Review Article

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Narcolepsy: Clinical features, co-morbidities & treatment

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Narcolepsy is a neurologic illness that typically begins in the second and third decades of life. It is chronic in nature and negatively impacts the quality of life of affected patients. The classic presentation is a tetrad of excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations. The exact cause remains unknown, but there is significant evidence that hypocretin deficiency plays an integral role. Some primary conditions that result in secondary narcolepsy include traumatic brain injury, congenital disorders, tumours, and strokes. Some medical and psychiatric disorders share characteristics of narcolepsy, at times leading to diagnostic inaccuracy. Other sleep disorders are commonly co-morbid. Diagnosis relies on patient history and objective data gathered from polysomnography and multiple sleep latency testing. Treatment focuses on symptom relief through medication, education, and behavioural modification. Both classic pharmacological treatments as well as newer options have significant problems, especially because of side effects and abuse potential. Novel modalities are being examined to expand options for treatment.

Key words Cataplexy - excessive daytime sleepiness - hypocretin - MSLT - narcolepsy

Narcolepsy is a disabling neurlogical illness that usually begins early in life. It manifests as sleep disturbances and REM sleep phenomena that intrude into the lives of affected individuals. There are two subtypes of the disorder: narcolepsy with cataplexy and narcolepsy without cataplexy. The cause is uncertain, but there is evidence of both genetic and environmental factors. The brain peptide hypocretin appears to be deficient in most cases involving cataplexy. There are several co-morbid conditions linked to narcolepsy, especially other sleep disorders. The symptoms overlap with many medical and psychiatric illnesses, which can result in misdiagnosis. Therefore, careful history along with objective sleep data gathered in polysomnography and multiple sleep latency testing are needed to make an accurate diagnosis. Stimulant medications, modafinil, and sodium oxybate target the excessive daytime sleepiness while antidepressants and sodium oxybate are useful for cataplexy. Therapies that focus on various neurotransmitter systems, immunomodulation, and hypocretin replacement are being evaluated.

Epidemiology

The prevalence of narcolepsy varies across countries and with different ethnic groups, and so the exact prevalence is not known. Discrepancies may relate in part to disease definitions, study designs, and age groups studied. Prevalence estimates have been reported to be between 168 and 799 per 100,000 in most studies, although Japanese studies have indicated a higher prevalence of 1600 per 100,000[1,2]. None of these studies used polysomnography in their diagnostic

approach, however, and instead relied on survey data. An estimated incidence of 0.74 per 100,000 person-years for a diagnosis of narcolepsy with cataplexy and 1.37 per 100,000 person-years for patients diagnosed narcolepsy with and without cataplexy was based on the incidence rates and prevalence of narcolepsy in Olmsted County, Minnesota between 1960 and 1989, as measured by the record linkage system of the Rochester Epidemiology Project[3]. The prevalence of narcolepsy without cataplexy is more difficult to ascertain, and these patients are more likely to be undiagnosed; this subgroup may represent 10 to 50 per cent of the narcolepsy population[4,5].

Narcolepsy can begin at any age, although the majority of the people diagnosed with narcolepsy begin to show symptoms between the ages of 10 and 25 yr[6]. There may be a bimodal distribution with a significant but smaller peak occurring in the fourth decade of life[7]. Younger populations report that excessive daytime sleepiness (EDS) is the first symptom to appear, whereas older cohorts report that cataplexy is the most common initial symptom[6]. Men seem to be more commonly affected, with narcolepsy occurring 1.6 times more often in men than in women[1].

Although the specific causes of narcolepsy remain unknown, it appears that there are both environmental and genetic factors contributing to the development of this disease. Supporting the evidence for an environmental influence is the fact that the disease is not apparent at birth, but instead commonly has its onset during the second decade of life. Additionally, there are apparent precipitating factors such as head trauma, infection, and changes in sleep-waking habits that have been identified in some cases[8]. A higher incidence of narcolepsy has been seen in people born in the month of March and a lower incidence among those born in September[9]. While most cases of narcolepsy are sporadic, there are multiple reports of familial narcolepsy[10]. First-degree relatives have an estimated a 1 to 2 per cent chance of developing narcolepsy[10]. Although small, it is substantially higher than the prevelance of narcolepsy in the general population.

Narcolepsy is associated with the HLA DR2 haplotype[11]. Because of this observation, it has been postulated that narcolepsy may result from an autoimmune process, though this has not been verified[11]. DNA analysis has revealed that there are several genes linked to narcolepsy. Moreover, different gene subtypes carry various levels of frequency, specificity, and relationship to ethnic backgrounds[10]. However, these genes can also be found in subjects who do not appear to have symptoms of narcolepsy. There has been a strong association observed with HLA DQB1 0602/DRB1 1501, which is particularly prevalent when cataplexy is present[11]; over 90 per cent of narcoleptics with cataplexy express this marker, but it is also seen in approximately 1/10 – 1/3 of the general population. Confounding this is the fact that there are rare patients with obvious cataplexy who do not have HLA DQ B1 0602, thus HLA typing is not useful as a diagnostic tool[10].

Role of hypocretin

Hypocretin is a peptide derived from the dorsolateral hypothalamus that has been linked to multiple regulatory functions including sleep/wake cycles, food intake, and pleasure seeking behaviour[12]. Sleep fragmentation is observed when there is a deficiency of hypocretin. There are currently two known variants, hypocretin 1 and 2, also known as orexin A and B, respectively. Hypocretin functions through two G protein coupled receptors. The cells containing hypocretin are linked to monoamine cell groups in the locus ceruleus, raphe nucleus, tuberomammillary nucleus, and ventral tegmental area corresponding to norepinephrine, serotonin, histamine, and dopamine respectively. Deficiencies of hypocretin can lead to abnormailities in the function of these monoamine systems, which in turn can mediate the symptoms of narcolespy. Dopamine has significant wakefulness promoting properties, as does histamine. Abnormalities related to rapid eye movement (REM) sleep can be produced with the changes to the adrenergic and serotonergic systems[13].

Animal studies provided some of the earliest evidence that hypocretin plays some role in narcolepsy[14]. Certain breeds of dogs, including Doberman Pinschers, can express the narcoleptic phenotype that is transmitted by an autosomal recessive gene. Study of these animals has revealed the presence of fragmented sleep, episodes thought to be similar to cataplexy, and short REM sleep latencies. Genetic analysis led to the discovery of a dysfunctional receptor in the neuropeptide system, specifically hypocretin 2 receptor. Studies in mice revealed a model in which mutations found in the preprohypocretin promoter produce the narcolepsy phenotype[14]. Hypocretin 2 receptor knockout mice also display episodes similar to cataplexy[15]. Animals without the hypocretin 1 receptor are not observed to have cataplexy-like behaviours, but do show fragmentation of their sleep.

With animal studies yielding evidence of a link between narcolepsy and abnormalities in the hypocretin system, attention has turned to hypocretin in human narcolepsy[16]. Human pathology studies have revealed reductions of Hcrt1, Hcrt2, and preproHcrt mRNA. However, only one report so far has found mutations in the *Hcrt* gene itself[16]. The resultant low level of hypocretin despite normal *Hcrt* genes lends some weight to the idea that narcolepsy is the result of an autoimmune process. Also in support of this idea is that narcolepsy has a typical onset in the second and third decades of life, which is common in many other autoimmune disorders. One report has identified monozygotic twins who were concordant for narcolepsy with cataplexy but found to have normal cerebral spinal fluid concentrations of hypocretin-1 and no mutations in the hypocretin gene or hypocretin receptor gene, suggesting that dysfunction of the hypocretin system may not be the only pathway to narcolepsy[17].

In human narcolepsy, the role of hypocretin system abnormality appears to be variable[16]. Many studies have found hypocretin to be absent or reduced in the cerebrospinal fluid of narcoleptics; over 90 per cent of patients show significant reductions in hypocretin levels when there is clear cataplexy and HLA positivity[12,18]. However, this association is not as clear when cataplexy is absent, with only approximately 20-40 per cent of non-cataplectic patients showing low hypocretin levels. The lack of low CSF hypocretin may represent an entirely different entity with pathology in another system versus a less severe form of the disease. Additionally, this may represent secondary narcolepsy resulting due to from tumours, traumatic brain injury, and encephalomyelitis[19]. Alterations in hypocretin have not been seen in other sleep disorders such as sleep apnoea, insomnia, and restless leg syndrome[11]. On the other hand, there are many other disorders with symptoms of daytime sleepiness or fatigue that have been associated with low CSF hypocretin levels such as encephalitis, multiple sclerosis, genetic disorders, tumours, and Guillian-Barre syndrome[12].

Clinical features

The classic tetrad of symptoms for narcolepsy includes excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, and hypnagogic hallucinations[8]. Not all symptoms are present in all patients and these may vary and in frequency and intensity over time[6,20]. Also, these symptoms can be found in other disorders, including other distinct sleep disorders[21].

Excessive daytime sleepiness includes spontaneous, recurring urges to sleep and a general sense of background sleepiness that is present much of the time; this is the most commonly occurring feature of the tetrad[22]. These episodes vary in length from seconds to over an hour. Patients with narcolepsy may experience multiple episodes of overwhelming sleepiness per day. The sleep attacks can occur at inappropriate times such as driving, when engaged in conversation, and other times the patient is active and participating in some task. This urge to sleep tends to be heightened by more monotonous activity or in low stimulation surroundings. Narcoleptics often report that taking a nap or succumbing to these sleep attacks help them, as they often feel refreshed upon waking, although usually only for a short period. Patients with narcolepsy generally do not spend a greater portion of their time asleep compared to people who do not have narcolepsy despite these recurring daytime sleep spells because their nocturnal sleep is often highly fragmented; this results in a loss of total sleep time at night so that the added daytime napping results in a "normal" amount of total sleep across the day[23]. The background level of sleepiness can also have significant impact on daytime functioning, impairing concentration, work and school performance, and general quality of life[24,25].

It is important to clarify that the narcoleptic patient is sleepy and not just fatigued, although both symptoms are often reported. Clinicians and patients often use these terms interchangeably, although these do not necessarily describe the same entity. Fatigue refers to lacking energy or feeling listless, as opposed to having a true tendency to fall asleep inappropriately. Fatigue is associated with many medical and psychiatric illnesses. Individuals who suffer from fatigue do not usually exhibit abnormal results on multiple sleep latency testing[24].

Cataplexy is a sudden decrease in or loss of muscle tone. It usually occurs bilaterally and is often in response to emotions such as humour, anger, surprise, and tremendous joy[22,23]. These attacks typically affect certain muscle groups but may be more generalized, resulting in the patient collapsing. Patients with narcolepsy are often aware of these attacks and take action such as propping themselves up or sitting down when as they perceive the attack coming on. There may be twitching of the facial muscles or limbs which can lead to a misdiagnosis of epilepsy[22]. In milder versions, patients may describe a general sense of weakness but still maintain control. Speech may be slurred or broken

as a result of muscle inhibition. Patients may also complain of simply feeling clumsy or unco-ordinated, particularly at times involving strong emotions. It is possible for cataplexy to emerge without the event being triggered by an emotion or stress, but this is more unusual. Typically, cataleptic episodes are brief, lasting a few seconds to a few minutes. In rare circumstances, these can persist for hours, resulting in status cataplecticus.

In normal sleep, NREM sleep always occurs first and then alternates with REM sleep. Because of the early onset REM periods and dissociation of certain components of REM sleep, a patient may experience other aspects of REM sleep during wakefulness [20,22,23]. In normal REM sleep, the body loses muscle tone, and dreaming occurs. Sleep paralysis occurs as a patient with narcolepsy is either falling asleep or awakening. This can be a frightening experience because the patient is unable to move limbs, open the eyes, or speak. These episodes are generally brief and patients are aware of their state. Often, hallucinations coincide with sleep paralysis.

Patients with narcolepsy may experience hallucinations at sleep onset (hypnagogic) and upon awakening (hypnopompic)[20,22,23]. Like normal dreams, these phenomena tend to be visual in nature but may also be auditory. Characteristically, these include simple forms, objects, animals, and people. Patients will sometimes respond to their hallucinations, particularly if they believe that an intruder is present or that they are in some form of danger. Patients also report other types of dream-like phenomena which might include levitation or out of body experiences.

In addition to the classic tetrad, patients also describe significant problems with insomnia, repeated awakenings, and complaints related to their level of tiredness such as blurry vision, diploplia, and trouble with concentration and memory[22,23,26]. There are often automatic behaviours that occur at the time of increasing sleepiness[22]. These automatic behaviours are generally related to routine activities that require little attention but may involve significant errors or risk, such as driving. Narcolepsy is often co-morbid with other sleep disorders such as REM sleep behaviour disorder, sleep apnoea, and periodic limb movement disorder[24,27]. The symptoms of narcolepsy and secondary effects of the disorder can have major negative effects on all aspects of life including the patient's education, work performance, ability to drive safely, relationships, mood, and overall wellbeing.

Of the four symptoms in the classic tetrad, excessive daytime sleepiness is the one most consistently reported by patients with narcolepsy[28]. Evaluating this complaint is problematic, however, because it is observed in numerous other disorders related to sleep and many general medical and psychiatric disorders. Several primary sleep disorders have daytime sleepiness as a symptom, including sleep deprivation, delayed sleep phase disorder, advanced sleep phase disorder, sleep disordered breathing, periodic limb movements, idiopathic hypersomnia, and Kleine-Levin syndrome.

Excessive daytime sleepiness is routinely linked to psychiatric disorders as well[24,28]. Epidemiologic studies have revealed significant co-morbidity of hypersomnia and psychiatric disorders. Dysthymia, atypical depression, seasonal affective disorder, and bipolar disorder are commonly associated with sleep dysregulation and complaints of hypersomnia. Several anxiety disorders may also impact the patient's sleep and should be evaluated and addressed[29,30].

Causes of narcolepsy

The exact cause of primary human narcolepsy remains unknown, although loss of hypocretin appears to play a role in most cases with cataplexy[12,18]. There are also other neurological insults that appear to have narcolepsy symptoms as a consequence[19]. Just as in primary narcolepsy, these entities may or may not include cataplexy as a symptom. Measurement of CSF hypocretin levels may reveal a broad range of variations in the low, normal, and intermediate range as well[8]. Lesions of the hypothalamus and nearby structures can produce narcolepsy-like symptoms. Multiple sclerosis, tumours, and strokes have all been associated with narcolepsy as well. More global insults such as traumatic brain injury, encephalomyelitis, and congenital disorders such as Neimann-Pick type C disease, myotonic dystrophy, and Prader-Willi syndrome are also associated with narcolepsy[8]. It is unknown if the changes in hypocretin levels are a consequence of the primary insult or a coincidental finding. Additionally, these changes can be transient, as the low levels found in many traumatic brain injury patients may return to normal after six months[12].

Diagnostic considerations

The International Classification of Sleep Disorders consists of two classifications of narcolepsy: with or without cataplexy[21]. The tetrad of EDS, cataplexy, sleep paralysis, and hallucinations is the hallmark of narcolepsy, though not all of the symptoms need be

present (Table I). Also, some of the symptoms may be present in isolation even if a patient has experienced the whole tetrad. For example, cataplexy may be seen without necessarily having a sleep attack, and sleep attacks do not necessarily include an episode of cataplexy. Because excessive daytime sleepiness is the most common feature in patients with narcolepsy, having methods to determine levels of sleepiness accurately is important. Several scales exist to measure sleepiness, including the Epworth Sleepiness Scale[31]. A common problem with subjective scales, however, is their inconsistent reliability to correlate with objective data.

The multiple sleep latency test (MSLT) is currently the accepted standard to obtain objective information regarding sleep drive and excessive sleepiness. It consists of five scheduled naps, each 20 min in length, that are scheduled every 2 h across the day. Ideally, the sleeping conditions are set so that the patients are best able to fall asleep. This requires appropriate temperature, limited stimulation, and making the nap as comfortable as possible given the obvious limitations of being in the lab and attached to recording equipment. Following each nap opportunity, the patient is to stay awake until the next scheduled nap. During the test, physiologic data are gathered such as the time it takes to fall asleep and the presence or absence of REM sleep. REM sleep that occurs within the first 15 min of sleep, an event termed sleep onset REM (SOREM), rarely occurs in normal individuals, but is common in narcolepsy. MSLT results may vary with the age of the patient [32]. The current criteria require falling asleep in less than eight minutes on average across the naps and having two SOREMs or the occurance of REM sleep within the 20 min naps[21]. There is some evidence that this criteria are not specific to narcolepsy. Having multiple SOREMs on the MSLT has been associated with other disorders with EDS such as sleep apnoea, shift work sleep disorder, and periodic limb movement disorder[33].

Table I . Primary and secondary aetiologies

Hypocretin deficiency
Hypothalamic lesion
Stroke
Tumour
Prader-Willi syndrome
Traumatic brain injury
Neimann–Pick disease type C
Myotonic dystrophy
Encephalomyelitis

Kleine-Levin syndrome, Prader-Willi, obsessive-compulsive disorder, and Parkinson's disease have also been linked to SOREMs[33]. Multiple SOREMs have rarely been seen in patients who were thought to be otherwise normal.

On the night prior to an MSLT, the patient is typically brought into the sleep laboratory in order to perform the nocturnal polysomnogram. The patient is monitored all night to gather data on breathing, movement, time in bed, time asleep, and heart rate. The patient also will have electroencephalogram (EEG) recorded throughout the night to monitor when the patient falls asleep and wakes up, as well as to provide information regarding what stages of sleep are attained and the length of those stages. While the EEG montage is limited, it has the potential to identify seizure activity. Patients may have audio and video monitoring to reveal snoring, sleep talking, and reveal movements or complex behaviours that the patient may be performing while asleep. The polysomnogram itself may reveal the aetiology of a person's excessive daytime sleepiness or other sleep pathologies. Narcolepsy can be co-morbid with other sleep disorders such as REM behaviour disorder, apnoea, and sleep related movement disorders. Conversely, the sleep study procedure may cause a person to have abnormal sleep because of the disruption of sleeping in a new environment and with the recording electrodes, thus potentially influencing the next day's MSLT, particularly if the patient had significant difficulty falling asleep or staying asleep in the laboratory. To minimize the effects of possible sleep deprivation, the American Academy of Sleep Medicine recommends that the patient have at least six hours of recorded sleep on the night prior to the MSLT[34]. This could still be insufficient for a given individual, however, and ideally a patient should sleep *ad libitum* for at least several days prior to being studied in the laboratory.

At its most basic level, an MSLT measures sleepiness. It does not determine what causes the observed sleepiness. Because of this, a condition that would promote one's ability to take multiple naps during the daytime could significantly interfere with the validity of using MSLT to diagnose narcolepsy. Further complicating the issue is that many of the symptoms of narcolepsy, with the exception of cataplexy, can be produced with sufficient sleep deprivation[35,36]. Co-morbid medical and psychiatric conditions could contribute to an increased tendency to fall asleep during the day. Numerous medications

can also interfere with the validity of the test. As data are gathered regarding REM sleep, medications that either suppress or promote REM sleep can affect test results. As such, medications that can alter alertness, sleep cycle, and other physiologic data that would be recorded during the test should be reduced or eliminated for at least several weeks prior to the test, if possible.

A significant confounder for the MSLT is insufficient sleep time since many people are chronically sleep deprived[35]. Therefore, a complaint of EDS requires taking detailed history and gathering data on a person's sleep[35]. To further assist in making the diagnosis, patients may be asked to keep a sleep diary in order to verify their sleep habits, time in bed, and attempt to learn how much time is spent sleeping each day. There is some evidence that such logs may be unreliable in comparison to actigraphy, which consists of wearing a motion sensitive device that records when there is motion and uses the lack of movement as a surrogate for time asleep.

There are no genetic tests currently available for clinical use to make a positive diagnosis of narcolepsy. Genetic testing may correlate best to narcolepsy when there is already clear cataplexy[8,12]. Additionally, the genes identified so far are specific to various ethnic backgrounds, further limiting their utility[10,37]. There are also no blood tests available to confirm a diagnosis. Analysis of CSF is useful in patients who also have typical cataplexy. Atypical cataplexy, which involves a cataplectic event that is not initiated by an emotional event such as laughter, is only associated with hypocretin deficiency in 20 per cent of cases[8]. In evaluating patients for narcolepsy with cataplexy, almost all cases with deficient hypocretin are also positive for HLA DQB1[8,11,18]. It is important to keep in mind that narcolepsy does not exclude other diagnoses from being co-morbid, and conversely, narcolepsy symptoms may be secondary to some other conditions such as traumatic brain injury, infection, tumour, or cerebrovascular accident[8]. Multiple sclerosis (MS) is particularly problematic because the common HLA DQB1 haplotype can be seen in MS, and plaques in the hypothalamus could potentially lead to secondary narcolepsy. It is reasonable to expect these chance plaques to be the cause of sleep related symptoms, because MS patients positive for HLA DQB1, but lacking plaques in the hypothalamus, do not show changes in hypocretin and do not exhibit the tetrad of narcolepsy symptoms.

Differential diagnosis

Narcolepsy shares many symptoms with psychiatric illnesses, which can sometimes lead to it being diagnosed as a psychiatric illness. According to the Fourth edition of the Diagnostic and Statistic Manual IV with text revision (DSM-IV-TR), nearly every psychiatric illness requires some level of functional impairment[30]. Patients with narcolepsy can exhibit significant problems in work, school, relationships, and their quality of life, and these types of impairments may bring them to psychiatric attention[19,25]. Common psychiatric illnesses such as major depressive disorder (MDD), bipolar disorder, and psychotic disorders have symptom overlap with narcolepsy[23]. Patients with mood disorders often have insomnia and/or hypersomnia[38]. Patients with MDD or who are in the depressed phase of bipolar disorder may experience EDS in addition to their fatigue[39]. Mood disorder patients in general can show polysomnographic findings of reduced REM latency when not taking REM suppressing antidepressants[38]. However, these generally do not result in SOREM periods as seen in narcolepsy. Mood disorders can be associated with psychosis, and hypnagogic/hypnopompic hallucinations may be interpreted as psychotic symptoms[40]. Patients with psychiatric illness and those with narcolepsy can express some level of impairment in cognitive performance[30,41]. In children, narcolepsy may present with just EDS[42]. Consequently, the behaviours observed as a result of the sleepiness may mimic that seen in children with attention deficit/hyperactivity disorder[43]. To further confound the diagnosis, both often respond to treatment with stimulant medications and there is evidence of improvement in paediatric patients with attention deficit hyperactivity disorder (ADHD) who take modafinil[44]. Malingering is another possibility, as patients may be seeking medical leave, disability, or seeking stimulants. Narcolepsy can also be misdiagnosed as a conversion disorder.

Schizophrenia and narcolepsy also share some features that can lead to misdiagnosis and thus inappropriate treatments[24]. Both tend to start in adolescence and young adulthood. Patients with schizophrenia can have alterations in the sleep cycle and complain of insomnia. Some schizophrenics may have reduced REM sleep latencies. Hallucinations are found in both, though a careful history and detailed assessment of these can help distinguish the two entities. Auditory hallucinations are experienced by both groups, though much more commonly in patients with schizophrenia. Conversely, visual hallucinations are reported by

patients with narcolepsy in rates as high as 83 per cent while seen by patients with schizophrenia only 29 per cent of the time[40]. Further, patients with narcolepsy usually report their hallucinations to be associated with sleep and those with schizophrenia do not generally link these phenomenon to their sleep. As opposed to the case of narcolepsy misdiagnosed as ADHD, the treatments of schizophrenia and narcolepsy do not often overlap. In fact, providing stimulants to a patient with schizophrenia may worsen their psychotic symptoms. Conversely, many antipsychotic medications may worsen EDS because of their sedative side effects. Depending on the neurotransmitters affected by a given agent, there can be myriad effects on sleep architecture that may be inadvertently beneficial. For example, REM sleep suppression may help with cataplexy and the hypnagogic hallucinations. Thus, the clinician and patient may be led astray by the resolution of the psychotic symptoms.

Several neurologic disorders should be considered when making the diagnosis of narcolepsy. Epilepsy is a commonly occurring condition that may be given as the initial diagnosis[45]. The cataplexy and sleep attacks may appear to an observer to be a seizure. Parkinson's disease and Alzheimer's disease both exhibit significant alterations in sleep and prominent EDS[46,47]. There is also an overlap in Parkinson's disease and narcolepsy because of their shared association with REM sleep behaviour disorder[46]. The presence of hallucinations may confuse patients and clinicians. Treatment strategies for these neurologic disorders may overlap, particularly with dopamine agonist medications, though such agents can also cause sleep attacks and worsen symptoms of Parkinson's disease.

Treatment of Narcolepsy

As a definitive cause of narcolepsy has yet to be identified, treatment strategies must focus on relief of symptoms. With EDS being the most prevalent and the most problematic issue for narcoleptics, most of the treatments target this particular symptom[8]. Stimulant medications have been the mainstay of therapy for many decades[4,13]. These medications primarily act by increasing monoaminergic activity. Those medications that influence dopamine and norepinephrine have been the most effective for managing EDS, but do not typically provide reflief from cataplexy, though some patients do find that amphetamines can reduce this symptom as well. Thus amphetamines and methylphenidate, in their various formulations, have been the most commonly utilized pharmacotherapy. Both of these mediations are available in immediate release and longer acting formulations. Adderall is given in doses of 10-60 mg per day, with 60 mg being the maximum total daily dose. Methylphenidate comes in numerous brands and dosage formulations. The usual dosages are between 10 and 60 mg per day, though this will depend on the actual brand and formulation chosen[4,13].

These medications can have profound side effects, and can be addictive[48,49]. Because of the noradrenergic effects, amphetamines can cause hypertension. Patients with high blood pressure, cardiac disease, symptomatic hyperthyroidism, and arteriosclerosis should use amphetamines with caution[49]. Both methylphenidate and amphetamines have been linked to significant substance abuse, in part thought to be mediated by their role with increasing dopamine levels. In some patients, stimulants can also produce or exacerbate co-morbid psychiatric complications such as anxiety, mania, and even psychosis. Because narcoleptic patients often have insomnia, the time of day when stimulants are taken must be monitored, so as not to produce even more sleep disturbance. Loss of appetite, sometimes with weight loss, and motor tics are associated with stimulants.

Modafinil is approved by the United States Food and Drug Administration for the treatment of excessive sleepiness related to narcolepsy, obstructive sleep apnoea/hypopnoea syndrome, and shift work sleep disorder[50]. Its mechanism of action is not fully understood, but it is believed to work through the dopaminergic, adrenergic, and histaminergic systems in the hypothalamus[13,51]. This difference led to it being termed a wakefulness promoting agent rather than a stimulant. While it appears useful for the treatment of EDS, it also seems to be beneficial for cataplexy[13]. The therapeutic range is 100 to 400 mg each day[50]. Dosing it multiple times per day can reduce residual EDS compared to a single daily dose[52]. One drawback, though, is compliance with the second daily dose, which may then hinder the true effectiveness of this medication. The most common side effects are headache, dry mouth, insomnia, nausea, and anxiety[50,52]. Some people also experience cardiovascular effects including tachycardia, palpitations, or chest pain. There can be serious dermatologic reactions and hypersensitivity including Stevens-Johnson syndrome and toxic epidermal necrolysis. Neurocognitive complaints include difficulty in concentrating, depression, and paresthesias. While no causative link

has been established, the literature reveals case reports of patients taking modafinil and experiencing suicidal ideation[50,53] . There are also reports linking modafinil to visual hallucinations in mania[50]. Modafinil is currently not scheduled as other stimulant medications. Compared to other medications useful for EDS, it does not appear to have the same level of abuse potential.

Multiple studies have been conducted in which modafinil is compared to traditional stimulant medication, with mixed results[4]. In studies involving a placebo, modafinil and stimulants were both superior in terms of reducing EDS. However, subjects already familiar with the effectiveness of amphetamines at times requested to be switched back to these medications, as they did not believe they were adequately treated with modafinil alone because of a subjective sense of sleepiness[4]. Additionally, some reported that they did not have a strong sense of control over their cataplexy and sleep paralysis. As amphetamines interact with the norepinephrine system they may show some additional benefits for these symptoms. Studies that revealed no particular difference between stimulants and modafinil generally used longer washout periods, and subjects received modafinil at its upper dosage limits[4]. With treatment, subjects reported improvements in quality of life, mood, and a higher level of satisfaction with modafinil compared to stimulants[54] (Table II).

Modafinil is not currently approved for treatment in children. However, it is prescribed to children and appears to be effective[55]. In a small study of modafinil in children ages 2-18 yr, it was associated with improvements in academic performance and further showed improvement in objective measures on MSLT[55]. There is some evidence that it is most effective when used in divided doses, with one in the morning and another in the afternoon[43]. Care should be taken not to administer modafinil in such a way that would impair the child's sleep.

Table II. Treatment - behavioural and pharmacological (for excessive sleepiness and cataplexy)

Behavioural
Ensure good sleep hygiene (avoid sleep deprivation)
Consider use of strategic napping
Pharmacological: For excessive sleepiness
Methylphenidate
Amphetamine
Modafinil
Selegiline (also anti-cataplectic)
Pharmacological: For cataplexy
Gamma-hydroxybutyric acid/sodium oxybate
Protriptyline
Desipramine
Imipramine
Clomipramine
Venlafaxine
Duloxetine
Selective serotonin reuptake inhibitors

Another medication found to be effective for the treatment of cateplexy and EDS is gamma-hydroxybutyric acid (GHB). It is produced for sale in the US as sodium oxybate, the salt form of GHB[43]. Historically, GHB has been utilized for many different conditions such as depression, insomnia, and alcoholism[56]. In the United States, it is currently only approved to treat cataplexy and EDS associated with narcolepsy and is the only medication approved by the US FDA for cataplexy[57]. The properties of GHB can appear to be paradoxical[56]. Because of its interaction with the GABA system, which is inhibitory, it can act as a sedative. However, in relative low doses it can stimulate dopamine release, and at higher doses inhibit dopamine release, thereby resulting in both inhibitory and stimulating central nervous system effects. It also appears to promote glutamate release, further enhancing its stimulating properties.

The effectiveness of sodium oxybate has been established in placebo controlled trials[4]. There are also studies in which subjects have taken sodium oxabate after being on other available treatments for EDS[58]. In this comparative study of modafinil versus sodium oxybate, both objective and subjective measures were assessed, utilizing the maintenance of wakefulness test and Epworth sleepiness scale, respectively. Findings from the study revealed that both subjective and objective effects of sodium oxalate were superior compared to treatment with modafinil[58]. The same study also found that modafinil did not separate from placebo, however.

GHB has been associated with significant abuse, dependence, and withdrawal[59]. Street users have called it “liquid ecstasy,” as it can produce euphoria and has been utilized in the nightclub scene[56]. It has also been called a date rape drug, being associated with sexual assault. It has been utilized by bodybuilders because of its ability to stimulate human growth hormone. It is contraindicated for use with other CNS depressants, and has synergistic effects with alcohol[57]. Abrupt discontinuation of GHB can result in life-threatening withdrawal[60]. Because of its shared agonism with

GABA, baclofen is very useful in the treatment of GHB withdrawal[61]. Overdoses of GHB can result in significant CNS sedation, respiratory depression, bradycardia, and seizures[57].

As sodium oxybate, it can have important cardiovascular effects secondary to water balance in the face of heightened sodium levels[57]. At the maximum recommended human dose of 9 g, it contains 1638 mg of sodium. As such, patients who have heart failure, hypertension, or renal impairment may need additional evaluation prior to starting sodium oxybate. It undergoes significant first pass metabolism in the liver, so patients with hepatic impairment should be started at one-half the usual dosage.

Common side effects of sodium oxybate include headache, nausea, dizziness, nasopharyngitis, somnolence, vomiting, and urinary incontinence[20,57]. There are also reports of obstructive sleep apnoea worsening while taking sodium oxybate. Somnambulism, or sleep walking, occurred in 4 per cent of the subjects in the clinical trials submitted for FDA approval[57]. However, in patients who had been exposed to the drug for up to 16 yr, the incidence of sleep walking increased to 32 per cent[57]. Because of the dangers inherent in somnambulism, patients must be cautioned regarding this potentially problematic effect.

Selegiline is another agent used to reduce EDS[4]. Selegiline is an irreversible monoamine oxidase inhibitor (MAOI) with selectivity for MAO-B[13]. As the dose increases, it can lose the selectivity and block both the A and B subtypes. It has wakefulness-promoting properties and can also reduce cataplexy, in part thought to be a result of its REM sleep suppressing properties. Selegiline has significant disadvantages though, as it requires a low tyramine diet and has numerous interactions with other medications. Patients should be counselled regarding the numerous foods and medications that are restricted with ongoing MAOI use. Many medications, including antidepressants which may have been used to control cataplexy, need a washout period prior to initiating an MAOI.

While modafinil and stimulants are the mainstay of treatment for EDS, these are not often effective for cataplexy[13]. In contrast, sodium oxybate improves nocturnal sleep, relieves EDS, and has anticataplectic properties as well. Aside from sodium oxybate, antidepressants (TCAs) used for decades. The exact mechanism for this effect is not fully known, but it is thought that the suppression of REM sleep is responsible. Other REM related symptoms (sleep paralysis and hypnagogic hallucinations) are improved with TCA usage. Routinely used TCAs include protriptyline, desipramine, and imipramine. Clomipramine causes the maximum serotonergic blockade, often resulting in substantial REM suppression. The significant side effects of TCAs such as their cardiovascular effects, especially conduction changes, may limit their use. Anticholinergic effects such as blurred vision, urinary retention, orthostatic hypotension, constipation, dry mouth, and dizziness are common as well. Sexual side effects occur frequently. In addition to the side effects, TCAs have important withdrawal complication, particularly for narcoleptics, in that patients may experience rebound cataplexy. In rare circumstances, the cataplexy may progress to status cataplecticus, impairing function for hours or days.

With the effectiveness of TCAs in treating cataplexy, it follows that other antidepressants may prove useful as well[13]. Selective serotonin reuptake inhibitors (SSRIs) have been shown to reduce cataplexy, but the literature base is limited. Like TCAs, these can suppress REM sleep. Other antidepressants are also reported to have effectiveness. Venlafaxine and duloxetine, both serotonin- norepinephrine reuptake inhibitors, have been used successfully[62]. However, venlafaxine usage is linked to tolerance and return of the symptoms[47]. In a small sample, duloxetine was not found to produce tolerance at one year of follow up[62]. The advantage that newer antidepressants hold over older TCAs is in their lesser side effects. Given the usual age of onset of narcolepsy, it is important to consider the potential moods changes in adolescents and young adults and the FDA warnings associated with antidepressant usage in this population[63]. Sexual side effects, headaches, gastrointestinal changes, and sleep changes are common with these medications. Venlafaxine is associated with sustained hypertension. Also, there are numerous possible drug-drug interactions with many of the antidepressants, particularly the older TCAs and MAOIs.

Given the possible immune mediated nature of narcolepsy, plasmapheresis and intravenous immunoglobulin are interesting potential options. In a small series, cataplexy was reduced using intravenous immunoglobulins (IVIG)[64]. In follow up, however, there was still a need for treatment of EDS[65]. Canine narcolepsy has responded to immunosuppresive agents such as steroids, azothiaprine, and methotrexate when

administered shortly after birth and the dogs raised in a controlled environment[66]. It appeared effective for cataplexy and consolidated sleep. A few human cases have been reported in which steroids have been used to treat for other conditions and then patients noticed that their narcolepsy symptoms also diminished[67,68]. Tiprolisant is an inverse histamine H(3)-receptor agonist that has been used in a small study of 22 subjects[68]. It appears to have wakefulness promoting properties, affecting the noradrenergic and histaminergic systems. Subjective sleepiness was reduced on the Epworth Sleepiness Scale (ESS) by nearly six points compared to one point with placebo. Hypocretin replacement therapies are also being explored[13,20]. Administration of hypocretin has not been efficacious so far because it does not cross the blood brain barrier.

In addition to the medication options for treatment, non-pharmacological approaches are important to provide optimal care of the patient with narcolepsy. The powerful sleep drive that results in the sleep attacks can be temporarily abated by taking naps. Napping for several minutes to an hour, though, does not generally suit the demands of most schedules and can seriously interfere with work or school. Nonetheless, naps may be necessary for some patients and arrangements should be made with employers and schools to accommodate a lunchtime nap and another in the late afternoon. Good sleep hygiene is a powerful component of successful treatment, as sleep consolidation and insomnia are prominent problems in narcolepsy. Patients should be counselled regarding the nature of the illness. Given the early onset and lifelong aspects, career counselling may be needed as well. Positions that require significant vigilance or concentration for extended periods of time may be unsuitable options. Shift work jobs and those with call schedules may also be problematic for narcoleptics. Driving restrictions are another important consideration. Because of the rebound cataplexy with discontinuation of medications, medication compliance becomes particularly vital in order to prevent accidents. Worsening EDS is also implicated in accidents and steps should be taken to promote wakefulness and reduce driving while sleepy[69]. In trying to determine what level of sleepiness is too sleepy to drive, multiple approaches have been taken, with conflicting results. In one large study, ESS predicted an increased risk of accidents when controlling for driver demographics, driving distance, weekly alcohol use, and the per cent of nighttime driving[69]. In another study, however, ESS and neuropsychiatric evaluation did not predict accidents when compared to driving simulations[70].

Summary

Narcolepsy is classically a tetrad of symptoms including EDS, cataplexy, sleep paralysis, and hypnagogic hallucinations. The exact pathophysiology is not yet known, but hypocretin deficiency appears to play a significant role, especially in cases with cataplexy. Narcolepsy is associated with several other sleep disorders as well as a variety of medical and psychiatric illnesses. The symptoms of narcolepsy can overlap with many other disorders, at times leading to misdiagnosis and inappropriate treatments. Diagnosis is made by taking a careful history along with polysomnography followed by an MSLT. While not definitive, having two periods of SOREM sleep is usually accepted as objective evidence to make the diagnosis. Stimulants have been the primary treatment of EDS and antidepressants are useful in the REM related aspects such as cataplexy. Attention to sleep hygiene and strategic use of daytime naps may also be helpful. Newer pharmacologic options are available that may have improved side effect profiles and/or greater efficacy in comparison to older treatments. Novel approaches are being explored to provide better resolution of symptoms.

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