



# UNIVERSITÀ DI PARMA

## ARCHIVIO DELLA RICERCA

University of Parma Research Repository

REM sleep behavior disorder in narcolepsy: a secondary form or an intrinsic feature?

This is the peer reviewed version of the following article:

*Original*

REM sleep behavior disorder in narcolepsy: a secondary form or an intrinsic feature? / Antelmi, Elena; Pizza, Fabio; Franceschini, Christian; Ferri, Raffaele; Plazzi, Giuseppe. - In: SLEEP MEDICINE REVIEWS. - ISSN 1087-0792. - (2019), p. 101254. [10.1016/j.smr.2019.101254]

*Availability:*

This version is available at: 11381/2871277 since: 2020-01-27T12:16:43Z

*Publisher:*

W.B. Saunders Ltd

*Published*

DOI:10.1016/j.smr.2019.101254

*Terms of use:*

Anyone can freely access the full text of works made available as "Open Access". Works made available

*Publisher copyright*

note finali coverpage

(Article begins on next page)

# Journal Pre-proof

REM sleep behavior disorder in narcolepsy: a secondary form or an intrinsic feature?

Elena Antelmi;, Fabio Pizza, Christian Franceschini, Raffaele Ferri, Giuseppe Plazzi



PII: S1087-0792(19)30222-9

DOI: <https://doi.org/10.1016/j.smrv.2019.101254>

Reference: YSMRV 101254

To appear in: *Sleep Medicine Reviews*

Received Date: 15 July 2019

Revised Date: 9 December 2019

Accepted Date: 9 December 2019

Please cite this article as: Antelmi; E, Pizza F, Franceschini C, Ferri R, Plazzi G, REM sleep behavior disorder in narcolepsy: a secondary form or an intrinsic feature?, *Sleep Medicine Reviews*, <https://doi.org/10.1016/j.smrv.2019.101254>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 Published by Elsevier Ltd.

**REM sleep behavior disorder in narcolepsy: a secondary form or an intrinsic feature?**

Elena Antelmi;<sup>1,2</sup> Fabio Pizza,<sup>1,2</sup> Christian Franceschini,<sup>3</sup> Raffaele Ferri,<sup>4</sup> Giuseppe Plazzi \*<sup>1,2</sup>

1. Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum, University of Bologna, Italy

2. IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy

3. Department of Medicine and Surgery, University of Parma, Italy

3. Sleep Research Centre, Department of Neurology IC, Oasi Research institute - IRCCS, Troina, Italy

Word count: summary: 244 ; main text: 5570

References: (#): 159

Tables: 2; Figures 2

**\*Corresponding author**

Giuseppe Plazzi

Department of Department of Biomedical and Neuromotor Sciences, University of Bologna

IRCCS Istituto delle Scienze Neurologiche di Bologna, Bellaria Hospital, Via Altura 3, Bologna, Italy

giuseppe.plazzi@unibo.it

**Financial disclosures related to the manuscript:** This study was partially supported by a fund from the Italian Ministry of Health "Ricerca Corrente" (RC n. 2751594) (Dr. Ferri)

**Conflict of interest related to the manuscript:** none

## Glossary of terms

**CSF:** cerebrospinal fluid; **GiV:** ventral gigantocellular reticular nucleus; **EDS:** excessive daytime sleepiness; **EEG:** electroencephalogram; **EMG:** electromyogram; **iRBD:** idiopathic/isolated RBD; **hcrt-1:** hypocretin 1; **MSLT:** multiple sleep latency test; **NT1:** Narcolepsy type 1; **NT2:** Narcolepsy type 2; **N-RBD:** RBD and narcolepsy; **RBD:** REM sleep behavior disorder; **PD:** Parkinson disease; **PSG:** polysomnography; **RSWA:** REM sleep without atonia; **RAI:** atonia index during REM sleep; **SLD:** subceruleus/sublaterodorsal nucleus; **SOREMPs:** Sleep onset in REM periods; **SINBAR** Sleep Innsbruck Barcelona group

## Summary

Disrupted nighttime sleep is one of the pentad of symptoms defining Narcolepsy. REM sleep behavior disorder (RBD) largely contributes to night sleep disruption and narcolepsy is the most common cause of secondary RBD. However, RBD linked to narcolepsy (N-RBD) has been insufficiently characterized, leaving unsolved a number of issues. Indeed, it is still debated whether N-RBD is an intrinsic feature of narcolepsy, as indubitable for cataplexy, and therefore strictly linked to the cerebrospinal fluid hypocretin-1 (CSF hcrt-1) deficiency, or an associated feature, with a still unclear pathophysiology. The current review aims at rendering a comprehensive state-of-the-art of N-RBD, highlighting the open and unsettled topics. RBD reportedly affects 30-60% of patients with Narcolepsy type 1 (NT1), but it may be seen also in Narcolepsy type 2 (NT2). When compared to idiopathic/isolated RBD (iRBD), N-RBD has been reported to be characterized by less energetic and quieter episode, which however occur with the same probability in the first and the second part of the night and sometime even subcontinuously. N-RBD patients are generally younger than those with iRBD. N-RBD has been putatively linked to wake-sleep instability due to CSF hcrt-1 deficiency, but this latter by itself cannot explain completely the phenomenon as N-RBD has not been universally linked to low CSF hcrt-1 levels and

it may be observed also in NT2. Therefore, other factors may probably play a role and further studies are needed to clarify this issue. In addition, therapeutic options have been poorly investigated.

**Keywords:** Narcolepsy; isolated RBD, secondary RBD; REM sleep behaviour disorder; disrupted sleep

## Introduction

Narcolepsy is a central hypersomnia, characterized by the pentad of excessive daytime sleepiness, cataplexy, hypnagogic or hypnopompic hallucinations, sleep paralysis, and disrupted nighttime sleep [1-3]. It is considered a chronic disorder, with a bimodal peak for age at onset, with a maximal rate of onset at 15 years and the second peak at 35 years [4], and with a mean global prevalence of approximately 30/100,000 [5,6].

The current classification [1] distinguishes Narcolepsy type 1 (NT1) and Narcolepsy type 2 (NT2). Both of them should present excessive daytime sleepiness, confirmed in electrophysiological sleep studies, while the cerebrospinal fluid hypocretin 1 level (CSF hcrt-1) of less than 110 pg/mL and the presence of cataplexy characterize only NT1. Therefore, NT1 is mandatorily linked to the loss of hypothalamic hcrt-1 neurons, while for NT2 the cause is less clear. Both genetic and environmental factors play a crucial role in the pathogenesis of narcolepsy. Almost all NT1 patients carry the HLA-DQB1\*0602 haplotype and a link to polymorphisms in other non-HLA genes that may affect the immune regulatory function and to several infectious triggers, supporting an autoimmune pathogenesis [2], as upheld also in recent cutting-edge studies [7,8].

The clinical fingerprint of NT1 is cataplexy, which is strictly linked to CSF hcrt-1 deficiency [9,10].

Disrupted nocturnal sleep, however, is a very prominent feature and has been reported since the first descriptions of the disease [11-12], but then somehow overlooked for decades. In particular, REM sleep behavior disorder (RBD) has been reported within the symptoms of narcolepsy since one of the first observations of this parasomnia by Schenck and Mahowald [13], but then poorly characterized within the scenario of narcolepsy.

RBD consists in repeated episodes of dream-enacting behavior, accompanied by loss of physiologic atonia during REM sleep [1]. RBD can be idiopathic/isolated (iRBD) or associated with other conditions linked to neurodegenerative, autoimmune or structural abnormalities [14]. It is now clear that, in at least 90% of patients, iRBD is a heralding symptom of impending neurodegeneration due to synucleinopathies [15-18]. The suspected mechanism underlying RBD is a lesion/dysfunction of the REM sleep atonia system, which is located in the pontomedullary brainstem [19]. The occurrence of RBD within narcolepsy (N-RBD) is a puzzling issue, whether or not it is an intrinsic feature, as evident for cataplexy, and therefore strictly linked to the hcrt-1 deficiency, or an associated feature, with a still unclear pathophysiology. In this regard, indeed, the occurrence of RBD has been reported not only in NT1, but also in NT2 [20-22] and in secondary narcolepsy [23,24] and not all the patients with NT1 (i.e. with reduced or absent CSF hcrt-1) suffer from RBD. Indeed, RBD is reported to occur in NT1 with a frequency ranging between 7% and 63% in different cohorts [21, 25-28], mirroring the pitfalls in study designs among the different groups. Of note, RBD may sometimes be the heralding symptom of NT1, forerunning the occurrence of cataplexy, especially in younger patients [26, 29-32], and in these cases a correct differential diagnosis with iRBD is important, also considering the different prognosis. Moreover, RBD is extremely rare in otherwise healthy children, and its presence should steer the clinician to investigate a possible narcolepsy or a complex neurodevelopmental disorder [33,34].

With this narrative review, we aimed at rendering a comprehensive state-of-the-art of N-RBD, paving the way for future studies helping in solving the current ambiguities and particularly highlighting aspects supporting or questioning RBD as an intrinsic feature of NT1.

We will also compare N-RBD versus iRBD heralding synucleinopathies, in order to depict their clinical, neurophysiological, and biological borders and discuss the relevance of N-RBD as well as the role of hypocretin neurotransmission in RBD pathophysiology.

### **Diagnosis and prevalence**

Because of the loss of physiological REM-related muscle atonia, patients with RBD act out their dreams, which are usually unpleasant in their content, with consequent and recurrent episodes of violent and energetic behaviors, emerging while sleeping [14,25]. According to the ICSD-3 [1], the diagnosis of RBD is based on the presence of four criteria, i.e.: (A) repeated episodes of sleep-related vocalization and/or complex motor behaviors; (B) these behaviors are documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep; (C) polysomnography-demonstrated REM sleep without atonia (RSWA); and (D) the disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance use. To some extent, even if the pattern of RBD has been reported to be milder, these criteria may be applied also to narcolepsy. However, there is still no consensus regarding the cut-off that should be used to diagnose RSWA [35-37]. This point is particularly tricky for N-RBD, as RSWA has been reported to be less affected than in iRBD consisting in phasic rather than in tonic muscle activation [38,39], with motor dyscontrol during REM sleep being intrinsic feature of NT1, independent of clinical RBD features on the other hand [39-40].

The prevalence of RBD is difficult to ascertain as it has been assessed with a variety of screening questionnaires that have provided different results in predicting the conversion to synucleinopathies [41], and rarely by adopting current criteria, i.e. including v-PSG for formulating the diagnosis [42]. Table 1 summarizes the most relevant studies on iRBD prevalence in the general population, detailing the methods used to establish the possible (screening questionnaires), probable (clinical assessment), or definite diagnosis when symptoms were confirmed by polysomnographic assessment. With these limits, the prevalence has been estimated by questionnaires to be between 2% and 5% in subjects above 50 or 60 years of age [42, 43-45], and up to 7-8% in older populations [46,47]. Conversely, when video-polysomnography (PSG) was used to confirm the clinical suspicion of RBD or to massively investigate otherwise healthy subjects, RBD prevalence definitely dropped down to 0.74-1.15% [42,43,48].

Narcolepsy seems to be the second most common cause of “secondary” RBD, accounting for about 10-15% of cases [14]. Clinical series of consecutive RBD patients indeed showed that narcolepsy accounts for up to 38% of secondary RBD in patients younger than 50 years, whereas synucleinopathies were more common in subjects aged above 50 years [30]. However, the prevalence has been reported in different studies with a large range-span, reflecting bias related to the different criteria used and inclusion of patients with NT1 and NT2 [23,49-52] or focus on NT1 only [32,53-54], and inclusion of patients taking anti-cataplectic drugs such as antidepressants that are another cause of RBD [26]. Even in the absence of clinical complaint of RBD, video-PSG may reveal an excessive increase in chin EMG tone or of EMG twitching during REM sleep associated with simple motor behavior [38,40,55]. The latter milder form of RBD can be easily overlooked, leading to an underestimation of the real prevalence. Overall, studies based on questionnaires/clinical interviews reported a prevalence of approximately 60-70% [21,27,52,54], which drops down to 2-50% in studies adopting video-PSG [21,25,28,32,39,51,54] (Table 1), also



considering the clinical overlap with nightmares and hallucinations. Studies are convergent in showing a higher occurrence of RBD in NT1, with similar prevalence rates in children and adults (nearly 30% of the cohort) [32,56,57].

### **Phenomenological aspect**

The original descriptions of narcolepsy highlighted the occurrence of sleep disruption. Rechtschaffen et al. [11] noticed that narcoleptics have more body movements during their sleep and wake up more frequently through the night. Similarly, Montplaisir [12] by comparing 20 narcoleptics (mean age 44.3 years) vs. 10 controls (mean age 43.6 years) confirmed that patients had more body movements during their sleep, which occurred preferentially during REM sleep. This abnormal motor control was originally ascribed to subcontinuous stage shifts and to what authors called “intermediate sleep”, to indicate the presence of REM characteristics in sleep stages other than REM sleep. Schenck et al. [13] reported for the first time RBD within the spectrum of symptoms of narcolepsy. Indeed, by using PSG data gathered over several years, they showed that 12% of 142 consecutive patients with narcolepsy had extensive motor dysregulation during REM sleep, and 7% met the criteria for RBD [13]. Therefore, since the original descriptions, it was clear that abnormal motor control during REM sleep ranges from subclinical to minor motor episodes to clear RBD [25]. However, only few studies have been published adopting v-PSG, aiming for the description of the phenomenological features of RBD in narcolepsy. The RBD pattern in NT1 patients has been reported to be calmer if compared to that of iRBD or of RBD within a neurodegenerative condition [40,55,58,59], even if a common pattern may be seen [60]. Within narcolepsy, RBD seems to have a sporadic occurrence and not to be an everyday phenomenon [21,26,55,61], but this might be also due to the fact that the pattern is gentler and behaviors may be easily overlooked [59]. Patients were reported to have simple and quiet motor

activity during REM sleep, which, differently from iRBD episodes (Figure 1), recurred both in first and the second half of the night (Figure 2) [40,55,59]. Even if a less violent pattern has been mainly reported [59], rare cases of violent RBD within narcolepsy have been also described [62] and these more violent episodes seem to occur more commonly in the latter part of the night recalling iRBD [55]. Of note, as in original descriptions [11,12], a recent study [59] reported that nocturnal motor activity/behaviors recurred throughout the whole night, in both NREM and REM sleep, and showed frequently an almost stereotyped pattern in the same subject [59]. This finding corroborates the hypothesis that N-RBD is a more complex phenomenon, likely linked to a motor and state of being instability more severe than that of iRBD.

Therefore, N-RBD has been reported to be more similar to REM-related motor episodes (Figure 2) [38,40,55,59] and to be less complex and energetic if compared to frank florid RBD (Figure 1). The phenomenology of N-RBD has been reported to be particularly severe in children, especially close to the disease onset. Antelmi et al. [32], by reviewing v-PSG recordings of children affected with NT1 observed, within 2 years from disease onset, the presence of a severe motor dyscontrol during REM sleep in almost 30% of them. Of these patients, six had episodes of RBD, while seven reported even a more severe phenotype, with subcontinuous patterned-gesturing, recurring every time they entered into a dissociated REM sleep state, throughout the whole nocturnal and daytime sleep. NT1 children with RBD had not only a more severe motor control during REM sleep, but also a more severe motor control dysfunction during daytime in terms of cataplexy (ranging from “cataplectic facies” to a subcontinuous generalized hypotonic status), hence suggesting somehow a link to the acute loss of hypocretin neurons. Of note, presence of N-RBD in children correlates with a lower atonia index during REM sleep (RAI), and therefore with a more severe dyscontrol of muscle tone during REM sleep, but not with sleep instability, as measured with stage-shift transitions or with lower CSF hcrt-1 levels.

### **Additional clinical aspects**

Demographic features do differ between iRBD and N-RBD and, indeed, the former occurs mainly in middle-aged men, while the latter affects children or young patients, without differences in sex distribution [1,14].

As far as additional symptoms/clinical aspects are concerned, patients with RBD associated with an idiopathic/neurodegenerative condition and those with N-RBD only share few overlapping features, but differ for several others.

Sleep attacks indeed are within the core symptoms of narcolepsy [1]; however, excessive daytime sleepiness (EDS) of narcoleptic type, with SOREMPs, hallucinations, sleep paralysis and even cataplexy-like phenomena have been reported also in patients with a parkinsonian condition [63-70]. EDS has been reported also within the symptoms of iRBD, however, it is likely that prominent EDS is a sign of an evolution of neurodegeneration, rather than an intrinsic feature of RBD [17,18,71].

Hypnagogic hallucinations are additional core symptoms of narcolepsy, brought by dissociated W-REM state [72]. Hallucinations may occur also in neurodegenerative conditions, although they are clearly different from those of narcolepsy, either because they are not sleep-related but also because they differ in quality [73].

Loss/reduction of olfaction as well is an important non-motor and prodromal symptom of PD, frequently seen in iRBD patients [17,18,59,71], but also reported in narcolepsy [59,73-75]. In iRBD, longitudinal studies showed that impaired olfaction and color vision are the most powerful predictors for conversion of iRBD into synucleinopathies [17,18]. In narcolepsy, reduction of olfaction has been hypothesized to be an intrinsic feature, not related to hcr1 level, because it

has been reported in both patients with and without cataplexy [75,76], nor to the presence of RBD [75].

Autonomic symptoms as well have been reported within the corollaries of narcoleptic symptoms [59,76,77], even being of different type and not as severe as reported in iRBD and PD [59,71,78].

Cognitive functioning, executive function in particular, has been reported to be impaired in both narcoleptic patients and iRBD patients [3,17,18,59,71,79] however, in NT1 patients attentive and executive function abnormalities are more likely linked to sleepiness [79].

Finally, PD/AD have been inconsistently reported in association with narcolepsy [80-84].

See Table 2.

### **Biomarkers of the disease**

The pathological hallmark of NT1 is loss/reduction of hcrt-1 in the cerebrospinal fluid (CSF) [1].

Therefore, all patients with NT1 should have CSF hcrt-1 <110 pg/mL and, clinically, cataplexy. CSF hcrt-1 levels have been reported to be lower, although not absent, also in PD patients [85-87]. CSF hcrt-1 reduction has been reported to be more prominent in PD patients with sleep symptoms versus those without. In one study, the hypocretin system in PD patients has been shown not to be selectively disrupted, with one study showing melanin concentrating hormone cell loss in the same patients with hcrt-1 loss [88]. It is likely that CSF hcrt-1 reduction in PD patients occurs secondary to collateral damage caused by a widespread neurodegenerative process involving also the hypothalamus [89-92], although also in this regard results are ambiguous [93,94]. To corroborate this finding, CSF hcrt-1 levels have been reported to be normal in iRBD patients [95]. Results are anyway confounding, and indeed in another cohort of PD patients, an increased

ventricular CSF hcr1-1 level has been correlated with the co-occurrence of RBD [96] and also the association between CSF hcr1-1 levels and sleepiness in PD has been questioned [97].

Results regarding searching for neurodegenerative markers in the CSF are also contradictory and confounding in both iRBD and NT1 patients and data are still too scarce to draw any conclusion on the predictive role of CSF biomarkers [98]. Overall, while there are some data supporting abnormalities in CSF neurodegenerative proteins in iRBD [98], this does not seem to be the case in NT1 patients [99].

Substantia nigra hyperechogenicity – a sonographic vulnerability marker for Parkinson's disease (PD) – has been reported in iRBD, while it has not been found in NT1, even if on CNS echography the brainstem raphe volume has been reported to be more reduced in narcoleptic subjects with RBD than in those without [100].

Even if several biochemical and histopathological differences do exist between the two conditions [59,99,101,102], ictal single-photon emission tomography studies exploring the RBD pathways in vivo showed similar bilateral activation in the premotor areas, interhemispheric cleft, periaqueductal area, dorsal and ventral pons and the anterior lobe of the cerebellum in patients with iRBD and in those with RBD due PD (PD-RBD) or N-RBD [103]. Therefore, it is reasonable to infer that even if the intrinsic cause of the phenomenon in the two conditions is different, it does act by activating/deactivating the same causal structures.

See Table 2.

## **Neuropathophysiology**

RSWA is the neurophysiological hallmark of RBD [1]. It is defined by the presence of sustained (tonic) loss of normal muscle atonia during REM sleep, and/or by intermittent (phasic) excessive electromyographic activity during REM sleep.

The quantification of RSWA is mandatory in order to objectively confirm RBD diagnosis, according to the latest ICSD [1].

Several visual/manual [35-37,50,104] and automated methods are available allowing, with similar accuracy, a reliable quantification of RSWA in patients with RBD. These methods have been used also for the comparison of neurophysiological features of RBD in narcolepsy and in other conditions [104, 106-113]. All the above studies demonstrated that there is substantial agreement in determining RAI between the automatic scoring method, i.e the RAI, and the Montréal and SINBAR visual scoring methods [109,111].

Studies on muscle tone during REM sleep in narcolepsy agree on reporting that both RBD and narcoleptic patients have a lower percentage of RSWA than controls [38,104], but narcoleptic patients were found to have a higher percentage of REM atonia and of phasic EMG density when compared to iRBD [38].

The higher the RSWA, the higher the possibility of having motor behaviors [32,40,53]; RSWA has also been reported to be a very good diagnostic biomarker of NT1 at all ages pointing to the intrinsic motor dyscontrol during REM sleep in narcolepsy [22,32,38,53,106].

Computerized quantitative analysis of the chin EMG tone during all sleep stages using the RAI disclosed that during REM sleep RAI was reduced in both iRBD and NT1 with RBD patient groups; on the contrary, during NREM sleep, atonia index (AI) was increased in iRBD patients but remained low in patients with NT1 and RBD [114]. Similarly, the number of chin EMG activations, reflecting the phasic activity, was increased during REM sleep in iRBD patients but was decreased during NREM sleep (especially during slow-wave sleep), differently from N-RBD patients in whom EMG

activations were always higher than controls. This study shows a clear different motor dyscontrol between the two conditions, with N-RBD patients presenting increased chin EMG tone and phasic activations in all sleep stages while iRBD patients seem to show only RSWA [113].

Several studies showed that hcr1-1 deficiency in NT1 is associated with nocturnal sleep state instability, a finding that has been shown in experimental models [114] and confirmed in adult patients by analyzing nocturnal sleep transitions at first as classified by the visual scoring of sleep stages [115,116], and subsequently by addressing quantitatively the polysomnographic signal [117]. This evidence indicates that REM sleep is a dissociated state in NT1, a finding consistent also with the high occurrence of RBD. However the only study addressing sleep transitions within the RBD spectrum in NT1 children failed in showing significant differences for a possible ceiling effect [32], suggesting the need for more in depth quantitative analyses to unravel the potential relation between levels of state instability and occurrence of RBD and that other factors over and above are probably implicated.

### **Etiopathophysiology**

N-RBD has been reported in association with history of parasomnia [25], HLA-DQB1\*0602 positivity [26,57], CSF hcr1-1 levels [27], cataplexy [21] and RSWA [27,32,55]. However, although it is more common in NT1, RBD has been reported also in NT2 [20,21,22] and in secondary narcolepsy [23,24,119] and not all the studies reported a correlation of RBD within narcolepsy and CSF hcr1-1 levels.

In iRBD and PD-RBD, several studies indicate that it is unlikely that RBD is due to a dysfunction of the dopaminergic nigrostriatal system and indeed RBD occurs in less than half of PD patients and the use of dopaminergic agents usually does not improve RBD. It is believed that RBD and RSWA are linked to a lesion of a sub-population of REM-on glutamatergic neurons of the locus

subceruleus/sublaterodorsal nucleus (SLD) responsible of inducing muscle atonia via their descending projections to the premotor GABA/glycinergic neurons of the ventral gigantocellular reticular nucleus (GiV) [119]. Loss of this function in iRBD seems to be related to brainstem degeneration linked to underlying synucleinopathy [17,18,70] and positive synucleinopathy, detected by means of peripheral nervous system biopsy, has been consistently reported to be a strong biological fingerprint of iRBD [120-124], particularly positive skin biopsy has emerged as the biological fingerprint of iRBD [121,122], but it has been recently shown to be always negative in N-RBD [59], supporting the hypothesis of a complete different pathophysiology between these two conditions.

N-RBD has been putatively linked instead to the reduction/absence of CSF hcrt-1 [19,125], although it cannot be completely ruled out that the SLD-GiV atonia pathway is damaged in these patients. It has been hypothesized that hypocretin neurons excite the SLD-GiV pathway during REM sleep, in particular during the muscle twitches induced by a phasic glutamatergic excitation of the motoneurons. Indeed, even if hypocretin neurons fire mainly during active wakefulness, they display bursts of activity during the twitches of REM sleep [126]. Moreover, microinjections of hcrt-1 and 2, in the SLD region induces REM sleep with atonia/active sleep [127].

The mediotegmental pontine area might be important for the pathophysiology of both narcolepsy and RBD, as pointed also by case reports of secondary subtypes of narcolepsy and RBD [128]. The pontine inhibitory area, which has been implicated in the pathogenesis of cataplexy, is in close proximity to the locus coeruleus [129], indicating that the degeneration of the hypocretin cell projections to these pontine area may be involved in the comorbidity of RBD and cataplexy in narcolepsy patients [129].

However, several controversial issues do exist, as hypocretin neurons are known to inhibit REM sleep and increase, rather than decrease, muscle tone [130] and therefore their role in



determining RBD appear controversial. Besides, not all the patients affected with NT1 present RBD, raising doubts on the intrinsic link between RBD and CSF hcrt-1 deficiency. Still, no lesion has been observed in patients with narcolepsy in the brainstem structures responsible for muscle atonia. Thus, the occurrence of RBD in patients with narcolepsy is challenging to explain, and no consensus is available for the mechanisms involved.

Alternatively, hypocretin cell loss may induce RBD by promoting dissociation of states and, indeed, along with the well-known wake-promoting role, hcrt-1 neuropeptides would also suppress REM sleep [131]. Therefore, CSF hcrt-1 reduction would facilitate the occurrence of REM sleep at any time of day in an opportunistic way, promoting the onset of dissociated states of being.

Overall, on the one side, iRBD and N-RBD share a few overlapping features, either from the clinical (i.e. hyposmia, autonomic, cognitive and neuropsychiatric symptoms, EDS, PLMs) [2,73,74,90,92,132] and biological (i.e. reduction of CSF-hcrt levels) [91,95] points of view. Moreover, ictal single-photon emission tomography studies exploring the RBD pathways in vivo showed similar activation in the bilateral premotor areas, interhemispheric cleft, periaqueductal area, dorsal and ventral pons and the anterior lobe of the cerebellum in patients with iRBD and in those with PD-RBD or N-RBD [103].

On the other side, however, a body of evidence supports a completely different etiopathogenesis of their underlying diseases [14,98,101,102].

The link with CSF hcrt-1 deficiency, as suggested by Luppi et al. [125], is somehow also supported by clinical observations. Indeed, video-PSG studies reported that patients affected with RBD, i.e. RSWA, are more likely to suffer also from cataplexy, i.e. loss of tone when awake [21,32].

Therefore, N-RBD can be seen as the nocturnal face of sleep-wake instability and REM dissociation, which characterizes this disease.

As introduced above, however, 70–90% of patients with narcolepsy without cataplexy may also present RBD with normal CSF hcrt-1 [20,21] and RBD within NT2 may be considered also as a marker of a possible progression toward the full-blown picture of NT1 [29]. Indeed, in these patients, the mechanisms underlying symptoms such as sleep attacks, hypnagogic hallucinations or RBD are unknown. However, a normal CSF hcrt-1 level in narcolepsy does not necessarily mean that the hypocretin system is spared and partial hypocretin neuron loss has been shown in a postmortem patient with NT2 [133]. In patients with secondary narcolepsy, the role of CSF hcrt-1 levels seem instead marginal [23,24], highlighting the possible involvement of alternative neurotransmitter pathways.

Overall, clinical and neurophysiological findings, i.e. a milder phenotype with phasic rather than tonic loss of muscle atonia during REM sleep in N-RBD versus iRBD, suggest that the underlying mechanisms are completely different.

### **RBD and dream content**

The phenomenology of enacted dreams seems to be different in iRBD and N-RBD, but still insufficiently studied. This is an intriguing issue, perfectly matching with the different neurophysiological substrates of these two conditions. Indeed, while in iRBD patterns of EMG of wakefulness emerge during REM sleep, in N-RBD also individual features of NREM, REM sleep and wakefulness appear in a mixed, dissociated fashion [32,71,134]. According to this concept, also dream mentation might be different.

It is common clinical experience and a general belief that iRBD patients frequently report dreams in which they are attacked by animals or unfamiliar people that they would fight back in self-defense or try to run away from. In iRBD, It has been also reported that fear and anger are the most common associated emotions, with a striking prevalence of aggression themes and less of

appetitive behaviors [135-137]; however, subsequent studies did not support this notion [138,139], even if the study by D'Agostino et al [138] had the limitation that 12 patients (i.e. 75% of the cohort) were taking clonazepam, that might affect the dream process and recall, as pointed in the comment letter to this article [140].

Regarding narcoleptic patients, Fosse et al. [141] reported that they had intensified REM-dream emotion. Dream mentation is also reported to be different between SOREMPs during daytime and SOREMPs and REM during the night. Indeed, total recall counts along with visual vividness, reflective consciousness, improbabilities and discontinuities are more frequent during daytime SOREMPs, while in controls all these variables, but reflective consciousness, are more numerous after late night REM sleep versus early night REM sleep. In addition, emotions were found to be more prevalent in SOREMPs than in REM [141-143], with positive and negative emotions equally present [143,144]. For nighttime REM, narcoleptic patients were found to have a higher level of joy/elation and anxiety/fear than healthy controls [141,142], but not of terror, as frequently reported in iRBD. Fosse et al. [141,143] suggested that dream mentation in narcolepsy might reflect an unstable REM process, with intermittingly elevated aminergic brain modulation that may lead to more activation of the prefrontal cortical areas.

Another report found that RBD episodes can occur repeatedly during SOREMPs and can be accompanied by dissociated REM-dreaming phenomena such as volitional control and awareness of dreaming, flying and out of body experiences. [144,145]. The enacted behaviors recorded during daytime SOREMPs were nonviolent (i.e., task oriented or reminiscent of lively interactions with other persons), similar to those of RBD episodes observed in the first part of the night in NT1 patients [55]. Overall, N-RBD is reported to be gentler and with a pattern more similar to that of "status dissociatus" [32,72] and less violent or energetic than that reported in iRBD. The different dream mentation might therefore be under the influence of the different

neurophysiological substrates of the two entities and for instance of their different physiopathology.

Concerning iRBD, it must be considered that negative emotions, misfortune, and threatening events are over-represented in dreams also in the general population, compared to positive emotions and peaceful activities [146-148]. Additionally, vivid dreams with physical aggression and animal-related content are often reported by patients with synucleinopathies and, particularly, in those with frontal dysfunction [149]. Therefore, the content of dream in iRBD or PD-RBD might be also related to a cortical involvement and it may be hypothesized that chronic RBD, as a part of a widespread neurodegenerative process, might lead to a release of ontogenetically early dream patterns.

Further studies are therefore mandatory to this regard because they might provide insights into the pathophysiology of these two different conditions.

### **Treatment**

Very few data are available on the impact of pharmacological or even behavioral treatments on N-RBD.

Antidepressants used to treat cataplexy could possibly be a factor in worsening or inducing RBD [25,26]. This aspect is of clinical interest given the current knowledge that RBD may be a side effect of antidepressant treatment, as well as of beta blockers, of anticholinesterase inhibitors, and of selegiline also in the general population [1,150]. Therefore, when RBD is a prominent and disabling symptom within NT1 (up to 35% of patients according to Schenck et al. [25]), the clinician should at first consider the possibility to modify drug treatment, in order to reduce the burden of RBD symptoms, by using alternative compounds for cataplexy/EDS.

The pharmacological treatment of iRBD, beside the recommendation to minimize the risk of injuries and the reported (not evidence-based) efficacy of non-pharmacological approaches (e.g. hypnotherapy, use of complex systems connected to a pressurized bed alarm) is mainly based on the use of clonazepam and melatonin [14]. While the mechanisms of action of the above drugs in iRBD are still debated [151,152], there are no studies at all testing their efficacy in N-RBD, thus calling for future research focused on this peculiar clinical population [153]. Indeed, a single study reported the use of melatonin in drug-resistant RBD patients associated with comorbid neurological conditions (2 with narcolepsy) and stated the possibility of a safe mid-term (i.e. one year) treatment without further detailing the clinical results in different neurological comorbidities [154]

Some anecdotal data may support the use of sodium oxybate for N-RBD. In a small uncontrolled case series of adult NT1 patients evaluated on consecutive nights (without and with low doses of sodium oxybate), two out of 16 patients showed complex episodes at the first nocturnal recording but not under treatment [155], without however disclosing a significant impact of the treatment on objective muscle tone measures. Indeed, registration trials and post-authorization studies on sodium oxybate considered EDS and cataplexy as primary outcomes, and only few data on the impact on sleep paralysis were reported but not on RBD symptomatology. However, sodium oxybate appeared to be useful for the clinical management of RBD in a single NT1 case [156], and induced a reduction of muscle activities during REM sleep in a large polysomnographic study that however did not include any information on RBD symptoms or motor episodes [157]. Some case reports also pointed at the potential efficacy of sodium oxybate on drug-resistant iRBD [158,159] and the evidence of an intrinsic link between RBD occurrence up to a status dissociatus condition and cataplexy severity in NT1 children [32]. Future studies may address the impact of sodium oxybate on 24-hour motor impairment in NT1 (cataplexy and RBD).

## Conclusion

Narcolepsy is the second most common cause of secondary RBD; indeed up to 60% of narcoleptic patients suffer from RBD [21,25,28,32,39,51,54], versus 1% of the general population [42-48], and RBD may be the heralding symptom of the narcoleptic pentad, especially in children, forerunning the appearance of cataplexy and the development of the full-blown NT1 phenotype.

However, not all patients with CSF hcr1-1 deficiency suffer from RBD and RBD can be seen also in NT2 patients or in secondary narcolepsy. To further corroborate this, N-RBD correlates with abnormal motor control during sleep [53,59] and particularly with increased muscle tone during REM sleep [32,53,106], but its correlation with CSF hcr1-1 levels still needs to be solved [27,32].

Even if iRBD and N-RBD share definitely some overlapping features, it appears that from both the clinical and neurophysiological standpoints they do have different features. Indeed, motor behaviors during REM sleep in narcoleptic patients are gentler, simpler and calmer, if compared to those seen in iRBD patients. Moreover, contrary to iRBD patients, narcoleptic patients may have abnormal movements also during NREM sleep [26,32]. Also neurophysiological studies corroborate this observation, showing a different motor dyscontrol between the two conditions, with N-RBD patients presenting increased chin EMG tone and phasic activations in all sleep stages and dissociated EEG features, while iRBD patients seem to show only RSWA.

Therefore, it can be speculated that N-RBD might be the nocturnal face of abnormal motor dyscontrol across the 24 hour, as a mirror of cataplexy during daytime but, differently from cataplexy, it does not seem to correlate directly with CSF hcr1-1 levels.

Studies are thus mandatory in order to elucidate the role of the hypocretin system in N-RBD, the possible involvement of additional factors and the pathogenesis of RBD within secondary narcolepsy with normal CSF hcrt-1.

Studies dealing with the treatment of N-RBD are completely lacking and are thus encouraged.

It is also unknown if the presence of RBD within narcolepsy might be linked to a different prognosis or to a discrete subtype of narcolepsy.

Finally, along with a gentler and milder motor pattern, also the anguished and nightmarish quality of dreams of iRBD seems to lack in N-RBD [59]. This is an intriguing issue still to be solved. For instance, REM sleep dissociation and, in particular N-RBD, offers a unique opportunity to study dream content, its meaning and its emotional correlates, but it can also offer a key to catch important pathophysiological issues.

### **Practice points**

- Narcolepsy is the second most common cause of secondary RBD
- In children the presence of RBD should raise the suspicion of an underlying narcolepsy
- Clinical, neurophysiological and biological markers do differ between iRBD and NRBD
- The neurophysiology of NRBD is still a vexing issue, but sleep-wake instability linked to hcrt-1 loss likely play a core role
- Pharmacological approaches aiming at improving NRBD are still to be investigated

### **Research agenda**

- To elucidate the ultimate role of the hypocretin system in the pathogenesis of N-RBD
- To better evaluate the prevalence of N-RBD in primary and secondary forms

- To evaluate the degree of motor dyscontrol during nighttime before and after medications for narcolepsy
- To study the prognosis of N-RBD, in regard to both narcolepsy and RBD
- To investigate the significance of RBD in NT2, also as a potential clinical marker for conversion in NT1
- To understand which is/are the generator/s of N-RBD
- To compare dream mentation in iRBD and N-RBD

**Figure 1:**

Hypnogram and RBD episodes (vertical bars) in a patient with iRBD.

S1-S2-S3-S4: stage 1, 2, 3 and 4 of NREM sleep; R: REM sleep; W: wakefulness.

**Figure 2**

Hypnogram and RBD episodes (vertical bars) in a patient with NT1.

S1-S2-S3-S4: stage 1, 2, 3 and 4 of NREM sleep; R: REM sleep; W: wakefulness.

**Table 1:**

IH: Idiopathic hypersomnia; NT1: Narcolepsy type 1; NT2: Narcolepsy type 2; iRBD: Isolated / Idiopathic RBD; pRBD: possible RBD; RBD: Rem sleep behavior disorder;; RBDSQ: RBD Screening questionnaire; RBDSQ-J: Japanese version of RBDSQ; RBD-I: Innsbruck RBD inventory; RSWA: REM sleep without atonia.vPSG: video polysomnography;

**Table 2**



CSF: cerebro-spinal fluid;EDS: excessive daytime sleepiness; F: females; yo: years old;M: males;  
MIBG: meta-iodobenzylguanidine; p- $\alpha$ -syn: phosphorylated.alpha-synuclein; RSWA: REM sleep  
without atonia; SN: substantia nigra SPECT: single-photon emission computed tomography .;

## References

1. American Academy of Sleep Medicine. The International Classification of Sleep Disorders: Diagnostic & Coding Manual. 2nd ed. Rochester, MN: American Academy of Sleep Medicine; 2005
2. Scammell TE. Narcolepsy. *N Engl J Med* 2015;373:2654-2662.
3. Postiglione E, Antelmi E, Pizza F, Lecendreux M, Dauvilliers Y, Plazzi G. The clinical spectrum of childhood narcolepsy. *Sleep Med Rev* 2018;38:70-85.
4. Dauvilliers Y, Montplaisir J, Molinari N, Carlander B, Ondze B, Besset A, Billiard M. Age at onset of narcolepsy in two large populations of patients in France and Quebec. *Neurology* 2001;57:2029-33.
5. Ohayon MM, Priest RG, Zulley J, Smirne S, Paiva T. Prevalence of narcolepsy symptomatology and diagnosis in the European general population. *Neurology* 2002;58:1826-33.
6. Partinen M, Kornum BR, Plazzi G, Jennum P, Julkunen I, Vaarala O. Narcolepsy as an autoimmune disease: the role of H1N1 infection and vaccination. *The Lancet Neurology* 2014;13:600-13.
7. \*Latorre D, Kallweit U, Armentani E, Foglierini M, Mele F, Cassotta A, et al. T cells in patients with narcolepsy target self-antigens of hypocretin neurons. *Nature*. 2018;562:63-8.

8. \*Luo G, Ambati A, Lin L, Bonvalet M, Partinen M, Ji X, Maecker HT, Mignot EJ. Autoimmunity to hypocretin and molecular mimicry to flu in type 1 narcolepsy. *Proc Natl Acad Sci U S A*. 2018;115:E12323-32.
9. Liblau RS, Vassalli A, Seifinejad A, Tafti M. Hypocretin (orexin) biology and the pathophysiology of narcolepsy with cataplexy. *Lancet Neurol* 2015;14:318-28.
10. Kaushik MK, Aritake K, Imanishi A, Kanbayashi T, Ichikawa T, Shimizu T, et al. Continuous intrathecal orexin delivery inhibits cataplexy in a murine model of narcolepsy. *Proc Natl Acad Sci U S A*. 2018;115:6046-51.
11. Rechtschaffen A, Dement W. Studies on the relation of narcolepsy, cataplexy, and sleep with low voltage random EEG activity. In: Kety S, Evarts E, Williams H, editors. *Sleep and Altered States of Consciousness*. Williams and Wilkins; Baltimore: 1967. pp. 488–505.
12. \*Montplaisir. Disturbed nocturnal sleep. In: *Narcolepsy; Advances in Sleep Research, Vol 3*; Ed Guilleminaul, Dement, Passouant, 1976 pp: 43-56.
13. Schenck CH, Milner DM, Hurwitz TD, Bundlie SR, Mahowald MW. A polysomnographic and clinical report on sleep-related injury in 100 adult patients. *Am J Psychiatry* 1989;146:1166-73.
14. Dauvilliers Y, Schenck CH, Postuma RB, Iranzo A, Luppi PH, Plazzi G, et al. REM sleep behaviour disorder. *Nat Rev Dis Primers*. 2018;4:19.
15. Iranzo A, Tolosa E, Gelpi E, Molinuevo JL, Valdeoriola F, Serradell M, et al. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. *Lancet Neurol* 2013;12:443-53.

16. Howell MJ, Schenck CH. Rapid eye movement sleep behavior disorder and neurodegenerative disease. *JAMA Neurol* 2015;72:707-12.
17. Postuma RB, Iranzo A, Hogl B, Arnulf I, Ferini-Strambi L, Manni R, et al. Risk factors for neurodegeneration in idiopathic rapid eye movement sleep behavior disorder: a multicenter study. *Ann Neurol* 2015;77:830-39.
18. Postuma RB, Iranzo A, Hu M, Högl B, Boeve BF, Manni R, et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. *Brain* 2019;142:744-59.
19. Luppi PH, Clement O, Sapin E, Gervasoni D, Peyron C, Léger L, et al. The neuronal network responsible for paradoxical sleep and its dysfunctions causing narcolepsy and rapid eye movement (REM) behavior disorder. *Sleep Med Rev* 2010;15:153-63.
20. \*Mignot E, Lammers GJ, Ripley B, Okun M, Nevsimalova S, Overeem S, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. *Arch Neurol* 2002;59:1553-62.
21. Nightingale S, Orgill JC, Ebrahim IO, de Lacy SF, Agrawal S, Williams AJ. The association between narcolepsy and REM behavior disorder (RBD). *Sleep Med* 2005;6:253-8.
22. Bin-Hasan S, Videnovic A, Maski K. Nocturnal REM Sleep Without Atonia Is a Diagnostic Biomarker of Pediatric Narcolepsy. *J Clin Sleep Med* 2018;14:245-252
23. Moghadam KK, Pizza F, La Morgia C, Franceschini C, Tonon C, Lodi R, et al. Narcolepsy is a common phenotype in HSAN IE and ADCA-DN. *Brain* 2014;137:1643-55.
24. Nevsimalova S, Malinova V. Cataplexy and sleep disorders in Niemann-Pick type C disease. *Curr Neurol Neurosci Rep* 2015;15:522.

25. \*Schenck CH, Mahowald MW. Motor dyscontrol in narcolepsy: rapid-eye-movement (REM) sleep without atonia and REM sleep behaviour disorder. *Ann Neurol* 1992;32:3-10.
26. Mayer G, Meier-Ewert K. Motor dyscontrol in sleep of narcoleptic patients (a lifelong development?). *J Sleep Res* 1993;2:143-8.
27. Knudsen S, Gammeltoft S, Jennum PJ. Rapid eye movement sleep behaviour disorder in patients with narcolepsy is associated with hypocretin-1 deficiency. *Brain*. 2010;133:568-79.
28. Luca G, Haba-Rubio J, Dauvilliers Y, Lammers GJ, Overeem S, Donjacour CE, et al; European Narcolepsy Network. Clinical, polysomnographic and genome-wide association analyses of narcolepsy with cataplexy: a European Narcolepsy Network study. *J Sleep Res* 2013;22:482-95.
29. Bonakis A, Howard RS, Williams A. Narcolepsy presenting as REM sleep behaviour disorder. *Clin Neurol Neurosurg* 2008;110:51-20.
30. Bonakis A, Howard RS, Ebrahim IO, Merritt S, Williams A. REM sleep behaviour disorder (RBD) and its associations in young patients. *Sleep Med* 2009;10:641-5.
31. \*Nevsimalova S, Prihodova I, Kemlink D, Lin L, Mignot E. REM behavior disorder (RBD) can be one of the first symptoms of childhood narcolepsy. *Sleep Med* 2007;8:784-6.
32. \*Antelmi E, Pizza F, Vandi S, Neccia G, Ferri R, Bruni O, et al. The spectrum of REM sleep-related episodes in children with type 1 narcolepsy. *Brain* 2017;140:1669-79.
33. Lloyd R, Tippmann-Peikert M, Slocumb N, Kotagal S. Characteristics of REM sleep behavior disorder in childhood. *J Clin Sleep Med* 2012;8:127-31.

34. Kotagal S. Rapid Eye Movement Sleep Behavior Disorder During Childhood. *Sleep Med Clin.* 2015;10:163-7.
35. Lapierre O, Montplaisir J. Polysomnographic features of REM sleep behavior disorder: development of a scoring method. *Neurology.* 1992;42:1371-4.
36. Montplaisir J, Gagnon JF, Fantini ML, Postuma RB, Dauvilliers Y, Desautels A, et al. Polysomnographic diagnosis of idiopathic REM sleep behavior disorder. *Mov Disord* 2010;25:2044-51.
37. Frauscher B, Iranzo A, Gaig C, Gschliesser V, Guaita M, Raffelseder V, et al.; SINBAR (Sleep Innsbruck Barcelona) Group. Normative EMG values during REM sleep for the diagnosis of REM sleep behavior disorder. *Sleep* 2012;35:835-47.
38. Dauvilliers Y, Rompré S, Gagnon JF, Vendette M, Petit D, Montplaisir J. REM sleep characteristics in narcolepsy and REM sleep behavior disorder. *Sleep* 2007;30:844-9.
39. Ferri R, Franceschini C, Zucconi M, Vandi S, Poli F, Bruni O, et al. Searching for a marker of REM sleep behavior disorder: submental muscle EMG amplitude analysis during sleep in patients with narcolepsy/cataplexy. *Sleep* 2008;31:1409-17.
40. Franceschini C, Ferri R, Pizza F, Ricotta L, Vandi S, Detto S, et al. Motor events during REM sleep in patients with narcolepsy-cataplexy: a video-polysomnographic pilot study. *Sleep Med* 2011;12:S59-63.
41. Skorvanek M, Feketeova E, Kurtis MM, Rusz J, Sonka K. Accuracy of Rating Scales and Clinical Measures for Screening of Rapid Eye Movement Sleep Behavior Disorder and for Predicting Conversion to Parkinson's Disease and Other Synucleinopathies. *Front Neurol* 2018;9:376.

42. Pujol M, Pujol J, Alonso T, Fuentes A, Pallerola M, Freixenet J, et al. Idiopathic REM sleep behavior disorder in the elderly Spanish community: a primary care center study with a two-stage design using video-polysomnography. *Sleep Med* 2017;40:116-121.
43. kang SH, Yoon IY, Lee SD, et al. REM sleep behavior disorder in the Korean elderly population: prevalence and clinical characteristics. *Sleep* 2013;36:1147-52.
44. Wong JC, Li J, Pavlova M, Chen S, Wu A, Wu S, Gao X. Risk factors for probable REM sleep behavior disorder: A community-based study. *Neurology* 2016;86:1306-12.
45. Ma JF, Qiao Y, Gao X, Liang L, Liu XL, Li DH, Tang HD, Chen SD. A community-based study of risk factors for probable rapid eye movement sleep behavior disorder. *Sleep Med* 2017;30:71-76.
46. Boot BP, Boeve BF, Roberts RO, Ferman TJ, Geda YE, Pankratz VS, et al. Probable rapid eye movement sleep behavior disorder increases risk for mild cognitive impairment and Parkinson disease: a population-based study. *Ann Neurol* 2012;71:49-56.
47. Mahlkecht P, Seppi K, Frauscher B, Kiechl S, Willeit J, Stockner H, et al. Probable RBD and association with neurodegenerative disease markers: A population-based study. *Mov Disord* 2015;30:1417-21.
48. Haba-Rubio J, Frauscher B, Marques-Vidal P, Toriel J, Tobback N, Andries D, et al. Prevalence and Determinants of REM Sleep Behavior Disorder in the General Population. *Sleep*. 2017 Dec 5. doi:10.1093/sleep/zsx197.
49. Del Rosso LM, Chesson AL Jr, Hoque R. Characterization of REM sleep without atonia in patients with narcolepsy and idiopathic hypersomnia using AASM scoring manual criteria. *J Clin Sleep Med*. 2013;9:675-80.

50. Frauscher B, Ehrmann L, Högl B. Defining muscle activities for assessment of rapid eye movement sleep behavior disorder: from a qualitative to a quantitative diagnostic level. *Sleep Med* 2013;14:729-33
51. Sasai-Sakuma T, Kinoshita A, Inoue Y. Polysomnographic Assessment of Sleep Comorbidities in Drug-Naïve Narcolepsy-Spectrum Disorders--A Japanese Cross-Sectional Study. *PLoS One* 2015;10(8):e0136988.
52. Suzuki K, Miyamoto M, Miyamoto T, Inoue Y, Matsui K, Nishida S, et al. The Prevalence and Characteristics of Primary Headache and Dream-Enacting Behaviour in Japanese Patients with Narcolepsy or Idiopathic Hypersomnia: A Multi-Centre Cross-Sectional Study. *PLoS One* 2015;10(9):e0139229.
53. Ferri R, Manconi M, Plazzi G, Bruni O, Vandi S, Montagna P, et al. A quantitative statistical analysis of the submentalis muscle EMG amplitude during sleep in normal controls and patients with REM sleep behavior disorder. *J Sleep Res* 2008;17: 89-100.
54. Mattarozzi K, Bellucci C, Campi C, Cipolli C, Ferri R, Franceschini C, et al. Clinical, behavioural and polysomnographic correlates of cataplexy in patients with narcolepsy/cataplexy. *Sleep* 2007;30:844-9.
55. Cipolli C, Franceschini C, Mattarozzi K, Mazzetti M, Plazzi G. Overnight distribution and motor characteristics of REM sleep behaviour disorder episodes in patients with narcolepsy-cataplexy. *Sleep Med* 2011;12:635-40.
56. Nevsimalova S, Jara C, Prihodova I, Kemlink D, Sonka K, Skibova J. Clinical features of childhood narcolepsy. Can cataplexy be foretold? *Eur J Paediatr Neurol* 2011;15:320-5.

57. Nevsimalova S, Pisko J, Buskova J, Kemlink D, Prihodova I, Sonka K, Skibova J. Narcolepsy: clinical differences and association with other sleep disorders in different age groups. *J Neurol* 2013;260:767-75.
58. Iranzo A, Santamaria J, Tolosa E. The clinical and pathophysiological relevance of REM sleep behavior disorder in neurodegenerative diseases. *Sleep Med Rev* 2009;13:385-401.
59. \*Antelmi E, Pizza F, Donadio V, Filardi M, Soserio L, Yuri, Incensi A. Biomarkers for REM sleep behavior disorder in idiopathic and narcoleptic patients. *Annals of Clinical and Translational Neurology* 2019 doi: DOI: 10.1002/ACN3.50833.
60. Oudiette D, Leu-Semenescu S, Roze E, Vidailhet M, De Cock VC, Golmard JL, Arnulf I. A motor signature of REM sleep behavior disorder. *Mov Disord* 2012;27:428-31.
61. Frauscher B, Gschliesser V, Brandauer E, Schönwald SV, Falkenstetter T, Ehrmann L, et al. Motor disturbances during non-REM and REM sleep in narcolepsy-cataplexy: a videopolysomnographic analysis. *J Sleep Res* 2011;20:514-21.
62. Ingravallo F, Schenck CH, Plazzi G. Injurious REM sleep behaviour disorder in narcolepsy with cataplexy contributing to criminal proceedings and divorce. *Sleep Med* 2010;11:950-2.
63. Rye DB, Bliwise DL, Dihenia B, Gurecki P. Daytime sleepiness in Parkinson's disease. *J Sleep Res* 2000;9:63e9.
64. Arnulf I, Konofal E, Merino-Andreu M, Houeto JL, Mesnage V, Welter ML, et al. Parkinson's disease and sleepiness: an integral part of PD. *Neurology* 2002;58:1019-24.
65. Roth T, Rye DB, Borchert LD, Bartlett C, Bliwise DL, Cantor C, et al. Assessment of sleepiness and unintended sleep in Parkinson's disease patients taking dopamine agonists. *Sleep Med* 2003;4:275e80.



66. Kaynak D, Kiziltan G, Kaynak H, Benbir G, Uysal O. Sleep and sleepiness in patients with Parkinson's disease before and after dopaminergic treatment. *Eur J Neurol* 2005;12:199e207.
67. Gjerstad, M. D., Alves, G., Wentzel-Larsen, T., Aarsland, D. and Larsen, J. P. Excessive daytime sleepiness in Parkinson disease: is it the drugs or the disease? *Neurology* 2006;67:853-8.
68. Monaca C, Duhamel A, Jacquesson JM, Ozsancak C, Destee A, Guieu JD, et al. Vigilance troubles in Parkinson's disease: a subjective and objective polysomnographic study. *Sleep Med* 2006;7:448e53.
69. Bliwise DL, Trotti LM, Juncos JJ, Factor SA, Freeman A, Rye DB. Daytime REM sleep in Parkinson's disease. *Park Relat Disord* 2013;19:101-3.
70. Ylikoski A, Martikainen K, Sarkanen T, Partinen M. Parkinson's disease and narcolepsy-like symptoms. *Sleep Med*. 2015;16:540-4.
71. Arnaldi D, Antelmi E, St Louis EK, Postuma RB, Arnulf I. Idiopathic REM sleep behavior disorder and neurodegenerative risk: To tell or not to tell to the patient? How to minimize the risk? *Sleep Med Rev*. 2017;36:82-95.
72. Antelmi E, Ferri R, Iranzo A, Arnulf I, Dauvilliers Y, Bhatia KP, et al. From state dissociation to status dissociatus. *Sleep Med Rev* 2016;28:5-17.
73. Leu-Semenescu S, De Cock VC, Le Masson VD, Debs R, Lavault S, Roze E, et al. Hallucinations in narcolepsy with and without cataplexy: contrasts with Parkinson's disease. *Sleep Med* 2011;12:497-504.

74. Stiasny-Kolster K, Clever SC, Möller JC, Oertel WH, Mayer G. Olfactory dysfunction in patients with narcolepsy with and without REM sleep behavior disorder. *Brain* 2007;130:442-9.
75. Bayard S, Plazzi G, Poli F, Serra L, Ferri R, Dauvilliers Y. Olfactory dysfunction in narcolepsy with cataplexy. *Sleep Med* 2010;11:876-81.
76. Klein G, Burghaus L, Vaillant M, Pieri V, Fink GR, Diederich N. Dysautonomia in narcolepsy: evidence by questionnaire assessment. *J Clin Neurol* 2014;10:314-9.
77. Donadio V, Liguori R, Vandi S, Pizza F, Dauvilliers Y, Leta V, et al. Lower wake resting sympathetic and cardiovascular activities in narcolepsy with cataplexy. *Neurology* 2014;83:1080-6.
78. Ferini-Strambi L, Oertel W, Dauvilliers Y, Postuma RB, Marelli S, Iranzo A, et al. Autonomic symptoms in idiopathic REM behavior disorder: a multicentre case-control study. *J Neurol* 2014;261:1112-8.
79. Zamarian L, Högl B, Delazer M, Hingerl K, Gabelia D, Mitterling T, et al. Subjective deficits of attention, cognition and depression in patients with narcolepsy. *Sleep Med* 2015;16:45-51.
80. Christine CW, Marks WJ, Ostrem JL. Development of Parkinson's disease in patients with Narcolepsy. *J. Neural Transm. Vienna Austria* 1996 2012;119:697-9
81. Economou NT, Manconi M, Ghika J, Raimondi M, Bassetti CL. Development of Parkinson and Alzheimer diseases in two cases of narcolepsy-cataplexy. *Eur Neurol* 2012;67:48-50.
82. Fialová M, Dvořák P, Dušek P, Kovalská P, Šonka K. Narcolepsy with cataplexy and Parkinson's disease. Case Report. *Neuro Endocrinol Lett* 2015;36:226-30.

83. Mayer G, Kesper K, Oertel W, Höffken H, Stiasny-Kolster K. REM Sleep behavior disorder (RBD) in narcolepsy patients as a predictor of neurodegeneration: results of a prospective clinical and imaging investigation. *Sleep* 2013;36:A236.
84. Antelmi E, Vandi S, Pizza F, Liguori R, Plazzi G. Parkinsonian tremor persisting during cataplexy. *Sleep Med* 2016;17:174-6.
85. Drouot X, Moutereau S, Nguyen JP, Lefaucheur JP, Creange A, Remy P, et al. Low levels of ventricular CSF orexin/hypocretin in advanced PD. *Neurology* 2003;61:540e3.
86. Fronczek R, Overeem S, Lee, S. Y. Hegeman IM, van Pelt J, van Duinen SG, et al. Hypocretin (orexin) loss in Parkinson's disease. *Brain* 2007;130:1577-85.
87. Thannickal TC, Lai YY, Siegel JM. Hypocretin (orexin) cell loss in Parkinson's disease. *Brain* 2007;130:1586e95.
88. Naganuma F, Bandaru SS, Absi G, Mahoney CE, Scammell TE, Vetrivelan R. Melanin-concentrating hormone neurons contribute to dysregulation of rapid eye movement sleep in narcolepsy. *Neurobiol Dis* 2018 Dec;120:12-20.
89. Baumann C, Ferini-Strambi L, Waldvogel D, Werth E, Bassetti CL. Parkinsonism with excessive daytime sleepiness: a narcolepsy-like disorder? *J Neurol* 2005; 252:139e45.
90. Buskova J, Klempir J, Majerova V, Picmausova J, Sonka K, Jech R, et al. Sleep disturbance in untreated Parkinson's disease. *J Neurol* 2011;258:2254e9.
91. Asai H, Hirano M, Furiya Y, Udaka F, Morikawa M, Kanbayashi T, et al. Cerebrospinal fluid-orexin levels and sleep attacks in four patients with Parkinson's disease. *Clin Neurol Neurosurg* 2009;111:341-4.

92. Wienecke M, Werth E, Poryazova R, Baumann-Vogel H, Bassetti CL, Weller M, et al. Progressive dopamine and hypocretin deficiencies in Parkinson's disease: is there an impact on sleep and wakefulness? *J Sleep Res* 2012;21:710-7.
93. Overeem S, van Hilten JJ, Ripley B, Mignot E, Nishino S, Lammers GJ. Normal hypocretin-1 levels in Parkinson's disease patients with excessive daytime sleepiness. *Neurology*. 2002;58:498-9.
94. Compta Y, Santamaria J, Ratti L, Tolosa E, Iranzo A, Muñoz E, et al. Cerebrospinal hypocretin, daytime sleepiness and sleep architecture in Parkinson's disease dementia. *Brain* 2009,132:3308-17.
95. Anderson KN, Vincent A, Smith IE, Shneerson JM. Cerebrospinal fluid hypocretin levels are normal in idiopathic REM sleep behaviour disorder. *Eur J Neurol* 2010;17:1105-7.
96. Bridoux A, Moutereau S, Covali-Noroc A, Margarit L, Palfi S, Nguyen JP, et al. Ventricular orexin-A (hypocretin-1) levels correlate with rapid-eye-movement sleep without atonia in Parkinson's disease. *Nat Sci Sleep* 2013;5:87-91.
97. Drouot X, Moutereau S, Lefaucheur JP, Palfi S, Covali-Noroc A, Margarit L, et al. Low level of ventricular CSF orexin-A is not associated with objective sleepiness in PD. *Sleep Med*. 2011;12:936-7.
98. Liguori C, Paoletti FP, Placidi F, Ruffini R, Sancesario GM, Eusebi P, et al. CSF Biomarkers for Early Diagnosis of Synucleinopathies: Focus on Idiopathic RBD. *Curr Neurol Neurosci Rep* 2019;19(2):3.

99. Jennum PJ, Østergaard Pedersen L, Czarna Bahl JM, Modvig S, Fog K, Holm A, et al. Cerebrospinal Fluid Biomarkers of Neurodegeneration Are Decreased or Normal in Narcolepsy. *Sleep* 2017;40(1).
100. Unger MM, Möller JC, Ohletz T, Stiasny-Kolster K, Oertel WH, Mayer G. Transcranial midbrain sonography in narcoleptic subjects with and without concomitant REM sleep behaviour disorder. *J Neurol* 2009;256:874-7.
101. Honda M, Arai T, Fukazawa M, Honda Y, Tsuchiya K, Salehi A, et al. Absence of ubiquitinated inclusions in hypocretin neurons of patients with narcolepsy. *Neurology* 2009;73:511-7.
102. Barateau L, Jausset I, Lopez R, Evangelista E, Chenini S, Benkiran M, et al. Cardiac Sympathetic Activity differentiates Idiopathic and Symptomatic Rapid Eye Movement Sleep Behaviour Disorder. *Sci Rep* 2018;8:7304.
103. \*Mayer G., Bitterlich M, Kuwert T, Ritt P, Stefan H. Ictal SPECT in patients with rapid eye movement sleep behaviour disorder. *Brain J Neurol* 2015;138, 1263-70.
104. Frauscher B, Iranzo A, Gaig C, Gschliesser V, Guaita M, Raffelseder V, et al and SINBAR (Sleep Innsbruck Barcelona) Group. Normative EMG values during REM sleep for the diagnosis of REM sleep behavior disorder. *Sleep* 2012;35:835-47.
105. Frauscher B, Gabelia D, Biermayr M, Stefani A, Hackner H, Mitterling T, et al. Validation of an integrated software for the detection of rapid eye movement sleep behavior disorder. *Sleep* 2014;37:1663-71.
106. Ferri R, Rundo F, Manconi M, Plazzi G, Bruni O, Oldani A, et al. Improved computation of the atonia index in normal controls and patients with REM sleep behavior disorder. *Sleep Med* 2010;11:947-49.

107. McCarter SJ, St Louis EK, Duwell EJ, Timm PC, Sandness DJ, Boeve BF, et al. Diagnostic thresholds for quantitative REM sleep phasic burst duration, phasic and tonic muscle activity, and REM atonia index in REM sleep behavior disorder with and without comorbid obstructive sleep apnea. *Sleep* 2014;37:1649-62.
108. McCarter SJ, St Louis EK, Sandness DJ, Duwell EJ, Timm PC, Boeve BF, et al. Diagnostic REM sleep muscle activity thresholds in patients with idiopathic REM sleep behavior disorder with and without obstructive sleep apnea. *Sleep Med* 2017;33:23-29.
109. Figorilli M, Ferri R, Zibetti M, Beudin P, Puligheddu M, Lopiano L, et al. Comparison between automatic and visual scorings of REM sleep without atonia for the diagnosis of REM sleep behavior disorder in Parkinson disease. *Sleep* 2017;40:zsw060.
110. Ferri R, Gagnon JF, Postuma RB, Rundo F, Montplaisir JY. Comparison between an automatic and a visual scoring method of the chin muscle tone during rapid eye movement sleep. *Sleep Med* 2014;15(6):661-5.
111. Cesari M, Christensen JAE, Kempfner L, Olesen AN, Mayer G, Kesper K, ET AL. Comparison of computerized methods for rapid eye movement sleep without atonia detection. *Sleep* 2018;41:zsy133.
112. Cooray N, Andreotti F, Lo C, Symmonds M, Hu MTM, De Vos M. Detection of REM sleep behaviour disorder by automated polysomnography analysis. *Clin Neurophysiol* 2019;130(4):505-14.
113. Ferri R, Zucconi M, Marelli S, Plazzi G, Schenck CH, Ferini-Strambi L. Effects of the chronic use of clonazepam on NREM sleep patterns in REM sleep behavior disorder. *Sleep Med* 2013;14:399-406.

114. Diniz Behn CG, Klerman EB, Mochizuki T, Lin SC, Scammell TE. Abnormal sleep/wake dynamics in orexin knockout mice. *Sleep* 2010;33:297-306.
115. Sorensen GL, Knudsen S, Jennum P. Sleep transitions in hypocretin-deficient narcolepsy. *Sleep* 2013;36:1173-7.
116. Pizza F, Vandi S, Ilioti M, Franceschini C, Liguori R, Mignot E, Plazzi G. Nocturnal Sleep Dynamics Identify Narcolepsy Type 1. *Sleep* 2015;38:1277-84.
117. +Stephansen JB, Olesen AN, Olsen M, Ambati A, Leary EB, Moore HE, et al. Neural network analysis of sleep stages enables efficient diagnosis of narcolepsy. *Nat Commun* 2018;9:5229.
118. Nishino S, Kanbayashi T. Symptomatic narcolepsy, cataplexy and hypersomnia, and their implications in the hypothalamic hypocretin/orexin system. *Sleep Med Rev* 2005;9:269-310
119. Fraigne JJ, Torontali ZA, Snow MB, Peever JH. REM Sleep at its Core - Circuits, Neurotransmitters, and Pathophysiology. *Front Neurol* 2015;6:123.
120. Vilas D, Iranzo A, Tolosa E, Aldecoa I, Berenguer J, Vilaseca I, et al. Assessment of  $\alpha$ -synuclein in submandibular glands of patients with idiopathic rapid-eye-movement sleep behaviour disorder: a case-control study. *Lancet Neurol* 2016;15:708-18.
121. Doppler K, Jentschke HM, Schulmeyer L, Vadasz D, Janzen A, Luster M, et al. Dermal phospho-alpha-synuclein deposits confirm REM sleep behaviour disorder as prodromal Parkinson's disease. *Acta Neuropathol* 2017;133(4):535-45.
122. Antelmi E, Donadio V, Incensi A, Plazzi G, Liguori R. Skin nerve phosphorylated  $\alpha$ -synuclein deposits in idiopathic REM sleep behavior disorder. *Neurology* 2017;88:2128-31.

123. Iranzo A, Borrego S, Vilaseca I, Martí C, Serradell M, Sánchez-Valle R, et al.  $\alpha$ -Synuclein aggregates in labial salivary glands of idiopathic rapid eye movement sleep behavior disorder. *Sleep* 2018;41(8).
124. Fernández-Arcos A, Vilaseca I, Aldecoa I, Serradell M, Tolosa E, Santamaría J, et al. Alpha-synuclein aggregates in the parotid gland of idiopathic REM sleep behavior disorder. *Sleep Med* 2018;52:14-17.
125. \*Luppi PH, Clément O, Sapin E, Garcia SV, Peyron C, Fort P. Animal models of REM dysfunctions: what they tell us about the cause of narcolepsy and RBD? *Arch Ital Biol* 2014;152:118-28.
126. Lee M.G., Hassani O.K., Jones B.E. Discharge of identified orexin/hypocretin neurons across the sleep-waking cycle. *J Neurosci* 2005;25:6716-20.
127. Xi MC, Fung SJ, Yamuy J, Morales FR, Chase MH. Induction of active (REM) sleep and motor inhibition by hypocretin in the nucleus pontis oralis of the cat. *J. Neurophysiol* 2002;87:2880-88.
128. Mathis J, Hess CW, Bassetti C. Isolated mediotegmental lesion causing narcolepsy and rapid eye movement sleep behaviour disorder: a case evidencing a common pathway in narcolepsy and rapid eye movement sleep behaviour disorder. *J Neurol Neurosurg Psychiatry*. 2007;78:427-9.
129. Kiyashchenko LI, Mileykovskiy BY, Lai YY, Siegel JM. Increased and decreased muscle tone with orexin (hypocretin) microinjections in the locus coeruleus and pontine inhibitory area. *J Neurophysiol* 2001;85:2008-16.
130. Mileykovskiy BY; Kiyashchenko LI; Siegel JM. Behavioral correlates of activity in identified hypocretin/orexin neurons. *Neuron* 2005;46:787-98.



131. Roman A, Meftah S, Arthaud S, Luppi PH, Peyron C. The inappropriate occurrence of rapid eye movement sleep in narcolepsy is not due to a defect in homeostatic regulation of rapid eye movement sleep. *Sleep* 2018;41(6).
132. Arnulf I, Leu S, Oudiette D. Abnormal sleep and sleepiness in Parkinson's disease. *Curr Opin Neurol* 2008;21:472-7.
133. Thannickal TC, Nienhuis R, Siegel JM. Localized loss of hypocretin (orexin) cells in narcolepsy without cataplexy. *Sleep* 2009;32:993-8.
134. Broughton RJ. Neurology and dreaming. *Psychiatr J University Ottawa* 1982;7:101-10.
135. Olson EJ, Boeve BF, Silber MH. Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. *Brain* 2000;123:331-9.
136. Fantini M, Corona A, Clerici S, Ferini-Strambi L. Aggressive dream content without daytime aggressiveness in REM sleep behavior disorder. *Neurology*. 2005;65:1010-5.
137. Borek LL, Kohn R, Friedman JH. Phenomenology of dreams in Parkinson's disease. *Mov Disord* 2006;22:198-202.
138. D'Agostino A, Manni R, Limosani I, Terzaghi M, Cavallotti S, Scarone S. Challenging the myth of REM sleep behaviour disorder: no evidence on heightened aggressiveness in dreams. *Sleep Med* 2012;13:714-19.
139. Valli K, Frauscher B, Peltomaa T, Gschliesser V, Revonsuo A, Högl B. Dreaming furiously? A sleep laboratory study on the dream content of people with Parkinson's disease and with or without rapid eye movement sleep behavior disorder. *Sleep Med* 2015;16:419-27.
140. Fantini ML, Ferini-Strambi L. Dream content in RBD: effect of clonazepam. *Sleep Med* 2012;13:11

141. Fosse R, Stickgold R, Hobson JA. Emotional experience during rapid-eye-movement sleep in narcolepsy. *Sleep* 2002;25:724-32.
142. Vogel G. Mentation reported from naps in narcoleptics. In: Guilleminault C, Dement WC, Passouant P, eds. *Narcolepsy*. New York: Spectrum; 1976: 161-8.
143. Fosse R. REM mentation in narcoleptics and normals: an empirical test of two neurocognitive theories. *Conscious Cogn* 2000;9:488-509.
144. Bellucci C, Vandi S, Iloti M, Pizza F, Russo PM, Tuozzi G, et al. Dissociated rapid eye movement sleep dream experiences in type 1 narcolepsy: a case report. *Sleep Med* 2016;19:150-2.
145. Hishikawa Y, Koida H, Yoshino K. Characteristics of REM sleep accompanied by sleep paralysis and hypnagogic hallucinations in narcoleptic patients. *Waking Sleeping* 1978;2:113-23.
146. Hall CS, Van De Castle R. *The content analysis of dreams*. New York: Appleton-Century-Crofts, 1966.
147. Domhoff GW. *Finding meaning in dreams: a quantitative approach*. New York: Plenum, 1996.
148. Revonsuo A. The reinterpretation of dreams: an evolutionary hypothesis of the function of dreaming. *Behav Brain Sci* 2000;23:793-1121.
149. Bugalho P, Paiva T. Dream features in the early stages of Parkinson's disease. *J Neural Transm (Vienna)*. 2011;118:1613-9.
150. Schenck CH, Mahowald MW, Kim SW, O'Connor KA, Hurwitz TD. Prominent eye movements during NREM sleep and REM sleep behavior disorder associated with fluoxetine treatment of depression and obsessive-compulsive disorder. *Sleep* 1992;15:226-35.

151. Ferri R, Zucconi M, Marelli S, Plazzi G, Schenck CH, Ferini-Strambi L. Effects of long-term use of clonazepam on nonrapid eye movement sleep patterns in rapid eye movement sleep behavior disorder. *Sleep Med* 2013;14:399-406.
152. Ferri R, Marelli S, Ferini-Strambi L, Oldani A, Colli F, Schenck CH, Zucconi M. An observational clinical and video-polysomnographic study of the effects of clonazepam in REM sleep behavior disorder. *Sleep Med* 2013;14:24-9.
153. Schenck CH, Montplaisir JY, Frauscher B, Hogl B, Gagnon JF, Postuma R, et al. Rapid eye movement sleep behavior disorder: devising controlled active treatment studies for symptomatic and neuroprotective therapy--a consensus statement from the International Rapid Eye Movement Sleep Behavior Disorder Study Group. *Sleep Med*. 2013;14:795-806.
154. Boeve BF, Silber MH, Ferman TJ. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. *Sleep Med* 2003;4:281-4.
155. Plazzi G, Pizza F, Vandi S, Aricò D, Bruni O, Dauvilliers Y, Ferri R. Impact of acute administration of sodium oxybate on nocturnal sleep polysomnography and on multiple sleep latency test in narcolepsy with cataplexy. *Sleep Med* 2014;15:1046-54.
156. Mayer G. Efficacy of sodium oxybate on REM sleep behavior disorder in a patient with narcolepsy type 1. *Neurology* 2016;87:2594-5.
157. Mayer G, Rodenbeck A, Kesper K; International Xyrem Study Group. Sodium oxybate treatment in narcolepsy and its effect on muscle tone. *Sleep Med* 2017;35:1-6.
158. Shneerson JM. Successful treatment of REM sleep behavior disorder with sodium oxybate. *Clin Neuropharmacol* 2009;32:158e9.

159. Moghadam KK, Pizza F, Primavera A, Ferri R, Plazzi G. Sodium oxybate for idiopathic REM sleep behavior disorder: a report on two patients. *Sleep Med* 2017;32:16-21.

Journal Pre-proof

Table 2:

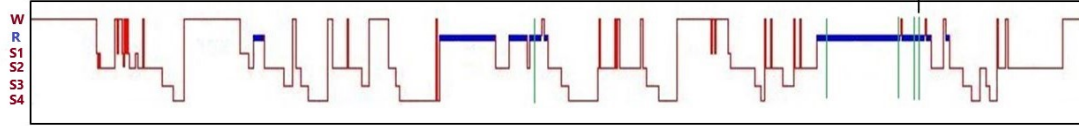
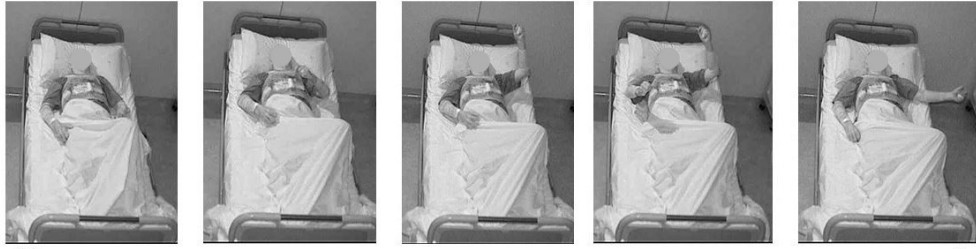
	iRBD	RBD-NT1
<b>DEMOGRAPHIC AND CLINICAL-POLYSOMNOGRAPHIC FEATURES</b>		
<b>GENDER</b>	M>F	M=F
<b>AGE AT ONSET</b>	50 yo	7-40 yo
<b>HYPOSMIA</b>	++	+
<b>CONSTIPATION</b>	++	-
<b>AUTONOMIC DYSFUNCTION</b>	++	+
<b>DEPRESSION</b>	++	+
<b>COGNITIVE DYSFUNCTION</b>	++	+/-
<b>EDS</b>	+	+++
<b>SLEEP ATTACKS/HALLUCINATIONS</b>	+	+++
<b>TIME OF OCCURRENCE OF THE EPISODES</b>	2nd half of the night	1 <sup>st</sup> and 2 <sup>nd</sup> half of the night
<b>FREQUENCY OF THE EPISODES</b>	Variable	Variable; even subcontinuous
<b>VIOLENT PATTERN OF RBD EPISODES</b>	+	+/-
<b>RBD FEATURES</b>	Complex motor behavior Verbalization, Laughter Episodic violent/active	Calmer Discrete motor activity Verbalization, not violent
<b>RSWA (%)</b>	>	<
<b>REM DENSITY</b>	<	>
<b>INSTRUMENTAL FINDINGS</b>		
<b>CARDIAC MIBG</b>	Abormal	Normal
<b>SN HYPERECHOGENICITY</b>	++	+/-
<b>ICTAL BRAIN SPECT</b>	Same pattern	Same pattern
<b>BIOCHEMICAL AND HISTOPATHOLOGICAL MARKERS</b>		
<b>LOSS OF HYPOCRETINERGIC CELLS</b>	+/-	+++
<b>LOSS OF DOPAMINERGIC CELLS</b>	+++	+/-
<b>CSH HYPOCRETIN LEVELS</b>	Normal (↓ in PD and LBD)	< 110 pg/mL
<b>CSF- AMYLOID AND B-AMYLOID</b>	↓ ?*	↓ ? *
<b>CSF- TAU AND P-TAU</b>	↓/= ?*	↓/= ?*
<b>UBIQUINATED NEURONAL INCLUSIONS</b>	+++	-
<b>CENTRAL P-A-SYN DEPOSITS</b>	+++	?
<b>PERIPHERAL P-A-SYN DEPOSITS</b>	+++	?

iRBD	Year	Author-Journal	Population	Studied Subjects	Overall Approach	Results
	2012	Boot et al, Ann Neurol [46]	Population study (70-89 yo)	727	Questionnaire completed by the usual sleeping partner	53 pRBD (7,3%)
	2013	Kang et al, Sleep [43]	Population study (> 60 yo)	348 out of 696 invited to vPSG study	Clinical examination + vPSG chin analysis + telephone confirmation of dream enactment behavior by bed partners	7 RBD + 18 Subclinical RBD (Overall=7.18%; RBD=2,01%; iRBD=1,15%; subclinical RBD=4,95%)
	2015	Mahlknecht et al, Mov Dis [47]	Bruneck Study Cohort (60-97 yo)	456 out of 488	Questionnaire assessment	pRBD prevalence of 4,6% (RBDSQ) and of 7,7% (RDB-I)
	2016	Wong et al, Neurology [44]	Kailuan Cohort Study (> 24 yo)	12784 out of 12990 subjects	Questionnaire assessment	pRBD prevalence of 5,9% in males, of 4,1% in women
	2017	Ma et al, Sleep Med [45]	Population study (> 50 yo)	3635 out of 3970 of Wuliqiao Cohort	Questionnaire assessment	98 pRBD (2,70%; 3,28% in males, 2,41% in women)
	2017	Pujol et al, Sleep Med [42]	Primary Care Centers (> 60 yo)	539	Stage 1: Screening Questionnaire; Stage 2: Neurological Assessment + vPSG	28 pRBD (5,2%); 4 iRBD at step 2 (0,74%)
	2018	Haba-Rubio et al, Sleep [48]	Hypnolus Cohort Study	1997	Questionnaire + Chin EMG analysis from PSG	368 pRBD (18.4%), 21 definite RBD (1,06%)
<b>NT1</b>	1993	Mayer et al, J Sleep Res [26]	Consecutive Series of 87 Narcolepsy patients	14 patients with history of dream-related motor behaviours vs 13 age/sex paired subjects	Clinical Assessment + vPSG	Narcolepsy patients with dream-related motor behavior history = 16%; association between RBD and use of antidepressants
	2005	Nightingale et al, Sleep Med [21]	Random Selection of Known Narcolepsy Patients with available contact details	55 out of 68 recruited patients	Questionnaire Screening + Interview + vPSG	Possible RBD in 39 out of 55 patients (71%) at questionnaire, 20 (36%) with probable RBD symptoms at telephone interview
	2008	Ferri et al, Sleep [39]	Narcolepsy Center Case	34 NT1 adults	Clinical Assessment + vPSG	17 out of 34 NT1 (50%) with clinical/PSG criteria for RBD

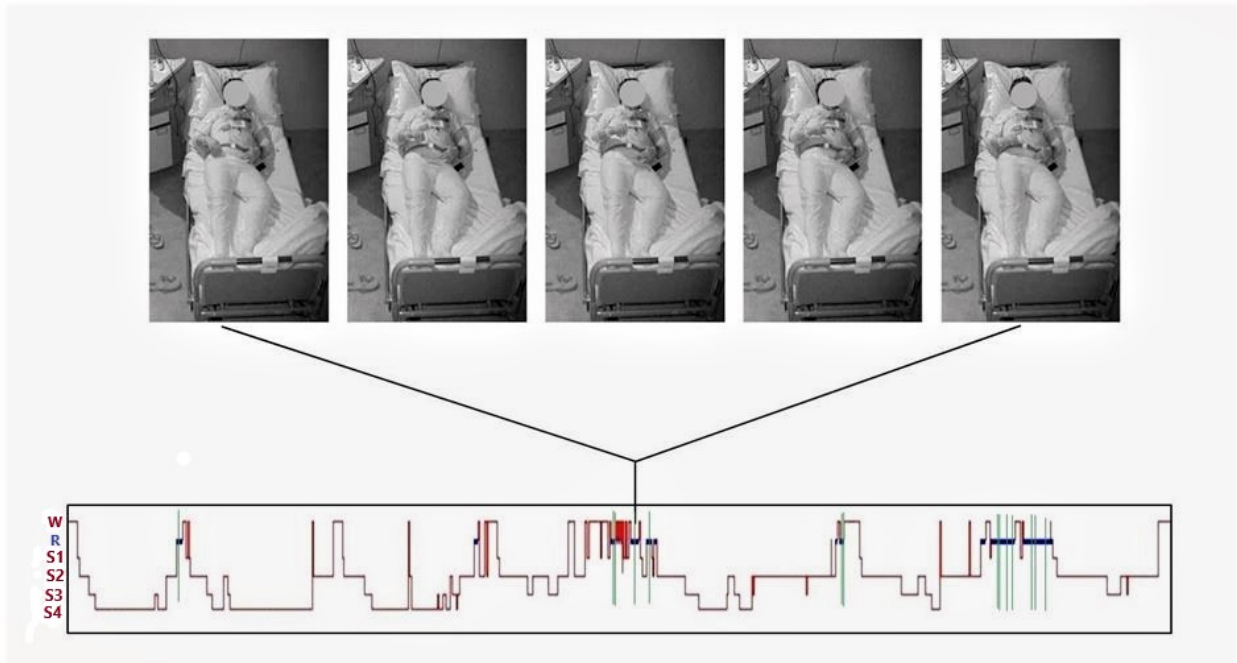
			Series (34 NT1, 35 controls, 18-75 yo)			
2007	Mattarozzi et al, Sleep Med [54]	Narcolepsy Center Case Series	44 NT1 adult patients	Questionnaire + Clinical assessment + vPSG	27 out of 44 (61%) reported RBD symptoms, 19 out of 44 (43%) had RBD at vPSG; RBD occurrence was not related to cataplexy frequency or gender, but more frequent in patients with longer disease course	
2010	Knudsen et al, Brain 2010 [27]	Adult Narcolepsy Center Case Series (63 patients)	48 NT1 patients (37±2 yo), 15 NT2 patients (29±3 yo)	Clinical Assessment + vPSG	RBD symptoms in 40 out of 63 (63.4%) patients, associated with cataplexy (71% vs 40%) or hypocretin deficiency (72% vs 41%), the latter remaining significant predictor at multivariate analyses suggesting that RBD and cataplexy are the intrinsic features of hypocretin deficiency.	
2013	Del Rosso, J Clin Sleep Med [49]	Retrospective vPSG review (8 narcolepsy, 8 IH)	Adults with narcolepsy (4 NT1, 4 NT2; 27,5 yo) and IH (n=8, mean age 33 y)	Clinical Assessment + vPSG	None of the patients showed abnormal REM behaviors at PSG	
2013	Frauscher et al, J Clin Sleep Med [50]	Sleep Center Consecutive Series of 100 adults with narcolepsy	100 narcolepsy patients (87 NT1, 13 NT2) aged 16-78 yo (median 39)	Clinical Assessment + vPSG	24% with RBD, none with primary RBD complaint at clinical evaluation	
2013	Luca et al, J Sleep Res [28]	European Narcolepsy Network Database	1099 NT1 patients, with available data on RBD comorbidity in 295 patients	Clinical Assessment + vPSG	Clinically suspected or vPSG confirmed RBD in 46% of men and 54% of women with NT1	
2013	Nevsimalova et al, J Neurol [57]	Adult Narcolepsy Center Case Series (148 patients)	Consecutive Narcolepsy Patients (age 41±20, range 7-85): 109 NT1, 39 NT2	Clinical Assessment + vPSG	Association between RBD and NT1 (37%) vs NT2 (15%), not correlated to patients' age	
2015	Sakai-Sakuma, Plos One [51]	Consecutive Series of Patients with CNS	Adult Cohort of consecutive patients with 158 NT1 (28±11 yo), 295 NT2 (26±9 yo), and	RBD diagnosed on vPSG findings	Higher RWA and occurrence of PSG diagnosable RBD in NT1 (2%) vs NT2 (0.3%) and IH (0%)	

			Hypersomnia	395 IH (29±9 yo)		
2015	Suzuki et al, Plos One [52]	576 consecutive outpatients with sleep disorders		68 narcolepsy and 35 IH patients vs 61 controls	Questionnaire Assessment	Positive RBDSQ-J in 60% of narcolepsy patients, 14% of IH and 11% of controls
2017	Antelmi et al, Brain [72]	Narcolepsy Center Case Series (40 NT1)		40 NT1 children (12±3 yo) and 22 Controls	Clinical Assessment + vPSG	32.5% of NT1 with Complex Behaviors in REM (RBD)
2018	Bin-Hasan, J Clin Sleep Med [22]	Pediatric Sleep Center Cohort (17 Narcolepsy)		Children aged 6-18: 11 NT1, 6 NT2, 12 IH, and 11 with subjective EDS	Clinical Assessment + vPSG	2 out of 11 NT1 (18%), and 2 out of 6 NT2 (33%); RWA proposed as good biomarker to identify narcolepsy (both type 1 and 2)





Journal Pre-proof



Journal Pre