# STUCK IN THE REVOLVING DOOR: CHALLENGES IN NARCOLEPSY

**Logan Schneider**

## Neurocircuitry

The relatively recent description of hypocretin deficiency in Narcolepsy type 1 (Na-1) has defined it as a critical moderator in the maintenance of wakefulness[1–3]. A modest population of ~70,000 cells in the lateral hypothalamic area (LHA) is the sole source of hypocretin in the brain, and is noted to be selectively destroyed in Na-1. Despite the limited number of hypocretinergic neurons, their sprawling projections reach all major arousal regions[4], with densest innervations being found in the locus ceruleus (LC) and tuberomammillary nucleus (TMN)[5,6]. However, hypocretin neurons do not project directly to the ventrolateral pre-optic nucleus (VLPO), suggesting that they serve more of a wake-state-stabilizing role external to the primary sleep-wake circuit. Hypocretin neurons are most active during wakefulness, and fall silent during NREM and REM sleep[7–13].

## Pathophysiology

The prevailing theory regarding the etiology of sporadic Na-1 is one of autoimmune destruction of the limited hypocretin cell population. Current evidence points to a heightened risk in patients with specific HLA-DQ1 locus alleles and TCRα polymorphisms. While genetic factors do not appear to be sufficient for developing narcolepsy, the ubiquity of *DQB1*0602* within narcoleptics suggest that they are setting the stage for an immunologic trigger. Given the cyclic variation in narcolepsy incidence following winter months, epidemiologic data has implicated specific pathogens (namely *Streptococcus pyogenes* and $H_1N_1$ influenza) as the likely culprits. While the genetic data points toward an autoimmune process mediating the destruction of hypocretin neurons in Na-1, only indirect evidence currently exists to support this claim[14]. The most compelling hypothesis is one in which hypocretin cellular destruction is mediated by $CD8^+$ T cells in patients with CD4+ T cell help, which involves the *HLA-DQB1*06:02* risk allele, after exposure to an environmental trigger.

## Clinical presentation

In the most recent edition of International Classification of Sleep Disorders (ICSD-3) the nosology of narcolepsy has been revised, subdividing the disorder into type 1 and type 2 narcolepsy (Na-2), rather than with and without cataplexy, respectively[15]. This change is in recognition of the fact that almost all cases of narcolepsy with cataplexy (and particularly those that will eventually develop cataplexy) have hypocretin deficiency, thereby restructuring the classification of the disorders in a more pathophysiologically informed framework. However, as CSF hypocretin-1 measurements are not routinely performed in clinical practice, a diagnosis of Na-1 can still be made on the basis of both cataplexy and a positive multiple sleep latency test (MSLT)[16].

The diagnosis of Na-1 is most often apparent from the clinical history alone, with most patients presenting with a clinical pentad of symptoms: excessive daytime sleepiness (EDS) and sleep attacks, cataplexy triggered by intense/unexpected emotional stimuli, sleep paralysis, hypnagogic and/or hypnopompic hallucinations, and nocturnal sleep fragmentation. However, around the time of symptom onset, there exist significant racial differences in manifestations of the cardinal features of narcolepsy, including those of cataplexy, sleepiness, and hypnogogic hallucinations[17]. In addition to having an earlier and more pronounced subjective sleepiness, African Americans with low CSF hypocretin-1 are 4.5x more likely to present without cataplexy, compared to Caucasians (28.3% vs 8.1%, respectively)[17]. Such symptomatic variability and lack of clinical familiarity with the disorder commonly results in delayed diagnosis[18,19].

## Diagnostic Criteria and Procedures

As mentioned, the most common initial symptom of Na-1 is excessive sleepiness. The Epworth Sleepiness Scale (ESS) is one of the most widely used, validated, self-administered questionnaires for assessing *subjective* sleepiness over a period of time[20]. However, the Pediatric Daytime Sleepiness Scale is more appropriate for use in pediatric populations[21].

*Objective* measures of sleepiness are central to the diagnostic evaluation of a sleepy patient. Several tests have been designed to objectively evaluate sleepiness, most notably the PSG-MSLT. To obtain a clinically valid MSLT, the test must be conducted under specific conditions[22]. In order to assess adequacy of sleep in the

period leading up to the MSLT, patients are often asked to complete a sleep diary and/or to wear a wrist actigraph for 2 weeks. Additionally, nocturnal polysomnography (nPSG) with ≥360 minutes of recorded sleep must be performed on the night preceding the MSLT to rule out inadequate sleep as a confounder[22]. Also, the PSG helps determine if there are other sleep disorders present that can cause sleepiness. Finally, the PSG may show a sleep-onset REM period (SOREMP) – REM sleep occurring within the first 15 minutes of sleep onset – which has high positive predictive value for Na-1 and is included in the diagnostic criteria[23]. Medications such as sedatives, stimulants, and those that affect the propensity to enter REM sleep, particularly tricyclic antidepressants and SSRIs/SNRIs, must be withheld for at least 2 weeks prior to the MSLT, to ensure validity of the test. A drug screen should be performed on the morning of the test to assess for any medications that could confound the results.

The MSLT has two main diagnostic features: the mean sleep latency (MSL) and the presence/absence of SOREMPs. The MSL is a calculated average of sleep latencies from the 4-5 naps (with sleepless nap opportunities ascribed a value of 20 minutes); an MSL of 10-20 minutes is generally found in healthy, rested subjects, while an MSL ≤ 8 minutes indicates excessive sleepiness. The 8-minute cutoff has a poor predictive value, as ~22% of the general population has an MSL ≤ 8 minutes[24]. More importantly, in narcolepsy, patients generally exhibit multiple SOREMPs over the course of the nPSG-MSLT evaluation. Combining the presence of ≥ 2 SOREMPs with the MSL cutoff greatly increases the diagnostic utility of the test, as this combination is only found in ~2-4% of the normal population[25]. Despite this, the nPSG-MSLT does have limitations, as SOREMPs can be found in patients who have disrupted circadian rhythms (e.g., shift workers and DSPD) or insufficient sleep. And, while the primary diagnostic utility has been validated in Na-1, it has been extended to the diagnosis of type 2 narcolepsy (Na-2) and idiopathic hypersomnia (IH), where the test-retest reliability of the test is extremely poor[26,27].

Genetic analyses are not commonly used in clinical practice, despite the aforementioned strong association between *HLA-DQB1*06:02* and Na-1, with 97% of patients possessing at least one allele[28]. Viewed another way, very few narcoleptics with hypocretin deficiency are *HLA-DQB1*06:02* negative[29]. However, this must be considered in light of the relatively poor specificity of the allele, given that ~40-50% of Na-2 patients carry *DQB1*06:02*, as does ~12-38% of the general population[28,30,31]. Nonetheless, a negative genetic test has diagnostic utility, particularly when attempting to differentiate Na-1 from Na-2, as no cases of narcolepsy without cataplexy were found to be hypocretin deficient when *HLA-DQB1*06:02* was negative[32]. Moreover, while Na-1 is often quite evident on clinical grounds alone, the clinical history and recommended diagnostic evaluations (i.e. nPSG-MSLT) occasionally produce equivocal or contradictory results. In fact, most cases with a positive MSLT are HLA negative, suggesting that they represent false positives. Repeating the MSLT and requiring two positive results after documentation of sufficient sleep prior to testing may be helpful, as the test-retest reliability of MSLTs in the general population[25] and in type 2 narcolepsy is very poor ($\kappa<0.3$) [27].

Incorporating CSF hypocretin level into the evaluation of narcolepsy, can significantly improve diagnostic certainty, particularly when differentiating Na-1 from Na-2[33,15]: a CSF hypocretin level ≤ 110 pg/mL is unambiguously tied to loss of hypocretin neurons and Na-1, unless associated with severe acute neurological disease such as TBI, Guillain Barre syndrome, encephalitis[34]. This assay may be particularly useful in African Americans, due to the higher prevalence of atypical cataplexy or non-cataplectic hypocretin-deficient narcolepsy[30,35]. This assay, however, is not currently widely available for clinical use, and can only be performed on specimens sent to the Stanford Narcolepsy Center research laboratory.

**Treatment strategies**

For patients with Na-1, behavioral modifications are a mainstay of therapy, with scheduled naps providing improved symptom control. Patient and family education can be augmented by helpful resources organized through patient advocacy support groups. Safety is paramount, and patients should be counseled regarding the risk and avoidance of driving while sleepy. Due to the potential for abuse and side effects, clinicians must be judicious in choosing a pharmacologic regimen, particularly in Na-2 and IH, which have little evidence to support the use of any particular agent[36–38].

Sodium oxybate (γ-hydroxybutyrate [GHB]) is now considered a standard therapy for narcolepsy. Sodium oxybate is a sedative anesthetic compound known to increase slow-wave sleep and, to a lesser extent, REM sleep, presumably through agonism at the GHB and $GABA_B$ receptors[39]. Sodium oxybate is FDA-approved for the treatment of cataplexy in Na-1, as well as for the treatment of EDS in Na-1 and Na-2. Sodium oxybate addresses multiple narcolepsy symptoms including EDS, disrupted nocturnal sleep, cataplexy, and sleep attacks, thereby improving patients' overall daytime function[40]. Full therapeutic benefit may take weeks to months to manifest fully.

Because of its potential for abuse and possible adverse effects with heavy sedation and respiratory depression, it is dispensed through a central pharmacy in the U.S. and requires patient *and* provider enrollment in the pharmaceutical company's management program (www.xyremrems.com/).

*Excessive daytime sleepiness (EDS)*

Modafinil (and the R-enantiomer armodafinil) is a non-amphetamine, wake-promoting agent that is often considered a first-line therapy for EDS in Na-1 and is FDA-approved for use in other disorders with hypersomnolence, such as shift-work disorder and residual EDS in OSA. Amphetamines and amphetamine-like compounds have been effectively used in the management of EDS in narcolepsy since 1935, but are currently considered second-line therapy due to their abuse potential. Due to the addictive nature of amphetamines/amphetamine-like stimulants, they should be prescribed at the minimum, effective dose, with preference for long-acting/extended-release agents.

*Cataplexy*

The emotion-triggered, REM-sleep-related atonia of cataplexy has been managed with REM-sleep-suppressing antidepressants since the 1970s. The early use of tricyclic antidepressants (TCAs) was limited by significant anticholinergic side effects, high risk in overdose, and the lack of FDA approval. The extended-release formulation of venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), is very effective and therefore commonly used as a first-line agent. Atomoxetine, primarily a norepinephrine reuptake inhibitor, is also used in the treatment of cataplexy and EDS, particularly in children.

*Future therapies and treatment of other hypersomnias*

Based on the presumed autoimmune mechanism of Na-1, much interest has been kindled in using immunotherapies to treat patients during an acute presentation (<9 months from symptom onset). Disappointingly, trials of intravenous immunoglobulin have had mixed results[41]. However, evidence that the pathophysiology may be T-cell-mediated rather than humoral[42,43] suggests that inhibiting T-cell entry into the CNS, with agents such as the α4-integrin monoclonal antibody, natalizumab, may be more appropriate. Finally, the development of CNS-penetrating hypocretin agonists has faced many biological hurdles, but their utility in the resolution of hypocretin-deficient narcolepsy has been established through replacement studies in animals[44,45].

Clinical trials are underway for a number of other agents that target novel pathways for wake promotion or sleep suppression. Pitolisant, an inverse agonist that promotes histamine release through inhibition of the presynaptic autoinhibitory $H_3$ receptor, is being explored as a treatment for EDS in Na-1 and Na-2. A phenylalanine derivative that enhances dopaminergic and noradrenergic neurotransmission, [R]-2-amino-3-phenylpropylcarbamate, is being investigated for the management of EDS in narcolepsy and OSA.

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