Narcolepsy: The Current Understanding and Treatment

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Abstract/Goals and Objectives

Narcolepsy was first identified and named in the late 1800 by a French physician. Over 200 years later the exact cause of narcolepsy is still unknown. Two subtypes of narcolepsy have been discovered, type 1 which has the presence of cataplexy and type 2 which has the absence of cataplexy. Many symptoms have been discovered including extreme daytime sleepiness, muscle weakness, hallucinations, and more. These symptoms are due to REM sleep disturbances and fragmented sleep. Diagnosis can be tricky, but there are a few different ways that a person can be diagnosed with narcolepsy including a multiple sleep latency test and assay of the cerebral spinal fluid. Narcolepsy disrupts the homeostasis of the sleep-wake cycle due to the death of the neuropeptide hypocretin. Treatment options are available that can vastly improve the quality of life. Treatments include stimulates to keep the sleepiness at bay and nighttime medication that improves the sleep homeostasis. The purpose of this paper is to inform readers about narcolepsy in a way that is simple to understand and inform about the treatment and need for more research especially for type 2 narcolepsy.

Perspective Statement

Earlier this year I was diagnosed with narcolepsy. I thought it was normal to be sleeping 14-16 hours a night and then a few hours after waking up to take a nap for a couple of hours. I was planning each of my days around when I would be able to take a nap because I knew I was going to be tired. Before starting on medications to handle daytime sleepiness the exhaustion I was feeling was deliberating. It was difficult to do anything without needing to go lie down. I couldn't do homework after coming home from class because I needed to go to sleep. I would choose to nap rather than hang out with friends, I would sleep rather than doing hobbies I really enjoy like knitting or reading. Once I started on the medication Xywav which is a form of sodium oxybate I realized how much of my life was consumed by sleeping. Now I am able to go a full day without having to take a nap or scheduling my days around when I am able to sleep. Before getting my diagnosis I thought there was no way I could have narcolepsy because I wasn't falling asleep randomly in the middle of conversations which is what I was led to believe narcolepsy was. There is a false definition of narcolepsy put out by the media that I think is stopping people from getting their diagnosis.

Introduction

Narcolepsy was first noticed in the late 1800s by a French physician by the name of Jean-Baptiste-Edouard Gelineau. He aptly named the phenomenon "narcolepsie" by combining two greek words: *narke*, meaning numbness or stupor and *lepsis* meaning attack (Golden et al., 2018). He observed this stupor-like state in a fisherman. In the next century as more doctors were treating narcolepsy a term was made to describe the common symptoms of this disorder. The term is "Gelineau tetrad", this tetrad includes excessive daytime sleepiness (EDS), cataplexy,

hypnagogic hallucinations, and sleep paralysis (Coelho, 2024). Today narcolepsy is defined in a few different ways. One way narcolepsy is defined is a chronic neurological disorder affecting the sleep-wake cycle in the brain (Anderson, 2021). Another way this condition can be defined is a primary disorder of the central nervous system that is defined as excessive daytime sleepiness (Coelho, 2024). The prevalence of Narcolepsy is thought to be about 1 in 2,000 people, but it is thought that narcolepsy is underdiagnosed (Golden et al., 2018). There is not an agreed upon definition of what narcolepsy exactly is and the cause was only recently discovered about 25 years ago (Mahoney et al., 2018). Narcolepsy can be treated in a variety of different ways.

Narcolepsy Subtypes

There are two defined subtypes of narcolepsy. The symptoms a person displays will determine which version of narcolepsy they have, type 1 or type 2. The main differentiating factor is the presence or absence of cataplexy. Cataplexy is the sudden onset of muscle weakness caused by extreme emotional responses such as laughing (Gandhi et al., 2024). Cataplexy can range from subtle weakness of the knees to collapsing. Type 1 is the presence of cataplexy and type 2 is the absence. In narcolepsy type 1 there is a loss of the vast majority of hypocretin neurons in the hypothalamus which leads to disruption in the sleep-wake cycle (Anderson, 2021). In type 2 narcolepsy there is not a loss of hypocretin, but one hypothesis for the cause of type 2 narcolepsy is impaired hypocretin receptors or an unknown mechanism (Slowik et al., 2023). There is much less known about narcolepsy type 2 than type 1. There is a chance that a person with type 2 narcolepsy can develop cataplexy and this would indicate a progression of the disease (Slowik et al., 2023).

Symptoms

The most notable symptom of both subtypes of narcolepsy is excessive daytime sleepiness (EDS). EDS is a constant sleepy feeling and a few times a day an overwhelming urge to sleep at inappropriate times such as driving (Gandhi et al., 2024). Sleep paralysis and auditory/visual hallucinations are also symptoms of narcolepsy. Sleep paralysis happens during the transition from or to a sleep state, it is the inability to move or speak and can last seconds to minutes (Anderson, 2021). Sleep paralysis does not only happen to people with narcolepsy as it can occur to people without a sleep disorder. Hypnagogic hallucinations are hallucinations that happen right before falling asleep, these experiences are often brief and vivid (Golden et al., 2018). Fragmented sleep is a common occurrence in people with narcolepsy. Although a person with narcolepsy is very tired they typically are unable to stay asleep for a long period of time, their sleep is fragmented and they will tend to wake up several times a night; this points to the unstable sleep-wake cycle of narcolepsy (Golden et al., 2018). Abnormal dreams are common in people suffering with narcolepsy. People with narcolepsy dream more often and vividly, this includes strange dreams, nightmares, and out of body experiences. Narcoleptics are better at being able to recall their dreams, but sometimes dream delusions, dreams that are mistaken for reality can occur (Thorpy et al., 2024). Weight gain and obesity are common symptoms as well (Slowik et al, 2024). Each symptom will show up differently in each case of narcolepsy. A person does not have to have every single symptom that has been listed to be diagnosed with narcolepsy and having one of these symptoms does not mean a person has narcolepsy.

Diagnosis

There are a few different steps to get a diagnosis of narcolepsy. The diagnosis is based on the guidelines set forth by the American Academy of Sleep Medicine. Clinical criteria of diagnosis is based on EDS associated with cataplexy, sleep paralysis, hallucinations, and sleep fragmentation (Coelho, 2021). Figure 1 is the Epworth Sleepiness Scale (ESS) which is used to measure EDS. The questionnaire is subjective, but it helps determine if further evaluation is needed which happens with a score of 11 or more (Anderson, 2021). The next step after the ESS would be to rule out other sleep disorders like sleep apnea using a polysomnography (Golden et al., 2018). After polysomnography rules out other disorders that can disrupt sleep, electrophysiological testing is the next step. The test that is administered is called the multiple sleep latency test (MSLT). This test will measure a person's ability or tendency to fall asleep. 5 opportunities to nap are given with 2 hours in between each nap and each nap lasting around 20 minutes (Anderson, 2021). A positive test will show a mean sleep onset latency of 8 minutes or less, meaning the person fell asleep in less than 8 minutes on average for all of the naps, and at least two sleep-onset REM episodes (SOREMP), meaning REM sleep was reached within 15 minutes of falling asleep (Anderson, 2021). The MSLT has a false negative rate of over 20% in diagnosing narcolepsy, the test may need to be repeated or other diagnosis methods must be used (Thorpy et al., 2024). Another way for narcolepsy to be diagnosed is to measure the amount of hypocretin a person has in their cerebrospinal fluid (CSF), this practice is not commonly used. The international Classification of Sleep Disorders, 3rd edition (ICSD-3) classifies how to differentiate the diagnosis between the two classes of narcolepsy.

Type 1- Excessive daytime sleepiness for at least the past three months along with one of the following: hypocretin 1 concentration of the CSF less than 110 pg/ml along with a mean sleep latency of less than 8 minutes and SOREMP reached 2 times on the MSLT or cataplexy

along with mean sleep latency of less than 8 minutes and SOREMP reached 2 times on the MSLT (Golden et al., 2018).

Type 2- Excessive daytime sleepiness for at least three months and mean sleep latency of less than 8 minutes and SOREMP reached 2 times on the MSLT (Golden et al., 2018).

The gene HLA-DQB1*0602 is present in 95% of people with narcolepsy type 1 and is present in 50% of people with type 2(Anderson, 2021). There is no testing diagnostic criteria for this gene (Coelho, 2024). The reason this gene is not used for diagnosis is because this gene is present in upwards of 38% of the general population (Golden et al., 2018).

There are other sleep disorders that are closely related to narcolepsy that a person could have if they do not meet the criteria set by the international Classification of Sleep Disorders, 3rd edition. One such disorder is idiopathic hypersomnia. The difference between narcolepsy and idiopathic hypersomnia is that during the MSLT a person with idiopathic hypersomnia will have fewer than two SOREMP. In narcolepsy naps tend to be refreshing, but this is not the case for idiopathic hypersomnia as even long naps are not helpful in restoring wakefulness. Idiopathic hypersomnia sleep is not fragmented and there are less night time awakenings (Golden et al., 2018). Another disorder a person could have is Kleine-Levin syndrome which is much rarer than narcolepsy. This disorder is considered episodic rather than a consistent sleepiness like in narcolepsy, behavioral changes are often seen is Kleine-Levin syndrome as well (Golden et al., 2018)

Sleep Neurobiology

Specific neural pathways in the brain regulate the human sleep wake cycle. These specific pathways originate from the hypothalamus in the brain (Andersone, 2021). The hypothalamus is

home to the neuropeptide hypocretin (also called orexin) and histamine neurons; hypocretin and histamine activate the wake-promoting neurons throughout the brain. Hypocretin has two recognized receptors called 1 and 2 (Coelho, 2021). Hypocretin specifically increases activity in areas of the brain that are responsible for suppressing rapid eye movement (REM) sleep (Anderson, 2021). Throughout the night hormones are secreted at intervals to create a cycle of REM sleep and non rapid eye movement (NREM) sleep, this creates a homeostasis (Anderson, 2021). During REM sleep hypocretin decreases which then decreases the activity of the Reticular Activating System (Slowik et al., 2023). The neurobiology of sleep includes more hormones and pathways than what was mentioned, but as of now they are not linked to narcolepsy.

Pathophysiology Hypothesis of Narcolepsy

Various theories have been put forth to explain the pathophysiology of narcolepsy as it is not completely understood. One theory is the premature degeneration of hypocretin producing cells, another one is that interaction with the environment causes the loss of the associated cell population (Coelho, 2024). One thing that is known is the underlying cause of narcolepsy type 1 is the low levels of hypocretin, which was discovered in 1998. As stated before the cause of destruction of the hypocretin cells is not yet known (Gandhi et al., 2024). Evidence shows that the cause of type 1 narcolepsy could be an autoimmune disorder brought about by CD4+ T cells, the immune response would be the CD4 cells destroying the orexin neurons (Gandhi et al., 2024). The loss of hypocretin may destabilize separation of the sleep and wake states, the mechanism of how hypocretin affects sleep and cataplexy along with the complementary effects are not fully understood (Thorpy et al., 2024). Narcolepsy type 2 most likely has a different

pathology than type 1 as people with type 2 have kept their hypocretin molecules. Not much is known about narcolepsy type 1 and even less about type 2.

In 2009 there was an increase in reports of narcolepsy type 1 in Europe following the H1N1 influenza pandemic. There also seemed to be a risk of developing narcolepsy after receiving the vaccine for this pandemic (Golden et al., 2018). The rise of narcolepsy after the pandemic sparked interest in narcolepsy being in autoimmune disorder as well as an association with upper respiratory infection (Golden et al., 2018).

Treatment of Narcolepsy

As of now there is no cure for narcolepsy, only management of symptoms to improve the quality of life. There are many different management types as each person's needs will vary greatly. Table 1 shows the treatments of different day time medication that can be taken to reduce excessive daytime sleepiness. Wake-promoting stimulant medications work by inhibiting the reuptake of dopamine. Examples of these are modafinil and armodafinil and these are often the first medications prescribed as they have less side effects and lower potential for abuse (Golden et al., 2018). Amphetamine is a nervous system stimulant and is a common medication prescribed that works by limiting dopamine and norepinephrine uptake (Martin, 2023). These medications have a potential for addiction and abuse so when prescribing them they should be used cautiously. Along with their addiction potential these medications also have more significant side effects than those mentioned earlier (Golden et al., 2018).

Figure 2 shows medications that can be prescribed to treat cataplexy. Sodium oxybate is the only FDA approved medication that is available to treat cataplexy (Amin et al., 2024). Sodium oxybate is the sodium salt of gamma hydroxybutyrate (GHB) . This medication is able to

increase slow-wave sleep, decrease EDS, and improve nighttime sleep quality (Anderson, 2021). The half life of this drug is very short so the administration is different from the other medications that are taken for narcolepsy. Sodium oxybate is taken in two doses throughout the night, the first dose is taken right before bedtime and the second is taken 2 ½ to 4 hours after the first dose (Golden et al., 2018). Since it is a nighttime drug a person will have to wake up in the middle of the night to take the second dose. This drug comes in a liquid form and has to be titrated to reduce adverse reactions before a person can take their needed dose. A doctor will prescribe their patient a low dose of this medication and each week they will take more until they reach their intended dose. Sodium oxybate is a central nervous system depressant with high abuse potential (Anderson. 2021). The mechanism of the medication and the way it treats cataplexy is unknown. There are a few other non nighttime medications that can reduce the effects of cataplexy like solriamfetol and pitolisant (Anderson, 2021). Antidepressants promote the action of norepinephrine that can suppress rem sleep. There are non medication treatments like scheduling short naps to improve alertness. Caffeine can also be used to reduce daytime sleepiness although a person can easily build caffeine tolerance or it might not help at all.

Discussion and Conclusion

As of now, there is a severe lack of understanding of narcolepsy especially narcolepsy type 2 and what is causing it. There is more research on narcolepsy type 1 than type 2. It seems like narcolepsy type 2 could be a whole different disease since people with type 2 still have hypocretin and this should be looked into. There have been breakthroughs throughout the past 30 years such as figuring out that narcolepsy type 1 is caused by the diminishing of hypocretin. Although understanding has come a long way since the late 1800s when it was discovered, there

are many aspects that aren't understood. There should be more research done to find out how the hypocretins are being lost and if there is a way to prevent or build back up the amount of hypocretins. It seems that the public isn't aware of what narcolepsy actually is and how debilitating it can be in everyday life.

Activity	*Chance of Dozing*			
	0 (Never)	1 (Slight)	2 (Moderate)	3 (High)
Sitting and Reading				
Sitting inactive in a public place (such as theater or meeting)				
As a passanger in a car for an hour without a break				
Lying down to rest in the afternoon				
Sitting a talking to someone				
Sitting quietly after lunch without alcohol				
In a car, while stopped for a few minutes in traffic				
Total score:				

Figure 1. shows the Epworth Sleepiness Scale questionnaire that is used to determine if further evaluation for sleep disorder is needed. The patient answers the question on a scale of 0-3 on how likely they would be to doze off while doing that activity.

TABLE 2

Drugs to treat excessive daytime sleepiness in narcolepsy

Medication	Dosage	Side effects and federal schedule
Modafinil	100–400 mg/day in 2 divided doses	Headache, anxiety, nausea, dry mouth, anorexia, diarrhea, reduction of efficacy of oral contraceptives, Stevens-Johnson syndrome (rare) Schedule IV[a]
Armodafinil	150-250 mg once daily in the morning	Same as modafinil Schedule IV
Methylphenidate	Immediate-release: 5 mg twice daily titrated up by 5-10 mg per dose weekly up to to 10-20 mg twice daily; once on stable dose, transition to extended- or sustained-release formulation	Headache, anxiety, nausea, anorexia, tremor, psychosis, cardiovascular effects like hypertension and arrhythmias, abuse (rare) Schedule II[b]
Dextroamphetamine	Short-acting: 5 mg twice daily titrated up by 5-10 mg per dose weekly up to 30 mg twice daily; once on stable dose, transition to long-acting formulation	Headache, anxiety, nausea, anorexia, tremor, psychosis, cardiovascular effects like hypertension and arrhythmias, abuse (rare) Schedule II
Amphetamine/dextroamphetamine	Short-acting: 5–10 mg daily titrated up by 10 mg weekly up to 60 mg/ day or satisfactory clinical response; may add additional doses 4–6 hours after first dose; once on stable dose, transition to long-acting formulation	Headache, anxiety, nausea, anorexia, tremor, psychosis, cardiovascular effects like hypertension and arrhythmias, abuse (rare) Schedule II

Figure 2. shows different medications that can be used to treat excessive daytime sleepiness along with the dosage and side effects (Golden et al., 2018).

TABLE 3

Medications to treat cataplexy in narcolepsy

Medication	Dose	Side effects
Sodium oxybate[a]	3 g/night in divided doses, once before bedtime and then 2.5-4 hours later, titrated up to 4.5-9 g in divided doses	Nausea, mood swings, enuresis, headache, weight loss, sedation, sleepwalking, worsening of obstructive sleep apnea; High salt content can worsen preexisting hypertension, heart failure, and renal impairment Schedule III, ie, moderate to low potential for physical and psychological dependence; see www.dea.gov/druginfo/ds.shtml
Venlafaxine	Short-acting: 37.5–75 mg twice daily; may transition to long-acting formulation once on stable dose	Nausea, dizziness, dry mouth, headache, insomnia, sexual dysfunction
Fluoxetine	20–60 mg once daily	Nausea, headache, dry mouth, diarrhea, sexual dysfunction
Sertraline	50–150 mg once daily	Nausea, headache, dry mouth, diarrhea, sexual dysfunction
Protriptyline	5–10 mg twice daily	Dry mouth, constipation, light-headedness, urinary retention

[a] Treats both daytime sleepiness and cataplexy.

Table 3 is medications for the treatment of narcolepsy with cataplexy. The graph also shows the dosage and common side effects (Golden et al.,2018).

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