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Review Article

The Role of Bio-Psychological Factors in Non-24-Hour Sleep-Wake Syndrome

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Abstract

Non-24-hour sleep-wake syndrome (N24) is a circadian rhythm sleep disorder in which the individual's biological clock is unable to synchronize with a 24-hour day. Instead of going to bed at roughly the same time each day, a person with N24 typically delays their bedtime minute by hour. Because most people are required to maintain a regular schedule for work, school, or other social obligations, the first symptoms of N24 syndrome that are usually observed are periodic insomnia at night and excessive sleepiness during the day. Due to the cyclical nature of this disorder, some sufferers tend to feel normal for a few days to a few weeks when their body rhythm is in sync with the rhythm of the society around them. All life on Earth has evolved on a 24-hour cycle of day and night (dark light). To anticipate this daily rhythm, organisms have evolved mechanisms to determine the time of their cellular and metabolic processes. As a result, in almost all cells of the human body there is a biological clock that is built on a cycle of DNA and protein. The activity of molecular clock gene has been seen in white blood cells and cells of the heart, brain, liver and many other tissues.

Keywords: Non-24-Hour Sleep-Wake Syndrome; Bio-Psychological Factors; Darkness; Light

Overview of Non-24-Hour Sleep-Wake Syndrome (N24)

Non-24-hour sleep-wake syndrome (N24) is a circadian rhythm sleep disorder in which the individual's biological clock is unable to synchronize with a 24-hour day. Instead of going to bed at roughly the same time each day, a person with N24 typically delays their bedtime minute by hour. They sleep in the following hours and later than the bedtime, until their sleep period covers the whole hour. (In very rare cases, the sleep rhythm progresses gradually instead of being delayed.) Body temperature cycles and hormonal rhythms of patients also follow a non-24-hour rhythm. Trying to fight this internal rhythm and sleep according to a regular schedule causes severe and cumulative sleep deprivation. N24 occurs in 55-70% of totally blind people, but it also occurs in an unknown number of sighted people [1].

Clinical Signs and Symptoms of Non-24-Hour Sleep-Wake Syndrome (N24)

Because most people are required to maintain a regular schedule for work, school, or other social obligations, the first symptoms of N24 syndrome that are usually observed are periodic insomnia at night and excessive sleepiness during the day. Due to the cyclical nature of this disorder, some sufferers tend to feel normal

for a few days to a few weeks when their body rhythm is in sync with the rhythm of the society around them. As the person's body resynchronizes from the rhythm of the night cycle (or circadian cycle) and the commitments that the person with N24 syndrome tries to maintain, insomnia and excessive daytime sleepiness return [1,2].

The sleep cycle of people with N24 syndrome usually ranges from more than 24 hours (eg 24.1 hours) to 28-30 hours in severe cases. Cases with a cycle of less than 24 hours (which would be expected to result in a gradually progressing rhythm) are very rare [1,2] (Figure 1).

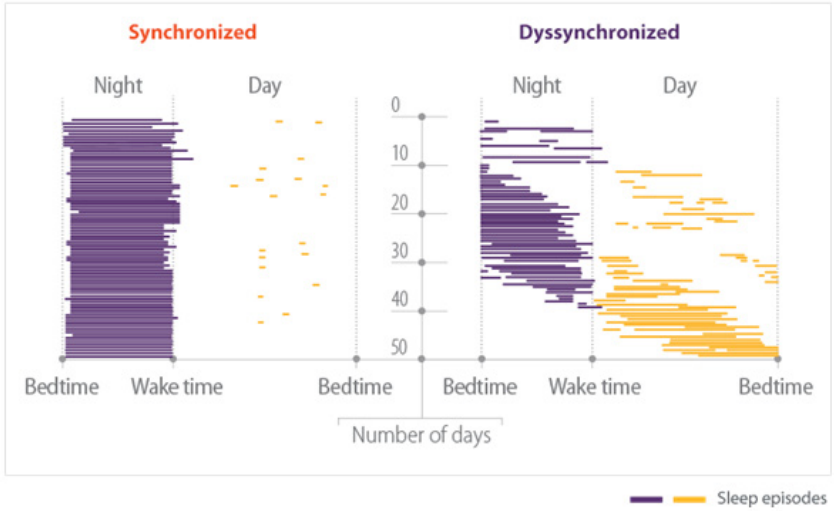

Figure 1: Schematic of a normal sleep-wake cycle (left) versus a disrupted sleep-wake cycle (right)[1].

When these people are allowed to sleep in their cycle, some people with N24 syndrome experience relief from their symptoms of insomnia and fatigue, at the cost of being able to maintain a socially and occupationally required schedule. However, some people with N24 syndrome will experience fatigue, lethargy, lethargy, and sleep disturbance on any schedule, possibly due to continued abnormal synchronization of their internal circadian rhythm. Recent research has documented that in addition to the biological clock in the brain, there is a molecular clock in almost every cell of the body, and scientists speculate that the misalignment of many clocks underlies these symptoms [1,3].

If N24 syndrome is not recognized and managed, and the person tries to fit into a 24-hour schedule, symptoms of chronic sleep deprivation such as excessive daytime sleepiness, fatigue, depression, difficulty concentrating, and memory problems accumulate. N24 syndrome can be extremely debilitating as it causes severe difficulty for a person trying to maintain their social and work commitments. Isolation and loneliness can also be due to being periodically awake while others are sleeping [1,3] (Figure 2).

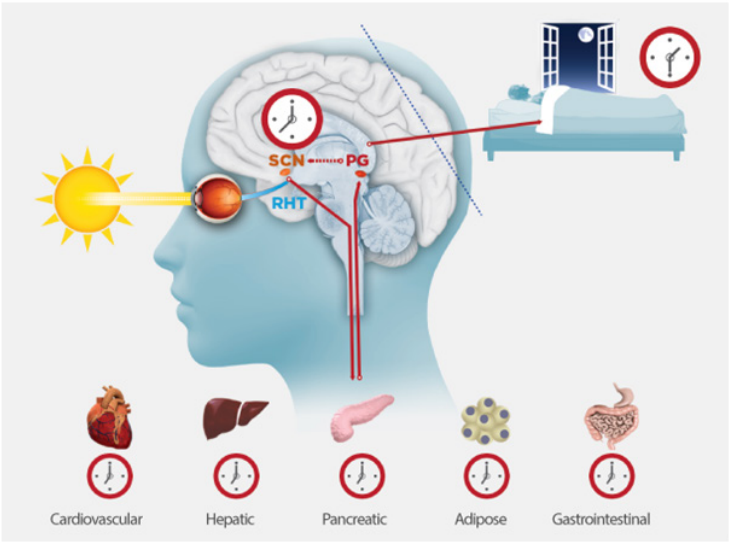

Figure 2: Schematic of the physiology of non-24-hour sleep-wake disorder[1].

Etiology of Non-24-Hour Sleep-Wake Syndrome (N24)

All life on Earth has evolved on a 24-hour cycle of day and night (dark light). To anticipate this daily rhythm, organisms have evolved mechanisms to determine the time of their cellular and metabolic processes. As a result, in almost all cells of the human body there is a biological clock that is built on a cycle of DNA and protein. The activity of molecular clock gene has been seen in white blood cells and cells of the heart, brain, liver and many other tissues[1,4].

Individual cellular clocks operate on a cycle that is close to 24 hours. This is known as a circadian rhythm ("circa-" = about and "dian" = relating to a day). But since the clock is not precise, the clocks of individual cells can be separated from each other or from the Earth's Day-night cycle. To keep these clocks on time, the master clock is located in the brain. In the same way that an orchestra conductor keeps musicians in sync with each other in time, this master clock keeps the body's cellular clocks on the same time cycle. [1,4]

The master clock is located in the suprachiasmatic nucleus (SCN), a part of the brain called the hypothalamus that regulates many of the body's basic functions. The SCN is composed of about 20,000 closely spaced cells whose rhythms are synchronized so that the signaling rates of the cells vary in a nearly 24-hour rhythm. Then the signaling of SCN cells is transmitted directly and indirectly to many other areas of the brain, and then this clock signal is transmitted to the rest of the body using neuro-biochemical and hormonal methods [1,4] (Figure 3).

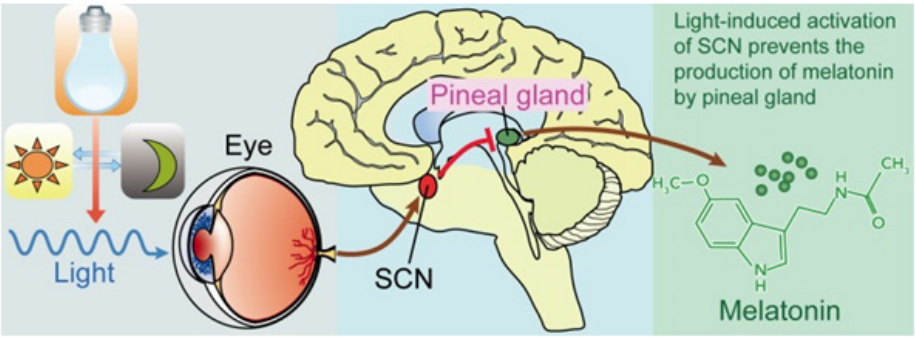

Figure 3: Schematic of the effect of light on the biochemical mechanism of melatonin hormone[1].

The two best rhythms determined by the clock signal are the body temperature cycle and the production of the hormone melatonin. The SCN regulates body temperature through connections with other regions of the hypothalamus. Body temperature varies in a wave-like pattern that reaches a maximum during the day and a minimum (or nadir) at night [1,5].

The SCN also sends a nerve signal that follows a complex polysynaptic pathway through the cervical spinal ganglion to regulate the activity of the pineal gland, which is responsible for melatonin production. Melatonin, sometimes called the "hormone of darkness," is produced in the dark at night. Melatonin is secreted by the pineal into the cerebrospinal fluid and then travels through the bloodstream to reach the cells of the body. It acts on specific melatonin receptors to directly regulate cell function. It also strengthens the temperature cycle by facilitating the nocturnal drop in body temperature. Another effect of this is to reduce the body temperature to prepare the brain and help the body to sleep [1,5] (Figure 4).

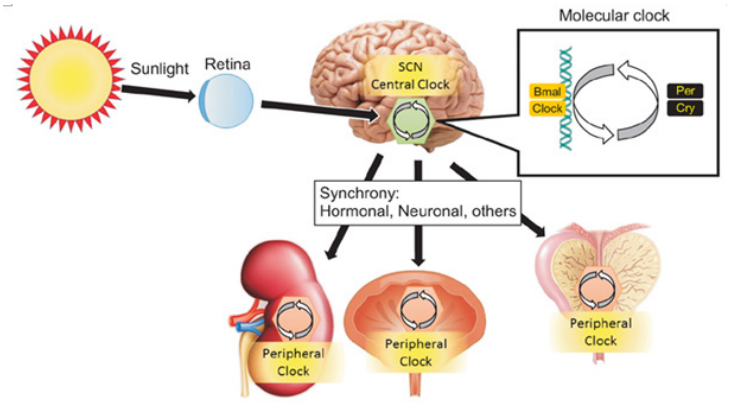

Figure 4: Schematic of the molecular clock of human sleep and wakefulness[1].

While the SCN functions to coordinate cellular clocks throughout the body, there is still a need to synchronize the SCN clock with the Earth's 24-hour period. If the SCN is left alone, it maintains a rhythm of nearly 24 hours. In healthy humans, the intrinsic period of the SCN clock is on average about 24.2 hours. If there was no way to correct this 24-hour cycle, the clock in the SCN would drift several minutes each day until it no longer kept correct time [1,6].

The primary means of correcting the SCN clock is through light-dark exposure. Specialized cells in the retina, which are different from the cells used in vision, register contact with light and dark and transmit this signal to the SCN through a neural pathway known as the retinohypothalamic tract. When the eyes are exposed to light in the early morning hours, this sends a signal that advances the clock in the SCN, thereby providing the necessary diurnal entrainment. When light is visible late at night, a delay signal is sent to the SCN. The diagram of the effect of light at different times of the day and night is known as a phase response curve and can be used to predict the effects of light on the biological clock. If the SCN clock is running for more than 24 hours, it tends to lag behind the circadian cycle, but exposure to morning light resets it. If the SCN clock runs less than 24 hours, exposure to light late at night will slightly delay it. That is, the SCN clock is kept on time by the light and dark cycle of the day and night. In healthy people, exposure to morning light causes the circadian rhythm to be neutralized [1,6] (Figure 5).

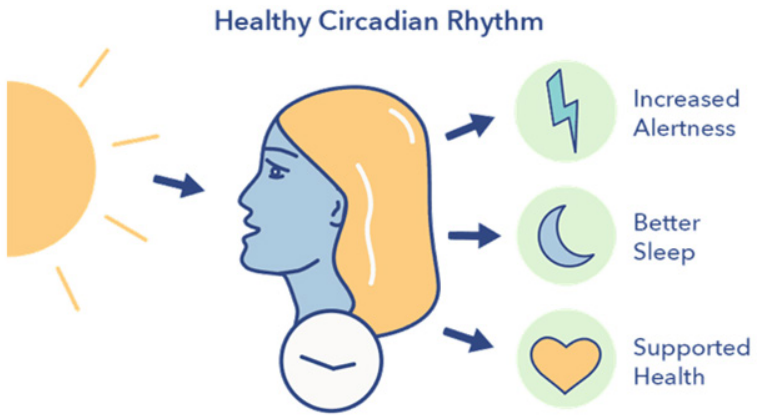

Figure 5: Schematic of the effect of sunlight on the quality of sleep and human comfort[1].

Retinal cells that register light for circadian functions use a pigment called melanopsin as a light sensor. Because melanopsin is particularly sensitive to blue light, that's why the light of that color has a greater effect on the circadian rhythm. Red, orange and yellow light have much less effect. Green light can also affect rhythms in some situations [1,7].

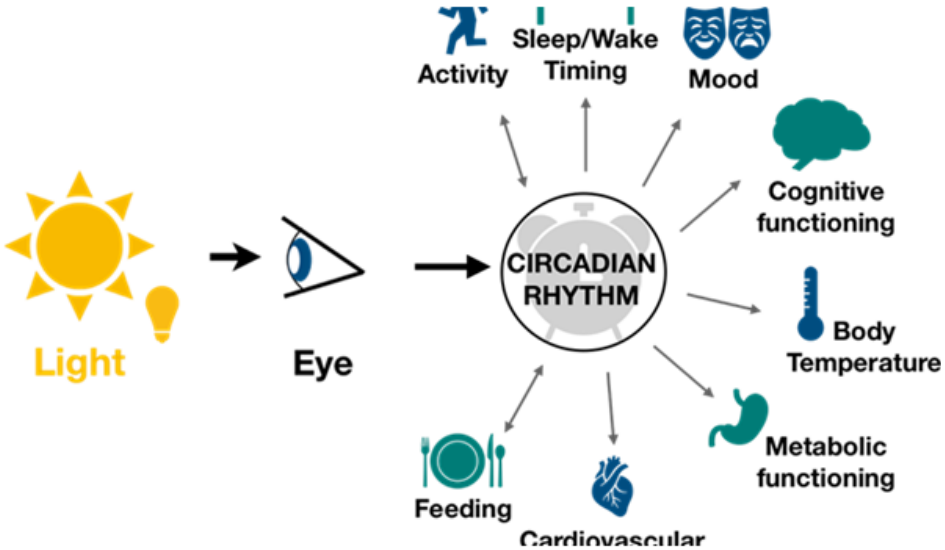

Figure 6: Schematic of the direct effect of sunlight on the rhythm of sleep and daily human activity[1].

Among the most important body rhythms controlled by the SCN is the sleep-wake cycle. This cycle is controlled by two processes, known as the homeostatic process and the circadian process. During sleep, the brain and body repair themselves and gather energy and metabolic resources for the day's activities. During the day, while the person is awake, these resources are gradually consumed. The gradual depletion of energy during the day creates an incentive to sleep to restore that energy. This is known as homeostatic sleep induction. If the homeostatic process is the only one, the person wakes up completely and gradually wears it out over the course of the day, like a dead battery. This means uneven alertness levels throughout the day, with dangerously low alertness in the afternoon and evening. To counter this issue, the SCN also regulates vigilance in a so-called circadian process. As the day wears on and energy wanes, the SCN compensates by sending stronger alertness signals to the brain and body. This alertness signal peaks in the two hours just before sleep. This zone of maximum alertness is known as the "no-sleep zone" because the signal of alertness makes sleep in that zone nearly impossible. As the normal sleep time approaches, the SCN begins to reduce its alertness signal so the body can sleep. In order to prevent early awakening, before night sleep, the circadian alertness signal decreases more during the night. This complex interaction between the circadian process and the homeostatic process allows the human organism to maintain a relatively high state of alertness during the day (with the occasional exception of a mid-afternoon nap period) and allows a period of 9 7 hours of night sleep should be established [1,7] (Figure 6).

When all the cells are working properly, the light signals recorded in the eyes keep the SCN with the 24-hour circadian cycle, and the SCN in turn synchronizes the pineal gland clocks and body cells. Like members of a well-ordered orchestra, all clocks keep a 24-hour cycle in sync with each other. Then, the circadian alertness signal is combined with the homeostatic process, and as a result, the person can sleep at night and maintain alertness during the day. But there are various things that can go wrong with this system and lead to a circadian disorder like N24 syndrome [1,8] (Figure 7).

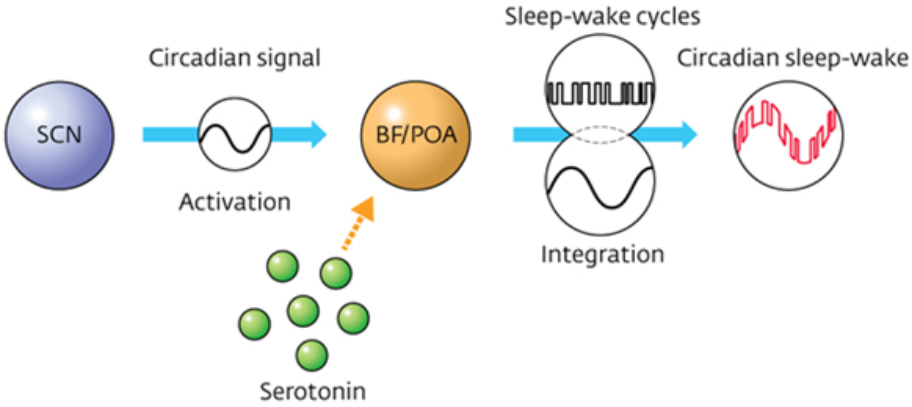

Figure 7: Schematic of the activation pathway of brain hormones in the human sleep and wake cycle[1].

Blindness: The best-known cause of N24 syndrome is that which occurs in blind people. People who are completely blind (without light perception) do not register the light signals that are needed to fine-tune the body clock 24 hours a day. If the SCN clock deviates from 24 hours, the blind person has no natural way to bring it back into sync without medical treatment. Because the intrinsic rhythm of the SCN is not always exactly 24 hours, the circadian timing system of a blind person moves slowly over time. Over time, they will cycle between periods of nighttime sleep and periods of daytime sleep. In the vast majority of cases, the sleep rhythm is gradually delayed, so this period is more than 24 hours, but there are cases of gradual progress and a period of less than 24 hours. The length of the circadian period in blind people with N24 syndrome is typically 23.8 to 25 hours [1,9].

Changes in sensitivity to light: In some sighted people, there may be sensitivity or insensitivity to the effects of light on the circadian system. The vision-producing areas of the eye and brain may function well, but the separate cellular pathway that transmits the circadian light signal may not. If they are completely insensitive to the circadian effects of light, their circadian situation is no different from that of a blind person. If they are not sensitive to light, light may affect their rhythm to some extent but may not be strong enough to correct the circadian drift in their particular light environment [1,9]. Conversely, some patients with delayed sleep phase disorder, a condition related to N24 syndrome, have been shown to be highly sensitive to the effects of light. If they are exposed to natural room light in the evening, it may cause an exaggerated delay in their circadian rhythm. If this delay becomes cumulative, the result is N24 syndrome [1,10].

Environment: Exposure to light in the environment may also play a role. Healthy individuals often fall into a non-24-hour rhythm when kept in isolation without any time cues and allowed to turn the lights on and off as they choose. The length of the rhythm not only exceeds the intrinsic 24.2-hour cycle of the SCN, but maybe as long as 25 hours or more. This is because exposure to light is self-selected and has a delayed effect later in the day.

However, this cannot be the only cause of N24 syndrome because light does not lead to N24 syndrome in all individuals in a non-isolated environment. In contrast, individuals with N24 syndrome are unable to maintain a 24-hour schedule even in a non-isolated environment with typical time cues [1,10].

Hormonal factors: In some cases, the hormone melatonin may play a role in the development or continuation of N24 syndrome. Some patients with N24 syndrome produce less melatonin than normal, which can be problematic because melatonin helps correlate sleep with the day-night cycle. On the other hand, too much melatonin can also cause problems. Antidepressants such as fluvoxamine, which greatly increase melatonin levels by inhibiting its metabolism, have been reported to cause DSPD, which is closely related to N24 syndrome. In some people, the ability to metabolize melatonin is abnormal, which can lead to higher than normal levels during the day, which may lead to disruption of the circadian clock [1,11].

Differences in cellular clock function: Other studies on the causes of circadian rhythm disturbances have focused on the cellular clock itself. Studies in healthy individuals have shown a correlation between the period of the cellular clock and the addition of a biological bubble, which refers to the biomusic concept of synchronizing organisms to a perceived external rhythm, such as music and human dance. Humans are the only species for which all individuals experience podiatry, although there are documented examples of nonhumans being tricked. Morning hours are shorter than evening hours. In N24 syndrome there may be an extreme "evening" extension in which the cellular rhythm may take more than 24 hours for exposure to natural light to correct it, a condition known as "out of the biological bubble". . The period of the human biological clock can be measured in two ways. First, the course may be examined under the normal life conditions of the subject. In that situation, the period of a normal person is 24 hours. Their sleep-wake cycle times do not change over time. A person with the definition of N24 syndrome will have a period longer than 24 hours, sometimes up to 25-26 hours [1,11]. Under normal conditions, the circadian clock is influenced by external factors, especially light. But under certain experimental conditions (fixed routines and forced synchronization) scientists can cancel out these external effects and find what they call the intrinsic period of the clock. This is the time that the watch maintains when isolated from external influences. For normal people, the intrinsic period of the clock is about 24.2 hours. Daily exposure to natural light compensates for the 0.2 difference, allowing normal people to stay in a 24-hour day [1,11].

Three small studies have examined the natural course of N24 syndrome patients. A study of 6 patients reported a 24.5-hour period, a study of 4 patients reported 24.9 hours, and a case report of one patient reported a 24.5-hour period. Therefore, these N24 syndrome patients need to regulate at least 0.5 to 0.9 hours per day to stay within a 24-hour cycle. Exposure to natural light is not enough to make this adjustment. If combined with other factors that trigger the biological clock later, it may be impossible to lock in a 24-hour day [1,12].

Other studies have also investigated the clock of muscle cells (fibroblasts) extracted and grown in culture. The period of the cells in the culture is related to the intrinsic period of the person from whom the cells were sampled. This suggests that the clock period is determined at the cellular level. For N24 syndrome patients this suggests that at least some of them may exhibit an underlying biochemical disturbance of the circadian clock, leading to a longer intrinsic period [1,12].

While the intrinsic course of N24 syndrome patients is longer than average, it overlaps with the course in a few individuals of the severe age type who do not have clinical N24 syndrome. Thus, while the long intrinsic period is clearly an important factor in the development of N24 syndrome, there may be other factors that differentiate between severe evening chronotype and free N24 syndrome [1,12].

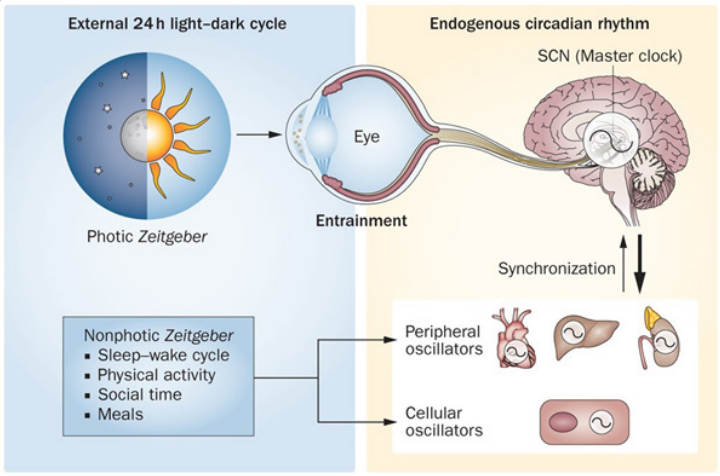

Figure 8: Schematic of the mechanism of the effect of light and darkness on the human eye to establish sleep and wakefulness in 24 hours a day[1].

Differences in sleep regulation: Another possible set of reasons for N24 syndrome is related to homeostatic and circadian sleep regulation. On average, patients with N24 syndrome need a little more sleep than normal. In some cases, this can be severe. While a healthy person may sleep for 8 hours and be awake for 16 hours, if someone needs 12 hours of sleep and then is awake for a normal 16 hours, their entire day will last 28 hours. Changes in the sleep cycle in turn cause changes in light exposure time, perpetuating a cycle of N24 syndrome. Likewise, if someone is sleep-deprived, they may sleep a normal 8 hours, but before enough homeostatic pressure builds up to have 20 hours of awake time, this amounts to 28 hours per day [1,13] (Figure 8).

Sleep timing associated with internal circadian rhythms, also known as the phase angle between sleep and circadian rhythms, is abnormal in many cases of N24 syndrome. Here the phase angle is described in terms of the relationship between sleep time and circadian rhythm, body temperature. In healthy people, the body temperature starts to decrease shortly before sleep onset and it reaches a minimum late in the sleep period, which is usually about 2 hours before waking up. People with N24 syndrome fall asleep very late in the temperature cycle, and therefore the time between the minimum temperature and the time of awakening (sleep compensation) may be 4 hours or more, even in severe cases up to 8 hours. Because the body's response to light-dark exposure is synchronized with internal rhythms (such as cell core temperature) and not with the sleep cycle per se, individuals with N24 syndrome have an abnormal relationship between sleep and circadian rhythms in the They sleep ahead of their clock phase and don't get the light they need during the day to reset their clocks. At the same time, since they wake up late relative to the temperature cycle, they are exposed to light during the phase delay portion of the phase response curve. This tends to push their circadian rhythm much longer than a normal day. This long-term intrinsic course effect strengthens N24 syndrome patients [1,13] (Figure 9).

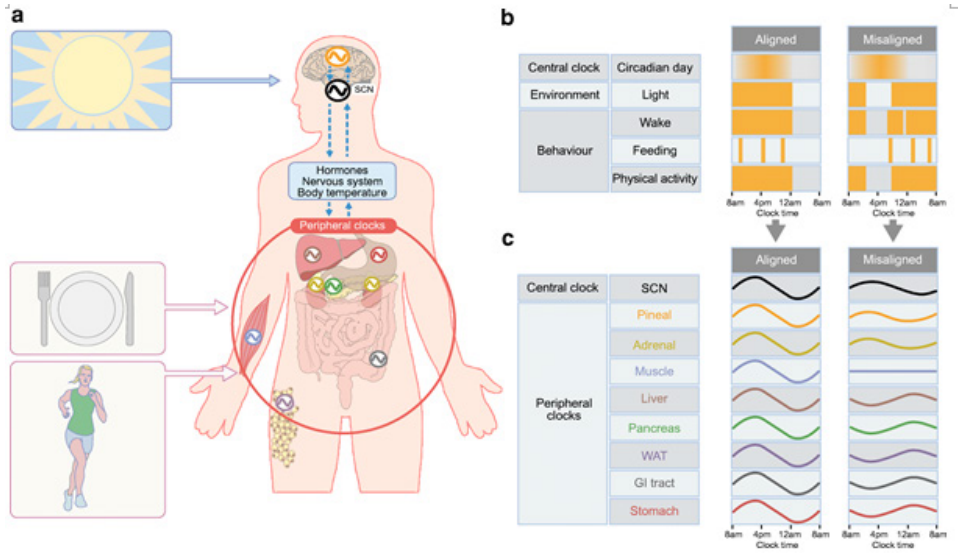

Figure 9: Schematic of the effect of sunlight on the physiological mechanism of the organs of the human body[1].

Regulating sleep around the clock is also important. Even healthy people have a "no-sleep zone" that occurs an hour or two before normal sleep and is associated with the maximum signal of circadian alertness. In people with N24 syndrome, this no-go zone occurs too late in the day and is too strong to allow sleep in a 24-hour cycle [1,14].

This pattern may be enhanced by specific effects of sleep and wakefulness on alertness. When people wake up after a long period of sleep, they are often in a state of less alertness, known as sleep inertia. In people with N24 syndrome, this state of slowness and revelry may be very powerful and last for hours. The more awake they are, the more alert they are. (This may be explained by the observation that brain cell circuits are awake the longer they become more excitable.) When it's time for them to sleep (if they want to stay on a 24-hour cycle) their alertness is as low as reaches high Their high energy state, even if it is short, does not allow them to fall asleep at a normal time. Additionally, patients with N24 syndrome may be reluctant to fall asleep at this time because they end up feeling more awake, alert, and productive [1,14] .

Development of sleep: The development of the brain, especially the circadian and sleep centers, is another factor in the dynamics of sleep and wakefulness. In pervasive developmental disorders such as autism, a relatively high frequency of N24 syndrome and other circadian rhythm and sleep disorders has been observed. It is assumed that the circadian and sleep centers of the brain did not develop properly or were affected by other biochemical or anatomical defects. Other people with N24 syndrome who do not have widespread developmental disorders may have developmental disorders limited to sleep and circadian brain centers [1,15].

Trauma: Physical injuries to the brain, such as head injuries, have been shown to lead to N24 syndrome in previously healthy

individuals. It is assumed that head injury damages the sleep and circadian centers of the brain such as the hypothalamus or the pineal gland. Similarly, brain tumors lead to N24 syndrome. Circadian sleep disorders have been observed in survivors of tumors affecting the pons and hypothalamus. Craniopharyngioma also leads to sleep disorders. In some cases, this damage is caused by the tumor itself, and in other cases, due to radiation therapy in the head. In one case, an aneurysm near the SCN resulted in a transient N24 syndrome. There is also a report of N24 syndrome following chemotherapy for Hodgkin's lymphoma. Trauma Under the heading of physical abnormalities, any factor that results in total blindness, whether through genes, disease, or injury, can lead to secondary N24 syndrome [1,15].

Iatrogenic: N24 can also result from attempts to treat the more common disorder, delayed sleep phase disorder (DSPD). One of the most widely used treatments for DSPD is chronotherapy, in which the patient is instructed to gradually delay their sleep and wake times by up to three hours a day until the circadian clock is set to one. Change the sleep and wake schedule that is more socially acceptable. In principle, this means the temporary adoption of the N24 program. Unfortunately, in some patients, once an N24 schedule is established, it is almost impossible to eliminate it. They have replaced a circadian rhythm disorder, DSPD, with a more debilitating disorder, N24. There are several reasons why it is difficult to separate from the N24 pattern. One involves sleeping time, relative to the temperature rhythm mentioned above. Another involves something called circadian flexibility. This means that when the organism is on a certain cycle, including a non-24-hour cycle, it remembers the circadian clock of that cycle and tries to continue it. The risk of post-treatment N24 has been known since the 1990s, but many doctors are still unaware of the risk of complications of this disease as they continue to use the wrong treatment.1,15

Genetics: There is increasing evidence of a genetic component to N24 syndrome. In most cases it is not a simple inherited genetic disease (inheritance model). Most patients with N24 syndrome do not have parents or close relatives with the disease. However, it appears that there are several genetic factors that can predispose someone to N24 syndrome [1,16].

One study showed specific genetic changes (single nucleotide polymorphisms, SNPs) in the BHLHE40 gene, located on the short arm of chromosome 3 at 3p26.1, in 4 patients with N24 syndrome. Because this gene encodes components of the cellular clock, such mutations may affect the function of the cellular clock and lead to the abnormalities noted in N24 syndrome [1,16].

A separate study of 67 N24 syndrome patients found an association with a polymorphism in the PER3 gene located on the short arm of chromosome 1 at 1p36.23. The PER3 gene also encodes an important component of the circadian cellular clock. Variations in the PER3 gene (both SNPs and repeat number) are believed to affect the free-running period (in animals), the homeostatic drive to sleep (in humans), and the response to light (in humans) [1,16]. DSPD, a disease related to the N24 syndrome, was associated in a family study with a mutation in the CRY1 gene, located on the long arm of chromosome 12 at 12q23.3, which is involved in the circadian clock [1,17].

Several genome-wide studies, genetic screening of more than 100,000 individuals, have shown genetic associations with human chronotypes. While these studies did not specifically involve N24 patients, N24 is closely associated with severe evening chronotype, suggesting that some of the same genetic factors may also be involved. Taken together, both gene-specific studies in Non-24 and general genetic studies of circadian rhythms strongly suggest that some individuals may have a genetic predisposition to develop N24 syndrome [1,17].

Frequency of Non-24-Hour Sleep-Wake Syndrome (N24)

While the total number of people living with N24 syndrome is unknown, researchers believe that more blind people have the syndrome than sighted people. It is estimated that 55-70% of all people who are totally blind have N24 syndrome. People who lack any optical perception (eg those whose eyes have been denucleated) are more affected than people who have some retinal function. The frequency of N24 syndrome in the world's sighted people is unknown, but so far 100 sighted people with N24 syndrome have been reported in the medical literature from around the world. Fifty-seven of these cases were reported in a Japanese study. Because the disease is not widely recognized, there may be a significant number of undiagnosed cases [1,18]. In published cases of sighted patients with N24 syndrome, about 75% are male. Studies of healthy adults show that, on average, men have longer circadian cycles than women. Among the support groups, the number of male and female patients is almost equal. The most common age of onset is late teens or early twenties, although N24 syndrome can occur at very young or older ages. This disorder seems to be lifelong. There are insufficient data to determine whether N24 syndrome is progressive. Anecdotal evidence from long-standing N24 syndrome sufferers suggests worsening of symptoms with age, along with increased day length, but this may be due to an interaction between N24 syndrome and age-related sleep disturbances. Clinical research on changes in the manifestations of N24 syndrome during the life cycle is currently lacking. N24 syndrome was first described in the medical literature by Elliott, Mills and Waterhouse in 1970 [1,18].

Disorders Associated with Non-24-Hour Sleep-Wake Syndrome (N24)

Symptoms of the following disorders can be similar to symptoms of N24 syndrome. Comparison may be useful for differential diagnosis of this syndrome:

Delayed sleep-wake phase disorder (DSPD) is a circadian rhythm disorder, much more common than N24 syndrome, in which the body's normal sleep-wake onset time is shifted several hours later than the affected individual. The difference between DSPD and N24 is that DSPD sufferers have a sleep phase delay that remains almost constant from day to day, whereas later N24 sufferers have a constantly changing sleep duration. For example, a person with DSPD may go to bed at 4 am most nights. The exact

time may fluctuate from day to day (eg 3am one day or 5am the next) but the delay will not be more than that. A person with N24 syndrome sleeps at 4 AM one day, 5 AM the next, 6 AM the next, 7 AM, etc., all day and night [1,19].

Researchers have theorized that some people who suffer from DSPD have biological clocks with circadian rhythms that are much longer than normal, just like people who suffer from N24 syndrome, but the former are still able to They have 24-hour absorption. According to this theory, it is this longer circadian rhythm that causes the biological clock of people with DSPD to shift the bio-bubble material to a later time. It is worth noting that people with DSPD later develop N24 syndrome [1,19].

Irregular sleep-wake rhythm disorder (ISWRD) is characterized by a lack of a circadian rhythm of sleep and wakefulness. Sufferers sleep at variable hours during the day and night, with or without a specific pattern. During a typical 24-hour day, there are often 3 or more sleep periods of varying length. ISWRD differs from N24 in that people with N24 syndrome have a distinct rhythmic pattern of sleep, but their rhythm period is longer than 24 hours. ISWRD patients have little or no rhythmic patterns of any kind. Patients with long-standing N24 syndrome have been observed to have disordered sleep as the disorder progresses, but usually retain at least some of the rhythmic pattern, which distinguishes them from ISWRD. ISWRD is more common among children with developmental disabilities and elderly patients with dementia. It can also be caused by head injury or brain tumors. ISWRD is also known as circadian rhythm sleep disorder, a type of irregular sleep [1,19].

Sleep apnea is a common sleep disorder characterized by temporary and frequent interruptions in breathing during sleep. Symptoms of this disorder include frequent sleep interruptions during the night, excessive daytime sleepiness, loud snoring, irritability, and poor concentration. Obesity, including a large neck and a narrow or congested airway, is commonly associated with sleep apnea. In obstructive sleep apnea syndrome, the most common form of sleep apnea, difficult breathing is interrupted by airway collapse. After that, there may be a partial awakening and the person is gasping for breath. Untreated sleep apnea is associated with high blood pressure, irregular heartbeat, and an increased risk of heart attack, heart failure, stroke, and diabetes. Because obstructive sleep apnea is so common, affecting approximately 24% of men and 9% of women, it is not uncommon for someone with N24 syndrome to also have sleep apnea [1,20].

Idiopathic insomnia is a rare condition that may be misdiagnosed as N24 syndrome or may be associated with N24 syndrome. While N24 syndrome appears due to an abnormal wakefulness period usually longer than 24 hours in a "day," a person's persistent insomnia may cause the person to indicate the time of sleep onset that if the person stays awake, He will sleep and wake up for a longer period of time. Idiopathic hypersomnia is characterized by episodes of severe sleepiness that occur for no apparent reason (idiopathic). Episodes may be chronic or persistent. Some people with idiopathic hypersomnia sleep for long periods of time (for example, more than 10 hours). Others sleep for less time (for example, less than 10 hours). Idiopathic insomnia can disrupt many aspects of life. Behavior modification and drugs are used to treat this disorder [1,20].

Narcolepsy is a neurological sleep disorder characterized by chronic bouts of excessive daytime sleepiness, sometimes called excessive daytime sleepiness (EDS). Drowsiness attacks may last for only a few seconds or minutes. The frequency of these episodes varies from a few episodes to several in a day. Nocturnal sleep patterns may also be disturbed. Three additional symptoms often associated with narcolepsy are severe muscle weakness (cataplexy), a specific type of hallucination that occurs just before falling asleep or waking up, and brief episodes of paralysis upon awakening. Narcolepsy may be associated with "automatic behavior", that is, performing automatic tasks without any previous memory or recollection of the task [1,20].

Kline-Lewin syndrome is a rare disorder characterized by the need for a large amount of sleep (excessive sleep) (ie, up to 20 hours a day). excessive consumption of food (compulsive hyperphagia); and behavioral changes such as unexpected abnormal sexual drive upon awakening, affected individuals may exhibit irritability, lack of energy (lethargy), or lack of emotion (apathy). They may also appear confused and hallucinate. The symptoms of Klein-Lewin syndrome are periodic. An infected person may live without symptoms for weeks or months. If present, symptoms may last for days to weeks. In some cases, the symptoms associated with Kline-Lewin syndrome eventually disappear with age. However, episodes may recur later in life. The exact cause of Klein-Lewin syndrome is unknown [1,20].

In addition, hypothyroidism, periodic limb movement disorder, depression, low blood sugar and other conditions can also cause excessive daytime sleepiness. Conditions associated with excessive nocturia such as heart disease, diabetes, prostate disorders, congestive heart failure, interstitial cystitis, systole, and other bladder problems may also lead to symptoms of disturbed sleep and wakefulness patterns as well as excessive daytime to be sleepiness [1,20] .

Diagnosis of Non-24-Hour Sleep-Wake Syndrome (N24)

Initial diagnosis is based on home sleep logs kept by the patient, which show non-24-hour sleep patterns. This is usually easier to detect if the patient's sleep time is not limited by social or work commitments [1,21].

Confirmation of the diagnosis can be obtained using an astiggraph, a device worn on the wrist that records movement and is used to track sleep time. The adhesive marker should be used long enough for the sleep cycle to complete at least one crossing of the clock, typically several weeks. Documenting the non-24-hour pattern of melatonin secretion may be a useful confirmation of diagnosis, although this method is currently used mostly for research purposes [1,21].

Clinical Trial

Sleep logs and stratification are the primary means of initial follow-up. Polysomnography (nocturnal sleep study technique) is not necessary to diagnose N24 syndrome but may be used to rule out related disorders. For polysomnography to be useful, it must be done at a time when the patient's cycle allows him to sleep [1,21].

Treatment Paths for Non-24-Hour Sleep-Wake Syndrome (N24)

In 2014, the US Food and Drug Administration (FDA) approved Hetlioz (tasimelteon), a melatonin receptor agonist, for the treatment of N24. Hetlioz, manufactured by Vanda Pharmaceuticals, Inc., is the first FDA-approved treatment for this disorder. The efficacy of Hetlioz was evaluated in two clinical trials on totally blind subjects with N24. Most recommended treatments for sighted patients with N24 syndrome include exposure to specific regimens of light (phototherapy) and darkness (scototherapy) [1,22].

Phototherapy usually involves the use of a light box. The lightbox is used early in the morning, typically for 2 hours, to stabilize the sleep cycle. Light therapy is best started when the patient's cycle is established at the desired waking time. Light is recorded by special cells in the retina that send a signal to the brain through the retinohypothalamus system. This signal suppresses melatonin output and alters sleep time. The phase response curve determines the best time for light exposure [1,22].

Dark therapy (scototherapy) is performed by preventing exposure to light at the end of the day. Even normal room light may have a phase delay, so patients should remain in dim light or use special dark glasses that reduce exposure during the day and night [1,22].

A combination of light and dark therapy is believed to be more effective than either alone. If a 24-hour cycle cavity is achieved with light and dark therapy, the patient must maintain their therapeutic regimen or they will return to the same sleep-wake state [1,22].The hormone melatonin may be used to stabilize the sleep-wake cycle. Melatonin is usually taken about 4-6 hours before the intended bedtime. While melatonin is often effective in blind patients with N24 syndrome, it is rarely successful as the sole treatment in sighted patients with N24 syndrome [1,22].

Investigational Treatments

Early case reports suggest that vitamin B12 can successfully treat some cases of N24 syndrome. Blue light has a special role in influencing the circadian rhythm. Blue-enriched light has been used in the treatment of DSPD-related disease and may be beneficial for N24, although no cases or trials have been published. Conversely, blue light avoidance using glasses that block all blue (and sometimes green) light has been shown to be successful as a widespread treatment in patients with N24 syndrome, but there are no published studies of this. There is no method. Additionally, instead of glasses, patients may use special red or amber lights (which do not extinguish blue or green light) for illumination at night [1,22]. There is considerable research on the basic biology and molecular genetics of circadian rhythms. Drugs that alter the timing of the biological clock are a promising avenue for future study, but none are yet ready for clinical use. Research on circadian and homeostatic control of sleep time in healthy individuals and patients with N24 syndrome and related disorders may also provide clues to future treatments [1,22].

Conclusion

The sleep cycle of people with N24 syndrome usually ranges from more than 24 hours (eg 24.1 hours) to 28-30 hours in severe cases. Cases with a cycle of less than 24 hours (which would be expected to result in a gradually progressing rhythm) are very rare. All life on Earth has evolved on a 24-hour cycle of day and night (dark light). To anticipate this daily rhythm, organisms have evolved mechanisms to determine the time of their cellular and metabolic processes. As a result, in almost all cells of the human body there is a biological clock that is built on a cycle of DNA and protein. The activity of molecular clock gene has been seen in white blood cells and cells of the heart, brain, liver and many other tissues. In 2014, the US Food and Drug Administration (FDA) approved Hetlioz (tasimelteon), a melatonin receptor agonist, for the treatment of N24. Hetlioz, manufactured by Vanda Pharmaceuticals, Inc., is the first FDA-approved treatment for this disorder. The efficacy of Hetlioz was evaluated in two clinical trials on totally blind subjects with N24. Most recommended treatments for sighted patients with N24 syndrome include exposure to specific regimens of light (phototherapy) and darkness (scototherapy). There is considerable research on the basic biology and molecular genetics of circadian rhythms. Drugs that alter the timing of the biological clock are a promising avenue for future study, but none are yet ready for clinical use. Research on circadian and homeostatic control of sleep time in healthy individuals and patients with N24 syndrome and related disorders may also provide clues to future treatments [1-22].

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Conflict of Interest

None.

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