Narcolepsy

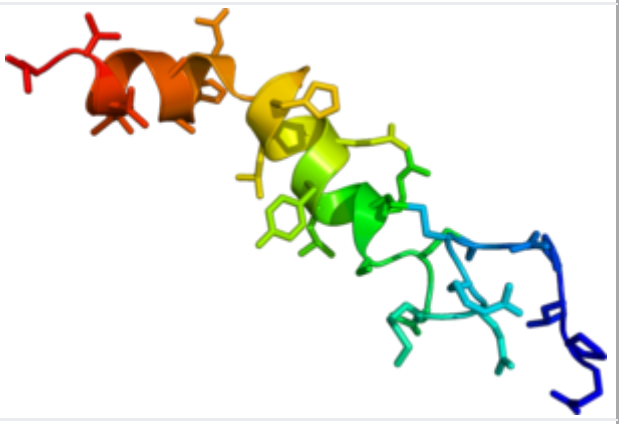
Narcolepsy is a long-term neurological disorder that involves a decreased ability to regulate sleep-wake cycles.[1] Symptoms often include periods of excessive daytime sleepiness and brief involuntary sleep episodes.[1] About 70% of those affected also experience episodes of sudden loss of muscle strength, known as cataplexy.[1] These experiences can be brought on by strong emotions.[1] Less commonly, there may be vivid hallucinations or an inability to move (sleep paralysis) while falling asleep or waking up.[1] People with narcolepsy tend to sleep about the same number of hours per day as people without, but the quality of sleep tends to be lessened.[1]

The exact cause of narcolepsy is unknown, with potentially several causes.[1][3] In up to 10% of cases, there is a family history of the disorder.[1] Often, those affected have low levels of the neuropeptide *orexin*, which may be due to an autoimmune disorder.[1] Trauma, infections, toxins or psychological stress may also play a role.[1] Diagnosis is typically based on the symptoms and sleep studies, after ruling out other potential causes.[1] Excessive daytime sleepiness can also be caused by other sleep disorders such as sleep apnea, major depressive disorder, anemia, heart failure, drinking alcohol and not getting enough sleep.[1] Cataplexy may be mistaken for seizures.[1]

While there is no cure, a number of lifestyle changes and medications may help.[1] Lifestyle changes include taking regular short naps and sleep hygiene.[1] Medications used include modafinil, sodium oxybate and methylphenidate.[1] While initially effective, tolerance to the benefits may develop over time.[1] Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) may improve cataplexy.[1]

About 0.2 to 600 per 100,000 people are affected.[2] The condition often begins in childhood, with males and females being affected equally.[1] Untreated narcolepsy increases the risk of motor vehicle collisions and falls.[1] The term "narcolepsy" is from

Narcolepsy



The concentration of orexin-A neuropeptides in the cerebrospinal fluid of narcoleptic individuals is usually very low

Pronunciation	/ˈnɑːrkəˌlɛpsi/
Specialty	Sleep medicine, psychiatry, neurology
Symptoms	Excessive daytime sleepiness, involuntary sleep episodes, sudden loss of muscle strength, hallucinations[1]
Complications	Motor vehicle collisions, falls[1]
Usual onset	Childhood[1]
Duration	Long term[1]
Causes	Unknown[1]
Risk factors	Family history[1]
Diagnostic method	Based on the symptoms and sleep studies[1]
Differential diagnosis	Sleep apnea, major depressive disorder, anemia, heart failure, drinking alcohol, not getting enough sleep[1]
Treatment	Regular short naps, sleep hygiene[1]
Medication	Modafinil, sodium oxybate, methylphenidate[1]
Frequency	0.2 to 600 per 100,000[2]

the French *narcolepsie*.[4] The French term was first used in 1880 by Jean-Baptiste-Édouard Gélineau, who used the Greek νάρκη (*narkē*), meaning "numbness", and λῆψις (*lepsis*) meaning "attack".[4]

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Signs and symptoms

There are two main characteristics of narcolepsy: excessive daytime sleepiness and abnormal REM sleep.[5] The first, excessive daytime sleepiness (EDS), occurs even after adequate night time sleep. A person with narcolepsy is likely to become drowsy or fall asleep, often at inappropriate times and places, or just be very tired throughout the day. Narcoleptics are not able to experience the amount of restorative deep sleep that healthy people experience – they are not "over-sleeping". In fact, narcoleptics live their entire lives in a constant state of extreme sleep deprivation.

Excessive sleepiness can vary in severity, and it appears most commonly during monotonous situations that don't require much interaction.[6] Daytime naps may occur with little warning and may be physically irresistible. These naps can occur several times a day. They are typically refreshing, but only for a few hours or less. Vivid dreams may be experienced on a regular basis, even during very brief naps. Drowsiness may persist for prolonged periods or remain constant. In addition, night-time sleep may be fragmented, with frequent awakenings. A second prominent symptom of narcolepsy is abnormal REM sleep. Narcoleptics are unique in that they enter into the REM phase of sleep in the beginnings of sleep, even when sleeping during the day.[5]

The classic symptoms of the disorder, often referred to as the "tetrad of narcolepsy," are cataplexy, sleep paralysis, hypnagogic hallucinations, and excessive daytime sleepiness.[7] Other symptoms may include automatic behaviors and night-time wakefulness.[5][8][9] These symptoms may not occur in all people with narcolepsy.

- Cataplexy is an episodic loss of muscle function, ranging from slight weakness such as limpness at the neck or knees, sagging facial muscles, weakness at the knees often referred to as "knee buckling",[10] or inability to speak clearly, to a complete body collapse. Episodes may be triggered by sudden emotional reactions such as laughter, anger, surprise, or fear. The person remains conscious throughout the episode. In some cases, cataplexy may resemble epileptic seizures.[11] Usually speech is slurred and vision is impaired (double vision, inability to focus), but hearing and awareness remain normal. Cataplexy also has a severe emotional impact on narcoleptics, as it can cause extreme anxiety, fear, and avoidance of people or situations that might elicit an attack. Cataplexy is generally considered to be unique to narcolepsy and is analogous to sleep paralysis in that the usually protective paralysis mechanism occurring during sleep is inappropriately activated. The opposite of this situation (failure to activate this protective paralysis) occurs in rapid eye movement behavior disorder.
- Periods of wakefulness at night[5]
- Sleep paralysis is the temporary inability to talk or move when waking (or less often, when falling asleep). It may last a few seconds to minutes. This is often frightening but is not dangerous.
- Hypnagogic hallucinations are vivid, often frightening, dreamlike experiences that occur while dozing or falling asleep. Hypnopompic hallucinations refer to the same sensations while awakening from sleep. These hallucinations may manifest in the form of visual or auditory sensations.[5]
- Automatic behaviors occur when a person continues to function (talking, putting things away, etc.) during sleep episodes but awakens with no memory of performing such activities. It is estimated that up to 40 percent of people with narcolepsy experience automatic behavior during sleep episodes.

In most cases, the first symptom of narcolepsy to appear is excessive and overwhelming daytime sleepiness. The other symptoms may begin alone or in combination months or years after the onset of the daytime naps. There are wide variations in the development, severity, and order of appearance of cataplexy, sleep paralysis, and hypnagogic hallucinations in individuals. Only about 20 to 25 percent of people with narcolepsy experience all four symptoms. The excessive daytime sleepiness generally persists throughout life, but sleep paralysis and hypnagogic hallucinations may not. A rare subset of narcoleptics also experience a heightened sense of taste and smell known as the supertaster phenomenon.

Many people with narcolepsy also suffer from insomnia for extended periods of time. The excessive daytime sleepiness and cataplexy often become severe enough to cause serious problems in a person's social, personal, and professional life. Normally, when an individual is awake, brain waves show a regular rhythm. When a person first falls asleep, the brain waves become slower and less regular, which is called non-rapid eye movement (NREM) sleep. After about an hour and a half of NREM sleep, the brain waves begin to show a more active pattern again, called REM sleep (rapid eye movement sleep), when most remembered dreaming occurs. Associated with the EEG-observed waves during REM sleep, muscle atonia is present called REM atonia.

In narcolepsy, the order and length of NREM and REM sleep periods are disturbed, with REM sleep occurring at sleep onset instead of after a period of NREM sleep. Also, some aspects of REM sleep that normally occur only during sleep, like lack of muscular control, sleep paralysis, and vivid dreams, occur

at other times in people with narcolepsy. For example, the lack of muscular control can occur during wakefulness in a cataplexy episode; it is said that there is an intrusion of REM atonia during wakefulness. Sleep paralysis and vivid dreams can occur while falling asleep or waking up. Simply put, the brain does not pass through the normal stages of dozing and deep sleep but goes directly into (and out of) rapid eye movement (REM) sleep.

As a consequence night time sleep does not include as much deep sleep, so the brain tries to "catch up" during the day, hence EDS. People with narcolepsy may visibly fall asleep at unpredicted moments (such motions as head bobbing are common). People with narcolepsy fall quickly into what appears to be very deep sleep, and they wake up suddenly and can be disoriented when they do (dizziness is a common occurrence). They have very vivid dreams, which they often remember in great detail. People with narcolepsy may dream even when they only fall asleep for a few seconds. Along with vivid dreaming, people with narcolepsy are known to have audio or visual hallucinations prior to falling asleep.

Narcoleptics can gain excess weight; children can gain 20 to 40 lb (9 to 18 kg) when they first develop narcolepsy; in adults the body-mass index is about 15% above average.[12][13]

Causes

The exact cause of narcolepsy is unknown, and it may be caused by several distinct factors.[1][3] Part of the mechanism involves the loss of orexin-releasing neurons within the lateral hypothalamus.[14][15] In up to 10% of cases there is a family history of the disorder.[1] There is a strong link with certain genetic variants.[14] In addition to genetic factors, low levels of orexin peptides have been correlated with a past history of infection, diet, contact with toxins such as pesticides, and brain injuries due to brain tumors or strokes.[5][14] Autoimmunity may also play a role.[16]

Genetics

The primary genetic factor that has been strongly implicated in the development of narcolepsy involves an area of chromosome 6 known as the human leukocyte antigen (HLA) complex.[14][17] Specific variations in HLA genes are strongly correlated with the presence of narcolepsy;[14] however, these variations are not required for the condition to occur and sometimes occur in individuals without narcolepsy.[14][18] These genetic variations in the HLA complex are thought to increase the risk of an auto-immune response to orexin-releasing neurons in the lateral hypothalamus.[14][15][18]

The allele HLA-DQB1*06:02 of the human gene HLA-DQB1 was reported in more than 90% of people with narcolepsy, and alleles of other HLA genes such as HLA-DQA1*01:02 have been linked. A 2009 study found a strong association with polymorphisms in the TRAC gene locus (dbSNP IDs rs1154155, rs12587781, and rs1263646).[19] A 2013 review article reported additional but weaker links to the loci of the genes TNFSF4 (rs7553711), Cathepsin H (rs34593439), and P2RY11-DNMT1 (rs2305795).[20] Another gene locus that has been associated with narcolepsy is EIF3G (rs3826784).[21]

H1N1 vaccine

A link between GlaxoSmithKline's H1N1 flu vaccine Pandemrix and narcolepsy has been found in both children and adults.[22] Finland's National Institute of Health and Welfare recommended that Pandemrix vaccinations be suspended pending further investigation into narcolepsy.[23][24]

Pathophysiology

Orexin, otherwise known as hypocretin, is a neuropeptide that acts within the brain to regulate appetite and wakefulness as well as a number of other cognitive and physiological processes.[14][25][26] While there are billions of cells in the human brain, only 10,000–20,000 neurons secrete orexin peptides;[5] all of these neurons project out of the lateral hypothalamus.[14] Loss of these orexin-producing neurons causes narcolepsy and most individuals with narcolepsy have a reduced number of these neurons in their brains.[14][15][18]

The neural control of normal sleep states and the relationship to narcolepsy are only partially understood. In humans, narcoleptic sleep is characterized by a tendency to go abruptly from a waking state to REM sleep with little or no intervening non-REM sleep. The changes in the motor and proprioceptive systems during REM sleep have been studied in both human and animal models. During normal REM sleep, spinal and brainstem alpha motor neuron hyperpolarization produces almost complete atonia of skeletal muscles via an inhibitory descending reticulospinal pathway. Acetylcholine may be one of the neurotransmitters involved in this pathway. In narcolepsy, the reflex inhibition of the motor system seen in cataplexy has features normally seen only in normal REM sleep.[1]

Diagnosis

Diagnosis is relatively easy when all the symptoms of narcolepsy are present, but if the sleep attacks are isolated and cataplexy is mild or absent, diagnosis is more difficult. It is also possible for cataplexy to occur in isolation.[27] Three tests that are commonly used in diagnosing narcolepsy are the polysomnogram, the multiple sleep latency test (MSLT), and administration of the Epworth Sleepiness Scale. These tests are usually performed by a sleep specialist. The polysomnogram involves continuous recording of sleep brain waves and a number of nerve and muscle functions during night time sleep. When tested, people with narcolepsy fall asleep rapidly, enter REM sleep early, and may often awaken during the night. The polysomnogram also helps to detect other possible sleep disorders that could cause daytime sleepiness.

The Epworth Sleepiness Scale is a brief questionnaire that is administered to determine the likelihood of the presence of a sleep disorder, including narcolepsy. For the multiple sleep latency test, a person is given a chance to sleep every two hours during normal wake times. The person is taken in usually for an overnight sleep study. The following day the person will have multiple tests where they will be told to nap after a full nights sleep (usually eight hours). Observations are made of the time taken to reach various stages of sleep (sleep onset latency). This test measures the degree of daytime sleepiness and also detects how soon REM sleep begins. Again, people with narcolepsy fall asleep rapidly and enter REM sleep early. Occasionally, a multiple sleep latency test can result in a false-negative for a narcoleptic.[28]

The system which regulates sleep, arousal, and transitions between these states in humans is composed of three interconnected subsystems: the orexin projections from the lateral hypothalamus, the reticular activating system, and the ventrolateral preoptic nucleus.[15] In narcoleptic individuals, these systems are all associated with impairments due to a greatly reduced number of hypothalamic orexin projection neurons and significantly fewer orexin neuropeptides in cerebrospinal fluid and neural tissue, compared to non-narcoleptic individuals.[15] Those with narcolepsy generally experience the REM stage of sleep within five minutes of falling asleep, while people who do not have narcolepsy (unless they are significantly sleep deprived)[29] do not experience REM until after a period of slow-wave sleep, which lasts for about the first hour or so of a sleep cycle.[1]

Measuring orexin levels in a person's cerebrospinal fluid sampled in a spinal tap may help in diagnosing narcolepsy,[30] with abnormally low levels serving as an indicator of the disorder. This test can be useful when MSLT results are inconclusive or difficult to interpret.[31]

Classification

There are four types of narcolepsy: narcolepsy with cataplexy, narcolepsy without cataplexy, narcolepsy unspecified, and narcolepsy due to a medical condition. The last one is only diagnosed when the direct cause is a medical or neurological disorder.[6]

The 2001 International Classification of Sleep Disorders (ICSD) divides primary hypersomnia syndromes between narcolepsy, idiopathic hypersomnia, and the recurrent hypersomnias (like Klein-Levin syndrome); it further divides narcolepsy into that with cataplexy and that without cataplexy. This ICSD version defines narcolepsy as a disorder of unknown cause that is characterized by "excessive sleepiness that typically is associated with cataplexy and other REM-sleep phenomena, such as sleep paralysis and hypnagogic hallucinations". It also establishes baseline categorical standards for diagnosis of narcolepsy, through two sets of well defined criteria, as follows.[32] Minimal narcolepsy diagnostic criteria set #2:

- A complaint of excessive sleepiness or sudden muscle weakness.
- Associated features that include: sleep paralysis; disrupted major sleep episode; hypnagogic hallucinations; automatic behaviors.
- Polysomnography with one or more of the following: sleep latency less than 10 minutes, REM sleep latency less than 20 minutes, an MSLT with a mean sleep latency less than 5 minutes, two or more sleep-onset REM periods (SOREMPs).
- No medical or mental disorder accounts for the symptoms. (see hypersomnia differential diagnosis)[32]

In the absence of clear cataplexy, it becomes much more difficult to make a firm diagnosis of narcolepsy. Various terms, such as essential hypersomnia, primary hypersomnia, ambiguous narcolepsy, atypical narcolepsy, etc., have been used to classify these people, who may be in the developing phase of narcolepsy.[32]

Since the 2001 ICSD, the classification of primary hypersomnias has been steadily evolving, as further research has shown more overlap between narcolepsy and idiopathic hypersomnia.[33] The 3rd edition of the ICSD is currently being finalized, and its new classification will label narcolepsy caused by orexin deficiency as type 1 narcolepsy, which is almost always associated with cataplexy. The other primary hypersomnias will remain subdivided based on the presence of SOREMPs. They will be labeled: type 2 narcolepsy, with 2 or more SOREMPs on MSLT; and idiopathic hypersomnia, with less than 2 SOREMPS.[34]

However, there is no evidence that the pathophysiology or therapeutic response is substantially different for hypersomnia with or without SOREMPs on the MSLT.[34] Given this currently understood overlap of idiopathic hypersomnia and narcolepsy, the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) is also updating its classification of the primary hypersomnias. It reclassifies narcolepsy without cataplexy as major somnolence disorder (MSD). Additionally, MSD will encompass all syndromes of hypersomnolence not explained by low orexin concentrations, including idiopathic hypersomnia (with and without long sleep time) and long sleepers (people requiring >10 hours sleep/day).[34][35][36]

Further complicating these updated classification schemes, overlap between narcolepsy *with* cataplexy and idiopathic hypersomnia has also been reported. A subgroup of narcoleptics with long sleep time, comprising 18% of narcoleptics in one study, had symptoms of both narcolepsy with cataplexy and idiopathic hypersomnia (long sleep time and unrefreshing naps). It is believed that this subgroup might have dysfunction in multiple arousal systems, including orexin and GABA (see idiopathic hypersomnia causes).[37]

Treatment

People with narcolepsy can be substantially helped, but not cured. Treatment is tailored to the individual, based on symptoms and therapeutic response. The time required to achieve optimal control of symptoms is highly variable and may take several months or longer. Medication adjustments are frequently necessary, and complete control of symptoms is seldom possible. While oral medications are the mainstay of formal narcolepsy treatment, lifestyle changes are also important. General strategies like people and family education, sleep hygiene and medication compliance, and discussion of safety issues for example driving license can be useful. Potential side effects of medication can also be addressed.[6] Regular follow-up is useful to be able to monitor the response to treatment, to assess the presence of other sleep disorders like obstructive sleep apnea, and to discuss psychosocial issues.[6]

The main treatment of excessive daytime sleepiness in narcolepsy is central nervous system stimulants such as methylphenidate, amphetamine, dextroamphetamine, modafinil, and armodafinil. In late 2007 an alert for severe adverse skin reactions to modafinil was issued by the FDA.[38]

Modafinil and sodium oxybate are the most effective treatment of sleepiness although they are only moderately effective.[6] Several studies also showed that sodium oxybate is effective to treat cataplexy.[6]

Another drug that is used is atomoxetine, a non-stimulant and a norepinephrine reuptake inhibitor (NRI), which has no addiction liability or recreational effects. In many cases, planned regular short naps can reduce the need for pharmacological treatment of the EDS, but only improve symptoms for a short duration. A 120-minute nap provided benefit for 3 hours in the person's alertness whereas a 15-minute nap provided no benefit.[39] Daytime naps are not a replacement for night time sleep. Ongoing communication between the health care provider, person, and their family members is important for optimal management of narcolepsy.

Another FDA-approved treatment option for narcolepsy is sodium oxybate,[40] also known as sodium gamma-hydroxybutyrate (GHB). It can be used for cataplexy associated with narcolepsy and excessive daytime sleepiness associated with narcolepsy.[40][41][6][42]

Narcolepsy has sometimes been treated with selective serotonin reuptake inhibitors and tricyclic antidepressants, such as clomipramine, imipramine, or protriptyline, as well as other drugs that suppress REM sleep.[43] Venlafaxine, an antidepressant which blocks the reuptake of serotonin and norepinephrine, has shown usefulness in managing symptoms of cataplexy,[44] however, it has notable side-effects including sleep disruption.[45]

Children

Pre-pubertal children are advised to have the school contacted and alert the teachers to their problems, as well as taking a nap at lunchtime and around 4 or 5 pm. They can take medications like modafinil, sodium oxybate, methylphenidate and atomoxetine against sleepiness and sodium oxybate, venlafaxine,

fluoxetine and clomipramine against cataplexy.[46] None of these medications have been tested by the FDA and none of them have been approved for younger children.

Pubertal children are also advised to contact the school and inform their teachers. They, too, should plan on taking a nap at lunch and around 4 or 5 pm. Further, it should be explained to them, how important a regular nocturnal sleep schedule is and that they should aim for 9 hours of sleep at night. Pubertal children can take several medications like modafinil, sodium oxybate, methylphenidate and atomoxetine against sleepiness and sodium oxybate, venlafaxine and fluoxetine against cataplexy.[47]

Epidemiology

In the United States, it is estimated that this condition afflicts as many as 200,000 Americans,[48] but fewer than 50,000 are diagnosed. It is as widespread as Parkinson's disease or multiple sclerosis and more prevalent than cystic fibrosis, but it is less well known. Narcolepsy is often mistaken for depression, epilepsy, or the side effects of medications. It can also be mistaken for poor sleeping habits, recreational drug use, or laziness. Narcolepsy can occur in both men and women at any age, although its symptoms are usually first noticed in teenagers or young adults. There is strong evidence that narcolepsy may run in families; around 10 percent of people diagnosed with narcolepsy with cataplexy have a close relative with this neurological disorder.[1] While narcolepsy symptoms are often confused with depression, there is a link between the two disorders. Research studies have mixed results on co-occurrence of depression in people with narcolepsy - the numbers quoted by different studies are anywhere between 6% and 50%.[49]

Narcolepsy has its typical onset in adolescence and young adulthood. There is an average 15-year delay between onset and correct diagnosis which may contribute substantially to the disabling features of the disorder. Cognitive, educational, occupational, and psychosocial problems associated with the excessive daytime sleepiness of narcolepsy have been documented. For these to occur in the crucial teen years when education, development of self-image, and development of occupational choice are taking place is especially devastating. While cognitive impairment does occur, it may only be a reflection of the excessive daytime somnolence.[50]

The prevalence of narcolepsy is about 1 per 2,000 persons.[48] It is a reason for people with narcolepsy to visits to sleep disorder centers, and with its onset in adolescence, it is also a major cause of learning difficulty and absenteeism from school. Normal teenagers often already experience excessive daytime sleepiness because of a maturational increase in physiological sleep tendency accentuated by multiple educational and social pressures; this may be disabling with the addition of narcolepsy symptoms in susceptible teenagers. In clinical practice, the differentiation between narcolepsy and other conditions characterized by excessive somnolence may be difficult. Treatment options are currently limited. There is a paucity in the literature of controlled double-blind studies of possible effective drugs or other forms of therapy. Mechanisms of action of some few available therapeutic agents have been explored but detailed studies of mechanisms of action are needed before new classes of therapeutic agents can be developed. Narcolepsy is an underdiagnosed condition in the general population. This is partly because its severity varies, so it can be mistaken for other illnesses very easily. Some people with narcolepsy do not suffer from loss of muscle control.

Society and culture

In 2015, it was reported that the British Department of Health was paying for sodium oxybate medication at a cost of £12,000 a year for 80 people who are taking legal action over problems linked to the use of the Pandemrix swine flu vaccine. Sodium oxybate is not available to people with narcolepsy through the National Health Service.[51]

Research

Histamine-directed medications

It remains to be seen whether H3 antagonists (i.e., compounds such as pitolisant that promote the release of the wakefullness-promoting molecule amine histamine) will be particularly useful as wake-promoting agents.[34]

GABA-directed medications

Given the possible role of hyper-active $GABA_A$ receptors in the primary hypersomnias (narcolepsy and idiopathic hypersomnia), medications that could counteract this activity are being studied to test their potential to improve sleepiness. These currently include clarithromycin and flumazenil.[52][53]

Flumazenil

Flumazenil is the only $GABA_A$ receptor antagonist on the market as of Jan 2013, and it is currently manufactured only as an intravenous formulation. Given its pharmacology, researchers consider it to be a promising medication in the treatment of primary hypersomnias. Results of a small, double-blind, randomized, controlled clinical trial were published in November 2012. This research showed that flumazenil provides relief for most people whose CSF contains the unknown "somnogen" that enhances the function of $GABA_A$ receptors, making them more susceptible to the sleep-inducing effect of GABA. For one person, daily administration of flumazenil by sublingual lozenge and topical cream has proven effective for several years.[52][54] A 2014 case report also showed improvement in primary hypersomnia symptoms after treatment with a continuous subcutaneous flumazenil infusion.[55] The supply of generic flumazenil was initially thought to be too low to meet the potential demand for treatment of primary hypersomnias.[56] However, this scarcity has eased, and dozens of people are now being treated with flumazenil off-label.[57]

Clarithromycin

In a test tube model, clarithromycin (an antibiotic approved by the FDA for the treatment of infections) was found to return the function of the GABA system to normal in people with primary hypersomnias. Investigators therefore treated a few people with narcolepsy with off-label clarithromycin, and most felt their symptoms improved with this treatment. In order to help further determine whether clarithromycin is truly beneficial for the treatment of narcolepsy and idiopathic hypersomnia, a small, double-blind, randomized, controlled clinical trial was completed in 2012.[53] "In this pilot study, clarithromycin improved subjective sleepiness in GABA-related hypersomnia. Larger trials of longer duration are warranted."[58] In 2013, a retrospective review evaluating longer-term clarithromycin use showed efficacy in a large percentage of people with GABA-related hypersomnia.[59] “It is important to note that the positive effect of clarithromycin is secondary to a benzodiazepine antagonist-like effect, not its antibiotic effects, and treatment must be maintained.”[34]

Orexin receptor agonists

Orexin-A (a.k.a. hypocretin-1) has been shown to be strongly wake-promoting in animal models, but unfortunately it does not cross the blood-brain barrier. Therefore, companies have developed orexin receptor antagonists, like suvorexant, for the treatment of insomnia. It is also likely that an orexin-A receptor agonist will be found and developed for the treatment of hypersomnia.[34]

L-carnitine

Abnormally low levels of acylcarnitine have been observed in people with narcolepsy.[60] These same low levels have been associated with primary hypersomnia in general in mouse studies. “Mice with systemic carnitine deficiency exhibit a higher frequency of fragmented wakefulness and rapid eye movement (REM) sleep, and reduced locomotor activity.” Administration of acetyl-L-carnitine was shown to improve these symptoms in mice.[61] A subsequent human trial found that people with narcolepsy given L-carnitine spent less total time in daytime sleep than people who were given a placebo.[62]

Animal model

Animal studies try to mimic the disorder in humans by either modifying the Hypocretin/Orexin receptors or by eliminating this peptide.[63] An orexin deficit caused by the degeneration of hypothalamic neurons is suggested to be one of the causes of narcolepsy.[64] More recent clinical studies on both animals and humans have also revealed that hypocretin is involved in other functions beside regulation of wakefulness and sleep. These functions include autonomic regulation, emotional processing, reward learning behaviour or energy homeostasis. In studies where the concentration of the hypocretin was measured under different circumstances, it was observed that the hypocretin levels increased with the positive emotion, anger or social interaction but stayed low during sleep or during pain experience.[65]

The most reliable and valid animal models developed are the canine (narcoleptic dogs) and the rodent (orexin-deficient mice) ones which helped investigating the narcolepsy and set the focus on the role of orexin in this disorder.[64]

Dog

Dogs as well as other species like cats or horses can also exhibit spontaneous narcolepsy with similar symptoms as the one reported in humans. The attacks of cataplexy in dogs can involve partial or full collapse.[64] Narcolepsy with cataplexy was identified in a few breeds like Labrador retrievers or Doberman pinschers where it was investigated the possibility to inherit this disorder in the autosomal recessive mode.[66] According to [63] a reliable canine model for narcolepsy would be the one in which the narcoleptic symptoms are the result of a mutation in the gene HCRT 2. The animals affected exhibited excessive daytime sleepiness with a reduced state of vigilance and severe cataplexy resulted after palatable food and interactions with the owners or with other animals.[63]

Rodent

Rodents are genetically engineered to lack orexin. In some mice studies, it was reported that during the dark phase (when normal mice are active), the animals seem to have abrupt transient episodes of behavioural arrest, the NREMs are more fragmented, a lot of REMs during the active phase and a decreased REMs latency.[64] A very reliable mouse mode would be the HCRT knockout one which

display narcolepsy like phenotype.[63] Cataplexy can be triggered in mice by social interaction, anticipation of food, locomotor activity, group housing or ultrasonic vocalizations.[64] Example of rodent models with their characteristics:[67]

- Prepro-orexin KO: Behavioural arrest (cataplexy) and severe sleep/wake fragmentation, direct transition of wakefulness to REM sleep
- OX1R KO: Mild sleep/wake fragmentation
- OX2R KO: Cataplexy and moderate sleep/wake fragmentation
- Orexin/ataxin-3 mice/rats: Cataplexy and severe sleep/wake fragmentation, direct transition of wakefulness to REM sleep

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External links

- "Narcolepsy Information Page" (https://www.ninds.nih.gov/Disorders/All-Disorders/Narcolepsy-Information-Page). National Institute of Neurological Disorders and Stroke.

Classification	**ICD-10**: G47.4 (http://apps.who.int/classifications/icd10/browse/2016/en#/G47.4) · **ICD-9-CM**: 347 (http://www.icd9data.com/getICD9Code.ashx?icd9=347) · **OMIM**: 161400 (https://omim.org/entry/161400) · **MeSH**: D009290 (https://www.nlm.nih.gov/cgi/mesh/2015/MB_cgi?field=uid&term=D009290) · **DiseasesDB**: 8801 (http://www.diseasesdatabase.com/ddb8801.htm)
External resources	**MedlinePlus**: 000802 (https://www.nlm.nih.gov/medlineplus/ency/article/000802.htm) · **eMedicine**: neuro/522 (https://e

medicine.medscape.com/neuro/522-overview)

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