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Central Disorders of Hypersomnolence
Focus on the Narcolepsies and Idiopathic Hypersomnia

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The central disorders of hypersomnolence are characterized by severe daytime sleepiness, which is present despite normal quality and timing of nocturnal sleep. Recent reclassification distinguishes three main subtypes: narcolepsy type 1, narcolepsy type 2, and idiopathic hypersomnia (IH), which are the focus of this review. Narcolepsy type 1 results from loss of hypothalamic hypocretin neurons, while the pathophysiology underlying narcolepsy type 2 and IH remains to be fully elucidated. Treatment of all three disorders focuses on the management of sleepiness, with additional treatment of cataplexy in those patients with narcolepsy type 1. Sleepiness can be treated with modafinil/armodafinil or sympathomimetic CNS stimulants, which have been shown to be beneficial in randomized controlled trials of narcolepsy and, quite recently, IH. In those patients with narcolepsy type 1, sodium oxybate is effective for the treatment of both sleepiness and cataplexy. Despite these treatments, there remains a subset of hypersomnolent patients with persistent sleepiness, in whom alternate therapies are needed. Emerging treatments for sleepiness include histamine H3 antagonists (eg, pitolisant) and possibly negative allosteric modulators of the gamma-aminobutyric acid-A receptor (eg, clarithromycin and flumazenil). CHEST 2015; 148(1):262-273

ABBREVIATIONS: AASM = American Academy of Sleep Medicine; CSF = cerebrospinal fluid; EDS = excessive daytime sleepiness; ESS = Epworth Sleepiness Scale; FDA = US Food and Drug Administration; GABA = gamma-aminobutyric acid; HLA = human leukocyte antigen; ICSD-3 = *International Classification of Sleep Disorders, Third Edition*; IH = idiopathic hypersomnia; MSL = mean sleep latency; MSLT = multiple sleep latency test; MWT = maintenance of wakefulness test; PSG = polysomnography; RCT = randomized controlled trial; REM = rapid eye movement; SOREMP = sleep-onset rapid eye movement period; SSRI = selective serotonin reuptake inhibitor

Sleepiness is a common experience, with the prevalence of excessive daytime sleepiness (EDS) occurring at least 3 d/wk ranging from 4% to 21%.[1] Such sleepiness may be caused by medical conditions, sleep disorders, illicit and prescribed substances, work and family demands (including shift work), and insufficient sleep time. Insufficient sleep is a particularly common cause of EDS, as more than one-third of Americans are sleep deprived.[2]

This review focuses on the central disorders of hypersomnolence, a group of sleep disorders characterized by EDS in the absence of disrupted nocturnal sleep or circadian rhythm disorders. The first of these disorders to be comprehensively described was narcolepsy, dating back to a

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case published in 1880 by Jean Baptiste Gélineau of a 38-year-old wine merchant with > 200 sleep attacks per day.[3] Idiopathic hypersomnia (IH) was then detailed by Bedrich Roth in a series of 642 patients seen over 30 years.[4] The classification, diagnosis, and treatment of the central disorders of hypersomnolence have evolved considerably since these early descriptions and will be the focus of this review. Together, these hypersomnolence disorders account for substantial morbidity and impairments in quality of life.[5-9]

Clinical Features, Diagnosis, and Classification

EDS is the cardinal feature of the central disorders of hypersomnolence. It is defined as the "inability to stay awake and alert during major waking episodes of the day, resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep."[10] It can be confused with fatigue, but while fatigue presents with a lack of energy without inadvertent or excessive sleep, sleepiness implies an increased propensity to sleep. The most recent version of the *International Classification of Sleep Disorders, Third Edition* (ICSD-3) subdivides the central disorders of hypersomnolence into eight categories (Table 1).[10] While insufficient sleep syndrome (ie, sleepiness caused by short sleep times and cured by sleep extension) is categorized as one of the eight hypersomnolence syndromes, insufficient sleep time must be excluded for the other diagnoses. This can be accomplished using patient-completed sleep logs or actigraphic monitoring over a 1- to 2-week period. In this version of the ICSD-3, there are three persistent hypersomnolence disorders not associated with another illness or substance: narcolepsy type 1, narcolepsy type 2, and IH (Table 2).

The classic symptom tetrad for narcolepsy is EDS, cataplexy, sleep paralysis, and hallucinations at sleep onset or offset (ie, hypnagogic or hypnopompic hallucinations, respectively). Cataplexy is defined as the sudden loss of muscle tone in response to a strong emotion, most typically when hearing or telling a joke. However, < 10% of patients exhibit all symptoms initially and this may contribute to the average diagnostic delay of 10½ years.[11] Cataplexy is present in 65% to 75% of individuals with narcolepsy.[12-14] It is quite specific; only rarely will cataplexy or cataplexy-like episodes occur in other disorders, including Coffin-Lowry syndrome, Norrie disease, and Niemann-Pick disease type C.[15-19] The presence or absence of cataplexy is a key distinguishing feature between the two types of narcolepsy, which are now recognized to be quite different entities despite their similar nomenclature. Cataplexy is present in narcolepsy type 1 (formerly known as narcolepsy with cataplexy) and absent in narcolepsy type 2 (formerly narcolepsy without cataplexy) (Table 2). Many patients with narcolepsy type 1 have fragmented nocturnal sleep, underscoring the fact that this type of narcolepsy reflects difficulty with state control.[20] In essence, patients with narcolepsy type 1 have difficulty remaining awake when desired, but also, at times, with remaining asleep when it is alternately desired.

Cataplexy can also be conceptualized as a problem of state control, such that a feature of rapid eye movement (REM) sleep (ie, the paralysis, or atonia, that typically accompanies normal REM sleep) suddenly intrudes into wakefulness.[20] REM behavior disorder, in which patients are able to act out dreams because their motor control during REM more closely resembles that of wakefulness (ie, they have a lack of paralysis, or lack of atonia), is another disorder of sleep-wake state control that is common in narcolepsy type 1.[21] Sleep fragmentation may also be a common feature of narcolepsy type 2,[22] but is very atypical for IH.

The remaining features of the narcolepsy tetrad, sleep paralysis and hallucinations, are common in patients with either type of narcolepsy, but sleep paralysis also occurs in healthy subjects (5%-40%)[23] and these features do not reliably distinguish among the major hypersomnolence syndromes (Table 3).[24-38] Patients with IH have EDS but never cataplexy, and have a clinical presentation more similar to those patients with narcolepsy type 2 than type 1. Sleep paralysis and hallucinations are variably present in IH. One-third to two-thirds of patients with IH experience what Roth described as "sleep drunkenness": a prolonged state after awakening in which motor functions return before full awareness or there is partial return of both.[10,32,39] Patients report great difficulty

TABLE 1] Central Disorders of Hypersomnolence[10]

Disorders
Narcolepsy type 1
Narcolepsy type 2
Idiopathic hypersomnia
Kleine-Levin syndrome
Hypersomnia due to a medical disorder
Hypersomnia due to a medication or substance
Hypersomnia associated with a psychiatric disorder
Insufficient sleep syndrome