Hypersomnia

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Case Vignette

Andrew is an 11-year-old boy with a history of ADHD and anxiety who presents to neurology clinic with persistent daytime sleepiness since age 9 years. Andrew sleeps approximately 9.5 h at night and falls asleep in class several times per week. Teachers also describe him as having poor attention and working memory and being easily distractible, especially in the afternoons. Mother says he is very irritable and moody in the evenings but does better if he naps for 1–2 h after school and before dinner. Epworth Sleepiness Scale score was 18/24, indicating moderate to severe daytime sleepiness. Andrew was diagnosed with attention-deficit/hyperactivity disorder and has been on 10 mg of Adderall XR since age 10 years. This medication has helped his attention problems and school performance to some degree but has not improved his daytime sleepiness. Mother wonders how much of Andrew's daytime sleepiness is affecting his attention, mood, and school performance and whether an underlying sleep disorder could contribute to his symptoms.

Introduction

Hypersomnia is defined as the inability to stay awake during typical wakeful times during the day and may present as unintended lapses into drowsiness or sleep as well as a persistent desire to sleep [1]. Children may not be aware of their degree of sleepiness so parent and teacher behavioral observations are critical in the evaluation process. Symptoms of daytime sleepiness, which involves a real propensity toward sleep, must be distinguished from fatigue. Fatigue is often described as feeling tired, rundown, never rested, lacking energy, and exhausted. While the sleepiness of hypersomnia may also be associated with fatigue, patients with fatigue generally don't report inadvertent lapses into sleep like hypersomnia patients. Use of open-ended questions, requesting examples of symptoms in specific situations (i.e., whether a child falls asleep in car rides or during boring classes), and obtaining behavioral observations from parents, peers, and teachers can help the clinician distinguish more concerning symptoms of hypersomnia from generalized fatigue. Sleepiness can vary in severity and range from propensity to sleep in low-stimulation environments and with monotonous activity all the way to sudden sleep attacks.

Differential Diagnosis of Hypersomnia

Primary Central Nervous System Hypersomnias

Primary central nervous system hypersomnias can be broadly categorized as either chronic or periodic conditions (Fig. 8.1). Chronic primary hypersomnias refer to conditions in which symptoms of excessive daytime sleepiness are present daily for at least a 3-month period and include narcolepsy type 1 (narcolepsy with cataplexy), narcolepsy type 2 (narcolepsy without cataplexy), and idiopathic hypersomnia. Periodic primary hypersomnias are episodic presentations of exces-

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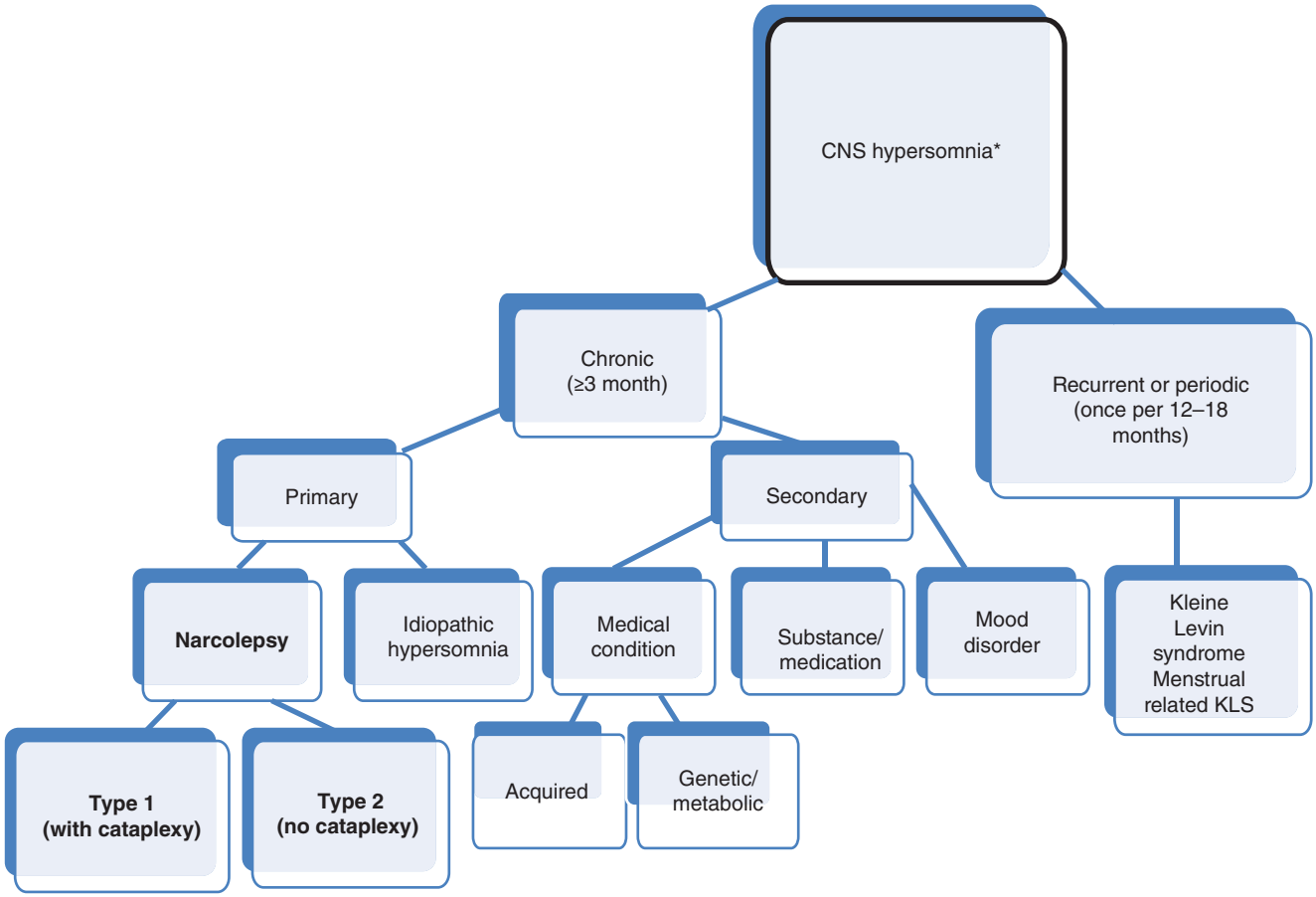

Fig. 8.1 Flowchart of primary and secondary hypersomnia conditions. *Excludes hypersomnia due to insufficient sleep or other primary sleep disorders

sive daytime sleepiness that are generally cyclical in nature and include menstrual-related hypersomnia and Kleine-Levin syndrome.

Narcolepsy Type 1

Narcolepsy type 1 is a rare sleep disorder, occurring in 0.025–0.05% of the population or 1 per 2000 people [2, 3] characterized by excessive daytime sleepiness, hypnagogic (sleep onset) and hypnopompic (sleep offset) hallucinations, sleep paralysis, and cataplexy. Fundamentally, these symptoms are thought to be related to increased rapid eye movement (REM) sleep pressure [4]. In normal REM sleep, dreams occur, and the body becomes functionally atonic, with the exception of eye muscles and the diaphragm. The sleep-related hallucinations and sleep paralysis experienced in narcolepsy are attributed to inappropriate transitions into REM sleep occurring close to waking periods. Similarly, cataplexy is believed to represent the functional atonia characteristic of REM sleep intruding into wake periods. The etiology of narcolepsy is due to loss of hypocretin neurons in the lateral hypothalamus though the cause of this neuronal loss is still unknown [5–7]. A strong association with narcolepsy type 1 and the HLA DQB1*0602 haplotype has been found suggesting an autoimmune etiology [8, 9].

Excessive daytime sleepiness is the core symptom of narcolepsy and is generally the first presenting symptom [10, 11]. In prepubertal children, symptoms of cataplexy have been reported to precede excessive daytime sleepiness though this is a rare presentation [12]. Narcolepsy symptoms most commonly develop in the second decade of life between ages 10 and 19 years of age with a second peak at ages 30–40 [2]. More recently, a rise in prepubertal onset of symptoms has been reported with more dramatic and sudden onset of symptoms [13, 14]. In these cases, excessive nocturnal sleep time, daytime sleepiness, atypical cataplexy, precocious puberty, and rapid weight gain have been noted. Unfortunately, the median time to diagnosis has been reported to be as high as 10.5 years and is attributed to lack of awareness of narcolepsy symptoms and signs [15, 16]. Pediatric narcolepsy can be a particular diagnostic challenge

because of associated neurobehavioral and psychiatric comorbidities discussed later in this section that can lead to misdiagnosis.

Cataplexy involves transient atonia that typically lasts seconds and is triggered by emotional stimuli such as laughter, anger, embarrassment, anticipation, and even pain. During classic cataplexy attacks, the axial muscles are affected, most commonly with transient weakness at the jaw, neck, shoulders, and/or knees. Consequently, cataplexy may be observed as episodic tongue protrusion, jaw slackening, change in speech, head bobbing/head drops, shoulder slumping, knee buckling, and/or falls. Cataplexy can be mistakenly diagnosed as epileptic seizures in the more severe cases, or children may be labeled clumsy in the more subtle presentations [12]. Cataplexy is reported in 65–75% of the patients with narcolepsy [17, 18] and distinguishes the condition of narcolepsy type 1 (narcolepsy with cataplexy) from narcolepsy type 2 (narcolepsy without cataplexy). Cataplexy onset is usually within 3 months to 1 year after onset of sleepiness [11, 19]. More recently, atypical forms of cataplexy have been reported, most notably in prepubertal children [20]. Atypical cataplexy may present with cataplectic facies (ptosis, jaw opening) and even positive motor phenomena resembling tics and/or dyskinesias such as grimacing and repetitive tongue protrusion [20]. This atypical presentation of cataplexy is not emotionally triggered and appears to be more chronic in nature, making it difficult to distinguish from other neurological conditions such as primary movement disorders or neuromuscular disease.

Narcolepsy Type 2

Narcolepsy type 2 shares the symptoms that mark narcolepsy type 1 – daytime sleepiness, hypnagogic or hypnopompic hallucinations, and sleep paralysis – with the exception of cataplexy. Despite this overlap in symptoms, only 24% of patients with narcolepsy type 2 have low CSF hypocretin levels (<110 pg/ml), and only about 40% are positive for the HLA DQB1*0602 haplotype. It has been suggested that this disorder may result from only partial loss of hypocretin neurons or that the disorder is different in etiology altogether [8, 21, 22]. Furthermore, cataplexy can occur years after daytime sleepiness symptoms, so in some cases, narcolepsy type 2 may simply be an early form of narcolepsy type 1. Diagnosis of narcolepsy type 2 can be challenging because symptoms of hypnagogic/hypnopompic hallucinations and sleep paralysis also occur in the general population, notably in settings of shift work and sleep deprivation [23, 24]. Thus, clinical history regarding symptoms, social history including work hours, stressors, sleep duration, and sleep quality are critical for making an accurate diagnosis of narcolepsy type 2. The revised International Classification of Sleep Disorders Manual specifies the diagnosis of narcolepsy (type 1 or type 2) requires typical symptoms and one of two confirmation studies: (1) a nocturnal polysomnogram and multiple sleep latency test (diagnostic of both type 1 and type 2) *or* (2) CSF hypocretin <110 pg/ml (diagnostic exclusively of type 1). The details of this sleep testing are discussed further in this chapter. It is estimated that narcolepsy type 2 represents 15–25% of all reported narcolepsy cases.

Idiopathic Hypersomnia

Idiopathic hypersomnia (IH) is also a condition of excessive daytime sleepiness, with patients reporting daily irresistible sleep periods over a period of at least 3 months without accompanying symptoms of hypnogogic hallucinations, sleep paralysis, or cataplexy. Patients with IH typically report symptoms of sleep drunkenness or sleep inertia (irritability and confusion upon being woken up with repeated returns to a sleep state) and unrefreshing naps [1]. Despite long sleep durations, on average greater than 10 h, patients with IH still have excessive daytime sleepiness. The etiology of this condition is unknown. Patients with IH generally have normal CSF hypocretin levels, and there has been no clear association with HLA typing or preceding infections [25]. In comparison to patients with narcolepsy types 1 and 2, individuals with IH have higher sleep efficiency on polysomnography, longer mean sleep latencies on the multiple sleep latency test, and a tendency to be older at the time of symptom onset [26, 27]. Some reports indicate a familial pattern of hypersomnia, as IH patients commonly report a relative with similar symptoms; however, there is little research about inheritance patterns of IH [1, 26]. Obstructive sleep apnea, delayed sleep phase syndrome, insufficient sleep, and drug use can all mimic the symptoms of idiopathic hypersomnia [25]; therefore close monitoring of typical sleep duration (by sleep charts or actigraphy) and performance of overnight polysomnography and multiple sleep latency testing are essential to provide an accurate diagnosis. Idiopathic hypersomnia typically develops in adolescence and in many cases self-resolves by young adulthood [1]. On the other hand, patients initially diagnosed with IH may later develop other symptoms typical of narcolepsy (hypnagogic/hypnopompic hallucinations, sleep paralysis). In these cases, their diagnoses may be changed to narcolepsy type 2 after repeat sleep diagnostic testing confirms the presence of abnormal sleep onset REM periods.

Kleine-Levin Syndrome (KLS)

KLS is characterized by periodic episodes of severe hypersomnia and behavioral, psychiatric, and cognitive disturbances [1]. It classically affects adolescents. Hypersomnia is the hallmark feature and patients typically report sleeping up to 18–20 h a day [28]. In addition to excessive sleepiness, episodes are marked by slowed processing speed, confusion, regression to childlike behaviors, altered perception/depersonalization, irritability, and anxiety [28–30]. Hyperphagia,

food hoarding, and anorexia have been reported with this condition, suggesting hypothalamic dysfunction. Episodes can last days to weeks interspersed by months of asymptomatic periods [30]. The frequency of episodes tends to decrease with age, and the condition frequently resolves during adulthood. Functional MRI (fMRI) studies have revealed hypoperfusion of the right dorsomedial prefrontal cortex and the right parietotemporal region as well as the hypothalamus, thalamus, and caudate [31].

The etiology of KLS is unknown. There is some evidence that KLS is of autoimmune etiology, though supporting data have been inconsistent in the literature. KLS onset often occurs after an infection, and on occasion subsequent relapses may be preceded by a similar illness [27]. A sample of individuals with KLS has also been noted to be more likely to be positive for the HLA DQB1*0201 haplotype than controls [32], although this finding did not carry over in studies with larger KLS cohorts [32, 33]. Other triggers for the periodic symptoms include travel, alcohol use, drug use, and head trauma [27]. Case studies have revealed that 5% of KLS patients have a family history of the disorder. Factors including prepubertal disease onset, male sex, or postadolescent onset result in longer duration of symptoms during episodes [1, 27]. KLS is so rare that there are limited data to inform treatment recommendations. Medications such as stimulants and antiepileptic medications such valproic acid have shown no or minimal benefit [33, 34]. Recently, one open-label, controlled study in 130 KLS patients showed that lithium treatment decreased the duration and frequency of symptomatic episodes [35]. This therapy is promising for future treatment. Important to management is supportive care with emphasis on maintaining good sleep hygiene (as sleep deprivation may trigger episodes) and educational support [29].

Secondary Causes of Hypersomnia in Children

The most common cause of excessive daytime sleepiness is insufficient amount of sleep [36]. The amount of sleep recommended for children at different ages has thus far been grounded in the results of population-based studies [37] in which typically developing, healthy school-aged children get a median 10 h on average per night and adolescents approximately 9 h. Yet, the average amount of sleep obtained by children per the National Sleep Health Foundation is notably lower. In a national poll of American children, 34% of toddlers, 32% of preschoolers, and 27% of school-aged children were reported to sleep fewer hours than what the parent/caregiver thought they needed [38]. More objective evidence confirms these concerns. In one research study using actigraphy, children ages 4–10 years slept on average 8 h per night compared to the recommended 10 h for this age range [39]. This growing trend of insufficient sleep among children certainly contributes to increased prevalence of daytime sleepiness, with up to 25% of students ages 4–12 reporting falling asleep in class [38]. There have been no large-scale studies of population data assessing sleep duration in children with neurodevelopmental disorders to clarify whether their sleep needs differ from what is recommended by chronological age. Other sleep disorders such as obstructive sleep apneas, periodic limb movements of sleep, nocturnal epilepsy, and parasomnias may sufficiently disturb the continuity of sleep and result in daytime sleepiness.

Developmental disorders such as attention-deficit/hyperactivity disorder (ADHD) and psychiatric disorders constitute up to 35% of total cases of children referred for sleep problems, [40] and thus fatigue and daytime sleepiness are common presenting concerns. Furthermore, clinical research has documented secondary narcolepsy-like symptoms in a number of neurogenetic conditions such as Prader-Willi syndrome [41], Norrie disease [42], Niemann-Pick C [43], and Coffin-Lowry syndrome [44]. Epilepsy, sedating medications, and predisposition to sleep apnea all may contribute to complaints of daytime sleepiness among children with developmental, genetic, and psychiatric conditions. In this section, we briefly review the incidence and potential causes of excessive daytime sleepiness among children with attention-deficit/hyperactivity disorder, depression, and two specific genetic disorders: Smith-Magenis syndrome and Prader-Willi syndrome.

Sleepiness in Children with ADHD

Sleep problems are a common comorbidity in ADHD. Based on parental report, 25–50% of children with ADHD have problematic sleep at night [45–49]. Sleep problems may be the result of hyperactivity, and difficulty settling down for sleep and/or medications used to treat ADHD may result in sleep problems [50]. These sleep disturbances often result in daytime sleepiness and fatigue. A retrospective study of 33 children and their polysomnograms by Goraya et al. revealed that children with ADHD had increased arousal indices, increased wake after sleep onset, and reduced sleep efficiency which correlated with excessive daytime sleepiness and hyperactivity [51]. Likewise, a meta-analysis conducted by Cortese et al. also suggested that children with ADHD have more daytime sleepiness, more movements in sleep, and higher apnea-hypopnea indexes compared to controls [52, 53]. While sleepiness has been reported in patients with primary ADHD [53, 54], it is also important to recognize that sleepiness in otherwise healthy children is well known to manifest as behavioral problems, educational difficulties, or symptoms of attention deficit or hyperactivity [37, 38]. Thus, primary sleep disorders resulting in daytime sleepiness have

the potential to mimic ADHD symptoms. Accordingly, it is important for clinical providers to ask about daytime fatigue and sleepiness and symptoms of primary sleep disorders such as narcolepsy when evaluating a patient with symptoms concerning for attention deficit disorders.

Sleepiness in Children with Smith-Magenis Syndrome (SMS)

Smith-Magenis syndrome (SMS) is a neurodevelopmental disorder caused by an interstitial deletion of chromosome 17p11.2 and associated with cognitive impairments, behavioral problems, dysmorphic features (brachycephaly, midface hypoplasia, "cupid's bow" mouth, prognathism), speech delays with/without hearing impairment, and peripheral neuropathy [55]. Significant sleep problems are reported in 65–100% of SMS patient by parents [56]. Early sleep onset and daytime sleepiness (including "sleep attacks" during which children abruptly fall asleep) are commonly reported in SMS cohort studies, even while patients have short total nocturnal sleep time and repetitive prolonged nocturnal wakings [57]. This atypical sleep pattern and daytime sleepiness are attributed to an inversion of melatonin onset and rise [58–60]: melatonin typically begins to rise in the early evening, and its secretion is then sustained through the night, but some children with SMS have been found to have paradoxically low levels of nocturnal melatonin and high levels of daytime melatonin [60]. Most notably, sleep disturbances were predictive of daytime behavior problems including tantrums and hyperactivity, and only mild improvements have been noted using medications to control behaviors or sleep [60]. Because the circadian rhythm of melatonin synthesis is regulated by the sympathetic nervous system, in one study SMS patients were given a B-adrenergic antagonist to reduce production of daytime melatonin. Results showed a dramatic improvement in both daytime melatonin concentrations and daytime behavior problems [61]. Such findings highlight a novel biological mechanism between sleep disturbances and problematic daytime behaviors in children.

Sleepiness in Children with Prader-Willi Syndrome (PWS)

Prader-Willi syndrome is most commonly caused by deletion in the paternally derived chromosome 15 (q11–q13), but maternal uniparental disomy, imprinting errors, and translocation have also been reported [62]. PWS is characterized by short stature, hypotonia, hyperphagia, early-onset obesity, impaired sexual development, and cognitive impairment [63]. Additionally, excessive daytime sleepiness is frequently noted, both by subjective report and by objective testing (multiple sleep latency testing) among children with PWS [64, 65]. Parents of children with PWS report that their children seem to nap excessively, fall asleep easily, and waken with difficulty [66]. Multiple sleep latency testing has revealed short sleep latency and presence of sleep onset REM periods consistent with narcolepsy in many cases [66–68]. Additionally, 16–28% of children with PWS may also have cataplexy, suggesting secondary narcolepsy due to global hypothalamic dysfunction and hypocretin neuropeptide loss [68]. Sleepiness may also be attributed to the high prevalence of sleep-disordered breathing, including hypoventilation, OSA [69], and central sleep apnea [70] reported among children with PWS. Interestingly, weight loss and reduction of sleep-disordered breathing with continuous positive airway pressure (CPAP) does not always result in reduction of the daytime sleepiness [71]. Use of modafinil, a wake-promoting agent described later in this chapter, has been shown to significantly improve daytime sleepiness among patients with PWS, though larger clinical trials are needed [72].

Hypersomnia and Depression

Depression is a common comorbid condition among children with neurodevelopmental disorders [73, 74] and is another contributing factor to the presentation of EDS. Change in sleep (either insomnia or hypersomnia) is listed as one of the diagnostic criteria of major depressive disorder (MDD) [75], but there have been a limited number of studies investigating the actual frequency of hypersomnia symptoms in MDD. Individuals who report hypersomnia in conjunction with MDD or other mood disorders most often have symptoms that include long sleep time, sleep inertia, and excessive daytime sleepiness [25]. Subjective assessments indicate a high frequency of hypersomnia in the presence of MDD with symptoms of hypersomnia often noted to precede a major depressive episode [25]. However, in the limited number of studies that have used objective measures such as multiple sleep latency testing (MSLT) to assess hypersomnia in mood disorders, mostly normal results are reported. Thus, it is possible that hypersomnia related to depression is a rarer subtype of depression and what patients report as sleepiness may actually be fatigue or lack of energy [25]. On the other hand, individuals with hypersomnia disorders of central origin such as narcolepsy type 1 have high rates of depression (discussed further below) suggesting a bidirectional relationship between hypersomnia and emotional health. Careful patient interview and diagnostic testing with polysomnography and multiple sleep latency testing are often necessary to establish the primary diagnosis.

Neurobehavioral and Neuropsychiatric Comorbidities Associated with Primary Narcolepsy

Children with narcolepsy types 1 and 2 have high rates of behavioral problems and psychiatric conditions. While it is commonly thought that these comorbidities are the results of excessive daytime sleepiness or secondary to poor coping mechanisms after development of chronic disease, it is also possible that these conditions are intrinsic to the disease state itself.

Attention-Deficit/Hyperactivity Disorder (ADHD) and Narcolepsy

ADHD symptoms are present at high rates among children with narcolepsy types 1 and 2 [76, 77]. A recent cross-sectional survey of children under 18 years of age found that 35.3% of children with narcolepsy reported ADHD symptoms compared to 4.8% of control subjects [76]. It is well known that sleep problems including sleep disturbances, insufficient sleep, and daytime sleepiness can result in poorer executive functioning, memory difficulties, inattention, and hyperactivity in children [53, 78, 79]; thus, symptoms of ADHD may be expected among children with narcolepsy. Indeed, excessive daytime sleepiness, insomnia, and fatigue scores among children with narcolepsy were all significantly associated with ADHD symptoms in this cross-sectional study [76]. However, the ADHD symptoms of narcolepsy patients were less likely to improve with treatment of stimulant medications, suggesting that sleepiness alone may not be driving these behaviors. Clinically, practitioners must be aware of the risk of cognitive and behavioral problems in children with narcolepsy and consider neuropsychological testing and formal academic supports in the form of 504 plans or Individualized Education Programs.

Schizophrenia and Narcolepsy

By one report, presentation of narcolepsy type 1 combined with schizophrenia seemed rare, occurring in 1–18 cases in a population of 2 million based on independent prevalence rates [80]. In contrast, another study showed that approximately 10% of adolescent patients with narcolepsy type 1 developed schizophrenia at an average age of 2.5 ± 1.8 years after narcolepsy symptom onset [81]. Patients with both narcolepsy and schizophrenia were younger than those with narcolepsy alone, and the authors suggested that younger age makes these patients more susceptible to "brain autoimmune disease" due to high prevalence of HLA DQB1*03:01/06:02 allele in patients with both narcolepsy and schizophrenia. While schizophrenia may be a potential comorbidity, use of high-dose stimulants has also been shown to be associated with adverse psychotic side effects among patients with hypersomnia conditions [80]. Auger et al. reported increased risk of psychosis (OR = 12), alcohol or polysubstance abuse (OR = 4.3), and psychiatric hospitalization (OR = 3.2) among patients with narcolepsy and idiopathic hypersomnia treated with high-dose stimulants (defined as dosage ≥120% of the maximum recommended by the American Academy of Sleep Medicine Standards of Practice Committee) [82]. Lastly, it is possible that there is a distinct subtype of narcolepsy with psychotic features, a claim which thus far has only been suggested by case reports [83]. Anti-NMDA receptor antibodies have been detected in patients with narcolepsy with psychotic features (with and without encephalitis symptoms), suggesting autoimmune etiology may result in broader neuropsychiatric symptoms [84]. Of great concern is the potential misdiagnosis of narcolepsy as schizophrenia based on reports of hallucinations. While hallucinations are experienced in both narcolepsy and schizophrenia, the hallucinations experienced by patients with narcolepsy are almost always associated with sleep onset/offset (hypnogogic/hypnopompic hallucinations) and more likely to be multimodal in presentation (both visual and tactile) [85].

Mood Disorders and Narcolepsy

Among both adults and children, primary mood disorders are reported in up to 1/3 of patients with narcolepsy and include depression, anxiety, obsessive-compulsive disorder, and social phobia [86]. Among children with narcolepsy, 25% of patients reported depressive symptoms on the Children's Depression Inventory [87]. Symptom burden tended to be higher in those reporting depression, with more frequent hypnogogic hallucinations and sleep paralysis, higher subjective sleepiness scores, and longer duration of symptoms before diagnosis compared with non-depressive patients. However, depressive feelings were not significantly different among patients based on treatment with stimulants for daytime sleepiness or venlafaxine for cataplexy.

These high rates of depression among patients with narcolepsy suggest that mood disorder may be intrinsic to the narcolepsy diagnosis. Interestingly, the sleep architecture of depressive patients without narcolepsy has been reported to include short REM onset latency, increased REM pressure with sleep onset REM periods, and sleep fragmentation – all findings similar to those reported in patients with narcolepsy. Hypocretin deficiency associated with narcolepsy induces cholinergic-monoaminergic imbalance with primary effect on alertness, but such dysregulation has been shown to

directly influence mood as well [88]. Clinically, screening for affective problems among patients with narcolepsy is important, as medications used to treat core symptoms such as stimulants may worsen underlying mood disorder symptoms. Ultimately, allying with mental health providers is often necessary for assessment and management of psychological health.

Evaluating and Diagnosing Hypersomnia

As mentioned above, obtaining a history of duration and quality of nocturnal sleep period is important as is detailed information about duration and frequency of daytime naps and whether such bouts of sleep are refreshing. Use of sleep logs or diaries can be helpful in obtaining longitudinal sleep and wake patterns, as can actigraphy. Physical exam should focus on craniofacial structure, as micro- and retrognathia as well as tonsillar hypertrophy may predispose children to develop obstructive sleep apnea and associated daytime sleepiness.

Questionnaires

There are number of validated questionnaires that are used in the clinical evaluation of hypersomnia. The Pediatric Daytime Sleepiness Scale is an eight-item, self-reported Likert-type questionnaire that measures daytime sleepiness in children ages 11–15 years, with possible scores ranging from 0 to 32. Higher PDSS scores indicate greater daytime sleepiness. Along with being easy to administer, score, and interpret, the PDSS has a high internal consistency and is commonly used in clinical practice [89]. The PDSS has been used in children with epilepsy [90, 91], autism [92], and ADHD [76]. The Cleveland Adolescent Sleepiness Questionnaire (CASQ) has been validated in a broader age range in students aged 11–17 years with known sleep-disordered breathing (primary snoring or obstructive sleep apnea) [93]. Internal consistency of the CASQ was slightly higher than the PDSS but to date has not been utilized in published research with children with neurological or neurodevelopmental disorders. Lastly, the modified Epworth Sleepiness Scale (ESS) is an eight-item questionnaire used to assess levels of EDS in children ages 6–16 years that allows both parents and children to rate the child's tendency to fall asleep during different scenarios [94]. Items are rated from zero to three, with higher scores indicating greater sleepiness. A total score is also obtained, with scores of 10 or more indicative of EDS and median scores of 14 reported specifically among patients with narcolepsy [95]. The modified version of the ESS has not been formally validated but has been used in a number of research studies assessing sleep-disordered breathing [94], hypersomnia associated with brain tumors [96], ADHD [97], multiple sclerosis [98], and narcolepsy [99].

Actigraphy

Actigraphs are watch-like devices that contain a computerized algorithm that measures limb movement to estimate sleep and wake patterns. The sleep onset latency, number and duration of nocturnal awakenings, time in bed, total sleep time, sleep efficiency, and number and duration of daytime naps can all be quantified using actigraphy in children. Actigraphy has been used in children with neurodevelopmental disorders such as ADHD [100, 101] and autism [102–104], though extra training on use and even desensitization protocols may be required [105]. Actigraphy can be helpful for evaluating for insufficient nocturnal sleep and circadian rhythm sleep disorders. Furthermore, actigraphy can confirm the presence of hypersomnia. In one study, group differences among children with narcolepsy type 1 and idiopathic hypersomnia and controls were detected in all actigraphic parameters except sleep onset latency and time in bed, and significant differences were even noted between participants with narcolepsy and idiopathic hypersomnia [106]. Unfortunately, actigraphy is not clinically reimbursed in many countries, limiting its use.

Nocturnal Polysomnography

Hypersomnia is one valid indication for an overnight polysomnogram (PSG), and others include concerns for obstructive sleep apnea, restless leg syndrome, frequent parasomnias, epilepsy, and nocturnal enuresis when an underlying sleep disorder contributing to EDS is suspected. If problems with sleep schedule or hygiene exist, they should be addressed, and hypersomnia reassessed before a sleep study is ordered. Per the International Classification of Sleep Disorders-3 [1], an overnight PSG and multiple sleep latency test (MSLT) are both indicated for the diagnosis of narcolepsy types 1 and 2, but ideally, potential sedating, alerting, or REM-suppressing medications (e.g., clonidine, guanfacine, stimulants, SSRI, SNRIs) need to be weaned off 2 weeks prior to testing. Alternatively, the ICSD-3 criteria permit narcolepsy type 1 diagnosis to be made if CSF hypocretin-1 concentration measured by immunoreactivity is either ≤110 pg/ml or <1/3 of mean values obtained in normal subjects with the same standardized assay.

In children, the specificity of a nocturnal sleep onset REM period (SOREMP, or REM onset latency of ≤15 min) for detection of narcolepsy type 1 is high at 97.3% (95% confidence interval [CI]: 92.2–99.4%), but the sensitivity was

moderate at 54.8% (95% CI: 38.7–70.2%). Overall, the positive predictive value of an SOREMP for the diagnosis of narcolepsy type 1 was 88.5% (95% CI: 69.8–97.4%) [107]. Given the high specificity of a nocturnal SOREMP on the PSG for the diagnosis of narcolepsy, the revised International Classification of Sleep Disorders-3 now allows the presence of a nocturnal SOREMP to be included in the two required SOREMPs for diagnosis of narcolepsy type 1 or 2, formerly factored in from multiple sleep latency testing only [1]. Insufficient amount of sleep and shift work have been associated with findings of nocturnal SOREMPs [108].

Mean Sleep Latency Test (MSLT)

A mean sleep latency test is considered a standard measure of sleepiness, based on the assumption that the length of time it takes an individual to fall asleep is directly related to their degree of sleepiness [109]. During an MSLT, the patient is offered up to five opportunities to nap during the day separated by 2-h intervals during which she/he is not permitted to sleep but may engage in other activities. At each nap interval, the patient is asked to lie down in bed in a dark room and given 20 min during which to fall asleep. Using EEG measures to assess for sleep onset, the mean sleep latency is calculated based on four to five nap periods, where a sleep latency of 20 min is used in calculations for any nap periods where the patient did not fall asleep. Sleep stages are also assessed during the MSLT to determine if the patient enters into a sleep onset REM period (SOREMP) during any of the naps. An MSLT is indicated in all cases where narcolepsy is suspected as well as in instances where a physician is attempting to differentiate between narcolepsy and idiopathic hypersomnia. If other sleep disorders are suspected such as obstructive sleep apnea (OSA) or insomnia, an MSLT is not indicated until an overnight polysomnogram (PSG) has been conducted to rule out these potential causes of sleepiness [109].

Per ICSD-3 criteria, a mean sleep latency of ≤8 min and two or more SOREMPs are required to make the diagnosis of narcolepsy. As noted above, one of these SOREMPs may now be observed on the nocturnal PSG.

Maintenance of Wakefulness Test (MWT)

The MWT is a test that requires a patient to try to stay awake in a dimly lit room over a series of 40 min periods with no stimulation. There are typically four periods in a protocol and patients "fail" if their mean sleep latency is <8 min [109]. This test is used to assess wakefulness and can be useful to determine treatment efficacy of medications used to treat hypersomnia disorders. There are no normative data for children.

Case Vignette, Continued

You refer Andrew to a pediatric sleep lab for testing for a repeat sleep study and multiple sleep latency test. His MSLT takes place approximately 5 months from the time of symptom onset. On his overnight sleep study, he again is noted to have a short sleep onset latency (3 min), a nocturnal SOREMP, periodic limb movements (index 21/h), and five obstructive events in all, for a total apnea-hypopnea index not consistent with OSA. In total, he slept 560 min. On the multiple sleep latency test, his mean sleep latency was 0.5 min, and SOREMPs were noted in all five nap periods. The test results confirm Andrew's diagnosis of narcolepsy in light of his clinical context.

Management of Hypersomnia

Practice parameters for the treatment of narcolepsy and other hypersomnia conditions are available through the American Academy of Sleep Medicine [110] and the European Federation of Neurological Societies [111], but there is little research specifically looking at safety and efficacy of these treatments in children with hypersomnia conditions. Consequently, most medications for hypersomnia are not approved by the Federal Drug Administration (FDA) for children. The guideline recommendations for treatment of narcolepsy and idiopathic hypersomnia conditions are reviewed below.

Daytime Naps/Sleep Hygiene

One to three daytime naps can be very refreshing for people with narcolepsy coupled with sufficient, regular nocturnal sleep. Clinical experience suggests naps should be kept brief, lasting 15–30 min, so patients are easier to wake.

Wake-Promoting Agents

Modafinil is generally considered first-line therapy for treatment of EDS in adults but is not approved for pediatric use because of case reports of Stevens-Johnson syndrome [112]. Although it lacks FDA approval for use in pediatric populations, it is frequently used in practice with good efficacy in children [113]. A few case series and a small double-blinded trial have supported its efficacy in treatment of pediatric narcolepsy [10, 113–115]. Modafinil has also been used successfully for treatment of excessive daytime sleepiness with

minimal side effects in children with Prader-Willi syndrome [72]. Modafinil is a central stimulant of postsynaptic alpha-1 adrenergic receptors [116] thought to work through direct and indirect actions on the dopaminergic system as well as serotoninergic and gamma-aminobutyric acid (GABA) pathways [117]. Side effects include headaches, anxiety, nausea, and insomnia, particularly at the start of treatment. It is a cytochrome p450 inducer so can affect metabolism of other medications. Of note, young women on oral contraceptives must be cautioned that modafinil may reduce the efficacy of the oral contraceptive and additional birth control may be needed.

There are no dosage guidelines in children, but doses ranging from 50 to 400 mg/day, taken in one to two doses in the morning and then at midday, have been successfully used [10, 118]. The *S*-enantiomer of modafinil has a half-life of 3–5 h and the *R*-enantiomer, armodafinil, has a longer half-life of 10–14 h. No head-to-head clinical trials between modafinil and armodafinil have been conducted for the treatment of narcolepsy [119, 120].

Stimulants

Traditional stimulants (D,L-amphetamines and methylphenidate) are evidence-based therapeutic treatments for improving wakefulness and alertness in patients with narcolepsy types 1 and 2 [121, 122]. Stimulants work primarily by increasing monoaminergic neurotransmitters including dopamine, norepinephrine, and serotonin to promote wakefulness. While this increase in norepinephrine and serotonin may help cataplexy, the effect is generally insufficient to eliminate cataplexy. Methylphenidate dosing usually starts at 10 mg each morning and can be titrated up to 40–60 mg, divided into morning and midday doses. Extended release formulations are also available. Amphetamine salts are also used in pediatric populations for treatment of excessive daytime sleepiness with comparable efficacy, and dosing is similar to methylphenidate, but maximum recommended dosing is 40 mg/day [117].

The most frequent side effects of traditional stimulants are loss of appetite, nervousness, tics, headaches, and sleep-onset insomnia. Increased anxiety can occur with these compounds, especially among patients predisposed to mood disorders, but a mood disorder is not a contraindication to use stimulants. At high doses, stimulants may precipitate psychosis and suicidal ideation [82, 123], and close clinical monitoring of efficacy and adverse reactions is recommended. Children who are prescribed these medications should be monitored with regard to blood pressure and weight.

Drug addiction is a common concern of parents with children who have narcolepsy and take stimulants. Reassuringly, one study has shown that patients with narcolepsy being treated with a stimulant had no significant differences in risk taking behaviors compared to patients not undergoing stimulant treatment [124].

Anti-cataplexy Medications

Tricyclic antidepressants (TCAs) were traditionally used for treatment of childhood cataplexy, but now selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and serotonin and selective norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine are more commonly used [19]. They are usually considered second-line treatment for cataplexy in adults [117]. Venlafaxine has also been successfully used for treatment of hypnagogic hallucinations and cataplexy in children [125, 126]. Venlafaxine has some adrenergic reuptake inhibition that may make it a slightly more alerting drug compared to standard serotonin reuptake inhibitors. Generally, however, this effect is insufficient to control daytime hypersomnia. Increased suicidal ideations have been reported with SSRI and SNRI use, and it is important to monitor mood and concerns of self-harm if used.

Atomoxetine, a norepinephrine reuptake inhibitor which has been used in treatment of ADHD symptoms, can also be considered for treatment of cataplexy in children, although efficacy and safety data are not yet established.

Sodium Oxybate

Sodium oxybate is efficacious for the treatment of cataplexy, EDS, and nocturnal sleep disruption in patients with narcolepsy [99, 114, 127] and is FDA approved for the treatment of adults with narcolepsy type 1 [114]. Its efficacy in children with narcolepsy has been shown in a number of studies for treatment of cataplexy and EDS [114, 127]. The FDA recently approved an indication for its use in children with narcolepsy 7–17 years old. The exact mechanism of how sodium oxybate works is unclear, but it stimulates GABA-B receptors, increasing slow-wave sleep [117]. Treatment is initiated with 2.25 g in two doses taken at night given 2–4 h apart and increased weekly up to maximal dosing of 4.5 g twice nightly or clinical effect.

Side effects of sodium oxybate can be more significant than those experienced with stimulants and include weight loss, dizziness, increased anxiety, hallucinations, and delusions. Of most concern, sodium oxybate can trigger sleep-disordered breathing and hypoventilation and could cause respiratory depression if mixed with alcohol. Hypernatremia-related side effects also need to be monitored. Training and registration processes are required of a provider prior to their prescribing sodium oxybate (Table 8.1).

Table 8.1 Commonly used medications for treatment of narcolepsy symptoms

Drug	Symptoms treated	Commonly used doses	Common side effects
Methylphenidate (IR, ER)	Excessive daytime sleepiness	10–60 mg divided into morning and midday doses	Loss of appetite, nervousness, tics, headaches, and sleep-onset insomnia. Monitor growth
D or L amphetamine (IR, ER)	Excessive daytime sleepiness	10–40 mg/day	Anxiety, depression, psychosis, and suicidal ideations
Modafinil	Excessive daytime sleepiness	100–400 mg/day taken in one to two doses in the morning and at midday	Headaches, anxiety, nausea, and insomnia. Possible Stevens- Johnsons syndrome
Armodafinil	Excessive daytime sleepiness	50–250 mg	Same as modafinil
Sodium oxybate	Excessive daytime sleepiness, nocturnal sleep disturbance, and cataplexy	2–9 g divided in two doses given at bedtime 2–4 h apart	Weight loss, sleep-disordered breathing and hypoventilation, increased anxiety, hallucinations, delusions. Can cause respiratory depression if mixed with alcohol
Protriptyline (TCAs)	Cataplexy	5–10 mg BID/TID	Dry mouth, mood changes, sleep disturbance, potential for QT prolongation, serotonin syndrome
Fluoxetine, paroxetine (SSRIs)	Cataplexy	Fluoxetine 10–40 mg	Sexual dysfunction, mood changes, sleep disturbances. Potential for prolonged QT cardiac interval and serotonin syndrome
Venlafaxine	Cataplexy	37.5–150 mg	Weight gain, mood changes, potential for prolonged QT interval and serotonin syndrome

ER extended release, *IR* immediate release.
Modified from [117, 128]

Back to Vignette: Treatment for Case

His school provided a 504 plan for Andrew to offer accommodations for his diagnosis of narcolepsy type 2. He has the option of taking a 30-min nap in the late morning and after lunch in the school nurse's office. With naps, he is more alert during the day and able to better participate in class and complete homework. He has started higher doses of stimulants (methylphenidate ER 27 mg each morning) for management of daytime sleepiness and ADHD symptoms. Mother reports improved alertness and academic functioning.

Future Directions

Treatment for narcolepsy and other disorders of hypersomnia in adults has been well studied [129], but there is a significant lack of placebo-controlled studies as to the safety and efficacy of these treatments in pediatric populations. Currently there are no evidence-based treatment guidelines for management of narcolepsy or hypersomnia symptoms specific to children, and most treatment recommendations are based on data from adult studies [117]. Several studies evaluating the safety and efficacy of methylphenidate and other stimulants in treating children and adolescents with ADHD exist [48], but there is limited data on their usefulness in treating hypersomnia. Considering that patients with primary hypersomnia conditions are dependent on lifelong medications, longitudinal studies assessing factors such as efficacy, tolerance, cardiovascular outcomes, and growth are needed [117, 129].

The MSLT is standard for assessing sleepiness in patients suspected of having hypersomnia disorders [109]. However, MSLT alone cannot confirm a diagnosis of hypersomnia or narcolepsy, as it must be evaluated in the context of the patient's history. A positive MSLT can be the result of other factors such as delayed sleep phase or insufficient sleep [109, 129, 130]. Future research may be directed to more biological assessments of sleepiness that would produce biomarkers that distinguish narcolepsy from other conditions that produce EDS.

Conclusions and Recommendations

EDS can result in executive functioning problems and behavioral difficulties. It is important to question parents about a child's sleep habits and symptoms of daytime sleepiness when assessing for conditions such as ADHD or problematic behaviors. Because sleepiness is often seen in conjunction with externalizing and internalizing behaviors such hyperactivity, inattention, and emotional dysregulation, disorders of hypersomnia including narcolepsy are often misdiagnosed as primary ADHD [16]. Office-based tools including the Pediatric Daytime Sleepiness Scale and the Epworth Sleepiness Scale can be useful in evaluating a patient's subjective feelings of sleepiness. These assessments can help

determine if the sleepiness is a factor and should prompt further query about typical sleep duration and quality and symptoms of other primary sleep disorders.

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