Exhibit 3:

NORD

Non-24-Hour Sleep-Wake Disorder

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Synonyms

- circadian rhythm sleep disorder, free-running type
- free-running disorder
- hypernychthemeral syndrome
- N24
- non-24
- non-24-hour disorder
- non-24-hour sleep-wake cycle disorder
- non-24-hour sleep-wake syndrome

Diseases Overview

Non-24-hour sleep-wake disorder (N24) is a circadian rhythm sleep disorder in which an individual's biological clock fails to synchronize to a 24-hour day. Instead of sleeping at roughly the same time every day, someone with N24 will typically find their sleep time gradually delaying by minutes to hours every day. They will sleep at later and later clock times until their sleep periods go all the way around the clock. (In extremely rare cases the sleep rhythm will gradually advance rather than delay.) Patients' cycles of body temperature and hormone rhythms also follow a non-24-hour rhythm. Attempts to fight against this internal rhythm and sleep on a typical schedule result in severe and cumulative sleep deprivation. N24 occurs in 55-70% of completely blind people, but also occurs in an unknown number of sighted people.

Signs & Symptoms

As most people are required to keep a regular schedule for work, school, or other social obligations, the first symptoms of N24 usually noticed are periodic night-time insomnia and excessive daytime sleepiness. Due to the cyclical nature of the disorder, some affected persons will tend to feel normal for periods of days to weeks when their body's rhythm is synchronized with the rhythm of society around them. As the individual's body once again desynchronizes from the rhythms of the light-dark cycle (or day-night cycle) and the obligations the individual with N24 is trying to maintain, the insomnia and excessive daytime sleepiness will return.

The sleep cycle of persons with N24 usually ranges from just over 24 hours (e.g. 24.1 hours) to as many as 28-30 hours in extreme cases. Cases with cycles less than 24 hours (which would be expected to result in a gradually advancing rhythm) are extremely rare.

When allowed to sleep on their own cycle, some individuals with N24 will find relief of their symptoms of insomnia and fatigue, at the cost of the ability to maintain a schedule required for social and occupational requirements. However, some people with N24 will continue to experience fatigue, grogginess, malaise and disrupted sleep on any schedule, possibly because of continued desynchronization of their internal circadian rhythms. Recent research has documented that in addition to the central clock in the brain, virtually every cell in the body has a molecular clock, and scientists speculate that desynchronization of multitude of clocks is what underlies these symptoms.

If N24 is not detected and addressed, and the person attempts to stay on a 24-hour schedule, the symptoms of chronic sleep deprivation will accumulate, such as excessive daytime sleepiness, fatigue, depression, difficulty concentrating, and memory problems. N24 can be severely disabling as it causes extreme difficulty for the individual attempting to maintain social and career obligations. Isolation and loneliness can also be issues due to periodically being awake when others are asleep.

Causes

All life on earth has evolved in conditions of a 24-hour day-night (light-dark) cycle. Organisms have evolved mechanisms to time their cellular and metabolic processes to anticipate this daily rhythm. As a result, within nearly all cells of the human body there is a biological clock based on a cycle of DNA and protein synthesis. Clock gene activity has been found within white blood cells and cells of the heart, brain, liver and many other tissues.

The individual cellular clocks run on a cycle that is close to 24 hours. This is known as a circadian rhythm ("circa-" = about and "dian" = pertaining to a day). But because the clocks are not exact, the clocks of individual cells can drift apart from each other or from the earth's day-night cycle. To keep these clocks in time there is a master clock located in the brain. In the same way that the conductor of an orchestra keeps the musicians playing in time with each other, this master clock keeps the body's cellular clocks to the same time cycle.

The master clock is located in what is called the suprachiasmatic nucleus (SCN), located in a part of the brain called the hypothalamus which regulates many basic body functions. The SCN is composed of about 20,000 closely networked cells whose rhythms are coordinated so that the firing rate of the cells varies together in a near-24-hour rhythm. The firing of SCN cells is then transmitted directly and indirectly to many other regions of the brain which then pass on this clock signal to the rest of the body by neurochemical and hormonal means.

Two of the best characterized rhythms driven by the clock signal are the body temperature cycle and the production of the hormone melatonin. The SCN regulates body temperature via connections to other areas of the hypothalamus. Body temperature varies in a wave-like pattern, which reaches a maximum during the day and a minimum (or nadir) during the night.

The SCN also sends a nerve signal that follows a complex poly-synaptic pathway via the cervical spinal ganglia to regulate the activity of the pineal gland, which is responsible for the production of melatonin. Melatonin, sometimes called "the hormone of darkness," is produced during the dark at night. It is secreted by the pineal into the cerebrospinal fluid and then travels in the bloodstream to reach the cells of the body. It acts upon specific melatonin receptors to directly regulate cell functions. It also reinforces the temperature cycle by facilitating the nocturnal drop in body temperature. Among other effects, this drop in body temperature helps ready the brain and body for sleep.

While the SCN serves to coordinate the cell clocks throughout the body, there is still a need to coordinate the SCN clock to the earth's 24-hour period. If left to itself, the SCN keeps a rhythm that is close to but not exactly 24 hours. In healthy humans the intrinsic period of the SCN clock averages about 24.2 hours. If there were no way to correct this cycle to equal 24 hours the clock in the SCN would drift by several minutes each day until it no longer kept correct time or stayed "entrained."

The primary means to keep the SCN clock set properly is via light-dark exposure. Specialized cells in the retina of the eye, which are different from the cells used for vision, register the exposure to light and dark and transmit this signal by a nerve path known as the retinohypothalamic tract to the SCN. When the eyes are exposed to light in the early morning hours this sends a signal that advances the clock in the SCN to an earlier time, thereby providing the necessary daily entrainment. When

light falls on the eyes late at night, a delay signal is sent to the SCN. A graph of the effect of light at different times of 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 runs longer than 24 hours, it tends to become delayed relative to the day-night cycle, but morning light exposure will reset it. If the SCN clock runs shorter than 24 hours, late night light exposure will delay it a bit. By this means, the SCN clock is kept in time with the light and dark cycle of day and night. In healthy individuals routine exposure to morning light works to keep circadian rhythms entrained.

The retinal cells that register light for circadian functions use a pigment known as melanopsin as a light sensor. Because melanopsin is particularly sensitive to blue light, light of that color has a greater effect in circadian rhythms. Red, orange and yellow light have much less effect. Green light can also affect rhythms under certain circumstances.

Among the most important of the body rhythms controlled by the SCN is that of 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 accumulate energy and metabolic resources for the activities of the day. During the day, while the person is awake, these resources are gradually consumed. The gradual loss of energy during the day produces a drive to sleep in order to restore that energy. This is known as the homeostatic sleep drive. If the homeostatic process were the only one involved, a person would wake up fully energized and then gradually wind down over the course of the day, like a battery losing power. This would mean an uneven level of alertness during the day, with dangerously low alertness in the afternoon and evening. To counterbalance this, the SCN also regulates alertness by what is known as the circadian process. As the day goes on, and energy winds down, the SCN compensates for this by sending a stronger alertness signal to the brain and body. This alertness signal reaches a peak in the two hours just before bedtime. This zone of maximum alertness is known as the “forbidden zone for sleep” since the alertness signal makes sleep nearly impossible during that zone. When the usual bedtime is reached, the SCN begins to turn down its alertness signal to allow the body to sleep. In order to prevent early awakening, before the night’s sleep is done, the circadian alertness signal declines further across the night.

This complex interplay between the circadian process and the homeostatic process allows the human organism to have a relatively level state of alertness during the day (with the occasional exception of a mid-afternoon nap period) and allows a 7-9 hour period of consolidated sleep at night.

When all is working well, light signals registered in the eyes keep the SCN on track with the 24-hour day-night cycle and the SCN in turn coordinates the clocks in the pineal gland and in cells throughout the body. All the clocks keep a 24-hour cycle in sync with each other like the members of a well-conducted orchestra. The circadian alertness signal then combines with the homeostatic process resulting in an individual who can sleep through the night and maintain alertness during the day.

But there are a number of things that can go wrong with this system and result in a circadian disorder such as N24.

1. Blindness. The most well-understood cause of N24 is what occurs in blind individuals. Persons who are completely blind (no perception of light) will not register the light signals which are needed to fine-tune the body clock to a 24-hour day. If the SCN clock starts to drift away from 24 hours, a blind person has no intrinsic way to bring it back in sync without medical treatment. Since the inherent rhythm of the SCN is not always precisely 24 hours, a blind person’s circadian timing system will slowly drift over time. They will cycle over time between periods of nighttime sleep and periods of daytime sleep. In the vast majority of cases the sleep rhythm gradually delays so the period is over 24 hours, but there are a few cases of gradual advances and a less-than-24-hour period. The length of the circadian period in blind persons with N24 is typically in the range of 23.8 to 25 hours.

2. Alterations in Light Sensitivity. In some sighted individuals there may be a subsensitivity 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 cell pathway that transmits the circadian light signal may not. If they are totally insensitive to the circadian effects of light, their condition, from a circadian point of view, is not different from that of a blind person. If they are subsensitive to light, light may produce some effect on their rhythms but it may not be strong enough to correct circadian drift in their particular lighting environment.

Conversely, some patients with delayed sleep phase disorder, a condition related to N24, have been shown to be supersensitive to the effects of light. If they are exposed to normal room light in the evening it may produce an exaggerated delay in their circadian rhythms. If this delay becomes cumulative, the result is N24.

3. Environment. Environmental exposure to light may also play a role. Healthy individuals, when kept in isolation without time cues and allowed to turn their lights on and off when they choose, will often fall into a non-24-hour rhythm. The length of the rhythm is not only longer than the intrinsic 24.2-hour cycle of the SCN, but may be up to 25 hours or more in length. This is because self-selected light exposure late in the day has a delaying effect. However, this cannot be the sole cause of N24 since light does not lead to N24 in all persons in a non-isolated environment. In contrast, persons with N24 cannot maintain a 24-hour schedule even in a non-isolated environment with normal time cues.

4. Hormonal Factors. In some cases the hormone melatonin may be involved in the development or perpetuation of N24. Some patients with N24 produce less melatonin than normal, which can be problematic since melatonin helps link sleep to the day-night cycle. On the other hand, too much melatonin may also cause problems. The antidepressant fluvoxamine, which greatly increases melatonin levels by inhibiting its metabolism, has been reported to cause DSPD, which is closely related to N24. Some individuals have an abnormality in their ability to metabolize melatonin, which can lead to higher-than-normal daytime levels that may result in circadian clock dysfunction.

5. Differences in Cellular Clock Function. Other studies of the causes of circadian rhythm disorders have focused on the cellular clock itself. Studies in healthy subjects show a correlation between the period of the cellular clock and the phase of entrainment. Morning persons have a shorter clock period than evening persons. N24 may be an extension of extreme “eveningness” in which the cellular rhythm may be too far from 24 hours for normal light exposure to correct it, a situation known as being “outside the range of entrainment”.

The period of the human biological clock can be measured in two ways. First one may examine the period under the usual living conditions of the subject. Under those conditions the period of a normal person is 24 hours. The timing of their sleep wake cycle does not change over time. A person with N24 by definition will have a period that is longer than 24 hours, sometimes as long as 25-26 hours.

Under normal circumstances the circadian clock is affected by outside factors, especially light. But under special experimental conditions (constant routines and forced desynchrony) scientists can cancel out these outside effects and find what is called the intrinsic period of the clock. This is the time the clock would keep if it were isolated from outside influences. For normal subjects the intrinsic period of the clock is around 24.2 hours. Daily exposure to normal light compensates for the 0.2 difference and allows normal subjects to stay on a 24-hour day.

Three small studies have looked at the intrinsic period of N24 patients. One study of 6 patients found a 24.5 hour period, a study of 4 patients reported 24.9 hours, and a case report of a single patient also found a 24.5 hour period. Thus these N24 patients require an adjustment of at least 0.5 to 0.9 hours per day to remain in a 24-hour cycle. Normal light exposure may not be enough to make this adjustment. When combined with other factors that push the clock later this may make entrainment to a 24-hour day impossible.

Other studies have also looked at the clock within muscle cells (fibroblasts) extracted and grown in culture. The period of cells in culture is correlated with the intrinsic period of the person from whom the cells were sampled. This shows that the clock period is determined on a cellular level. For N24 patients this suggests that at least some may be manifesting a fundamental malfunction of the biochemical basis of the circadian clock, which results in a longer intrinsic period.

While the intrinsic period of N24 patients is longer than average, it overlaps with the period found in a few extreme evening type subjects who do not have clinical N24. Thus, while the long intrinsic period is clearly a major contributing factor to the development of N24, there may also be additional factors involved, which make the difference between an extreme evening chronotype and free-running N24.

6. Differences in the Regulation of Sleep. Another possible set of causes of N24 is related to the homeostatic and circadian regulation of sleep. On average patients with N24 have a slightly greater sleep requirement than normal. In some cases this can be extreme. While a healthy person may sleep 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 day will last 28 hours total. The change in the sleep cycle will in turn change the timing of light exposure, perpetuating an N24 cycle. Similarly, if someone is deficient in the homeostatic drive for sleep they may sleep a normal 8 hours but require 20 hours of awake time before sufficient homeostatic pressure accumulates to permit sleep, again resulting in a 28 hour day.

The timing of sleep in relation to internal circadian rhythms, also known as the phase angle between sleep and circadian rhythms, is abnormal in many cases of N24. Here phase angle is described in terms of the relationship between sleep timing and the circadian rhythm of body temperature. In healthy individuals the body temperature starts to drop shortly before sleep onset and reaches a minimum late in the sleep period — usually about 2 hours before waking. Persons with N24 tend to fall asleep very late relative to their temperature cycle and so the time between the temperature minimum and time of waking (sleep offset) may be 4 hours or more, even up to 8 hours in extreme cases. Since the body's response to light-dark exposure is synched with the internal rhythms (such as core temperature) rather than the sleep-cycle per se, N24s with an abnormal relationship between sleep and circadian rhythms will sleep through the phase advance portion of their clock and not get the light they need on a daily basis to reset their clock. At the same time since they are awake late relative to their temperature cycle, they are exposed to light during the phase delay portion of the phase response curve. This tends to push their circadian rhythm in the direction of a much longer than normal day. This amplifies the effect of the already prolonged intrinsic period of N24 patients.

The circadian regulation of sleepiness is also important. Even healthy individuals have a "forbidden zone for sleep" that occurs an hour or two before normal bedtime and is associated with the maximum circadian alertness signal. In persons with N24 this forbidden zone occurs too late in the day and is too strong to permit sleep on a 24-hour cycle.

This pattern may be reinforced by certain effects of sleep and wake on alertness. When individuals wake after a prolonged period of sleep, they are often in a state of reduced alertness known as sleep inertia. In people with N24 this state of sluggishness and grogginess may be very powerful and persist for many hours. The longer they are awake the more alert they become. (This may be explained by an observation that brain cell circuits become more excitable with longer time awake.) When it comes time for them to sleep (if they are trying to stay on a 24-hour cycle) their alertness will have reached a high point and their heightened state of energy, even if brief, will not permit them to fall asleep at a normal time. In addition, patients with N24 may not want to try to fall asleep at this time because they finally feel awake, alert and productive.

7. Development. Development of the brain, and in particular the circadian and sleep centers, is another factor. In pervasive developmental disorders such as autism a relatively high frequency of occurrence of N24 and other circadian rhythm and sleep disorders has been noted. It is assumed that the circadian and sleep centers of the brain did not properly develop or are affected by other neurochemical or anatomical deficits. It may be that other N24s who do not have pervasive developmental disorders may have impaired development limited to the sleep and circadian brain centers.

8. Trauma. Physical damage to the brain, such as occurs from head injury has been noted to lead to N24 in previously healthy individuals. It is assumed that the head injury damages the sleep and circadian centers of the brain such as the hypothalamus or pineal gland. Similarly, brain tumors have been noted to lead to the development of N24. Circadian sleep disorders have been noted in survivors of tumors affecting the pons and the hypothalamus. Craniopharyngiomas are particularly likely to lead to sleep disorders. In some cases the damage is due to the tumor itself and in other cases to the effects of radiation treatment to the head. In one case an aneurysm near the SCN resulted in transient N24. There has also been a report of N24 following chemotherapy for Hodgkin's lymphoma.

Under the heading of physical abnormalities, any factor that leads to total blindness, whether via genes, disease or injury, can lead to secondary N24.

9. Iatrogenic. N24 can also arise from attempts at treatment of the more common disorder, delayed sleep phase disorder (DSPD). One of the widely used treatments for DSPD is chronotherapy, in which the patient is instructed to gradually delay their bedtime and wake time up to three hours a day until they go around the clock to a more socially acceptable sleep-wake schedule. In essence this means temporarily adopting an N24 schedule. Unfortunately, in some patients, once an N24 schedule has been established it becomes nearly impossible to break. They have exchanged one circadian rhythm disorder, DSPD, for an even more disabling one, N24. There are several reasons why the N24 pattern is hard to break out of once established. One involves the timing of sleep relative to the temperature rhythm mentioned above. The other involves what is called the plasticity of the circadian system. That means that once an organism has been placed on a particular cycle, including a non-24-hour cycle, the circadian clock remembers that cycle and tries to continue it. The risk of N24 after chronotherapy has been known since the 1990s but many doctors continue to be unaware of the risk when recommending chronotherapy.

10. Genetics. There is increasing evidence of a genetic component to N24. In most cases it is not a simple inherited genetic condition (Medelian inheritance). Most patients with N24 do not have parents or close relatives with the condition. However, there do seem to be several genetic factors which can predispose someone to the development of N24.

One study found specific genetic changes (single nucleotide polymorphisms, SNPs) in the gene *BHLHE40* in 4 patients with N24. As this gene encodes components of the cellular clock, such mutations may affect clock function leading to the abnormalities noted in N24.

A separate study of 67 N24 patients found an association with polymorphisms in the *PER3* gene. *PER3* also encodes a crucial component of the circadian clock. The same polymorphisms were associated with extreme evening chronotype – a genetic predisposition to functioning better late in the day, a tendency which is also noted in Non-24s. Variations in the PER3 gene (both SNPs and repeat numbers) are believed to affect free-running period (in animals), the homeostatic drive for sleep (in humans) and the response to light (in humans). All of these factors have been hypothesized, with some evidence, to be abnormal in N24.

DSPD, a condition related to N24, has been linked to the presence of a mutation in the CRY1 gene, which plays a role in the circadian clock, in a study of one family.

Several genome-wide association studies – genetic screenings of over 100,000 persons — have shown genetic associations with human chronotypes. While these studies did not involve N24 patients specifically, N24 is closely related to extreme evening chronotype, suggesting some of the same genetic factors may be relevant.

Taken together, both the specific studies of genes in Non-24 and the more general genetic studies of circadian rhythms strongly suggest that some individuals may have a genetic predisposition to the development of N24.

Affected Populations

While the total number of people living with N24 is unknown, researchers assume that more blind people are affected than sighted people. It is estimated that 55-70% of all people who are totally blind have N24. People who lack any light perception (for example those whose eyes are enucleated) are more likely to be affected than those with some retinal function. The frequency of N24 among the sighted is unknown but the world-wide medical literature provides case studies of roughly 100 sighted individuals with N24. Fifty-seven of these cases appear in a single Japanese study. The Circadian Sleep Disorders Network (see under “organizations”) has 98 members who have indicated they or a family member have N24. The Facebook N24 group has over 500 members but it is not known how many are actual patients. As the condition is not widely known, there may be a significant number of undiagnosed cases.

In published cases of sighted patients, around 75% are male, although it is not known if this is representative of the ratio in the overall patient population. Studies in healthy adults show that on average men have longer circadian periods than women. Among support groups the numbers of male and female patients are roughly equal. The most frequent age of onset is late teens or early twenties, although N24 can manifest at a much younger or older age. The disorde ars to be life-long. Insufficient data exists to determine whether N24 is progressive. Anecdotal evidence offered by g-term sufferers indicates

a worsening of symptoms with age, along with an increase in the day length, however this may be due to the interaction between N24 and age-induced sleep disruptions. Clinical research on changes in the manifestation of N24 throughout the life cycle is absent at present.

N24 was first described in the medical literature by Eliott, Mills, and Waterhouse in 1970.

Related Disorders

Symptoms of the following disorders can be similar to those of N24. Comparisons may be useful for differential diagnosis.

Delayed sleep-wake phase disorder (DSPD) is a circadian rhythm disorder, far more common than N24, in which the body's time of sleep onset and natural awakening are shifted several hours later than that of unaffected individuals.

The difference between DSPD and N24 is that those with DSPD have a delay in their sleep phase that remains roughly constant from day to day, while the sleep time of someone with N24 is constantly shifting later. For example someone with DSPD might go to bed around 4 am most nights. The exact time may fluctuate from day to day (e.g. 3am one day or 5am another) but the delay is not cumulative. Someone with N24 will fall asleep at 4am one day, 5am the next, then 6am, 7am, etc., all the way around the clock.

Researchers have theorized that some persons who suffer from DSPD have biological clocks set to a much longer circadian rhythm than normal, just like persons suffering from N24, but the former still have the ability to entrain to a 24-hour day. According to this theory, it is the longer circadian rhythm that causes the biological clock of the individual with DSPD to shift entrainment to a later time. Persons with DSPD sometimes later develop N24, either as a progression of their disorder or as the consequence of chronotherapy (see under "causes"), supporting the idea that the underlying biology is the same in some cases.

Irregular sleep-wake rhythm disorder (ISWRD) is characterized by the lack of a clearly defined circadian rhythm of sleep and wake. Sufferers sleep at variable times throughout the day and night with little or no apparent pattern. There are often 3 or more sleep periods of variable length during a typical 24-hour day. ISWRD is different from N24 in that individuals with the latter have a defined rhythmic pattern to their sleep but the period of their rhythm exceeds 24-hours. ISWRD patients have little or no rhythmic pattern of any kind. Patients with long-standing N24 have been observed to have more disorganized sleep as the disorder progresses, but usually retain at least some rhythmic pattern, which distinguishes them from ISWRD. ISWRD is most common among children with developmental disabilities and elderly patients with dementia. It also can result from head injury or brain tumors. ISWRD is also known as circadian rhythm sleep disorder, irregular sleep type.

Sleep apnea is a common sleep disorder characterized by temporary, recurrent interruptions of breathing during sleep. Symptoms of the disorder include frequent interruptions of sleep during the night, excessive sleepiness during the day, loud snoring, irritability, poor concentration and/or cognition. Obesity, including a large neck and a narrow or crowded airway are commonly associated with sleep apnea. In obstructive sleep apnea syndrome, the most common form of sleep apnea, labored breathing is interrupted by airway collapse. Partial awakening may then occur and the person may gasp for air. Untreated sleep apnea is associated with high blood pressure, irregular heart-beats, and increased risks for heart attack, heart failure, stroke and diabetes. Since obstructive sleep apnea is so common, affecting approximately 24% of men and 9% of women, it would not be unusual for someone with N24 to have comorbid sleep apnea.

Idiopathic hypersomnia is a rare condition that may be misdiagnosed as N24 or may be co-morbid to N24. While N24 normally manifests as a "day" longer than 24 hours due to an abnormally long wake period, chronic, ongoing hypersomnia may also cause an individual to exhibit a sleep onset time that shifts later daily if the individual remains awake for a normal amount of time while sleeping for an abnormally longer period of time. Idiopathic hypersomnia is characterized by episodes of extreme sleepiness that occur for no identifiable reason (idiopathic). Episodes may be chronic or constant. Some individuals with idiopathic hypersomnia sleep for long periods (e.g. more than 10 hours); others sleep for shorter periods (e.g. fewer than 10 hours). Idiopathic hypersomnia can disrupt many aspects of life. Behavioral modification and ·ations are used to treat the disorder.

Narcolepsy is a neurological sleep disorder characterized by chronic, excessive attacks of drowsiness during the day, sometimes called excessive daytime sleepiness (EDS). Attacks of drowsiness may persist for only a few seconds or several minutes. These episodes vary in frequency from a few incidents to several during a single day. Nighttime (nocturnal) sleep patterns may also be disrupted. Three additional symptoms often associated with narcolepsy are sudden extreme muscle weakness (cataplexy), a specific type of hallucination that occurs just before falling asleep or upon awakening, and brief episodes of paralysis while waking up. Narcolepsy also may be associated with "automatic behavior", i.e. doing something automatically without any memory afterward. (For more information choose "Narcolepsy" as your search term in the Rare Disease Database.)

Kleine-Levin syndrome is a rare disorder characterized by the need for excessive amounts of sleep (hypersomnolence), (i.e. up to 20 hours a day); excessive food intake (compulsive hyperphagia); and behavioral changes such as an abnormally uninhibited sexual drive. When awake, affected individuals may exhibit irritability, lack of energy (lethargy), and/or lack of emotions (apathy). They may also appear confused (disoriented) and experience hallucinations. Symptoms of Kleine-Levin syndrome are cyclical. An affected individual may go for weeks or months without experiencing symptoms. When present, symptoms may persist for days to weeks. In some cases, the symptoms associated with Kleine-Levin syndrome eventually disappear with advancing age. However, episodes may recur later during life. The exact cause of Kleine-Levin syndrome is not known. (For more information, choose "Kleine-Levin" as your search term in the Rare Disease Database.)

Additionally, hypothyroidism, periodic limb movement disorder, depression, hypoglycemia, and other conditions can also cause excessive daytime sleepiness. Conditions linked to excessive nocturia such as heart conditions, diabetes, prostate disorders, congestive heart failure, interstitial cystitis, cystoceles, and other bladder issues may also lead to symptoms of disturbed sleep and wake patterns as well as excessive daytime sleepiness.

Diagnosis

Initial diagnosis is based on home sleep logs kept by the patient that show a non-24-hour sleep pattern. This is usually more easily distinguished if the patient's sleep times are not constrained by social or occupational obligations.

Confirmation of diagnosis may be obtained by the use of an actigraph, a device worn on the wrist that registers movement which is used to track the timing of sleep. The actigraph should be worn for sufficient time for the sleep cycle to complete at least one pass around the clock, typically several weeks.

Documenting a non-24-hour pattern of melatonin secretion may be a useful confirmation of the diagnosis, though this procedure is currently more commonly used for research purposes.

Clinical Testing and Work-Up
Sleep logs and actigraphy are the main means for initial work up and follow up. Polysomnography (an overnight sleep study) is not necessary for diagnosis of N24 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 or her to sleep.

Standard Therapies

Treatment
In 2014, The U.S. Food and Drug Administration (FDA) approved Hetlioz (tasimelteon), a melatonin receptor agonist, to treat N24. Hetlioz, manufactured by Vanda Pharmaceuticals, Inc., is the first FDA approved treatment for the disorder. The effectiveness of Hetlioz was evaluated in two clinical trials of totally blind individuals with N24.

The most widely recommended treatments for sighted patients involve exposure to specific regimens of light (phototherapy) and dark (scototherapy).

Phototherapy usually involves the use of a lightbox. The lightbox is used in the early morning, typically for a duration of 2 hours, in order to stabilize the sleep cycle. Light treatment is best started when the patient's cycle already has them arising at the desired wake time. Light is registered by special cells in the retina of the eye which send a signal to the brain via the retinohypothalamic tract. This signal suppresses the output of melatonin and shifts the timing of sleep. A phase-response curve determines the best time for light exposure.

Dark therapy (scototherapy) is accomplished by avoiding light exposure late in the day. Even ordinary room light may have phase-delaying effect so patients should remain in dim light or use special dark goggles that reduce light exposure during the evening and night.

A combination of light and dark therapy is believed to be more effective than either alone. If entrainment to a 24-hour cycle is achieved with light and dark therapy, the patient must maintain the treatment regimen or entrainment will be lost.

The hormone melatonin may be used to stabilize the sleep-wake cycle. Melatonin is usually taken about 4-6 hours before the desired sleep time. While melatonin is often effective in blind patients with N24, it is rarely successful as the sole treatment in sighted patients.

Investigational Therapies

Early case reports suggested that vitamin B12 could successfully treat some cases of N24; however, a double-blind placebo-controlled trial found it was not significantly better than placebo for treatment of N24 or DSPD.

Blue light plays a particular role in affecting circadian rhythms. Blue-enriched light has been used in treatment of the related condition, DSPD, and may be useful for N24, although there are no published cases or trials.

Conversely, avoidance of blue light using goggles which block out all blue (and sometimes green) light has become a widely used treatment among patients with N24 with anecdotal success, but as of yet there are no published studies of this approach. In addition to, or in place of goggles, patients may use special red or amber lights (which do not put out blue or green light) in the evening for illumination. They do not use standard room light and avoid sunlight by using shades or shutters in the evening.

There is considerable ongoing research on the basic biology and molecular genetics of circadian rhythms. Drugs which alter the timing of the biological clock are a promising avenue for future study but as of yet none are near being ready for clinical use. Research on the circadian and homeostatic control of sleep timing in healthy subjects and patients with N24 and related disorders may also offer clues to future treatments.

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. Government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Toll-free: (800) 411-1222
TTY: (866) 411-1010
Email: prpl@cc.nih.gov

Some current clinical trials also are posted on the following page on the NORD website:
https://nord1dev.wpengine.com/for-patients-and-families/information-resources/news-patient-recruitment/

For information about clinical trials sponsored by private sources, contact:
www.centerwatch.com

For information about clinical trials conducted in Europe, contact:
https://www.clinicaltrialsregister.eu/

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Programs & Resources

RareCare® Assistance Programs

NORD strives to open new assistance programs as funding allows. If we don't have a program for you now, please continue to check back with us.

Additional Assistance Programs

MedicAlert Assistance Program

NORD and MedicAlert Foundation have teamed up on a new program to provide protection to rare disease patients in emergency situations.
https://rarediseases.org/patient-assistance-programs/medicalert-assistance-program/

Rare Disease Educational Support Program

Ensuring that patients and caregivers are armed with the tools they need to live their best lives while managing their rare condition is a vital part of NORD's mission.
https://rarediseases.org/patient-assistance-programs/rare-disease-educational-support/

Rare Caregiver Respite Program

This first-of-its-kind assistance program is designed for caregivers of a child or adult diagnosed with a rare disorder.
https://rarediseases.org/patient-assistance-programs/caregiver-respite/

Patient Organizations

No patient organizations found related to this disease state.

IAMRARE® Patient Registry

Powered by NORD, the IAMRARE Registry Platform® is driving transformative change in the study of rare disease. With input from doctors, researchers, and the US Food & Drug Administration, NORD has created IAMRARE to facilitate patient-powered natural history studies to shape rare disease research and treatments. The ultimate goal of IAMRARE is to unite patients and research communities in the improvement of care and drug development.

Understanding Rare Disease	Living with a Rare Disease	Community Support	Advancing Research	Driving Policy	Get Involved