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ABSTRACT

Narcolepsy is mainly associated with excessive daytime sleepiness, but the characteristic feature is abnormal rapid eye movement (REM) sleep phenomena. REM sleep disturbances can manifest as cataplexy (in narcolepsy type 1), sleep paralysis, sleep-related hallucinations, REM sleep behavior disorder, abnormal dreams, polysomnographic evidence of REM sleep disruption with sleep-onset REM periods, and fragmented REM sleep. Characterization of REM sleep and related symptoms facilitates the differentiation of narcolepsy from other central hypersomnolence disorders and aids in distinguishing between narcolepsy types 1 and 2. A circuit comprising regions within the brainstem, forebrain, and hypothalamus is involved in generating and regulating REM sleep, which is influenced by changes in monoamines, acetylcholine, and neuropeptides. REM sleep is associated with brainstem functions, including autonomic control, and REM sleep disturbances may be associated with increased cardiovascular risk. Medications used to treat narcolepsy (and REM-related symptoms of narcolepsy) include stimulants/wake-promoting agents, pitolisant, oxybates, and antidepressants; hypocretin agonists are a potential new class of therapeutics. The role of REM sleep disturbances in narcolepsy remains an area of active research in pathophysiology, symptom management, and treatment. This review summarizes the current understanding of the role of REM sleep and its dysfunction in narcolepsy.

1. Introduction

Narcolepsy is a chronic, orphan, neurologic disorder characterized by excessive daytime sleepiness (EDS) and abnormal rapid eye movement (REM) sleep phenomena, especially cataplexy in narcolepsy type 1 (NT1); many patients exhibit other symptoms related to impaired REM sleep, including sleep-related hallucinations (SRH), sleep paralysis (SP), and abnormal dreams, but also disrupted nighttime sleep [1,2]. Symptom onset typically occurs between 10 and 25 years of age, peaking at approximately 15 years of age; however, narcolepsy can develop from infancy to old age [3,4]. Although EDS commonly presents first, cataplexy and other symptoms can emerge in different order or time spans [5]. Limited awareness among physicians about narcolepsy and its symptoms, and attribution of symptoms to other diseases or comorbidities, contributes to diagnostic delays of 8 years or more [3,4].

Current diagnostic guidelines have relied heavily on electrophysiological signatures of REM sleep initiation, contributing to a multiple sleep latency test (MSLT) false negative rate over 20 % in diagnosing narcolepsy (especially for older patients) [6,7]. Many patients do not meet strict electrophysiological criteria, despite clinical evidence of REM sleep disruption and presence of other characteristics strongly associated with narcolepsy (eg, low cerebrospinal fluid [CSF] hypocretin levels; HLA-DQB1*06:02 positivity) [6]. Additionally, abnormalities on objective sleep testing occur in healthy people under circumstances like shift work, antidepressant intake, or sleep deprivation [8], potentially leading to misdiagnosis of narcolepsy (ie, false positives). Consensus is growing that diagnostic accuracy for narcolepsy is hindered by over-reliance on testing methods with unacceptably low reproducibility, and under-reliance on clinical symptom presentation [9].

A variety of REM sleep-related abnormalities are observed in people with narcolepsy (Fig. 1) and animal models (Fig. S1 [10]), including sleep-onset REM periods (SOREMPs). REM sleep-related abnormalities are also evident clinically as cataplexy (in animal models and humans with NT1), SRH (particularly hypnagogic hallucinations), SP, other symptoms believed to represent intrusion of REM sleep into wake (eg, REM muscle atonia or muscle fasciculations), and unusual dreams [2,11].

Increased understanding of REM sleep abnormalities in narcolepsy, including those evidenced as clinical symptoms, may enable improved

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Abbreviations

ASM	American Academy of Sleep Medicine
BP	blood pressure
CeA	central amygdala
CSF	cerebrospinal fluid
DR	dorsal raphe
EDS	excessive daytime sleepiness
EEG	electroencephalogram
GABA	γ-aminobutyric acid
GHB	γ-hydroxybutyrate
GPCR	G protein-coupled receptor
$Hcrt_1R$ (OX_1R)	hypocretin (orexin) receptor type 1
$Hcrt_2R$ (OX_2R)	hypocretin (orexin) receptor type 2
HR	heart rate
ICSD	*International Classification of Sleep Disorders*
ICSD-3	*International Classification of Sleep Disorders – Third Edition*
LC	locus coeruleus
LH	lateral hypothalamus
LPT	lateral pontine tegmentum
MM	medial medulla
mPFC	medial prefrontal cortex
mRNA	messenger ribonucleic acid
MSLT	multiple sleep latency test
NE	norepinephrine
NREM	non–rapid eye movement
NSS	narcolepsy severity scale
NT1	narcolepsy type 1
NT2	narcolepsy type 2
PPT	pedunculopontine nucleus
PSG	polysomnography
RBD	rapid eye movement sleep behavior disorder
REM	rapid eye movement
RSWA	rapid eye movement sleep without atonia
SLD	sublaterodorsal tegmental nucleus
SOREMP	sleep-onset rapid eye movement period
SP	sleep paralysis
SRH	sleep-related hallucinations
SubC	subcoeruleus
SXB	sodium oxybate
TMN	tuberomammillary nucleus
vlPAG	ventrolateral periaqueductal gray
VLPO	ventrolateral preoptic area

diagnostic criteria and potentially impact classification of narcolepsy and other sleep disorders [12]. This review describes the role of REM sleep in the clinical features and pathophysiology of narcolepsy, as well as the effects of medications on REM sleep-related symptoms.

2. Literature search

This review focuses on publications from the last 10 years, but necessarily includes older articles encompassing animal and human data. To identify literature data on the clinical features of narcolepsy, PubMed search strings contained narcolepsy AND [REM, cataplexy, hallucination, dream, or "sleep paralysis"]. REM sleep-related topics not specific to narcolepsy were identified by targeted searches. Articles describing the effects of narcolepsy medication on REM sleep and the clinical features of narcolepsy were located by searches for narcolepsy AND [medications or their classes].

3. REM sleep in animals and humans

Healthy controls typically have 4 to 6 non-REM (NREM)–REM sleep cycles throughout the night, which increase in duration from approximately 70−100 min to approximately 90–120 min. The duration of REM sleep episodes increases during each cycle (Fig. 1) [13]. Beyond rapid eye movements, REM sleep is characterized by reduction in

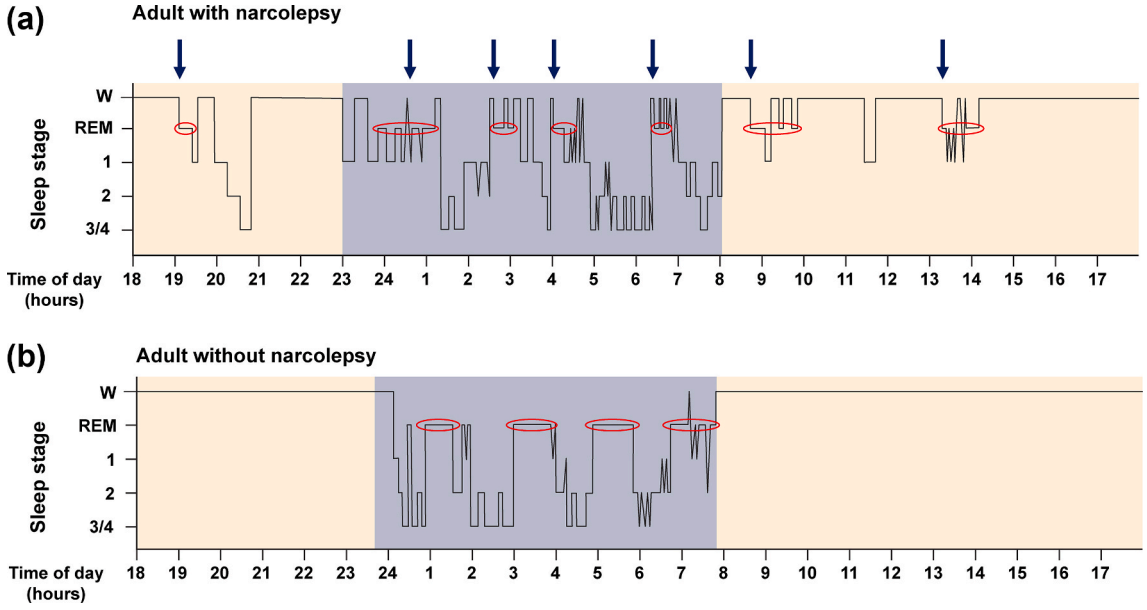

Fig. 1. Representative 24-h hypnograms for sleep in adults with and without narcolepsy
Red circles indicate REM episodes, which are shorter, fragmented, and occur during waking hours in narcolepsy. Blue arrows indicate SOREMPs. Yellow shading indicates day. Blue shading indicates night.
1, stage 1 sleep; 2, stage 2 sleep; 3/4, stage 3/4 sleep (slow-wave sleep); REM, rapid eye movement; SOREMP, sleep-onset REM period; W, wake. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

electroencephalogram (EEG) amplitude, autonomic changes related to heart rate (HR) and blood pressure (BP), and muscle atonia [14–17]. Dreaming often occurs during REM sleep, but also during NREM sleep [18]; dreams during REM sleep are reported as more vivid and of longer duration than dreams during NREM sleep [19].

REM sleep occurs in many mammals, excluding those with unihemispheric "sleep," including cetaceans [20]. Fur seals, which spend most of their life in the sea, show almost no REM sleep for consecutive days or weeks while in the water [21]. After this prolonged, near-complete elimination of REM sleep, they display minimal or no REM sleep rebound upon returning to baseline conditions on land [20,21]. In placental mammals, durations of REM and NREM sleep are significantly correlated with each other [22]. The amount of REM sleep is inversely correlated to core body temperature across homeotherm orders [22]. Thus, "primitive" egg-laying mammals, like the echidna and platypus, have body temperatures of 31 °C and REM durations averaging 7.5 h/day [22]. Marsupial mammals have core temperatures of 35 °C and average REM durations of 4.4 h/day. Placental mammals (including humans) have body temperatures of about 37 °C and average 2 h of REM sleep/day; birds have body temperatures of 41 °C and 0.7 h/day of REM sleep. Mammals with experimentally disconnected forebrain and midbrain do not thermoregulate, and when body temperature is reduced, experience increased amounts of REM sleep. Therefore, although difficult to determine experimentally, it is plausible that REM sleep evolved to maintain brain temperature and metabolism, which are reduced in NREM sleep, thereby preserving brainstem function for awakening [22]. In humans with narcolepsy (primarily NT1), there are conflicting findings related to overall and diurnal variation in core body temperature, and timing of core body temperature fluctuations relative to onset of sleep or REM sleep, compared with controls [23–27]; however, studies have consistently shown an altered diurnal skin temperature profile [23–27]. In people with NT1, artificial modulation (normalization) of core body and skin temperature (via hot/cold food and drinks and thermosuit) was associated with improved vigilance and sleepiness [28,29], and narcolepsy treatment (sodium oxybate) was associated with normalization of core body and skin temperature profile [30].

Human infants, who sleep approximately 16–18 h/day, experience large amounts of both REM sleep and SOREMPs. REM accounts for approximately 50 % of their sleep time, decreasing to approximately 20 %–25 % by early childhood [27,29]. The percentage of time spent in REM sleep again increases from childhood to adolescence, but then decreases throughout adulthood by approximately 0.6 % per decade [31]. Total sleep time also typically decreases with age [32,33], but the percentage of time spent in N1/N2 sleep increases with age. In healthy adults, REM sleep accounts for approximately 20 % of sleep, with a latency of approximately 94 min; both the percentage and duration of REM sleep decrease with age [33]. Older adults (≥60 years of age) experience 4 % less REM sleep than younger adults, a difference that could complicate diagnosis if not considered [33,34].

REM sleep and BP are related. Normal BP oscillates from higher morning and daytime values to lower nocturnal values. Arterial BP generally decreases during NREM sleep relative to wake and increases during REM sleep relative to NREM [33]. Sleep state–dependent modulation of arterial BP is related to integration of cardiovascular reflexes and central autonomic control of vasoconstrictor tone [35]. Sleep deprivation may elevate BP in healthy individuals. A systematic review found reports of generally increased BP differences on the night of sleep deprivation, on the day following sleep deprivation, or both, as well as some reports of no differences [36]. Another study showed that differences in BP did not vary during wakefulness, suggesting that changes in BP associated with sleep deprivation may manifest primarily during sleep [37]. At night, BP typically declines ≥10 %, termed "dipping" [37]. Environmental (eg, auditory and vibratory) stimuli increase BP during NREM and, to a lesser extent, REM sleep [14]. Diastolic BP non-dipping is associated with lesser amounts of REM sleep (as a percent of total sleep) in healthy people and those with NT1 [15,16].

3.1. Neurobiology and pathways of REM sleep generation

An intricate system of pathways and neurotransmitters (including γ-aminobutyric acid [GABA], dopamine, norepinephrine, histamine, hypocretin, acetylcholine, and serotonin) is responsible for the initiation and maintenance of, and transitions between, wakefulness, REM sleep, and NREM sleep (Fig. 2). Briefly, it was hypothesized approximately 30 years ago that wakefulness and REM sleep are regulated by reciprocal interactions between mesopontine cholinergic and monoaminergic neurons; however, it is now believed that non-cholinergic and non-monoaminergic REM-off and REM-on regions also contribute by forming a "flip-flop" wake–REM sleep switch [38]. The excitatory hypocretin system in the posterior hypothalamus provides input throughout the brain [39]. These topics, and others such as the influence of circadian rhythm on REM sleep, are discussed in detail in the Table S1 and Fig. S1. Loss of hypocretin innervation contributes to aberrant timing of REM sleep and resulting clinical features that contribute to NT1 and its diagnosis [11].

4. Narcolepsy

4.1. Electrophysiological measurement of REM sleep

In a meta-analysis, mean REM latency was 31.4 min after sleep onset in 1008 patients with narcolepsy (NT1 and narcolepsy type 2 [NT2]) and 93.6 min in 902 healthy controls [34]. Patients with narcolepsy have high sleep instability compared with healthy controls, with more transitions between states (eg, REM–wake, mean [SD] 30.9 [15.4] vs 13.9 [8.2] for NT1 and healthy controls, respectively) [40]. Accordingly, hypocretin deficiency (ie, ≤110 pg/mL) in the CSF is associated with significantly higher overall transitions between sleep stages and, in particular, transitions between wake–REM in patients with hypersomnolence [41]. A REM latency of ≤15 min has high specificity (82.2 %–99.6 %) for predicting hypocretin deficiency, although sensitivity is low (35.7 %–57.4 %), in patients with NT1 [42]. Further, hypocretin deficiency (ie, ≤110 pg/mL) in the CSF was associated with higher numbers of wake bouts (43.0 vs 25.0, $P < 0.0001$), sleep bouts (43.0 vs 25.5, $P < 0.0001$), and REM sleep–wake transitions (8.0 vs 5.0, $P < 0.0001$) compared with hypocretin concentrations that were not deficient in patients with hypersomnolence [41].

Tools including polysomnography (PSG) and MSLT are widely used to assess REM sleep and for diagnosis of narcolepsy and other sleep disorders; however, they must be interpreted carefully to produce reliable narcolepsy diagnoses. PSG is typically performed over a single night to rule out other sleep disorders and identify irregularities in sleep stage timing and progression during nocturnal sleep, including a SOREMP (defined as a REM sleep period occurring within 15 min of sleep onset). An MSLT the next day measures sleep onset latency and SOREMPs during naps in a sleep laboratory setting [43,44]. A five-nap MSLT is typical, but a four-nap MSLT can be used if >1 SOREMP occurs in the first four naps, or if mean sleep latency is <5 min or >10 min after the first four naps [45]. Extended PSG protocols may better characterize sleep patterns [46,47], and refining cutoff values for MSLT parameters has resulted in more specific and sensitive identification of narcolepsy. For example, hypocretin deficiency can be identified in patients with hypersomnolence using a mean REM sleep duration on the MSLT of

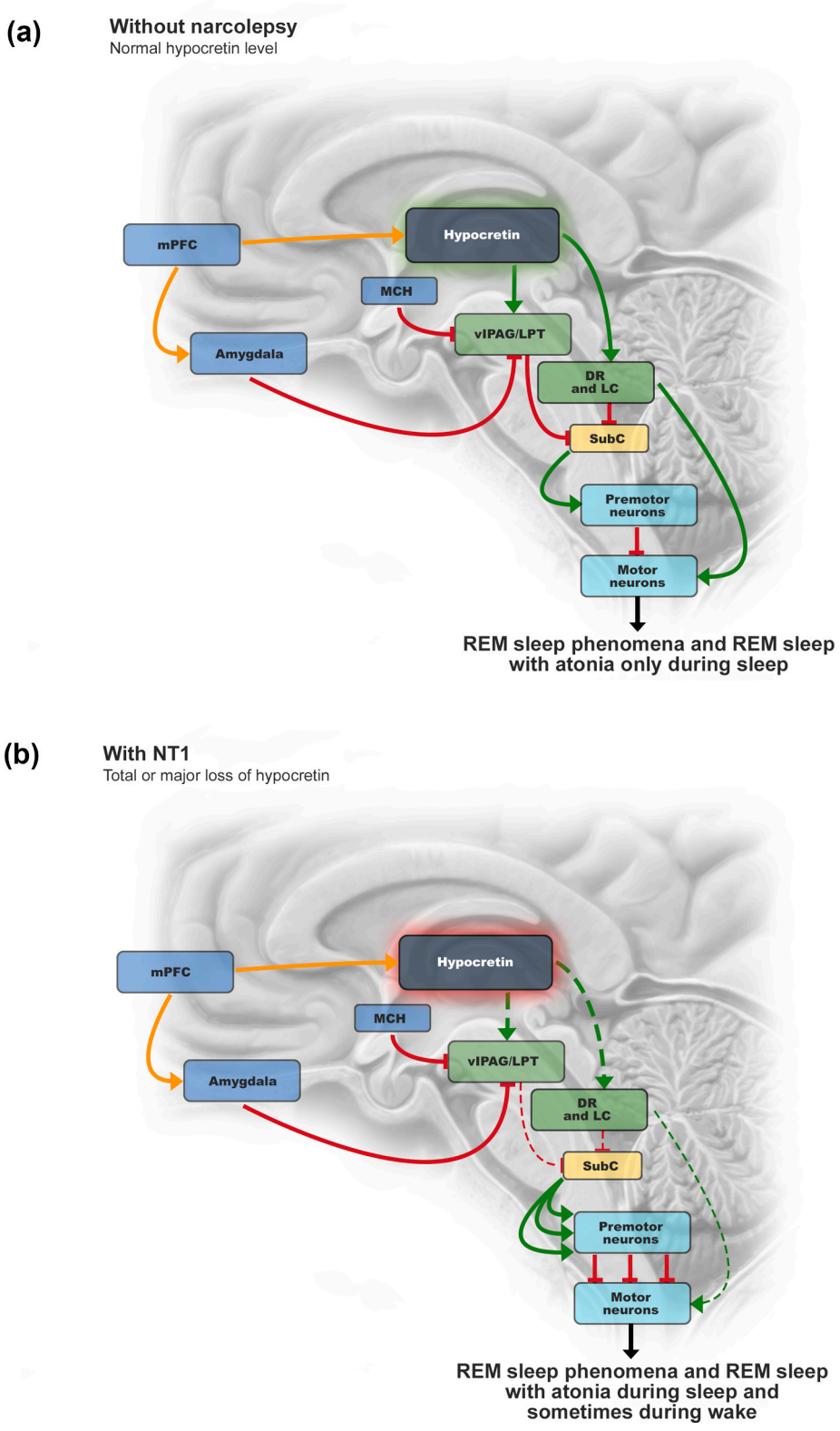

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Fig. 2. Neurobiological pathways underlying REM-related clinical features in humans without (A) or with (B) narcolepsy type 1
Model of circuits controlling cataplexy in the human brain. Activation during wakefulness of neural circuits involved in REM sleep paralysis is thought to underlie cataplexy. In REM sleep, muscle tone is suppressed by inhibition of LC neurons, which maintain muscle tone in waking by releasing norepinephrine onto motoneurons. In waking, LC activity is maintained by hypocretin neurons which are maximally active during positive emotions and which excite the LC. In the absence of hypocretin, as occurs in NT1, LC activity is unstable in waking. MCH neurons act in opposition to hypocretin neurons. Emotional stimuli result in activation of amygdalar neurons via the mPFC, and subsequent disinhibition of the SubC. A second pathway begins below (ventral to) the LC: the SubC. This pathway projects to the medial medulla, where it excites neurons containing GABA and glycine which project to and inhibit motoneurons. Together this combination of disfacilitation and inhibition is responsible for both the suppression of muscle tone in REM sleep and the loss of muscle tone in waking in NT1; the phenomenon is called cataplexy. The pathophysiology of NT2 is unclear, as hypocretin levels may be intermediate or normal, and normal function of the pathways may be partially preserved, leading to impaired REM but not cataplexy. Green lines ending with arrows indicate downstream activation, red lines ending with rectangular blocks indicate inhibition, and orange lines ending with arrows indicate activation due to emotional stimuli. Thick solid lines indicate normal function, thin lines indicate weakened function, and dashed thin lines indicate absent function.
DR, dorsal raphe; GABA, γ-aminobutyric acid; LC, locus coeruleus; MCH, melanin-concentrating hormone; mPFC, medial prefrontal cortex; NT1, narcolepsy type 1; NT2, narcolepsy type 2; REM, rapid eye movement; SubC, subcoeruleus, also called SLD, sublaterodorsal tegmental nucleus; vlPAG/LPT, ventrolateral periaqueductal gray/lateral pontine tegmentum (including the laterodorsal tegmental nucleus). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

≥4.1 min, and in patients with narcolepsy, a cutoff of ≥5.7 min [12]. In patients with hypersomnolence and cataplexy, having ≥1 direct REM sleep transition episode (ie, an abrupt transition from wake to REM, unlike SOREMPs which occur within 15 min of sleep onset and may be preceded by NREM sleep) during MSLT enhanced identification of hypocretin deficiency [12].

4.2. Diagnostic criteria

The standard for diagnosing narcolepsy has evolved over time. Earlier editions of the *International Classification of Sleep Disorders* (ICSD) relied heavily on clinical REM sleep features of narcolepsy. The third edition (ICSD-3), published in 2014, emphasized PSG and MSLT results in addition to clinical criteria [48]. ICSD-3 diagnostic criteria for NT1 and NT2 included daily periods of irrepressible need to sleep or daytime lapses into sleep and mean sleep latency ≤8 min and ≥2 SOREMPs on MSLT. A SOREMP detected on the preceding nocturnal PSG could replace one of the SOREMPs on the MSLT. Diagnosis of NT1 additionally required evidence of cataplexy and/or CSF hypocretin concentration ≤110 pg/mL (or <1/3 of the mean of normal subjects) [43,44]. The 2023 ICSD-3 *Text Revision* update changed NT1 diagnostic criteria related to the MSLT and SOREMPs. Cataplexy with mean sleep latency ≤8 min and ≥2 SOREMPs remains a valid criterion; however, cataplexy and a single SOREMP during the nocturnal PSG is now an independently sufficient criterion [2]. NT1 without cataplexy is uncommon and may be associated with subtle cataplexy that is not readily apparent [2]. For diagnosis of NT2, cataplexy must be absent and CSF hypocretin concentration (if measured) must be >110 pg/mL (or >1/3 of the mean of normal subjects) [2]. Additional symptoms (disrupted nighttime sleep, SRH, SP, and abnormal dreams) are supportive features for both types of narcolepsy [2]. The narcolepsy severity scale (NSS) and narcolepsy severity scale-2 (NSS-2) can be useful for quantifying the main symptoms and overall disease burden of NT1 and NT2, respectively [49–51].

4.3. Pathophysiology

NT1 is characterized by hypocretin deficiency, with selective loss of approximately 85 %–95 % of hypothalamic hypocretin-producing neurons and associated reductions in CSF hypocretin levels [2,52]. CSF hypocretin ≤110 pg/mL has high specificity (98 %) but not sensitivity (60 %) for NT1 [53]. Rarely, patients with narcolepsy with typical cataplexy have intermediate levels of CSF hypocretin (111–200 pg/mL) [54]. In NT2, CSF hypocretin levels are typically normal; there are limited data on hypocretin cell populations [2]. One postmortem study of brains from two patients with NT2 showed reduced hypothalamic hypocretin cells, but further studies are needed [55]. NT2 may have a different underlying pathophysiology than NT1, or it might represent an intermediate form of narcolepsy with partial hypocretin deficiency or potentially stem from autoimmune responses [56]. Considerable evidence suggests that NT1 has an autoimmune component. The HLA-DQB1*06:02 allele is more prevalent in people with NT1 (generally >95 %) [57–59] than NT2 (approximately 40 %–50 %) [58,59]. One large study showed that NT1 is not associated with increased risk of comorbid immune disorders, in favor of a potentially unique pathophysiology [60]. Autoimmunity is also suggested by the finding of autoreactive $CD4^+$ and $CD8^+$ (anti-hypocretin) T cells in people with NT1. Additionally, increased incidence of narcolepsy (and increased proportion of NT1 vs NT2 among total narcolepsy cases) in China after the H1N1 influenza pandemic [61,62] and increased incidence of NT1 following Pandemrix vaccination against H1N1 in Europe potentially implicate the immune system in the development of the disease [63,64]. This autoimmune hypothesis warrants further exploration.

Hypocretins (orexins) act primarily as excitatory neurotransmitters and are involved in regulating a variety of functions, including sleep and arousal [65]. Loss of hypocretin signaling may destabilize separation of the sleep and wake states [66,67]. The mechanisms by which hypocretin receptors affect sleep and cataplexy, and any synergistic or complementary effects between them, are not fully understood. REM sleep disturbances without loss of hypocretin may occur for a variety of causes; however, such disorders are beyond the scope of this review [11].

Histamine is a wake-promoting monoaminergic neurotransmitter that plays a role in sleep–wake regulation [68–70]. Histamine is released from neurons in the tuberomammillary nucleus, which has excitatory projections throughout the brain. Histamine cells are active during wakefulness, but much less so during REM or NREM sleep; this population is increased by up to 94 % in people with narcolepsy [71,72].

The neurobiological basis of cataplexy is not fully understood. Most cataplexy attacks immediately follow feelings of strong, positive emotions, suggesting a role for the amygdala [73,74], and neuroimaging studies have demonstrated similar patterns of activation during cataplexy and REM sleep [75,76]; specifically, the pathways that produce sleep paralysis may underlie cataplexy.

5. Clinical REM sleep dysfunction in narcolepsy

Some narcolepsy symptoms (Table S1) may result from intrusion of REM sleep into wake, such as SRH, inappropriately timed REM atonia (cataplexy), or SP [11]. Although these phenomena are nonspecific to narcolepsy (with the exception of cataplexy, which is pathognomonic of NT1) and occur in the general population, particularly in people with psychiatric disorders, they are more frequent in narcolepsy [8,77,78].

5.1. Disrupted nighttime sleep

Disrupted nighttime sleep in narcolepsy (NT1 or NT2) is reported by patients as frequent awakenings, early morning awakening, or sometimes unrefreshing sleep, and can be confirmed by objective measures like actigraphy or PSG [79]. PSG can assess reduced total sleep time,

increased time awake after sleep onset and number of awakenings and arousals, reduced sleep efficiency, and frequent sleep stage transitions. In a study of drug-free patients with NT1, more severe self-reported disrupted nighttime sleep was associated with increased SOREMPs, lower sleep efficiency, longer wake after sleep onset, and more numerous sleep stage transitions [80].

A study of drug-free patients with hypersomnolence found that hypocretin has a stabilizing effect on nocturnal sleep, with increased number of sleep–wake transitions in hypocretin-deficient participants. Post hoc analyses also revealed a robust dose-response effect of CSF hypocretin levels [41,80]. In patients with NT1, extremely low CSF hypocretin levels (<30 pg/mL) were associated with more fragmented sleep as assessed by actigraphy, compared with CSF hypocretin levels ≥30 to <110 pg/mL [81].

5.2. Cataplexy

Cataplexy is thought to arise from intrusion of REM sleep atonia into wakefulness; it primarily affects facial and neck muscles, sparing diaphragm and extraocular muscles as in REM sleep [59,82]. Cataplexy can also be complete, with whole body atonia that can cause falls, but this is infrequent; partial attacks, where one or more limbs or the head and neck are involved, are more common [59]. Cataplexy affects most people with NT1 but, by definition, does not occur in NT2 [2]. Cataplexy attacks can be very heterogeneous, affecting different muscle groupings, lasting for short or long durations (typically seconds to 1–2 min), and occurring multiple times daily or somewhat infrequently (usually at least once per month).

5.3. REM sleep behavior disorder

REM sleep behavior disorder (RBD) is characterized by the absence of normal muscle atonia during REM sleep (also called REM sleep without atonia [RSWA]), which allows for muscle movement during REM sleep, and can result in acting out of dreams [2]. RSWA is common in NT1 and may be a reliable biomarker for that disorder, in fact occurring during a greater percentage of sleep in individuals with narcolepsy compared with RBD [83]. In an unreplicated study of participants with narcolepsy (NT1 and NT2), the duration of REM sleep was significantly and positively correlated with RSWA based on chin and leg electromyography [84]. The prevalence (95 % confidence interval) of diagnosed RBD in the general population is 0.68 % (0.38, 1.05), and probable RBD is 5.65 % (4.29, 7.18) [85]. RBD affects approximately 30 %–60 % of patients with NT1 but is also seen in patients with NT2 [86,87]; the estimated prevalence may vary by method of determination (eg, video-PSG vs questionnaires or clinical interviews) [88]. The frequency of RBD is independent of the frequency of cataplexy [89]; however, hypocretin deficiency independently predicted risk of RBD (diagnosed by semi-structured interviews) in patients with narcolepsy (NT1 or NT2) [90].

5.4. Abnormal dreaming

Dreaming is also dramatically affected in narcolepsy. Patients with NT1 and NT2 dream more often and vividly, and report bizarre dreams and more frequent nightmares, and dreams that are recurrent, enchained (wherein the same dream can be resumed after an extended period of waking), and lucid, compared with people without narcolepsy. These dreams can include reports of out-of-body experiences and flying [90–92]. Patients with NT1 and NT2 also are better able to recall their dreams [93]. In one study, nightmares occurred in approximately one-third of patients with either NT1 or NT2, although non-negatively charged but vivid dreams were more frequent in NT1 [91]. In another study, patients with narcolepsy (NT1 or NT2) reported mean (standard error of the mean) frequency of lucid dreams of 6.9 (1.0) per month, compared with 0.7 (0.1) in controls; interestingly, 33 % of patients reported they were able to achieve relief from nightmares through lucid dreaming [94]. A dream study showed that dreams of flying occurred in 67 % of patients with NT1, compared with 15 % of controls ($P < 0.001$) [95]. Emotions experienced by patients with NT1 during SOREMPs were more common and intense than during nighttime REM sleep [92]. Dream delusions, in which dreams are mistaken for reality, were far more prevalent in patients with NT1 compared with controls (83 % vs 15 %, respectively) [93]. Patients with NT1 or NT2 who also had RBD were significantly more likely to have nightmares compared with those without RBD [93].

5.5. Sleep-related hallucinations

SRH are typically visual but can be auditory perceptions that occur while falling asleep (hypnagogic) or awakening (hypnopompic) [96,97]. They can occur in nocturnal sleep, daytime naps, or when there is strong REM sleep pressure while awake [97]. Because REM sleep is normally less likely to occur at nocturnal sleep onset, hypnagogic hallucinations are more diagnostic of narcolepsy than hypnopompic hallucinations [43,97]. The frequency and intensity of hypnagogic hallucinations can be assessed with the NSS and NSS-2 [50,51]. SRH are common in narcolepsy, although less common in NT2 compared with NT1. One study reported significantly more hypnagogic hallucinations in patients with NT1 compared with NT2 (61.1 % vs 29.4 %; $P < 0.05$) [90], and a retrospective analysis reported SRH in 54 % and 23 % of participants with NT1 and NT2, respectively [98]; in a study using the NSS-2, SRH were reported by 39.5 % of untreated patients with NT2 [51]. Similarly, SRH were reported by 80.0 % and 53.5 % of drug-free and treated participants with NT1, respectively [50]. Another study found that SRH were more frequent in NT1 (mean [SD] of 10 [13] per month) than in NT2 (mean [SD], 3 [5] per month) [99]. In a study of Japanese patients with narcolepsy (type unspecified; $N = 170$), hypnagogic hallucinations were highly variable, occurring as infrequently as once or twice per year or as frequently as every day [100].

5.6. Sleep paralysis

SP is experienced by patients with narcolepsy (NT1 or NT2), including most patients with NT1 [2,101], and can occur at sleep onset or persist for several minutes after waking, in both nocturnal sleep and daytime naps [11,97,102]. SP was reported by 58.7 %–72.7 % and 36.4 %–44.1 % of drug-free and treated participants with NT1, respectively. Because REM sleep is normally less likely to occur at nocturnal sleep onset than upon awakening, SP at the beginning of the night is more suggestive of a diagnosis of narcolepsy [49,50]. Frequency and severity of SP can be assessed with the NSS and NSS-2 [50,51].

5.7. Associations with autonomic dysfunction

Blunted nocturnal BP dipping, which is common in NT1 [16] and associated with increased risk of cardiovascular mortality in the general population, regardless of 24-h BP [103], is correlated with REM sleep percentage, number of SOREMPs, and mean sleep latency on MSLT. The association of blunted nocturnal dipping with NT1 suggests that hypocretin deficiency may play a role in the elevated cardiovascular risk seen in NT1 (evidenced by increased rates of cardiovascular disease, stroke, atrial fibrillation, myocardial infarction, cardiac arrest, heart failure, and major adverse cardiac event [MACE] in people with versus without narcolepsy in medical claims data analyses) [16]. Heart rates are also highly variable in NT1 [104]. Indeed, the hypothalamus and nucleus of the solitary tract receive dense projections from the hypocretin system; thus, disruptions to hypocretin signaling to hypothalamic structures that impact autonomic function may underlie the cardiovascular abnormalities observed in NT1 [39]. Other autonomic issues, such as thermoregulatory (eg, cold or heat intolerance) and gastrointestinal (eg, constipation) complaints, are also more prevalent in patients with NT1

than in controls [39].

6. Changes in REM sleep and related symptoms with narcolepsy medications

Given the wide range of neurotransmitter systems involved in generation, maintenance, and abolition of REM sleep, it is unsurprising that medications that treat narcolepsy and its REM-related symptoms act on diverse neurotransmitter systems (Table 1). Although more than half of patients in one study who were taking medications for their narcolepsy (NT1) reported improvement in disrupted nighttime sleep, and sleepiness and sleep transitions were reduced [105], this likely depends on type of medication.

6.1. Oxybate

There is a relatively large amount of data on the effects of sodium oxybate (SXB; sodium oxybate oral solution; Xyrem®), a high-sodium salt of γ-hydroxybutyrate (GHB), on disrupted nighttime sleep [79,106–108]. The precise mechanism of action of SXB remains unclear; however, it is thought to act on $GABA_B$ receptors [109]. GHB has been shown to reduce the frequency of SRH and SP in patients with NT1 or NT2 [110,111]. In pivotal trials, SXB treatment had significant efficacy for EDS and cataplexy attacks, compared with placebo [112,113]. In

Table 1
Medications used to treat narcolepsy and their effects on REM-related narcolepsy symptoms.

Class	Treatment	Mechanism [97,160]	Effect on REM sleep	Effect on REM-related narcolepsy symptoms
Oxybate	High-sodium oxybate	$GABA_B$ actions at noradrenergic, dopaminergic, and thalamocortical neurons (hypothesized)	Reduced REM duration (80.5 vs 43.75 min after 8 weeks of treatment), percentage (mean [SD], %; 23.1 [7] vs 13.1 [6.5]), and stage transitions (−7.6 REM to N1/Wake shifts/hour after 8 weeks of treatment) [1,115,116,161,162]	Reduces cataplexy, SP, HH; may improve RBD [110,111,114,116,162,163]
	Low-sodium oxybate	$GABA_B$ actions at noradrenergic, dopaminergic, and thalamocortical neurons (hypothesized)	Unknown, but presumed similar to high-sodium oxybate because of same active moiety	Reduces cataplexy [102,120]
	Once-nightly high-sodium oxybate	$GABA_B$ actions at noradrenergic, dopaminergic, and thalamocortical neurons (hypothesized)	Reduced REM duration (76.7 vs 60.6 min after 3 weeks of treatment) [126]	Reduces cataplexy [126]
Wake-promoting agent	Modafinil	DAT inhibitor	No change on REM duration (78.75 vs 78.5 min after 8 weeks of treatment) [115]	Unknown
	Armodafinil	DAT inhibitor	No change on REM duration (78.75 vs 78.5 min after 8 weeks of treatment) [115]	
	Solriamfetol	DAT/NET-inhibitor	Unknown	Unknown
Pitolisant		H_3-receptor antagonist/inverse agonist	Unknown	Reduces cataplexy, HH, SP [129–131,134]
Alerting agent	Amphetamine salts	DAT-mediated inhibition of DA reuptake and increase in DA release; also (to a lesser extent) NET-mediated inhibition of NE reuptake, and inhibition of serotonin [109,160]	Unknown	Unknown
	Dextroamphetamine	DAT-mediated inhibition of DA reuptake and increase in DA release [160]	Unknown	May reduce cataplexy and SP [143]
	Methylphenidate	DAT inhibitor; inhibition of NE and serotonin reuptake (to a lesser extent) [109]	Unknown	Unknown
Antidepressant	Fluoxetine	SSRI	Reduced REM duration, fragmented REM sleep [68]	Reduces cataplexy; may reduce SP/HH; contributes to rebound cataplexy and potentially RBD [140,147–149,164–166]; may induce cataplexy rebound on withdrawal [148]
	Venlafaxine	SNRI	Reduced REM duration [68]	
	Atomoxetine	SNRI	Unknown	
	Reboxetine	SNRI	Increased REM latency (mean [SD] 39.4 [32.1] vs 108.1 [72.7] min) after 1 week of treatment [165]	
	Clomipramine	TCA	Initial reduction of REM sleep; gradual return of REM sleep [167]	
	Imipramine	TCA	Initial reduction of REM sleep; gradual return of REM sleep [167]	Reduces cataplexy; may reduce SP/HH; may induce cataplexy rebound on withdrawal; can cause sedation [148,149,168,169]
	Phenelzine	MAOI	Complete reduction or absence of REM sleep [151,168]	

DA, dopamine; DAT, dopamine transporter; EDS, excessive daytime sleepiness; GABA, γ-aminobutyric acid; HH, hypnagogic/hypnopompic hallucinations; MAOI, monoamine oxidase inhibitor; N1, non–rapid eye movement sleep stage 1; NE, norepinephrine; NET, norepinephrine transporter; RBD, REM sleep behavior disorder; REM, rapid eye movement; SD, standard deviation; SNRI, serotonin and norepinephrine reuptake inhibitor; SP, sleep paralysis; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

addition, SXB reduced the occurrence of SP but not SRH in patients with NT1; this reduction was observed only in participants taking a 6 g dose (4.5 g and 9 g were also tested), although low baseline symptom frequency may have contributed to the apparent lack of significant findings [114]. In a double-blind study in patients with narcolepsy (NT1 or NT2; N = 222), SXB treatment significantly decreased REM sleep compared with placebo [115]. When participants with NT1 were treated with SXB with or without modafinil for 8 weeks, the numbers of shifts from N2/3/REM and REM to N1/wake were significantly reduced, whereas modafinil monotherapy did not reduce the number of transitions compared with placebo [1]. A post hoc analysis of 159 participants who received SXB for 8 weeks revealed dose-dependent reductions in the number of N2/3/REM and N2/3 to N1 stage shifts [116]. Further, the correlation between number of cataplexy attacks and shifts from REM sleep was numerically higher with increasing doses of SXB [116]. Importantly, in a post hoc analysis of a 12-month, open-label extension of SXB treatment, maximal effects on sleepiness and cataplexy were not fully realized for several months, suggesting that there may be benefits of long-term treatment with SXB [117]. In an interview-based dream study, participants with narcolepsy (NT1 or NT2) taking SXB had significantly lower frequency of dream recall and nightmares, but not lucid dreams, when compared with previous drug-free periods [91]. In a structured telephone-interview–based study, there were no differences in medication usage (eg, alerting agents, antidepressants, and SXB) between participants with NT1 with and without dream delusions [92]. SXB is approved by the US Food and Drug Administration and European Medicines Agency for the treatment of cataplexy or EDS in children with narcolepsy aged 7 years and older, as well as adults with narcolepsy [118,119].

Low-sodium oxybate (calcium, magnesium, potassium, and sodium oxybates oral solution; Xywav®), which contains the same active moiety as SXB (and thus has the same mechanism of action), improves EDS and cataplexy but has not been evaluated for its effects on REM sleep in narcolepsy [102,118–124]. A high-sodium once-nightly SXB (sodium oxybate for extended-release oral suspension; Lumryz™) has been approved by the US Food and Drug Administration for treatment of EDS or cataplexy in adults with narcolepsy [125]. After 3 weeks of treatment with once-nightly SXB, patients with NT1 or NT2 had less REM sleep than those taking placebo, as well as reduced cataplexy and EDS [126].

6.2. Pitolisant

Pitolisant is a histamine-3-receptor antagonist/inverse agonist [127]. Pitolisant consistently reduces cataplexy and is approved to treat that symptom, as well as EDS, in adult patients with narcolepsy in the United States, and is approved for the treatment of narcolepsy in children and adolescents (age ≥6 years) and adults with narcolepsy in the European Union [128–133]. Pitolisant also reduces SRH and SP in patients with NT1 or NT2 [134].

6.3. Wake-promoting agents

Wake-promoting agents such as solriamfetol, modafinil, and armodafinil are commonly used to treat EDS in patients with narcolepsy. Solriamfetol is a dopamine and noradrenaline reuptake inhibitor [135]. The mechanism of action of modafinil is unclear, but it is believed to block dopamine transporters and increase extracellular dopamine levels [109]. Each of these drugs has been shown to improve EDS in adult patients with narcolepsy (NT1 and NT2) [101,136–139]. The effects of solriamfetol on cataplexy are unclear, with one study reporting no significant effects; however, a small population of patients with cataplexy was assessed, which may have resulted in a lack of power. Another study reported that armodafinil had no significant impact on nocturnal PSG findings in patients with NT1 or NT2 [136].

6.4. Traditional stimulants

Although much of the existing literature suggests that alerting agents (eg, amphetamines and methylphenidates) do not affect cataplexy or REM sleep–associated symptoms [140], guidance from the American Academy of Sleep Medicine (AASM) conditionally recommends dextroamphetamine to reduce cataplexy and EDS in patients with NT1 or NT2 [141–143]. Why an amphetamine might decrease cataplexy is unknown, but could be related to reduction of REM sleep pressure. Furthermore, amphetamines could suppress cataplexy via inhibiting dopamine reuptake through their effects on the dopamine transporter [109,144]. The AASM Task Force found that dextroamphetamine had a clinically significant impact on reducing EDS and cataplexy despite very low-quality evidence and determined that the potential benefits outweigh the risks [141,142]. However, patients with NT1 treated with psychostimulants or wake-promoting agents have higher diastolic BP and HR than untreated patients, and the percentage of REM sleep is associated with 24-h hypertension regardless of treatment status [145].

6.5. Antidepressants

Antidepressants are used to treat cataplexy [140]. Many antidepressants (eg, selective serotonin reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors) are generally believed to suppress the percentage of REM sleep, and may depend on dosing and timing of medication [68]. Interestingly, however, in the community-based Wisconsin Sleep Cohort, adults with multiple SOREMPs were significantly more likely than those without SOREMPS to have been taking non–REM-sleep-suppressing antidepressants [146].

Antidepressants such as venlafaxine may also cause RBD in patients with narcolepsy; withdrawal may induce rebound cataplexy [140,147,148]. Indeed, a recent study confirmed that, even with gradual tapering over a period of up to 7 weeks, withdrawal from anticataplectic antidepressants was associated with increased cataplexy frequency in participants with NT1 who switched from SXB to low-sodium oxybate [120]. Desmethylimipramine and imipramine are effective in reducing cataplexy, SP, and SRH [149]. Several antidepressants suppress REM sleep in various ways and also inhibit nocturnal SOREMPs and promote nocturnal transitions to N1 or wakefulness [68,150]. Monoamine oxidase inhibitors, such as phenelzine at 30−90 mg/day, completely suppressed REM sleep in most patients with major depressive disorder, compensated for by an increase in N2 sleep [151]. Antidepressant treatment is also associated with RSWA in people without narcolepsy [152,153].

It is important to consider the REM-sleep-suppressing action of antidepressants when using MSLT to diagnose narcolepsy. One retrospective study showed that patients who underwent MSLT (including but not limited to patients with narcolepsy) and tapered off REM-sleep-suppressing antidepressants (eg, trazodone, nefazodone, mirtazapine, and bupropion) at least 2 weeks prior to MSLT assessment had more SOREMPs, and were more likely to have ≥2 SOREMPs on the MSLT, compared with those who had not [154]. Even after accounting for a variety of confounders (including age, sex, body mass index, depression, type of drug use at time of assessment, total sleep time, and arousal index), patients who tapered off REM-sleep-suppressing antidepressants remained more likely to have reduced mean sleep latency and increased

likelihood of having ≥2 SOREMPs compared with those who were not taking REM-sleep-suppressing antidepressants at initial assessment [154].

6.6. Hypocretin agonists

Currently, no hypocretin agonists are approved for the treatment of narcolepsy, although many are in development [155]. Preliminary evidence indicates that hypocretin receptor type 2 ($Hcrt_2R$) agonists can be very effective in suppressing cataplexy and improving daytime sleepiness in narcoleptic mice and in humans with NT1 [156]. A recent phase 2 trial reported that an orally administered selective $Hcrt_2R$ agonist resulted in substantial improvement in measures of sleepiness and cataplexy over a period of 8 weeks in patients with NT1; however, the treatment was associated with hepatotoxic effects [157]. No information is currently available on their effect on nocturnal sleep or REM sleep.

7. Conclusions and future directions

REM sleep disruption in narcolepsy manifests in many ways, including electrophysiologically (eg, SOREMPs and RSWA) and clinically (eg, cataplexy [in NT1] as well as RBD, SP, SRH, and unusual dreams [in some patients]). Studying REM sleep in narcolepsy provides insight into the consequences of disruption of this important sleep process, not only in the affected patients, but also potentially in patients with other disorders and the general population.

Future research must address several important issues. First, considering that NT1 and NT2 are typically chronic and lifelong (although NT2 may remit [6]), there is a need for long-term, effective, safe, and tolerable treatments. Although multiple treatment options have demonstrated benefits on cataplexy, there is a general paucity of data on the effects of existing treatments on REM sleep or clinical manifestations of REM sleep dysfunction besides cataplexy. In particular, further investigation into the varying effects of antidepressants on suppression of REM sleep and their individual mechanisms of action may lend additional insight. More work is needed in this area, perhaps facilitated by use of tools for assessing REM-related symptoms in a reproducible way, such as the NSS [49,50]. Second, while the impact of EDS and cataplexy on functioning and quality of life in people with narcolepsy has been well documented, the impact of other REM-related symptoms remains relatively unknown [158,159]. Symptoms such as SRH, SP, or nightmares are frightening and can further disrupt the already compromised sleep in patients with narcolepsy. Hence, it might be expected that these symptoms contribute to impairment of quality of life and functioning.

Finally, the neurobiology of REM sleep disruption in narcolepsy is largely unknown. Hypocretin disruption is hypothesized to play a role, but this does not explain why REM-related phenomena other than cataplexy are observed in people with NT2, in whom CSF hypocretin levels are typically not low but instead intermediate to normal. The prevalence and pathophysiology of NT2 are poorly understood; therefore, more research is needed to develop a better understanding of REM sleep–related symptoms and their treatment in both types of narcolepsy.

Practice points

- Rapid eye movement sleep–related symptoms in narcolepsy may evolve over time and manifest themselves in complex ways
- Patients can be distressed by rapid eye movement sleep–related symptoms, which could impair quality of life, although this is not well characterized except for cataplexy
- Robust evidence supports the efficacy of oxybates in improving all narcolepsy symptoms, including rapid eye movement sleep–related symptoms; however, pitolisant and antidepressants also can control rapid eye movement sleep–related symptoms

Research agenda

- More research, possibly using additional tools (such as the narcolepsy severity scale), is needed on treatments that may ameliorate rapid eye movement sleep–related symptoms of narcolepsy
- The impact of rapid eye movement sleep–related symptoms on quality of life and functioning of patients with narcolepsy should be better characterized
- The neurobiology of rapid eye movement sleep disruption in narcolepsy type 1 and narcolepsy type 2 should be further explored and compared, particularly regarding the role that hypocretin deficiency plays in pathophysiology
- Little is known about the pathophysiology of narcolepsy type 2; therefore, additional research is needed

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