Nature and Science of Sleep

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REVIEW

Living with Narcolepsy: Current Management Strategies, Future Prospects, and Overlooked Real-Life Concerns

This article was published in the following Dove Press journal:
Nature and Science of Sleep

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Abstract: Narcolepsy is a neurological disorder of the sleep-wake cycle characterized by excessive daytime sleepiness (EDS), cataplexy, nighttime sleep disturbances, and REM-sleep -related phenomena (sleep paralysis, hallucinations) that intrude into wakefulness. Dysfunction of the hypocretin/orexin system has been implicated as the underlying cause of narcolepsy with cataplexy. In most people with narcolepsy, symptom onset occurs between the ages of 10 and 35 years, but because the disorder is underrecognized and testing is complex, delays in diagnosis and treatment are common. Narcolepsy is treated with a combination of lifestyle modifications and medications that promote wakefulness and suppress cataplexy. Treatments are often effective in improving daytime functioning for individuals with narcolepsy, but side effects and/or lack of efficacy can result in suboptimal management of symptoms and, in many cases, significant residual impairment. Additionally, the psychosocial ramifications of narcolepsy are often neglected. Recently two new pharmacologic treatment options, solriamfetol and pitolisant, have been approved for adults, and the indication for sodium oxybate in narcolepsy has been expanded to include children. In recent years, there has been an uptick in patient-centered research, and promising new diagnostic and therapeutic options are in development. This paper summarizes current and prospective pharmacological therapies for treating both EDS and cataplexy, discusses concerns specific to children and reproductive-age women with narcolepsy, and reviews the negative impact of health-related stigma and efforts to address narcolepsy stigma.

Keywords: narcolepsy, cataplexy, sleepiness, hypersomnia, solriamfetol, pitolisant, sodium oxybate, children, pregnancy, lactation, stigma

Introduction

Narcolepsy is a chronic neurologic disorder that affects the stability of sleep and wakefulness.[1] All individuals with narcolepsy have excessive daytime sleepiness (EDS), and most experience sleep paralysis, hypnogogic and/or hypnopompic hallucinations, and/or disrupted sleep at night.[2] Cataplexy, a phenomenon of sudden, brief loss of muscle tone during wakefulness, is another defining feature of narcolepsy.[1] Additionally, many people with narcolepsy report difficulties with concentration, cognition, and daytime fatigue.[3]

Diagnosis of narcolepsy requires confirmation of EDS with a multiple sleep latency test (MSLT)—defined as an average sleep latency of <8 minutes during 5 sleep opportunities across the day—as well as two or more REM-onset naps.[4] Because of converging evidence that narcolepsy with cataplexy results from

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dysfunction in the neural hypocretin/orexin pathways that contribute to sleep-wake regulation,[5] low hypocretin-1 levels (≤110 pg/mL) measured in cerebrospinal fluid (CSF) can also be used to diagnose narcolepsy in centers where the test is available. At the time of publication, clinical testing for Orexin-A/Hypocretin-1 in Spinal Fluid is available through Mayo Clinic Laboratories.[6] Narcolepsy is categorized into two types based on clinical presentation and associated underlying biomarkers. Narcolepsy Type 1 (NT1) is defined by the presence of cataplexy and is nearly always associated with low hypocretin levels and/or impaired hypocretin signaling, whereas Narcolepsy Type 2 (NT2) is diagnosed when cataplexy does not occur and hypocretin deficiency/dysfunction is not observed. Partial deficiency of hypocretin can exist in the absence of cataplexy, however, indicating that some cases of NT2 may be caused by less-extensive impairment to hypocretin signaling.[7] Moreover, the scant neuropathology data in NT2 suggest that although hypocretin neuronal dysfunction is implicated in both types of narcolepsy, hypocretin neuron damage is more circumscribed in NT2 than in NT1.[7] NT2 is a challenge to diagnose due to non-specificity of symptoms, limitations of diagnostic tests and absence of useful biomarkers, and much remains to be understood about the pathophysiology of this hypersomnia subtype.[8] Whether NT2 is an entity distinguishable from idiopathic hypersomnia (IH) is also a topic of intense interest, and although this continues to be debated, some differentiating features have been advanced, eg, more disrupted nocturnal sleep and better restorative response to naps in NT2 than IH.[8,10]

Although the exact causes of narcolepsy are still under investigation, evidence points to an immune process that results in damage and/or dysfunction of the hypocretin-producing neurons in the lateral-posterior hypothalamus as a plausible etiology for NT1.[5] Observations that support immune-mediated NT1 pathophysiology include the association of NT1 development with major histocompatibility complex genes, particularly the HLA-DQB1*06:02 allele,[11] influenza A and streptococcal infections, and the Pandemrix H1N1 vaccine.[12] Other areas of active investigation into the causes of narcolepsy include examination of the histamine system, search for other immune mediators, and studies of "secondary narcolepsy" attributed to hypothalamic injury from traumatic, infectious, or demyelinating processes.

Prevalence estimates indicate that narcolepsy affects between 25 and 50 people per 100,000,[13] with higher rates observed in Japanese[14] and African American[15] cohorts and lower rates in Israel.[16] A 2019 study of an insurance database comprised of >18 million people found a prevalence rate of 79.4 per 100,000 persons and an incidence rate between 4.87 and 7.67 per 100,000 persons per year.[17] Variation in prevalence estimates is attributed to differences in case definition across studies and to differences in genetic susceptibility to narcolepsy among different subgroups.[13] Historically, narcolepsy had been reported to be more common in men than in women,[18] though more recent epidemiologic evidence shows equal prevalence of narcolepsy between genders or higher prevalence in women.[17,19,20] Women with narcolepsy report earlier symptom onset than men, and fall asleep more quickly on the MSLT.[20] Furthermore, in the Doberman Pinscher canine narcolepsy model, cataplexy was at least twice as severe in females as in males.[21]

Diagnostic and Treatment Challenges

The first symptoms of narcolepsy typically occur between the ages of 10–35 years, though cases of earlier and later presentations have been described. A major challenge is the time from symptom presentation to diagnosis. Studies examining the duration from the first signs of NT1 to diagnosis show a range of 8.4 to 22.1 years with an average delay of ~15 years.[22] It is estimated that up to 50% of people with narcolepsy are undiagnosed.[2] One study of 52 people with NT1 found the average time gap between symptom onset and medical consultation was 3.2 ± 5.1 years and the time from medical presentation to diagnosis was 8.9 ± 11.0 years.[23] It is encouraging, however, that delays appear to be decreasing over the last 5 decades.[22,23] Although no gender difference in the age of narcolepsy symptom onset has been observed, women may experience a delay in diagnosis compared to men; one study showed a duration of 16 years from the onset of symptoms to diagnosis in men and 28 years in women.[20]

Even when the narcolepsy is suspected, diagnosis can be elusive. Short sleep latencies and sleep onset REM periods can be seen in conditions other than narcolepsy,[24,25] and although test–retest reliability is high in NT1, more variable MSLT results are observed among individuals with NT2 and idiopathic hypersomnia.[26] A short REM latency (≤15 minutes) during nocturnal polysomnography (NPSG) has high specificity for NT1

and can aid in diagnosis,[27,28] though short REM latency on NPSG can also be observed in people with other untreated sleep disorders, night-shift workers, and individuals with insufficient sleep.[29] From a practical standpoint, many individuals with excessive sleepiness take medications that interfere with multiple sleep latency testing, and tapering and withholding these medications in preparation for the MSLT can cause safety concerns and decrements to quality of life. Measurement of a CSF hypocretin-1 level is a definitive test for NT1,[30] but challenges remain, such as access and acceptability among individuals with possible narcolepsy. Innovative testing methods using neuroimaging techniques such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), and magnetic resonance spectroscopy (MRS) are being investigated as possible tools for improving diagnosis of narcolepsy.[31]

People with narcolepsy have a higher incidence of certain comorbid conditions, including obesity, depression, anxiety, and other sleep disorders. For instance, a community-based study that compared 68 individuals with narcolepsy to age- and sex-matched controls at diagnosis and after an average follow-up period of 9.9 years found higher rates of obesity, psychiatric conditions, obstructive sleep apnea, endocrine disorders, and low back pain among those with narcolepsy.[19] A larger study of insurance-coding data that included 9312 people with narcolepsy, found excess rates of anxiety disorders, diabetes, headaches, depression, obesity, periodic limb movement disorder, obstructive sleep apnea, REM behavior disorder, and restless legs syndrome.[32] Won et al[20] examined gender differences in comorbid conditions among people with narcolepsy and found that men were significantly more likely to have a diagnosis of attention-deficit-hyperactivity disorder (ADHD), whereas women were more likely to be diagnosed with a neurologic or autoimmune disorder.

A limited number of studies have examined the relationship between age and the core symptoms of narcolepsy. Findings suggest that symptoms are dynamic over time and that EDS, cataplexy, and night-time sleep quality may improve with age.[33,36] Age-related increase in MSLT sleep latency and decrease in sleep onset REM periods (SOREMPs) have been observed in NT1.[34] Cataplexy has been observed to be significantly less frequent in individuals with NT1 age 65 or older, compared to those younger than 65 years.[33] Additionally, a 10-year longitudinal study reported improvement and even resolution of cataplexy, along with improved ESS and night-time sleep quality in a large proportion of individuals with NT1.[36] Another longitudinal study found that in a majority of individuals with NT1, EDS changed little over the 5 years of observation; nevertheless, spontaneous improvement in EDS was observed in 15% of the cohort, and was tied to milder hypocretin deficiency and more consolidated night-time sleep.[35] These studies challenge prior assumptions that narcolepsy symptoms are stable and unremitting over time.

Individuals with narcolepsy have higher rates of accidental injury than matched controls, including burns,[37] bone fractures[38] and automobile crashes.[39] In a study that compared car crashes between 282 individuals with NT1, NT2, or idiopathic hypersomnia (IH) and 470 controls, 22.7% of people with a hypersomnolence condition reported an auto accident in the previous 5 years compared with 14% of controls.[39] Crashes were predicted by higher levels of subjective sleepiness, use of caffeinated energy drinks, and reports of daytime napping. Interestingly, those with narcolepsy or IH who had been treated for 5 years or more did not have higher rates of automobile accidents than controls. In the European Union, national restrictions regulate that fitness to drive is assessed prior to issuance or renewal of driving licenses for individuals with certain sleep disorders, including NT1 and NT2.[40] In the US, most state motor vehicle bureaus expect driving license applicants to self-report conditions that may compromise fitness to drive, but do not make reporting of medical conditions mandatory and may or may not require further documentation if a condition is self-reported. Only a handful of states require mandatory reporting of a medical condition, including narcolepsy, that may impair driving, as well as documented assessment of fitness to drive.[41]

Treatment Landscape for Narcolepsy

In 2013, the FDA hosted a patient-focused drug development initiative (PFDDI) for narcolepsy to gather perspectives from individuals living with this condition. Some of the reported therapeutic challenges for the narcolepsy community included variable responsiveness and limited access to available treatment options, as well as intolerable drug side effects.[42] The Maski et al[43] report of the Unite Narcolepsy survey, administered in conjunction with the PFDDI meeting, indicated that 57.1% of people with narcolepsy experienced daytime sleepiness or fatigue three or more times per day in spite of treatment while only 3.9%

reported no daytime sleepiness in response to treatment. The lack of perceived efficacy, as well as side effects, drug interactions, and high costs, likely contribute to inconsistent medication use. A study of 116 people with narcolepsy found that while 55.2% of study participants took their medications at least 80% of the time, 12.9% took their medications only 50–80% of the time and 31.9% took their prescribed medications less than 50% of the time.[44]

It is striking that until recently, only 5 medications had been indicated for the treatment of narcolepsy in the US, reflecting an ongoing need for increased treatment options to combat EDS and cataplexy in narcolepsy. Increased understanding of narcolepsy pathophysiology is enabling exploration of other candidate molecules and in 2019 two new compounds, pitolisant and solriamfetol, were approved in the US for treatment of excessive daytime sleepiness in narcolepsy. Alternative formulations of current treatments aim to increase convenience and adherence to regimens and extended indications are expanding options for the pediatric population. Additionally, prospective treatments, such as orexin agonists, are showing promise in clinical trials and may soon find their way into the armamentarium of treatment options. Non-pharmacological therapies are likely to be effective adjunctive treatment for narcolepsy.

Historic and Current Pharmacologic Treatments

Historically, stimulants, antidepressants and hypnosedatives have been used to treat EDS and cataplexy associated with narcolepsy. The first compound to demonstrate significant improvement for excessive sleepiness in narcolepsy was amphetamine in 1935 and it is still prescribed today and indicated for that purpose.[45,46] Methylphenidate has been used to treat EDS in narcolepsy since the 1950s and is considered to have a more favorable safety profile than amphetamine. Methylphenidate and amphetamine are recommended as second- and third-line therapeutics for EDS. They are mechanistically similar, promoting wakefulness by increasing presynaptic dopamine release.[45]

Tricyclic antidepressants (TCAs), including imipramine, clomipramine, desipramine and protriptyline were reported to improve cataplexy symptoms as early as 1960. They are included as suggested treatments for cataplexy by the American Academy of Sleep Medicine (AASM) and European Federation of Neurological Societies, although rigorous randomized, placebo-controlled clinical trials have not been performed.[46,47] Intolerable side effects with TCAs are common, as well as rebound cataplexy upon withdrawal.[45] Although no antidepressants are FDA-approved for the treatment of cataplexy, classes other than TCAs have shown efficacy in reducing cataplexy, and are often better tolerated. Venlafaxine, a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is a first-line recommended therapeutic for cataplexy and shows fewer side effects but has similar withdrawal concerns as TCAs. Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), and selegiline, a monoamine oxidase type B inhibitor, are also common antidepressant-class recommended treatments for cataplexy.[45,47]

Currently, sodium oxybate, the sodium salt of gamma hydroxybutyrate, is the only medication indicated for both EDS and cataplexy. It is recommended as the first-line therapy for both of these indications, based upon rigorous randomized, placebo-controlled clinical trials, and its indication was recently expanded to include treatment of children (≥7 years of age) with narcolepsy after a placebo-controlled, double-blind, randomized clinical trial demonstrated the efficacy, safety, and tolerability of sodium oxybate in children and adolescents with narcolepsy.[48] For individuals who cannot take sodium oxybate, first-line recommended wake-promoting agents are modafinil and armodafinil, in part because their potential for abuse and dependency are lower than amphetamine. Modafinil has been shown to control EDS in narcolepsy at a comparable level to sodium oxybate, but is ineffective in reducing cataplexy, compared to placebo.[49]

New and Prospective Pharmacologic Treatments

Solriamfetol

Solriamfetol, a derivative of phenylalanine, is a dopamine and norepinephrine reuptake inhibitor recently approved in the US for the treatment of EDS in adults with narcolepsy or obstructive sleep apnea. In Phase 2 and 3 clinical trials, solrimfetol was shown to significantly improve wakefulness and reduce sleepiness in these patient populations compared to placebo as shown by Maintenance of Wakefulness Test (MWT) sleep latency and by Epworth Sleepiness Scale (ESS) scores.[50,53] Solriamfetol inhibits reuptake of the monoamines via interaction at both the dopamine transporter and the norepinephrine transporter and thus by a mechanism distinct from that of the wake-promoting agent modafinil,

which is thought to bind primarily at the dopamine transporter to inhibit dopamine reuptake.[54] Solriamfetol also differs mechanistically from the amphetamines as it does not promote the release of norepinephrine.[51,55,56] These distinctions may account for differences in therapeutic effects between solriamfetol and other wake-promoting drugs.[56,57] Unlike modafinil, armodafinil and pitolisant (see below), solriamfetol does not interfere with the efficacy of oral contraceptive pills,[58] potentially offering a more convenient option of non-amphetamine wake-promoting agent to women with narcolepsy passing through their child-bearing years. Solriamfetol treatment also shows no evidence of drug-induced rash, a potential side effect of the wake-promoting agents modafinil and armodafinil.[59]

Pitolisant

Pitolisant is an antagonist/inverse agonist of the histamine H_3 receptor that was approved for the treatment of narcolepsy with or without cataplexy in the European Union in 2016[60] and in the US for the treatment of EDS in adults in August 2019.[58] The histaminergic system in the central nervous system modulates processes including wakefulness, feeding, and learning and memory consolidation via histamine receptors, H_1, H_2, H_3 and H_4.[61] Blocking histamine synthesis, or histamine receptor H_1, has been shown to increase cortical slow waves and enhance sleep. Conversely, enhancing the neurotransmission of histamine has been shown to promote wakefulness. The histamine H_3 receptor controls the release, synthesis and turnover of histamine and the neuronal activity of histaminergic cells.[62] Thus, pitolisant acts to promote wakefulness by blocking H_3 receptors, which, in turn, increases synaptic histamine release via H_1 receptors.[63]

Randomized and open-label clinical trials have demonstrated efficacy of pitolisant in decreasing ESS scores and increasing MWT scores compared to placebo in people with narcolepsy with or without cataplexy, as well as in decreasing severity of cataplexy compared to placebo in people with NT1.[64,66] These studies also demonstrated that pitolisant is noninferior to modafinil in reducing EDS in people with narcolepsy with or without cataplexy.

Alternative Sodium Oxybate Formulations

Multiple investigations are underway to identify alternative formulations of sodium oxybate to increase the options with this standard therapy for both EDS and cataplexy.[47,58] To address the twice-nightly dosing of sodium oxybate, which some individuals find difficult to time correctly or to be an inconvenience, a once-nightly dosing regimen of an extended-release sodium oxybate formulation that uses micropump technology (FT218) is being tested for safety and efficacy. FT218 recently completed Phase III clinical development for treatment of EDS associated with narcolepsy and cataplexy, evaluating safety and efficacy of daily doses of 4.5, 6.0, 7.5 and 9.0 g sodium oxybate compared to placebo. Outcomes include MWT sleep latency, Clinical Global Impression of Change (CGI-C) and mean number of cataplexy attacks. If approved, FT-218 will be the first once-nightly treatment to address both EDS and cataplexy in narcolepsy.[67]

A low-sodium alternative to sodium oxybate, JPZ-258, is a recently developed mixed salts oxybate oral solution. Sodium load for the maximum therapeutic dose of sodium oxybate (9.0 g) is equivalent to 1640 mg sodium intake,[68] 71% of the 2300 mg maximum recommended sodium intake by the American Heart Association, and exceeding the 1500 mg recommended for individuals with conditions associated with sodium sensitivities.[69] The new formulation, JPZ-258, would reduce sodium intake by up to 92% and may thus present a safer alternative for people with narcolepsy who also have heart failure, hypertension or renal impairment or for those carrying risk factors for such conditions. Recently completed Phase 3 clinical trials evaluated safety and efficacy in people with narcolepsy with cataplexy and demonstrated significant differences in weekly number of cataplexy attacks as well as improved ESS scores compared to placebo.[70,71] The US Food and Drug Administration accepted a New Drug Application for JZP-258 for the treatment of cataplexy and EDS in people with narcolepsy ages 7 years and older in March 2020 and it is anticipated it will be commercially available in 2020.

Hypocretin/Orexin-Based Therapies

Because the pathophysiology of narcolepsy involves deficiency of the neuropeptide hypocretin-1,[72] multiple modes of hypocretin ligand-replacement strategies have been pursued as potential therapies for narcolepsy.[47] Penetration of the blood-brain barrier has proven the greatest challenge in hypocretin-replacement therapy. Considering significant barriers to hypocretin-replacement approaches, non-peptide small molecule hypocretin receptor agonists represent another avenue for targeting hypocretin deficiency in narcolepsy. TAK-925 is a hypocretin/orexin 2 receptor-selective agonist that is under development and has been shown to promote wakefulness in mice.[73] Phase 1 studies indicate that intravenous TAK-925 is well tolerated in

people with narcolepsy type 1 and increases wakefulness compared to placebo as measured by MWT and Karolinska Sleepiness Scale.[74,75] An oral hypocretin/orexin 2 receptor-selective agonist TAK-994 has also shown increased wakefulness and decreased cataplexy in mouse models and is progressing in phase 1 and phase 2 clinical trials.[76,78] These strides suggest a promising future for hypocretin/orexin receptor agonism in the treatment of narcolepsy with cataplexy.

AXS-12 (Reboxetine)

Reboxetine is a selective norepinephrine reuptake inhibitor approved for treatment of depression in 40 countries outside of the U.S.[58] A formulation of reboxetine, AXS-12, is under development for the treatment of EDS and cataplexy in narcolepsy. AXS-12 has demonstrated efficacy in reducing sleep and cataplexy in mice[79] and decreasing EDS and cataplexy in a pilot study in individuals with narcolepsy.[80] A recently completed phase 2 randomized, double-blind, placebo-controlled, crossover trial in individuals with narcolepsy and cataplexy compared AXS-12 with placebo and measured EDS, cataplexy, cognitive function, and sleep quality.[81] Phase 3 trials are planned, and if AXS-12 proves efficacious in the treatment of both EDS and cataplexy, it may be an alternative for individuals who do not tolerate or respond to other regimens. AXS-12 may also be useful to individuals with NT1 and comorbid depression.[58]

Non-Pharmacologic Treatments: Lifestyle Changes and Psychological Therapies

Lifestyle changes for treating narcolepsy symptoms are prescribed routinely to complement pharmacologic treatments. These most often include implementing scheduled naps and maintaining a regular sleep routine.[82] Many studies demonstrate the positive impact of naps on alertness in people with narcolepsy.[83] Other lifestyle alterations may be recommended including modifying work schedules based on individual needs, avoiding sleep-inducing situations and identifying sources of psychosocial support.[83,84] A study of 42 people with narcolepsy (NT1: n=32, NT2: n=10) showed decreased cardiopulmonary fitness compared to age- and sex-matched controls and higher levels of sleepiness and more frequent cataplexy episodes were associated with lower levels of exercise tolerance.[85] Although causality cannot be determined from this cross-sectional study, these finding raise the question of whether regular exercise may help improve narcolepsy symptoms in patients who are able to safely implement an exercise routine.

Narcolepsy symptoms have been shown to have significant impact on not only the physical but also the mental and social health of persons with narcolepsy.[86,88] Thus, counseling and psychological therapies have also been suggested as potential treatment approaches to address both the symptoms of narcolepsy, as well as the associated psychological impact that can accompany the diagnosis.[83,84,89] Although there is a shortage of controlled studies examining the benefits of non-pharmacological and lifestyle adjustments to treat narcolepsy, reports indicate that a large proportion of individuals rely on alternative treatment modalities to supplement medication.[83] Medication alone is often insufficient for alleviating narcolepsy symptoms and psychological and lifestyle approaches should be considered more broadly and tested rigorously.[42]

Challenges and Prospects for Specific Populations with Narcolepsy

Children and Adolescents with Narcolepsy

Narcolepsy may be diagnosed in children as young as 5 or 6 years of age, with a peak incidence around 15 years of age.[90] Most children with narcolepsy are brought to their physicians' attention because of their excessive daytime sleepiness, similar to adults.[91] Some children may restart taking naps after having given them up. The naps may not be refreshing, which may differ from adults, who often characterize their naps as refreshing. Some older children are able to realize they have cataplexy or muscle weakness with strong emotions, whereas others only realize what has been happening when discussing this with their physician. Parents may note the muscle weakness, yet not realize it to be cataplexy, such as when a child's head and tongue protrudes or thrusts forward while laughing which may also include ptosis (occulobuccofacial weakness), or may wonder why their child keeps falling to the floor when laughing.[92] Children are sometimes so frightened by the hypnagogic and hypnopompic hallucinations that they may not volunteer that information unless specifically asked. Similarly, sleep paralysis can be difficult to verbalize for children. Sleep logs and video recordings showing cataplexy are helpful if the child and parent have difficulty articulating the pentad signs of narcolepsy.

Diagnosis is by the same "adult" criteria with in-lab polysomnography and multiple sleep latency testing, using

the same cut-offs for the mean sleep latency of </=8 minutes and 2 sleep-onset REM periods (or sleep onset REM latency of </=15 minutes on overnight polysomnography) as described in detail earlier. Hypocretin levels can also be measured in children.

Treatment is also similar to adults with age-specific considerations.[93] Lifestyle treatment is as important as medication. Children are advised to continue to maintain a good sleep-wake routine (consistent bedtimes and wake times) and live an active lifestyle, full of the usual extracurricular activities. Sports activities keep the child moving and improve alertness and energy levels. Parents are counseled to be especially vigilant regarding safety while using playground equipment, swimming, cooking, or any other activities during which if cataplexy occurred, the child could sustain significant harm. It is recommended that children with narcolepsy are always supervised during these types of 'potentially dangerous' activities. For teens who are old enough to drive, the young drivers are educated on the importance of first assessing if they are alert enough, driving only when necessary, driving short distances if possible, and driving in the right lane in case they need to pull over abruptly.

Parents are educated on the importance of healthy eating as some children may have substantial weight gain at the onset of their narcolepsy. Additionally, parents are instructed to look for signs of precocious puberty, which is associated with narcolepsy, and may need to be evaluated by an endocrinologist.[94]

Children and teens with narcolepsy are at higher risk for depression, social and emotional distress, aggressive behavior, and difficulty with focus and attention resulting in poor school performance.[87,95,96] Treatment can substantially improve quality of life.

Most teachers are able to make accommodations for children to have one or more brief scheduled naps within the school day if needed, and otherwise, it is advised that children take a brief nap after school. Job counseling is also provided to teens with narcolepsy (with or without cataplexy) to avoid professions that require quiet, sedentary work, night-shift work, a commercial driver's license, or other jobs including but not limited to pilot, military personnel, security personnel. Additionally, for teens with cataplexy, counseling is provided to avoid jobs that include heavy machinery or heights.

Despite lifestyle changes, medications are almost always necessary to help children with narcolepsy stay awake and alert during the day. Parents may be hesitant to start medications; however, it is of paramount importance for the child to be alert, focused and able to keep up with their schoolwork. At the time of publication, there are no evidence-based guidelines or consensus guidelines for treatment of narcolepsy in children. Therapy is individualized for each child's symptoms. Typically, stimulants are first-line medications, followed by wake-promoting agents, including modafinil or armodafinil, and lastly, sodium oxybate. Cataplexy may be treated with sodium oxybate and antidepressant medications in the SSRI or SNRI classes. Sodium oxybate is now approved to treat EDS and cataplexy in children and adolescents age 7 years and older,[48] the wake-promoting medications modafinil and armodafinil are approved for children 17 years of age and older, and pitolisant is being tested in pediatric populations.[97] It is also important to discuss with older teens to avoid alcohol, which can worsen sleep quality and also possibly interact with medications.

Individuals of Childbearing Potential

The limited amount of information regarding narcolepsy during pregnancy and lactation and potential effects of common narcolepsy medications on the human fetus and neonate present challenges both to women with narcolepsy when facing decisions concerning family planning as well as to physicians treating this population of narcolepsy patients. A survey-based study evaluating narcolepsy specialists around the world indicated that most physicians stopped medications at the time of conception, during pregnancy and during breastfeeding.[98] This report suggested that based on the available literature, perceived risks of narcolepsy medications might be overestimated,[98] however current studies indicate the potential of teratogenicity of certain therapies and treatment of narcolepsy during pregnancy should consider all potential risks and benefits and should include informed collaboration between patient, sleep doctor and obstetrician.[99,100] Challenges for women with narcolepsy who choose to go without medication during pregnancy and lactation are likely to include compromised safety to both mother and fetus/infant as well as increased work absences and potential for unemployment for working women due to poor symptom control.[101] Simply anticipating these challenges could make embarking on family life a difficult consideration for young adult women with narcolepsy and may, in part, explain the increased age at first pregnancy for NT1 women and increased likelihood for single-pregnancy discovered in recent retrospective cohort and case–control studies.[102,103]

A recent finding of particular relevance to this population of people with narcolepsy is the demonstration of emission of sodium oxybate, first-line therapy for NT1, in the milk of lactating women taking sodium oxybate.[104,105] Our study in 2 women with NT1 representing 3 pregnancies, and a case report in a woman with NT1 indicated the possibility of avoiding infant exposure to elevated levels of gamma-hydroxybutyric acid (GHB) by delaying feeding expressed milk until exogenous GHB can be presumed to be absent from the milk. Larger, confirmatory studies should be undertaken; however, this information should be considered when evaluating therapeutic options for NT1 women who elect to breastfeed and respond well to sodium oxybate therapy. This option may be less feasible for women who have limited support for night-time infant care and feedings. It is significant that in the retrospective cohort study by Maurovich-Horvat et al,[102] 60.1% of women who developed narcolepsy before or during pregnancy reported neonatal care to be adversely affected by narcolepsy symptoms. Reported struggles in the puerperium included excessive sleepiness, sleep attacks during feeding or nursing, fear of being impaired by symptoms, and cataplexy while holding the baby. Improved options for safely treating postpartum NT1 women with sodium oxybate might help to eschew these dangers.

Considering the burden the above challenges could pose for the duration of pregnancy and breastfeeding in childbearing women with narcolepsy, it is requisite that this population be presented with a comprehensive understanding of their options, and sufficient guidance from their physician throughout the family planning process.

Studies examining the impact of narcolepsy on intimate relationships and sexuality are limited, but shed light on unique challenges to which practitioners should demonstrate sensitivity. Women and men with narcolepsy have reported forms of sexual dysfunction, including cataplexy with orgasm (termed orgasmolepsy) and erectile dysfunction with narcolepsy treatment, suggesting that individuals with narcolepsy may experience distinct challenges associated with sexual intimacy.[106,109] Orgasmolepsy episodes have been described as involving complete loss of muscle tone, but not lasting more than 30 seconds. Case studies indicate that cataplexy treatments may be effective in reducing orgasmolepsy for some patients, but rigorous studies in this area have not been pursued.[107] A further consideration, which receives little mention in the literature, is the potential impact of other symptoms of narcolepsy and narcolepsy treatments on intimate relationships and sexuality.[110] Excessive sleepiness, strict sleep regimens and sedating properties or sexual dysfunction side effects of narcolepsy therapies are only a few of the aspects of disease presentation and management that could pose challenges to sexual intimacy and intimate partner relationships. Future research in this area could aid to increase sleep specialist-awareness of some underaddressed psychosocial challenges in narcolepsy.

Acknowledging and Addressing Narcolepsy Stigma

Public understanding of narcolepsy is limited and often inaccurate, with entertainment and media portrayals associating narcolepsy with humorously falling asleep rather than with a serious health condition requiring medical attention.[111] As a result, people with narcolepsy face significant delays in proper detection and diagnosis.[22] Misperceptions of narcolepsy also perpetuate stigma and being labeled by teachers, co-workers, supervisors, and others as antisocial, lazy, careless, or faking.[42]

Significant prior research over the past 38 years and across various cultures well established that narcolepsy significantly impacts health-related quality of life (HRQOL) and psychosocial wellbeing, e.g.[88,112,119] People with narcolepsy report feeling socially isolated (even within their own families), inferior to others, and hesitant to disclose their disorder to others, fearing the consequences and reaction they would receive.[112] Despite these descriptions of diminished quality-of-life, health-related stigma was not studied as a potential underlying mechanism impacting people with narcolepsy until 2015.[120] Defined as a social process, experienced or anticipated, characterized by exclusion, rejection, blame or devaluation that results from experience, perception or reasonable anticipation of an adverse social judgment about a person or a group,[121] health-related stigma has been reported in a number of chronic conditions, and is a potential predictor of lower HRQOL. Kapella et al (2015) found that young adults with narcolepsy reported feeling significantly more stigma than those without narcolepsy in all domains, including social rejection, financial insecurity, internalized shame, and social isolation and that the levels of health-related stigma observed in this sample were comparable to those found in people living with HIV.[120] These high levels of health-related stigma are significant, especially with growing evidence that stigma contributes to economic disparities and difficulties with social relationships, and can affect

access to and the quality of health care as well as adherence to a medication regimen.[122] In addition to high levels of perceived stigma, people with narcolepsy reported lower levels of quality of life, especially in physical, vitality and social functioning roles, and greater anxiety and depression than young adults in the comparison group. The major factors impacting social functioning were depression, sleepiness, and social rejection. Conversely, less depression, sleepiness and perceived social isolation predicted significantly better social functioning. Further, the authors proposed that health-related stigma likely affects social functioning both directly and indirectly through depressed mood.

Addressing Stigma at an Individual Level

Further research is needed to examine other levels of stigma (societal, organizational, and individual perspectives) and across a broader age range. From this, evidence-based strategies could be developed for predicting vulnerable individuals and implementing effective strategies to mitigate the deleterious impacts of stigma. Health-related stigma interventions in other chronic illness communities suggest benefits from using educational programs, skill-building, cognitive behavioral therapy and support groups.

Kapella et al ground-breaking first study on narcolepsy and stigma highlights that living with this condition is a multifaceted experience involving a complex web of social dynamics that extends beyond managing the basic symptoms of narcolepsy.[120] Thus, treating the full scope of narcolepsy's impact requires a multidisciplinary care approach including pharmacologic treatments, scheduled naps, lifestyle changes (such as diet, exercise, and sleep hygiene) and social support (such as counseling, support groups, conferences, and educational and skill-building programs).

Connecting people with narcolepsy and their loved ones to patient advocacy organizations is another key way to support the social experiences of those living with narcolepsy. Patient advocacy organizations offer a variety of resources, events, support services and educational programming that can help to foster connection and reduce stigma. For example, sharing one's illness story with others is a powerful method of creating reflection and connection, and finding meaning and understanding.[123] Particularly for "invisible illnesses" like narcolepsy, having one's voice heard can be an incredibly validating experience.[124] Thus, there is great value in programs like Wake Up Narcolepsy's Narcolepsy 360 Podcast[125] and Narcolepsy Network's Annual Conference.[126] In addition to formal in-person and video support groups run through these organizations, there are additional formal and informal online support groups via platforms like Facebook and Patients Like Me.

Addressing Stigma at a Societal Level

During the FDA's narcolepsy meeting in 2013, people with narcolepsy and their loved ones consistently expressed the need for more to be done to help narcolepsy gain acceptance and understanding in schools, workplaces, and other social and professional settings.[42] Thus, efforts aiming to raise accurate awareness and debunk societal misperceptions of narcolepsy will help to reduce stigma and reduce unnecessary delays to diagnosis.

Better public education may also reduce the restrictions that people with narcolepsy face in professional and educational settings. For example, a diagnosis of narcolepsy is listed as a disqualifying condition for serving in the US military and those with narcolepsy must apply for a medical waiver to enlist or continue to serve.[127] Furthermore, sleep disorders, including narcolepsy, are associated with more auto accidents and medical errors in healthcare workers.[128] In the United States, legal protections under the Americans with Disabilities Act of 1990 (ADA) can help people with narcolepsy to receive educational and employment accommodations. Determining whether a particular person with narcolepsy qualifies for educational or employment accommodations should be an individualized process that takes into consideration the person's particular circumstances. Likewise, while educational and employment accommodations both involve the ADA and use some overlapping terminology – different factors, processes and protections are in play in these two areas. Learning about the legal protections empowers people with narcolepsy and their doctors and caregivers to help those with narcolepsy to obtain appropriate accommodations and succeed at school and in the workplace.

Research indicates that audiences are more likely to engage with and retain information when it is delivered by someone with lived experience, giving a "face" to medical terminology and statistics.[129] For example, In Our Own Voices (IOOV) is a public education program developed by the National Alliance on Mental Illness (NAMI) that trains individuals living with mental illness to deliver public presentations of their personal stories of illness and recovery. Studies have found that presentations by IOOV trainees are effective in increasing knowledge and

correcting misperceptions among the general public, college students, and healthcare professionals alike.[130,132]

Following these best practices, Project Sleep created the Rising Voices of Narcolepsy program[133] in 2017 to train people with narcolepsy to share their story effectively via speaking or writing. In just three years, the program has trained over 60 speakers and writers around the world. This program aims to empower advocates while also raising awareness, reducing stigma and reducing delays to diagnosis. Other patient advocacy organizations in the US include:

Hypersomnia Foundation:
https://www.hypersomniafoundation.org/
Narcolepsy Network:
https://narcolepsynetwork.org/
Project Sleep:
https://project-sleep.com
Wake Up Narcolepsy:
https://www.wakeupnarcolepsy.org/

Conclusion

Although narcolepsy is not a prevalent condition, it is one of the most common causes of excessive daytime sleepiness.[2] Nevertheless, it is under-recognized by the general public and medical providers and people with narcolepsy often experience protracted delays in diagnosis. Testing for narcolepsy has relied on behavioral testing and clinical history but advances in biomarkers such as CSF hypocretin-1 levels and neuroimaging may make narcolepsy easier to diagnose and shed light on pathophysiologic differences between NT1 and NT2. Until recently, few pharmacologic treatment options were available, and most medications used to treat narcolepsy were not developed for this disorder and had not undergone vigorous testing in this population. New pharmaceuticals that are now available and those in development provide novel options to treat EDS and cataplexy. In the last decade, the experiences of people with narcolepsy are playing a more prominent role in management of this condition. Innovations in pharmacologic therapies, lifestyle modifications and behavioral strategies, and personalized care for specific populations are changing the outlook for management of narcolepsy. Finally, the acknowledgement of health-related stigma associated with narcolepsy and efforts to reduce the impact of this bias are allowing individuals with narcolepsy to enjoy a better quality of life.

Disclosure

Dr. Emily C. Barker is a medical writer and has worked as an independent contractor generating reports and summaries for medical advisory board meetings and round-table discussions for Jazz Pharmaceuticals and has also received speaker honoraria from Jazz Pharmaceuticals. Julie Flygare, JD is employed as the President & CEO of Project Sleep, a 501(c)(3) non-profit organization dedicated to raising awareness about sleep health and sleep disorders. As a patient-perspective expert, Ms. Flygare has consulted on patient-centricity and health communications best practices with drug developers including Harmony Biosciences, Jazz Pharmaceuticals, Avadel Pharmaceuticals and Takeda Pharmaceuticals. She also receives royalties from sales of her book, Wide Awake & Dreaming: A Memoir of Narcolepsy. Dr. Shalini Paruthi is a clinical educator and sleep medicine physician, with focus in pediatrics. She gives professional lectures and receives honoraria from conference organizers and royalties from UpToDate. Dr. Paruthi is an uncompensated member of the Board of Directors of the Restless Legs Syndrome Foundation. Dr. Katherine M. Sharkey is a sleep medicine physician; she recently participated in an early-access patient program for pitolisant sponsored by Harmony Biosciences. As an academic physician, she gives professional talks and receives honoraria from conference organizers and royalties from UpToDate. Her research is funded through grant support from NIH and the Hassenfeld Institute. Dr. Sharkey is an uncompensated founding member of TIMES UP Healthcare. The authors report no other conflicts of interest in this work.

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