tranquilizers or non-benzodiazepines. Amphetamine, Modafinil and caffeine were mentioned in the stimulant category. The third category of drugs that is mainly described is melatonin. This paper is based on the classification of drugs that regulate circadian rhythm disorders. For each category, at least several representative drugs are proposed and their characteristics are described. It contains basic information about the drug, its properties, mechanism of action, side effects and so on. In the description of drug characteristics, there are also some parts of this article that compare drug effects horizontally. The section on stimulant function discusses how long three different drugs can help to maintain a state of arousal, Differences in side effects were also compared.

Keywords: circadian disorder, drug therapy, classification.

1. Introduction

Nowadays, the number of people with circadian rhythm sleep disorders (CRSD) or circadian rhythm disturbance, continues to rise in many people with wide age ranges. Survey studies from an article called circadian rhythm sleep disorders illustrate that more than 3% of adults have CRSD. The data on circadian sleep disorders with other similar rhythm disorders diseases like insomnia was aggregated, since CRSD can't be accurately summarized in the data collection process, about 10% of adults and 16% of teenagers may have CRSD. Although a part of diseases may be self-limiting, others will cause medical, psychological, social consequences [1]. It is 57 percent of Chinese adults and 36 to 50 percent of adults in Europe and the United States. In terms of prevalence, disorders related to circadian rhythm are worthy of attention and require a series of measures to prevent and treat.

For the treatment of circadian rhythm disturbance, drug therapy is the most common and effective one, as well as the one with high understanding and popularity. Sleeping pills are relatively well known, whether important or western medicine can bring certain effects, but also have relative side effects and drawbacks. The main pharmacological effects of sleeping pills are hypnotic and relatively inconspicuous sedative. Its inhibitory effect on various parts of the central nervous system, to treat insomnia and circadian rhythm disorders, while effectively regulating the symptoms of mood disorders and nervous disorders, which is why many sleeping pills and antidepressants are similar. Most sleeping pills are health drugs, relatively less dependent and safer, but there are also highly dependent drugs.

The research on drugs to treat circadian rhythm disorders is relatively mature, but there is still room for improvement such as reducing side effects or increasing the number of drugs to prevent resistance from developing. There are three stages of medication for insomnia, barbiturates,

benzodiazepines, tranquillizer and non-benzodiazepines. The goal is to make the treatment more efficient with fewer side effects. The first generation of sleeping pills, barbiturates, appeared earlier, the relative therapeutic index is relatively low, and the probability of drug resistance is high, and the role of dependence or addiction is large. The next day after taking it has great influence, and now it is used less; The second class of antipsychotic drugs (benzodiazepines) can quickly return patients to sleep, reduce the number of awakenings, improve sleep quality, light sleep time is shorter. The third class of non-benzodiazepines is diverse and has been shown to induce rapid sleep and reduce the next day's effects [2]. This article focuses on summarizing the effects and side effects of the above three drugs, as well as illustrating the various categories. Two other drugs that regulate circadian rhythm disturbances, such as stimulants and chronotropic drugs, are also described. On this basis, the research directions of different drugs will be compared, and the realistic improvement directions in the future research of such drugs will be evaluated and discussed.

2. Sedative hypnotics

Different drug classifications are used in both private decision-making and clinical studies, and the classification methods are varied, mainly based on the restrictive factors during drug use. Most systems are organized around therapeutic mechanisms, organ systems, diseases, and chemical properties. There are four pharmacologic categories of sleep and circadian disorders that have been found to be comprehensive, including sedatives, hypnotics, stimulants, chronotropic drugs, and other drugs that cannot be grouped into the first three categories [3].

2.1. Barbiturates

Sedative hypnotic drugs are the treatment of choice for most insomnia patients in China, although there are widespread drugs in the market with long treatment period and slow onset of effect. Small doses of hypnotic drugs have a sedative effect, when the dose increased to a certain amount of hypnotic effect, but should not be used in large quantities. The effects of sedative and hypnotic drugs on the central nervous system changed from quantitative to qualitative. There are many different types of sedatives and hypnotics, and they are grouped into three categories, mainly according to the source of the drug extraction, chemical form, and so on.

The first is barbiturates. Barbiturates are a series of drugs made by taking barbiturates as the parent nucleus and then extending them. These drugs can be divided into different types due to the difference in fat solubility and metabolism elimination in the body, including long-acting, medium-acting, short-acting and ultra-short-acting, which mainly refers to the difference in the speed of action. The principle of its action is mainly caused by blocking the ascending activation system of the brain stem reticular structure. The main mechanism of action of barbiturates causes post-outburst enhancement of GABA, which interacts with the alpha and beta subunits of GABA-A receptors and can also increase chloride ion levels, leading to post-outburst and central nervous system inhibition [4]. Barbiturates are universal central depressants. Like other universal central inhibitory drugs, the inhibitory effect of barbiturates changed from weak to strong with the increase of dosage. The corresponding effects of barbiturates are sedation, relief of bad mood, hypnosis, anti-shock, anti-seizure, and anesthesia. The side effects and adverse reactions of barbiturates are opposed to the sedative effects of the drugs. The first is the sequelae, after taking the drug may appear dizziness, lethargy, fatigue, concentration loss, memory loss, mental inactivity and a series of reactions. The second is drug tolerance, which can be developed by short-term use; After taking many drugs for a long time, there will be withdrawal reaction, and even drug dependence. On top of that, there may be other adverse reactions. Like allergic reactions. Even acute poisoning may cause respiratory and cardiovascular problems all the time, even death.

2.2. Benzodiazepines

The second generation of sedative hypnotics is Benzodiazepines. This class is based on benzodiazepines, derived from a large class of related drugs such as antipsychotic drugs. These drugs have been used since the 1960s and are widely used in European countries such as Spain and Belgium. The prescription rate of benzodiazepines in Australia changed from 56.6 per cent to 41.8 per cent between 2011 and 2018, and use of these drugs declined among older people outside Australia in the United States and Canada between 2010 and 2016. The overall trend is down but the overall share is still very high [2]. Benzodiazepines work by increasing gamma aminobutyric acid (GABA), a neurotransmitter in the brain that slows down the nervous system and has relaxing and calming effects, as well as reducing anxiety.

2.3. Non-benzodiazepine and tranquilizers

The third-generation sedative hypnotics includes non-benzodiazepine and tranquilizers, or called antipsychotic drugs and so on. They are still under development. This class has no obvious distinction, here is to mention some drugs that do not fit into the first two categories. Antipsychotic drugs are a kind of central nervous drug, can make patients in the awake condition, to achieve a state of mental stability. In the treatment of circadian rhythm disorders such as insomnia, only antipsychotic drugs are used. And the strong effect of antipsychotic drugs mainly responsible for the treatment of schizophrenia, mania and other psychiatric diseases. Non-benzodiazepine sedative hypnotic drugs compared with the first two, the characteristics of rapid onset, short half-life, associated with repeated administration of no accumulation effect. There is no obvious aftereffect the next day after taking it. It belongs to a short-acting hypnotic. It has been suggested that non-benzodiazepine hypnotics may be more tolerant and have fewer side effects than benzodiazepines because they selectively bind to the alpha-1 subunit of the GABA receptor [3].

2.4. Side effects

In addition, the side effects and abuse of sedative hypnotic drugs are very noteworthy, but there are still some users who do not have such awareness and do not use according to medical advice, which is also related to the sale and control of sleeping pills. Sedative hypnotic drugs have a certain dependence. Drug dependence includes physical dependence and mental dependence. Among them, the body is in the state of physiological adaptation after repeated drug use, mainly manifested as tolerance and withdrawal reaction; Mental dependence is a strong desire for drugs, a need to constantly use, abuse, and repeat the experience of psychological pleasure. Take benzodiazepines as an example. Although the drugs work quickly, they are mainly responsible for short-term treatment. When used over a long period of time it can develop conditions such as tolerance, or rebound insomnia. Severe phase symptoms, including physical and psychiatric symptoms such as photophobia, nausea, anxiety, and depression, occur in 15%-44% of long-term users who suddenly stop using benzodiazepines. According to the 2021 National Survey on Drug Use and Health, 21.4 percent of the 276 million people in the United States have abused illegal drugs in the past year, including 62 million people who have abused sedatives and hypnotics [2]. The main reason for the abuse of sedative hypnotics may be that after taking them, they can affect the increase of dopamine neuron firing, leading to addiction. But the addictive effects of drugs have been focused on according to the development of drugs, so in the study of the third generation of sedative hypnotic drugs, scientists intentionally adjusted to make such drugs have a short duration of action, rapid excretion, no accumulation effect, so the chance of getting tolerance and the chance of addiction will decrease [5].

3. Stimulants

Beside of sedative hypnotics, stimulants are also a useful drug for adjust circadian rhythm. Stimulants play a different role in regulating circadian rhythm than hypnotic drugs, which mainly increase alertness and improve mental activity. Stimulants work primarily by increasing wakefulness

and alertness. Therefore, they are effective symptomatic treatment of various excessive sleep disorders and hypnotic drugs are similar or even consistent.

3.1. Amphetamine

Amphetamine is an example of a stimulants which can treat circadian disturbance. It belongs to a class of drugs used to treat ADHD and narcolepsy, a class of central nervous system stimulants. Its mechanism of action is mainly related to its efficacy, as a central nervous system stimulant, amphetamine can increase the number of monoamine neurotransmitters by increasing the levels of dopamine, norepinephrine, and serotonin in the synaptic space, and by entering the peri-terminus via the transporter's latic acid, thereby inhibiting the vesicular monoamine transporter 2 and disrupting the function of related transporters[6].It can also metabolize a monoamine neurotransmitter through consistent monoamine oxidase, and other related roles. Amphetamine also stimulates the cellular receptor TAAR1 to internalize DAT or reverse the transporter. The effects of TAA1 may also extend to NET and SERT. The above activities be increasing dopamine outflow into the synaptic cleve and inhibiting reuptake in the synaptic cleve through DAT internalization and direct competition [7]. Amphetamine can cause a lot of adverse reactions, such as overexcitement, restlessness, insomnia, tremor, tension, irritability and other symptoms. The human body tolerates such drugs so quickly that long-term users must take higher and higher doses. Taking large amounts of amphetamine can also cause toxic neuropathy. So, the amount of drug taking when amphetamine is acting as a treatment medicine will be controlled specifically. It has been concluded that the dosage of amphetamine for narcolepsy is approximately 5 to 40 mg per episode and should not exceed 60 mg, which is already the maximum dose given to some adults. Should not be used for a long time, great dose [4].

3.2. Modafinil

Modafinil is another kind of circadian stimulants, it is a non-amphetamine central nervous system stimulant with wakefulness promoting properties. It is mainly used for the treatment of excessive daytime narcolepsy, narcolepsy, sleep shift disorder, obstructive sleep apnea and other similar diseases [8]. Modafinil is a weak inhibitor. According to available experimental results, increased concentrations of NE and 5HT were observed in the prefrontal cortex and hypothalamus after administration, which may be an indirect effect of increased extracellular dopamine. Another result shows that Modafinil controls non-explicit induction of c-fos gene expression in the brain's hypothalamus and activates alpha1 adrenergic receptors as central agonists to induce alertness. In addition, modafinil has many pharmacochemical and mechanochemical effects, but has little to do with circadian rhythm. In terms of pharmacokinetics, Modafinil is characterized by easy absorption. The metabolic method is liver metabolism, in which 80% of the dose is obtained by reabsorption in the form of metabolites. It has a half-life of about 15 hours [8].

3.3. Caffeine

The third stimulants which should be mentioned is caffeine. Caffeine is a naturally occurring methylxanthine class of central nervous system stimulant, which is the most widely used psychostimulant worldwide. Its half-life is about 5 hours, but not for pregnant women or those on birth control pills, caffeine's half-life can be extended to 11 hours, a smoker's half-life is shortened by up to 50 percent. The pharmaceutical use of caffeine is a metabolic and central nervous system stimulant, also used in life to reduce fatigue and maintain vigilance. Caffeine's main mechanism is that it acts on adenosine receptors in the brain. Caffeine molecules dissolve both fat and water, so they can cross the blood-brain barrier. There are four opposite adenosine receptor subtypes, A1, A2a, A2b, and A3, and these drugs have antagonistic effects on all four. But it is the antagonism on the A2a receptor that is responsible for caffeine's wakefulness. Unlike the first two stimulants, caffeine acts on adenosine receptors that are not limited to the central nervous system, but are found throughout the body. Caffeine metabolism occurs primarily in the liver through the cytochrome p450 oxidase system, most notably the CYP1A2 enzyme, which metabolizes one of the three dimethyl

xanthines [9]. These metabolites are then further metabolized in the body and excreted by the urinary system.

3.4. Effects

To sum up the comparison of the efficacy of caffeine, Modafinil, and amphetamine, it was noted in several experiments that amphetamine had the longest duration of effective restoration of alertness in healthy adults who had been awake for 44 hours when given 20 mg of D-amphetamine, 600 mg of caffeine, and 400 mg of modafinil. At 13.5 hours, caffeine was the shortest at 5.5 hours and Modafinil lasted 11.5 hours. But amphetamine was also the only drug that had an adverse effect on restorative sleep [10].

In addition to the effects of drugs, drug side effects and some of the negative consequences also need to be known. The first is about amphetamine. Amphetamines are also common drugs of abuse because of the euphoric effects they can produce when taken. The specific mechanism is that after taking amphetamine, it will have a direct effect on DAT and VMAT2 and increase the concentration of dopamine. After prolonged use, a diminished physiological dopamine response can further exacerbate abuse. Acute amphetamine severity is a common symptom caused by abuse. Symptoms include hypertension, tachycardia, shortness of breath, hyperthermia, tremors, and psychosis. About Modafinil, it is a well-tolerated stimulant. The most common adverse effects of Modafinil occur in only 10% of users and include headaches, nausea and decreased appetite. Other adverse effects occur in 5 to 10 percent of the population and include anxiety, insomnia, dizziness, and diarrhea [8]. There is a risk of abuse with these drugs, because it still produces a euphoric state of mind. There have also been studies showing a stage effect of modafinil, in which patients do not develop stage symptoms when treatment is stopped, but narcoleptic patients will return to symptoms of drowsiness. The degree of side effects of caffeine varies depending on the dose consumed and the body's sensitivity to the drug, resulting in symptoms ranging from mild to severe and even fatal. Mild symptoms include anxiety, irritability, increased urination, muscle twitching, and increased heart rate. In more severe cases, it can lead to disorientation, hallucinations, psychosis, seizures, arrhythmias, ischemia, etc.

4. Chronobiological drugs

Chronobiological drugs are substances that can cause changes in circadian rhythm regulation, which can prevent and adjust the circadian rhythm of animals, mainly mammals, which has been damaged and disturbed by the natural environment, or substances that can maintain long-term differences or short-term separation of day and night. Chronobiotics/Time drugs are a general term for drugs that regulate the human circadian rhythm, the most promising of which is melatonin. Such drugs reset the body clock in the suprachiasmatic nucleus of the hypothalamus, thus bringing the circadian rhythm in line with the circadian cycle. While such drugs can increase alertness or promote sleep, they only work if the symptoms are caused by a mismatch between the circadian cycle and the 24-hour day.

4.1. Melatonin

However, at present, there is no specific time drug for adjusting rhythm disorders in the market, and melatonin is a feasible method. In the human body, melatonin is secreted by the hormone melatonin. The human pineal gland is a small, highly vascularized secretory neuroendocrine organ of about 100-150 mg. Its main function is to periodically produce melatonin through the dark period, which has the characteristics of light sensitivity [11]. When the SCNS in the retina receive light information, they send signals to other hypothalamic regions. SCH secretion of gamma aminobutyric acid inhibits the opposite neuron, and disruption of pineal signaling results in melatonin not being secreted when light intensity is high. In the dark, SCN regulate the secretion of glutamic acid, which is responsible for transmitting signals to the pineal gland, so that melatonin can be secreted. In conclusion, light and pineal function are closely related to melatonin secretion, and the longer the

night, the longer the secretion time. Its secretion rhythm is also mediated by the interaction of clock genes in SCNS [12]. According to current research, the target of melatonin and its mechanism of action have not been fully studied, but something that scientists know is the target targets of melatonin are central and peripheral. There are many binding sites in the brain, in the immune system, in the kidneys, in the cardiovascular system, and the location varies by species. Melatonin has a half-life of about one hour, which is shorter than the drugs mentioned above, including hypnotic sedatives and stimulants. It is more effective in treating early insomnia than in treating maintenance and advanced insomnia. But its advantages are also very significant, it has few side effects, high safety. It is less likely to cause dependence, or the hangover effects or withdrawal effects that come with repeated use. The most common side effects of melatonin include headache, dizziness, nausea, and daytime sleepiness [13]. Rare, more severe reactions include seizures, confusion or disorientation, irritability, and lingering short-term depression.

5. Other treatment

In addition to the above three categories, there are several drugs can also have a positive effect on circadian disorders. These drugs generally work to reduce or alleviate the severity of sleep-related disorders, but whether they can be cured remains to be seen. Sodium oxybate/sodium hydroxybutyrate falls into this category. sodium oxybate is the sodium salt of gamma hydroxybutyrate, and GHB is an endogenous metabolite that inhibits the neurotransmitter GABA. Cataplexy in narcoleptic patients or excessive daytime sleepiness for the age of seven and above is now allowed to be treated. The mechanism of action of sodium oxybutyrate is not fully explained. One explanation for the improvement in sleep is that sodium hydroxybutyrate increases the amount of time spent in the N2 and N3 stages of sleep, while decreasing the amount of time spent in the N1, REM and awake transitions. It is possible that sodium hydroxybutyrate as a sodium salt of GHB influences the GABA-B receptor agonist Mars. These drugs have a half-life of about 0.5 to 1 hour and are metabolized almost entirely through biological conversion to carbon dioxide, which is then exhaled from the body [14]. Side effects of sodium oxybutyrate include dizziness, incontinence, confusion. But more common are nausea and vomiting. More severe cases can lead to acute psychosis, anxiety and possibly suicidal ideation. The source of most serious side effects is the consumption of illegal drugs, and in some country's sodium hydroxybutyrate is a drug when available over the counter. The most severe can result in respiratory depression, seizures, altered mental state or even death. Taking such drugs can also lead to weight loss, but this could be a benefit. Some of the medications mentioned above for regulating circadian rhythms should not be used with sodium hydroxybutyrate. For example, sodium oxybutyrate and sedative hypnotic drugs cannot be used at the same time, and not suitable for patients who drink alcohol.

6. Conclusion

In summary, first, the first class of circadian rhythm regulation drugs are sedative and hypnotic drugs, which are mainly regulated by central nervous system inhibitors. The second stimulant mainly stimulates the central nervous system, but the third stimulant, caffeine, is somewhat different from the first two in that it works somewhat with adenosine receptors, mainly the A2a receptor. The third time drug, melatonin, works by accepting daily light signals through the eyes. The difference in light between day and night stimulates SCN conduction signals and leads to the secretion of melatonin. Artificial intake of melatonin can regulate the circadian disorder in general. In terms of side effects, the last drug is relatively safe, because the human body also produces melatonin, but excessive influence is unhealthy, and will lead to a series of related side effects. There are also drugs that can cause severe withdrawal such as amphetamines, benzodiazepines, and many of them are also used for psychiatric purposes, so the dosage needs to be carefully controlled. Unresolved issues, such as the specific mechanism of action of melatonin, or whether side effects of artificially produced rhythm-

regulating drugs have been reduced and why they have been achieved, have not been discussed in great detail. This is also a question that needs to be continued in the future.

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