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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • REVIEW

REM obstructive sleep apnea: risk for adverse health outcomes and novel treatments

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Abstract

Rapid eye movement (REM) sleep was discovered nearly 60 years ago. This stage of sleep accounts for approximately a quarter of total sleep time in healthy adults, and it is mostly concentrated in the second half of the sleep period. The majority of research on REM sleep has focused on neurocognition. More recently, however, there has been a growing interest in understanding whether obstructive sleep apnea (OSA) during the two main stages of sleep (REM and non-REM sleep) leads to different cardiometabolic and neurocognitive risk. In this review, we discuss the growing evidence indicating that OSA during REM sleep is a prevalent disorder that is independently associated with adverse cardiovascular, metabolic, and neurocognitive outcomes. From a therapeutic standpoint, we discuss limitations of continuous positive airway pressure (CPAP) therapy given that 3 or 4 h of CPAP use from the beginning of the sleep period would leave 75% or 60% of obstructive events during REM sleep untreated. We also review potential pharmacologic approaches to treating OSA during REM sleep. Undoubtedly, further research is needed to establish best treatment strategies in order to effectively treat REM OSA. Moreover, it is critical to understand whether treatment of REM OSA will translate into better patient outcomes.

Keywords Rapid eye movement · Sleep · OSA · Cardiovascular · Neurocognitive · Diabetes · Memory · Mood · Treatment · Pharmacologic

Abbreviations

AHI	Apnea-hypopnea index
AHI4%	Apnea-hypopnea index using 4% oxygen desaturation criteria
AHI3%a	Apnea-hypopnea index using 3% oxygen desaturation criteria and/or arousal
BMI	Body mass index
CPAP	Continuous positive airway pressure
DREADD	Designer receptor exclusively activated by designer drugs
EDS	Excessive daytime sleepiness
EPAP	Expiratory positive airway pressure
GIRK	G protein coupled inward rectifying potassium channels
MSLT	Multiple sleep latency test
Non-REM	Non-rapid eye movement sleep
PSG	Polysomnography
REM	Rapid eye movement

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Introduction

Obstructive sleep apnea (OSA) occurs when the muscles and tissues surrounding the upper airway collapse partially or completely during sleep, resulting in a period where breathing stops or is significantly attenuated before the airway opens again. This phenomenon occurs repeatedly during sleep; in individuals with severe OSA, it can occur nearly every minute or more. In many people, several factors converge making OSA more severe during rapid eye movement (REM) sleep. The body naturally loses muscle tone during REM sleep, perhaps most significantly at the level of the genioglossus due to cholinergic mediated inhibition, and it becomes easier for

muscles surrounding the upper airway to collapse [1]. There is also a reduction in the hypoxic and hypercapnic ventilatory drive [2, 3]. The worsening of OSA during REM can be manifested in a number of ways, including more frequent events, longer duration events, and greater oxygen desaturation associated with events [4–6]. Figure 1 highlights the mechanisms linking REM sleep to adverse health outcomes. Exactly how these transient events during sleep lead to persistent daytime consequences remains to be fully determined. In one of the first experimental demonstrations that OSA is causally linked to persistent daytime hypertension, it was determined that chronic sleep fragmentation alone was insufficient to elicit the same increases in daytime blood pressure as chronic experimentally induced OSA [7]. Additionally, in this canine model of OSA, the maximal daytime hypertension response took 4–5 weeks to develop, and when the experimentally induced OSA was discontinued, nocturnal blood pressure immediately returned to baseline levels; however, the daytime blood pressure took about 3 weeks to normalize. This dichotomy in the timing of return to baseline blood pressure levels between sleep and wake argues for a mechanism related to hypertension that is tied to state and therefore likely mediated by plastic neural input to vessel walls.

OSA has been clearly linked to a number of adverse cardiovascular, endocrine, and neurocognitive outcomes, but whether the risks associated with these adverse outcomes depend on the stage of sleep in which the events occur has remained a matter of debate. The concept that REM OSA can be associated with increased risks is based on at least two possibilities that are not mutually exclusive. The first idea is that REM OSA induces intermittently severe disease, and that severe disease, even in limited doses, is sufficient to increase risks associated with adverse outcomes. This argument would suggest that a person who spends 25% of total sleep time in REM sleep, with a non-REM apnea hypopnea index (AHI) using 4% oxygen desaturation criteria (AHI4%) of 4/h and REM AHI4% of 24/h with an overall AHI4% of 9/h, would experience increased risk in comparison to an individual with an overall AHI4% of 9/h composed of REM and non-REM AHI4% that are each 9/h. Of note, this conceptual framework that intermittently severe disease carries increased risks would be true for positional OSA as well, where severity of OSA in the supine position is often greater than severity in the non-supine position. The other idea is that REM sleep constitutes some state in which the brain and other end organs are particularly vulnerable, due to its physiological features including the precise brain neurochemical milieu, degree of neuronal synchrony, frequency of cortical local field potential oscillations, and autonomic tone, which summate to influence heart rate and rhythm and control blood flow to end organs.

In this review, we discuss attempts to capture the epidemiology of REM OSA before evaluating the specific adverse outcomes of REM OSA on the cardiovascular, endocrine, and neurocognitive systems and how these determinations were derived within the context of assumed comorbid risks associated with non-REM OSA. Finally, we discuss some of the particular cellular and molecular mechanisms associated with REM inhibition of muscle tone, which may lead to novel drug targets for REM OSA.

Epidemiology of REM OSA

Determining how frequently REM OSA occurs in a population depends in part on having a definition of what constitutes REM OSA. This is somewhat problematic as there is no standard consensus for what constitutes REM OSA by any AHI cutoff, and using the AHI3% and/or arousal (AHI3%a) criteria instead of the AHI4% can lower the prevalence of REM OSA [8]. Additionally, how much REM sleep needs to be captured on any given sleep study in order to feel confident that the REM AHI is likely to generalize across nights is a matter of some debate [9]. In the research setting, 30 min of REM sleep has been largely accepted as the minimum required to make meaningful statements about REM OSA by the REM AHI [9], although in some studies, a duration as low as 10 min is used. Similarly, many research studies employ a ratio of REM AHI/non-REM AHI > 2 as a working definition of REM OSA. It is important to point out that there are several inherent limitations in just using a ratio of rates (i.e., events/h in REM sleep divided by events/h in non-REM sleep) when classifying REM OSA. First, classifying patients with OSA based on the REM AHI/non-REM AHI ratio by itself is problematic because it will undoubtedly designate some patients as having REM-related OSA when, in fact, there is also substantial disease during non-REM sleep. For example, a patient with a REM AHI of 80 events/h and a non-REM AHI of 35 events/h would be classified as having REM OSA when, in fact, severe OSA is also present during non-REM sleep. The REM AHI/non-REM AHI ratio does not accurately depict the occurrence of OSA predominantly during REM sleep because it can be high due to (1) a high REM AHI, (2) a low non-REM AHI, or (3) a combination of both [9]. To overcome this limitation, some studies add additional criteria of a total AHI minimum (usually 5/h) and non-REM AHI maximum (typically between 8 and 15/h).

One of the earliest studies to examine REM OSA prevalence included patients with a total AHI between 5/h and 25/h, a non-REM AHI < 15/h, and REM AHI/non-REM AHI > 2. This occurred in 24% of 632 men and 62% of 206 women with polysomnography (PSG)-identified OSA [10]. A similar pattern in which increased prevalence of REM OSA was observed in women was recapitulated in subsequent studies in which 21.0% of men and 40.8% of women expressed REM OSA in 2486 OSA patients [11] or 4% of men and 35% of women among 45 severely obese patients [12]. In studies that

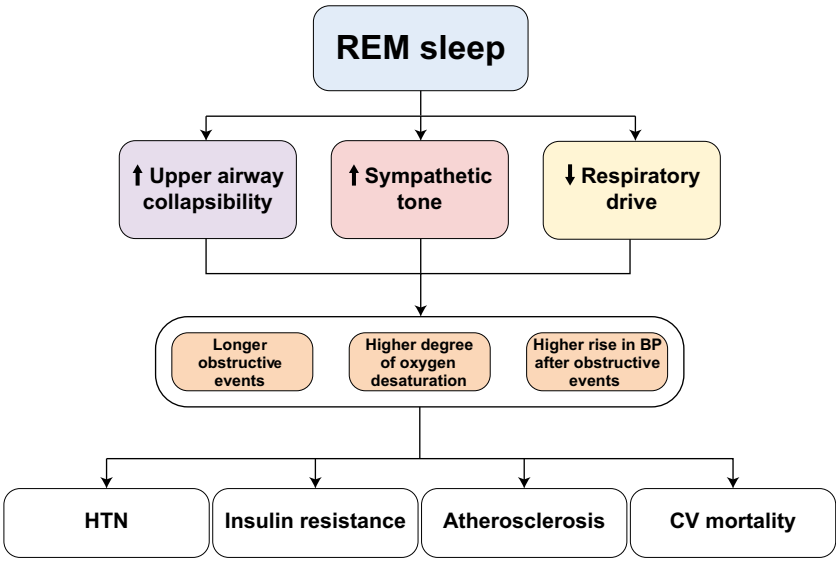

Fig. 1 Multiple mechanisms by which REM sleep can lead to increased frequency and severity of obstructive respiratory events and disproportionately toxic consequences on health outcomes. BP blood pressure, HTN hypertension, CV cardiovascular

did not segregate by sex, REM OSA was observed in 36.4% of 415 OSA patients using a sole criterion of REM AHI/non-REM AHI > 2 [13] and in 14.4% of 1540 OSA patients when stricter criteria were added [14]. Indeed, the precise effect of altering the definition of REM OSA was assessed in 931 patients with a minimum total AHI3%a of 5/h [15]. REM OSA was observed in 36.7% when only REM AHI/non-REM AHI > 2 was used, 24.4% when the criterion of non-REM AHI3%a < 15/h was added, and 13.5% when the criterion of non-REM AHI3%a < 8/h was added.

While these prevalence estimates are from patients referred to a sleep center for evaluation, REM OSA prevalence estimates have also been derived from large community-based epidemiological studies, although different criteria for REM OSA were typically employed. In the Wisconsin Sleep Cohort, among 2953 sleep studies with 30 min of REM and a non-REM AHI4% ≤ 5 events/h, 12% demonstrated a REM AHI ≥ 15 events/h [16]. Furthermore, among studies where the total AHI4% was less than 15 events/h, 22% demonstrated a REM AHI4% ≥ 15 events/h. In the Sleep Heart Health Study, among 3265 subjects with at least 30 min of REM sleep and a non-REM AHI4% < 5 events/h, 27.7% had a REM AHI4% of 5.0–14.9 events/h, 13.0% had a REM AHI4% of 15.0–29.9 events/h, and 5.5% had a REM AHI > 30 events/h [17]. Furthermore, among 4648 subjects with 30 min of REM sleep and all levels of OSA severity, 464 (10%) had a non-REM AHI4% < 5 events/h and REM AHI4% > 15 events/h [18]. In 2044 older men > 65 years of age in the Osteoporotic Fractures in Men (MrOS) study with a total AHI4% < 15 events/h, 20% had a REM AHI4% of 15–30 events/h and 6.5% had a REM AHI4% > 30 events/h [19]. In the HypnoLaus study, among 2074 subjects with at least 30 min of REM sleep, 40.8% had a REM AHI3a ≥ 20/h [20]. In sum, although REM OSA definitions may vary, REM OSA is prevalent in both community-based and clinic population samples.

Cardiovascular outcomes and REM OSA

OSA has been shown to be associated with several adverse cardiovascular outcomes including hypertension [15, 21], myocardial infarction [22, 23], and stroke [24, 25] in both community-based and clinic-based studies. In longitudinal studies of incident hypertension in the Wisconsin Sleep Cohort, OSA severity at baseline predicted the presence of hypertension 4 years later in a dose-dependent manner after controlling for several potential confounding factors [26]. In the Vitoria study, a large community-based study of middle-aged adults in Spain, OSA severity was not associated with incident hypertension over a 7-year follow-up [27]; however, a subsequent reanalysis demonstrated that moderate to severe OSA was associated with the incidence of more severe forms of hypertension in men, but not women [28]. In the Sleep Heart Health Study, OSA severity was associated with incident hypertension, but this association appeared to be significantly driven by obesity, as the strength of the association was significantly weakened when BMI was included as a covariate [29]. Given this heterogeneity, it seems plausible that not all apnea influences hypertension equally, and because REM sleep is associated with greater sympathetic activity, lower vagal tone, and more cardiovascular instability compared to non-REM sleep [30], obstructive events during REM sleep could disproportionately lead to hypertension and other adverse cardiovascular outcomes. It is theoretically possible that the increased sympathetic tone during REM sleep creates a ceiling effect, whereby obstructive events during this stage do not add much additional sympathetic tone. However, this is not well supported by studies examining sympathetic tone quantified by both sympathetic burst frequency and amplitude in subjects with and without OSA. In subjects without OSA, burst frequency during wake was 24 bursts/min and increased to 34 bursts/min during REM sleep. Burst amplitude during

REM sleep was 215% of the average value obtained during wake [31]. In individuals with OSA, wake burst frequency was already significantly elevated in comparison to subjects without OSA at 59 bursts/min. While burst frequency was not significantly different during REM sleep in individuals with OSA, burst amplitude increased nonetheless to 141% on average during REM sleep [30].

Indeed, analyses of REM OSA in the Wisconsin Sleep Cohort [16], the Men Androgens Inflammation Lifestyle Environment and Stress (MAILES) study [32], and the HypnoLaus study [20] suggest it is significantly associated with hypertension, independent of non-REM OSA. In the analysis of the Wisconsin Sleep Cohort comprising 1451 individuals completing 4385 sleep studies, REM AHI4% considered as a categorical variable (AHI4% 1–4.9/h, 5–14.9/h, and ≥ 15/h versus reference AHI4% < 1/h) was associated with significantly increased risk of prevalent hypertension, after controlling for age, sex, race, body mass index, waist-to-hip ratio, smoking alcohol, and non-REM AHI4% expressed as a continuous variable. Additionally, in a subset of individuals with ambulatory blood pressure monitoring data and a non-REM AHI4% < 5 events/h, REM AHI4% considered either categorically or continuously was significantly associated with increasing hypertension prevalence. Notably, non-REM AHI4% did not significantly predict prevalent hypertension in any models. Finally, longitudinal assessment of hypertension in 428 individuals whose hypertension status changed from absent to present (or vice versa) revealed a significant association of REM OSA severity by REM AHI4% categories and development of incident hypertension over time after controlling for non-REM AHI4% [16].

In a separate follow-up study, 269 adults enrolled in the Wisconsin Sleep Cohort Study who completed two or more 24 h ambulatory blood pressure studies over an average of 6.6 years were evaluated for non-dipping blood pressure [33]. Blood pressure ordinarily dips 10–20% across sleep, and when this does not occur, there is increased risk for the future development of hypertension in normotensive adults, as well as increased risk for cardiac damage, including left ventricular hypertrophy, angina, myocardial infarction, and cardiovascular death [34, 35]. In subjects with at least 30 min of REM sleep, REM AHI4% by category was significantly associated with increased risk for incident non-dipping of both systolic and diastolic blood pressure when controlling for non-REM AHI4% and other covariates.

In the MAILES study, a community-based study of adult men in Australia, 739 men with at least 30 min of REM sleep on polysomnography had completed prior clinical assessments for hypertension between the years 2002 and 2010. REM OSA severity by REM AHI3%a evaluated categorically was significantly associated with both prevalent and recent-onset hypertension, particularly in those with a REM AHI3%a ≥ 20 events/h, when controlling for a variety of potential confounders, including non-REM AHI3%a. In the subset of men with non-REM AHI3%a < 10 events/h, hypertension was also significantly associated with REM AHI3%a by category, similar to the observations in the Wisconsin Sleep Cohort. Also similarly, hypertension was not associated with non-REM AHI3%a. In the MAILES study, mean REM oxygen desaturation (i.e., mean of the drop in oxygen saturation per obstructive event) was significantly associated with prevalent hypertension independent of mean non-REM oxygen desaturation, and non-REM mean oxygen desaturation showed no significant associations with prevalent hypertension.

In assessing multiple polysomnographic variables that predict hypertension in the Multi-Ethnic Study of Atherosclerosis (MESA), REM OSA variables exhibited the largest absolute differences between groups when subjects were dichotomized by median systolic and diastolic blood pressures. This possibly suggests that to detect a difference between median BPs, a larger change in REM AHI versus NREM AHI is needed [21]. That said, REM AHI4% indices did not remain associated with BP in the final multivariate regression models in this analysis, whereas overall, AHI4% and arousals associated with periodic limb movement of sleep were.

HypnoLaus is a community-based study of men and women in Switzerland who are middle aged (median age 56 years) and largely white and non-obese. In 2074, individuals with at least 30 min of REM sleep, REM AHI3a, considered categorically in those with REM AHI3a ≥ 20/h, were associated with increased risk for hypertension after controlling for age, sex, BMI, waist-to-hip ratio, total sleep time, smoking, alcohol consumption, and non-REM AHI3a [20].

Given the strong association of hypertension with other adverse cardiovascular outcomes, a logical extension of the established relationship between REM OSA and hypertension would include a potential role for REM OSA in outcomes such as angina, myocardial infarction, stroke, and heart failure. Additionally, OSA-driven sympathetic surges associated with paroxysmal arrhythmias may occur most frequently in REM sleep, due to significantly higher sympathetic tone, heart rate, and heart rate variability in REM versus non-REM sleep [36, 37]. Atrial arrhythmias in particular could lead to atrial embolus generation and stroke. The possibility of REM OSA being tied to such cardiovascular outcomes was evaluated in a study of subjects from the Sleep Heart Health Study [17]. In this study, 3265 participants were evaluated who had at least 30 min of REM sleep and no significant OSA during non-REM sleep (non-REM AHI4% < 5/h). The participants were mostly older adults (mean age 62 ± 11 years) who were slightly overweight (BMI 28 ± 5 kg/m^2), and mostly women (63% female). Subjects were followed for 9.5 years on average, and a composite adverse cardiovascular outcome, including myocardial infarction, coronary artery revascularization, congestive heart failure, or stroke, was evaluated for prevalence and incidence. In participants with prevalent cardiovascular

disease at baseline ($n = 452$), the hazard ratio for the composite cardiovascular endpoint was 2.56 (95% CI, 1.46–4.47) for severe REM OSA (REM AHI4% > 30 events/h) compared to no OSA during REM sleep (REM AHI < 5 events/h) after adjusting for age, sex, race, body mass index, smoking status, prevalent hypertension, and diabetes. The association was much weaker in participants without prevalent cardiovascular disease. As noted by the authors, the overall number of individuals with prevalent cardiovascular disease at baseline and REM AHI4% > 30/h was relatively small ($n = 33$), and a separate study evaluating "REM OSA" as a phenotype from cluster analysis of a largely male veteran population did not observe increased cardiovascular risk in this cluster [38], so caution is warranted in interpretation of this finding. Nonetheless, these findings potentially offer an explanation for the divergent observations that OSA is significantly associated with adverse cardiovascular outcomes and yet that continuous positive airway pressure (CPAP) treatment of OSA in randomized clinical trials has yielded ambiguous or negative results [39, 40]. In such trials, the average duration of CPAP use is typically much lower than the expected total sleep duration. Because REM sleep is significantly weighted toward the second half of sleep, and especially in the minutes just prior to waking, it is likely that subjects assigned to CPAP treatment still had significant periods of untreated REM OSA. Such a hypothesis is supported by a subanalysis of the SAVE trial, where 561 patients with nightly CPAP adherence > 4 h/night had significantly lower risk for cerebrovascular events compared to propensity-score-matched subjects with usual care alone. Additional work appears to be needed to evaluate the specific effect of treatment of REM OSA on hypertension and cardiovascular outcomes.

Endocrine outcomes and REM OSA

Sleep and endocrine function are neuroanatomically linked through the hypothalamus, and lateral hypothalamic neurotransmitters orexin and melanin concentrating hormone (MCH) have strong and reciprocal effects on both feeding behaviors [41–43] and promotion of REM sleep [44]. Disruptions to sleep, such as short sleep duration [45] and OSA [46–48], have been associated with insulin resistance, glucose intolerance, and development of diabetes (for a comprehensive review see Reutrakul and Mokhlesi [49]). A role for OSA in diabetes is confounded by the mutual strong associations of OSA and diabetes with obesity. Nonetheless, OSA has been found to be associated with diabetes development even in non-obese populations [50, 51].

A specific role for REM sleep in this process has been observed in human subjects and animal models. In non-diabetic human subjects, continuous glucose monitoring combined with polysomnography revealed steep drops in the interstitial glucose concentration across periods of REM sleep [52], and rodents experiencing acute REM sleep disruption showed reduced activity of enzymes that typically break down glucose, including hexokinase and glucose-6-phosphatase [53]. Additionally, intermittent hypoxia has been demonstrated to impair pancreatic beta cell function [54, 55], and severity of hypoxemia correlated with HbA1c levels in subjects with OSA and no previously recognized diabetes [56]. Taken together, these observations suggest that REM OSA may play a substantial role in the development of insulin resistance and diabetes, given that obstructive events during REM sleep significantly fragment REM sleep quality and are often associated with the greatest oxygen desaturations during sleep [4, 6].

Several studies lend credence to this specific hypothesis. First, continuous glucose monitoring across sleep in subjects with untreated OSA demonstrated that the occurrence of OSA in REM sleep abrogated the expected decline in interstitial glucose concentration across REM sleep, whereas OSA in non-REM sleep had no effect on interstitial glucose concentration [57]. In obese type 2 diabetics with and without OSA undergoing continuous glucose monitoring during sleep, the mean glucose level was 38% higher during REM sleep in those with OSA versus those without OSA. These smaller studies were bolstered by the observations from larger population-based studies. In the Sleep Heart Health Study consisting of middle-aged and older subjects, REM AHI4% treated as a continuous variable was significantly associated with increasing levels of insulin resistance by homeostatic model of insulin resistance (HOMA-IR), after controlling for age, sex, race, body mass index, waist circumference, sleep duration, and enrollment site [58]. In contrast, non-REM AHI4% was significantly associated with both fasting and post-prandial glucose levels. In a prospective study of obese subjects with type 2 diabetes, increasing quartiles of REM AHI3%a were significantly associated with increasing levels of HbA1c after adjustment for age, sex, BMI, race, years of type 2 diabetes, insulin use, and non-REM AHI3%a [59]. The mean adjusted HbA1c increased from 6.3% in subjects with REM AHI < 12.3 events/h (lowest quartile) to 7.3% in subjects with REM AHI > 47 events/h (highest quartile), suggesting a clinically significant effect. Importantly, increasing levels of non-REM AHI3%a quartiles were not associated with HbA1c. Overall, the development and maintenance of diabetes are likely multifactorial with potentially differential effects of OSA in individual sleep stages, but nonetheless, OSA during REM sleep appears to confer specific risks toward this end point.

Neurocognitive outcomes and REM OSA

One of the most obvious, immediate, and mostly reversible [60] adverse neurocognitive outcomes associated with OSA is

excessive daytime sleepiness (EDS). EDS can be measured subjectively with questionnaires such as the Epworth sleepiness scale and Stanford sleepiness scale and objectively with measurements such as the sleep latency of a multiple sleep latency test (MSLT) or mean reaction time and number of lapses on a psychomotor vigilance test. While sleepiness tends to correlate with overall OSA severity, most studies examining a specific role of REM OSA have found little evidence for association with EDS. In a clinic-based study of 1146 patients undergoing both PSG and MSLT, OSA severity was found to explain 11% of the MLST result variance, with non-REM OSA severity explaining 10.8% and REM OSA severity explaining just 6% [61]. In another clinic-based study of 1821 subjects with both PSG and MSLT, REM OSA severity was not associated with daytime sleep propensity by sleep latency on the MSLT after controlling for age, gender, body mass index, and the duration of non-REM and REM sleep [62]. In contrast, non-REM OSA severity was associated with daytime sleep propensity. In the community-based Sleep Heart Health Study of 5649 subjects, REM AHI4% was not associated with daytime sleepiness by the Epworth sleepiness score after controlling for demographics, BMI, and non-REMAHI4%, whereas non-REM AHI4% did associate with Epworth sleepiness scores after controlling for demographics, BMI, and REM AHI4% [63]. Finally, in 18 subjects with severe OSA treated chronically with therapeutic CPAP, withdrawal of CPAP exclusively during REM sleep recapitulated severe REM OSA while maintaining normal sleep breathing in non-REM sleep [64]. Following induction of severe OSA in REM sleep, there was no change in mean reaction time or number lapses on morning psychomotor vigilance testing compared to ordinarily consolidated sleep, suggesting no significant increase in sleepiness or alertness.

Studies linking REM OSA to changes in mood have been more mixed. While one recent large clinic-based study of 1281 individuals with OSA demonstrated an association of REM OSA severity with worsened mood by Beck Depression Inventory scores in men but not women [65], assessment of older men in the MrOS cohort demonstrated no association of REM OSA severity with depression scores on the Geriatric Depression Scale-15 [19]. Similarly, in 142 predominantly male clinic patients, having REM AHI > non-REM AHI was not associated with increased Beck Depression Inventory depression scores [66]. Of note, although REM OSA does not generally appear to be associated with sleepiness, the comorbid presence of depressive symptoms predicted sleepiness assessed by the Epworth sleepiness scale in subjects with REM OSA [67].

Memory processing has long been suspected to be a significant function of sleep, and evidence is building that sleep may impart not only consolidation but also more complex and nuanced cognitive functions such as rule learning, pattern separation, gist extraction, and even forms of creativity [68, 69]. Because REM sleep differs from non-REM sleep in several crucial features that are important for neural processing, including the neurochemical milieu, the prominent frequencies of cortical field potentials, and the degree of synchrony among cortical regions, the precise mnemonic functions subserved by REM sleep, and their vulnerability to REM OSA, may be unique from those supported by non-REM sleep. While REM sleep has been implicated in the processing of perceptual [70], procedural [71, 72], probabilistic [73], and emotional memory [74–76], effects of REM OSA on these functions have not been investigated.

A role for REM sleep in spatial navigational memory in rodents dates back to at least 1972 [77], and more recently, optogenetic suppression of hippocampal theta rhythm during REM (but not non-REM) impaired spatial object placement learning [78]. These observations raise the possibility that REM OSA in human subjects could impair the processing of spatial navigational information that ordinarily occurs during sleep. In subjects with severe OSA well treated with therapeutic CPAP, performance on a 3D virtual navigation task improved by an average of 30% across normally consolidated sleep. When REM OSA was induced in these same subjects via CPAP withdrawal exclusively during REM sleep, this benefit of sleep was abolished, and in fact subjects' performance worsened by an average of 5% overnight [64]. Importantly, as noted above, there were no changes in psychomotor vigilance associated with apnea-induced REM sleep disruption, suggesting that any spatial navigation performance deficits were unlikely to be due to any sleepiness or inattention that may have resulted from the intervention.

Finally, it bears noting that sleep disturbances may not only impair cognitive function acutely, but also increase risk in the long term for cognitive dysfunction through neurodegenerative processes including Alzheimer's disease [79, 80]. A recent intriguing report investigating older subjects from the Sleep Hearth Health Study (average age 67 years), followed longitudinally for an average of 12 years, demonstrated that lower REM sleep percentage and longer REM sleep latency were both associated with a higher risk of incident dementia after controlling for age and sex [81]. Notably, the effect between REM sleep percentage and dementia was reduced after excluding subjects with a high number of arousals from REM sleep due to hypopneas, suggesting a possible contributing role of REM OSA. Additional work will be needed to help clarify the potential role of REM OSA in both memory and risk for neurodegenerative disease.

Nonpharmacological and pharmacological intervention for REM OSA

Treatment options for OSA are varied and include variants of positive airway pressure (PAP), oral appliances providing

Table 1 Cumulative minutes of REM and non-REM sleep over 8 h of bedtime

Time after lights turned off (h)	Cumulative minutes of non-REM sleep (mean ± SD)	Cumulative percentage of non-REM sleep (%)	Cumulative minutes of REM sleep (mean ± SD)	Cumulative percentage of REM sleep (%)
1	38 ± 14	13	2 ± 6	2
2	81 ± 18	27	11 ± 11	13
3	123 ± 23	41	20 ± 16	25
4	161 ± 27	54	33 ± 20	40
5	201 ± 31	67	44 ± 23	53
6	236 ± 36	79	58 ± 29	71
7	272 ± 37	91	72 ± 32	87
8	298 ± 39	100	82 ± 34	100

Data are summarized as mean ± SD of cumulative REM and non-REM sleep minutes from lights off to lights on in 115 subjects with type 2 diabetes who underwent in-laboratory polysomnography with 8 h of total recording time. The mean duration of REM and non-REM sleep in this cohort was 82 and 298 min, respectively. Using CPAP for 3 h or 4 h from the time lights are turned off will cover only 25% or 40% of REM sleep, respectively, and will leave most obstructive events during REM sleep untreated. In contrast, 7 h of CPAP use would treat 87% of REM sleep. Data extracted from Grimaldi et al. [59]

mandibular advancement, positional therapy, hypoglossal nerve stimulator, nasal expiratory positive airway pressure (EPAP), and a variety of upper airway surgeries. PAP is generally viewed as the gold standard treatment and appears to have the greatest efficacy, particularly in severe REM OSA; however, long-term adherence to PAP is often poor [82]. In clinical practice, 4 h of nightly CPAP use for 70% of the nights is considered adequate adherence to therapy. This translates into an average CPAP use of 2.8 h every night. Indeed, it is plausible that reduced CPAP adherence and the predominantly untreated OSA during REM sleep (which prevails during the latter hours of normal nocturnal sleep) may explain the negative or modest effects of CPAP therapy on blood pressure control in randomized clinical trials. Indeed, using CPAP for 3 or 4 h from the time lights are turned off will cover only 25% or 40% of REM sleep, respectively, and will leave most obstructive events during REM sleep untreated [59] (Table 1). As such, in order to effectively treat REM OSA, patients need to use CPAP during most of their sleep period. Given that many patients cannot achieve such high levels of CPAP adherence, it is imperative to explore alternative treatment strategies or even combine less effective therapeutic approaches (e.g., oral appliance plus nasal EPAP) in order to achieve clinical efficacy in lowering REM AHI.

Although there are no prospective clinical trials designed to explore treatment strategies in patients with REM OSA, a few studies have reported changes in both REM and non-REM AHI. In a placebo-controlled randomized clinical trial of patients with mostly mild to moderate OSA, 1 week of nasal EPAP significantly decreased REM AHI from a median of 26.5 to 8.7 events/h ($p < 0.05$) in 97 patients. At 3 months, there was data on 66 participants and the REM AHI with nasal EPAP device off and on was 25.3 events/h and 11.7 events/h ($p < 0.01$) [83]. In an observational long-term follow-up study of nasal EPAP, after 1 year of therapy, the REM AHI decreased from 16.8 to 3.7 events/h ($p < 0.001$) in 30 participants [84].

Two randomized controlled trials for oral appliances have explored OSA improvement in both REM and non-REM sleep [85, 86]. The first one used a cross-over randomized trial design of 37 patients and found that therapeutic oral appliance decreased the non-REM AHI by an average of 58%, whereas REM AHI decreased by 43% (from 34.2 ± 19.4 to 19.3 ± 15.5 events/h; $p = 0.01$) [85]. The second study randomized patients to either CPAP ($n = 18$), therapeutic oral appliance ($n = 20$), or a sham oral appliance ($n = 19$). CPAP reduced both supine and non-supine REM AHI by approximately 86% whereas therapeutic oral appliance decreased supine REM AHI by 51% (reduction in supine REM AHI of 12.5 ± 34.8 events/h from a baseline of 24.6 ± 31.5 events/h). The non-supine REM AHI was reduced by 49% (reduction in non-supine REM AHI of 7.5 ± 13.0 events/h from a baseline of 24.6 ± 31.5 events/h) [86]. The limited data from these two studies suggests that oral appliance therapy may be less effective in treating REM OSA than OSA during non-REM sleep.

The hypoglossal nerve stimulator was assessed in 126 carefully selected participants in the STAR randomized clinical trial [87]. After 1 year of therapy, both REM and non-REM AHI decreased to the same degree. The REM AHI decreased from 28.9 ± 17.4 to 14.7 ± 16.1 events/h ($p < 0.0001$). In contrast, the non-REM AHI decreased from 32.2 ± 12.6 to 15.3 ± 16.8 events/h ($p < 0.0001$).

Pharmacotherapy for OSA has consequently been a long sought-after goal, but most attempts at drug treatment of OSA have been ineffective [88]. It has been recently argued that greater success with pharmacotherapy might stem from appropriate OSA phenotyping where distinct physiological drivers of OSA and its repetitive, self-maintaining quality might be identified [89, 90]. In broad strokes, the two main approaches endorsed involve identifying targets that improve the pharyngeal

dilator muscle activation and/or upper airway anatomy in general and identifying targets that reduce the sensitivity of ventilatory control (or raise the arousal threshold). REM OSA is arguably a distinct phenotype of OSA [38] and, given the atonia in REM, might be particularly suitable to the former approach. While the natural history of REM OSA is not well studied, approaches that target reducing the number of events in REM sleep would be useful even if an individual eventually converts from having REM OSA to non-specific OSA.

Early studies suggested histamine increased tonic genioglossus muscle activity across vigilance states [91], but given its role in wake promotion, drugs targeting the histamine system might suffer from off-target wake-promoting effects. A major step forward in the understanding of the molecular mechanisms driving REM atonia of pharyngeal motoneurons was the identification of the requirement for muscarinic receptor-driven activation of G protein coupled inward rectifying potassium channels (GIRKs) [1]. Although there are numerous families of neuronal potassium channels [92], GIRKs have particular biophysical properties, making drug targets that block these channels a feasible possibility. Furthermore, one member of the GIRK family, Kir2.4, is expressed almost exclusively in cranial motor nuclei [93, 94], and thus, drug targets of Kir2.4 would offer some level of anatomical specificity. Although specific inhibitors of Kir2.4 remain under development, proof of concept of selectively pharmacologically manipulating cholinergic hypoglossal motoneurons was achieved with a chemogenetic approach using a virally transduced designer receptor exclusively activated by designer drugs (DREADD) [95, 96]. Systemic administration of clozapine-*N*-oxide, an otherwise biologically inert ligand for DREADD, resulted in sustained increases in tongue muscle activity and marked dilation of the pharynx without effect on sleep architecture or diaphragm and postural muscle activity in rodents.

Based on the expression of inhibitory cannabinoid receptors in the vagal nodose ganglion [97] and the theory that dampening vagal input to the medulla might stabilize respiratory pattern generation and raise activation of upper airway dilating muscles during sleep [98], interest in dronabinol, a nonselective agonist of cannabinoid type 1 and 2 receptors, as a potential treatment for OSA has risen. After some initial encouraging results in both rodents [99, 100] and human subjects [101], a fully blinded, parallel groups, placebo-controlled, randomized trial of dronabinol in people with moderate or severe OSA was completed [102]. Dronabinol was found to dose-dependently reduce the AHI3%a by 11–13 events/h and reduce subjective scores on the Epworth sleepiness scale following 6 weeks of treatment. Of particular note to REM OSA, the effect of dronabinol at the higher dose (10 mg/day) on the REM apnea index was the largest treatment effect size for any event type in any sleep stage after controlling for age, gender, race, ethnicity, and baseline AHI3%a. Furthermore, analysis of treatment responders, arbitrarily defined as those subjects with a final on-treatment AHI3%a of ≤ 15 events/h plus a reduction from baseline AHI3%a of $\geq 50\%$, demonstrated that responders had a significantly higher REM AHI3%a and ratio of REM AHI%3a to total AHI3%a versus non-responders. The mean decrease in REM AHI%3a in responders was 33 events/h while the mean decrease in non-REM AHI3%a in responders was 10 events/h. These tantalizing observations should prompt a further specific assessment of dronabinol in individuals with REM OSA.

The role of REM-sleep suppressing medications such as tricyclic antidepressants, monoamine oxidase inhibitors, or serotonin/norepinephrine reuptake inhibitors in the management of REM OSA has not been explored in human subjects. That said, combined use of the tricyclic antidepressant trazodone combined with L-tryptophan resulted in a dose-dependent decrease in OSA in an English bulldog model. Obstructive events during REM sleep in particular were reduced by 63% at the highest dose compared to placebo [103].

Conclusions, knowledge gaps, and future directions

REM OSA is quite prevalent and is associated with adverse cardiovascular, metabolic, and neurocognitive outcomes. The literature suggests that obstructive apneas and hypopneas during REM sleep are more toxic than those in non-REM sleep. One ongoing gap in knowledge is whether this is related to the intermittently more severe obstructive events during REM, a fundamental property of REM physiology, or both. Evidence suggesting that, for example, supine OSA severity is associated with adverse health outcomes would at least lend credence to concept that intermittently severe OSA can be harmful. CPAP therapy of 3–4 h per night may leave the majority of REM OSA untreated. While the concept of "effective AHI" has been explored [104], which estimates an individual's residual AHI based on their baseline severity and hours of CPAP use, systematic study of timing of CPAP use in relation to sleep onset and offset is lacking. We suggest that this type of research should not only require time series analysis of nightly CPAP use but also require concomitant actigraphy data in order to ascertain time of sleep onset. Further research is needed to explore novel therapeutic approaches, or combination of currently available non-CPAP therapies, in patients with REM OSA. Moreover, outcomes studies are necessary to demonstrate that effective treatment of REM OSA leads to better patient outcomes. While we await new research, clinicians should recognize the importance of REM OSA severity, even when overall OSA severity is significantly lower, and also emphasize the need for more prolonged CPAP usage in order to cover the second half of the sleep period when REM sleep predominates.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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