Clinical Neurophysiology 130 (2019) 1825–1832

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Frequency and characteristic features of REM sleep without atonia

Femke Dijkstra [a,b,c,*], Mineke Viaene [a,d], David Crosiers [b,c,e], Ilse De Volder [b,c,f], Patrick Cras [b,c,e]

[a] Laboratory for Sleep Disorders, St Dimpna Regional Hospital, Geel, Belgium
[b] Faculty of Medicine and Health Sciences, Translational Neurosciences, University of Antwerp, Antwerp, Belgium
[c] Department of Neurology, Antwerp University Hospital, Edegem, Belgium
[d] Department of Neurology, St Dimpna Regional Hospital, Geel, Belgium
[e] Institute Born-Bunge, University of Antwerp, Antwerp, Belgium
[f] Multidisciplinary Sleep Disorders Center, Antwerp University Hospital, Antwerp, Belgium

ARTICLE INFO

Article history:
Accepted 12 July 2019
Available online 27 July 2019

Keywords:
REM sleep without atonia
Polysomnography
Lewy body disease
Prodromal Parkinson's disease

HIGHLIGHTS

- REM sleep without atonia (RSWA) is a common finding in polysomnographic studies.
- Secondary RSWA was most frequently observed in the context of antidepressant use.
- Excessive daytime sleepiness was more frequently seen in isolated RSWA patients.

ABSTRACT

Objectives: Isolated REM sleep without atonia (iRSWA) is regarded as prodromal phase of REM sleep behavior disorder (RBD) and synucleinopathies. Other factors, however, have also been described to cause RSWA, including sleep apnea, antidepressants use and narcolepsy. We investigated the frequency of RSWA and its different etiologies.
Methods: We investigated RSWA in patients that underwent a clinical video polysomnography. In iRSWA subjects, we examined polysomnography indication and two markers of prodromal Parkinson's disease: excessive daytime sleepiness and depressive symptoms, with a case-control design.
Results: Of the 864 included polysomnographies, 188 were positive for RSWA (21.8%), 17 for RBD (2.0%) and 48 for iRSWA (5.6%). Mean Epworth Sleepiness Scale scores were 9.8 ± 4.8 (iRSWA subjects) and 7.5 ± 4.9 (controls), $p = 0.014$. Mean Beck Depression Inventory-II scores were 11.3 ± 7.9 (iRSWA subjects) and 9.5 ± 8.4 (controls), $p = 0.229$. Excessive daytime sleepiness was more often the polysomnography indication in the iRSWA group ($p = 0.006$).
Conclusions: RSWA is a frequent finding in the context of antidepressant use or synucleinopathies. iRSWA subjects reported increased excessive daytime sleepiness and more often had excessive daytime sleepiness as polysomnography indication.
Significance: Our study provides evidence for high frequency of RSWA, underscoring the need for longitudinal studies in iRSWA patients, with interest for conversion to synucleinopathies.

1. Introduction

REM sleep without atonia (RSWA, Fig. 1) is the polysomnographic (PSG) finding of increased tonic or phasic muscle activity during REM sleep (Berry et al., 2017). Together with dream-enacting behavior (DEB), it is an essential feature of REM sleep behavior disorder (RBD), which is regarded as an early phase of Parkinson's disease (PD), dementia with Lewy Bodies (DLB) and multiple system atrophy (MSA) (Iranzo et al., 2016). RSWA without DEB (isolated RSWA [iRSWA]), usually is a coincidental PSG finding of which the relevance is still unknown. It is hypothesized to be a prodromal phase of RBD and subsequently of an underlying neurodegenerative disorder (Högl et al., 2018), but major confirmative follow-up studies are lacking. In the few previously performed studies, iRSWA patients showed several other prodromal biomarkers such as hyposmia, decreased heart rate variability, substantia nigra hyperechogenicity, cognitive impairment and decreased striatal tracer uptake on ^{123}I-Ioflupane Single Photon Emission

* Corresponding author at: Department of Neurology, Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem, Belgium.
E-mail address: Femke.Dijkstra@uza.be (F. Dijkstra).

https://doi.org/10.1016/j.clinph.2019.07.018
1388-2457/

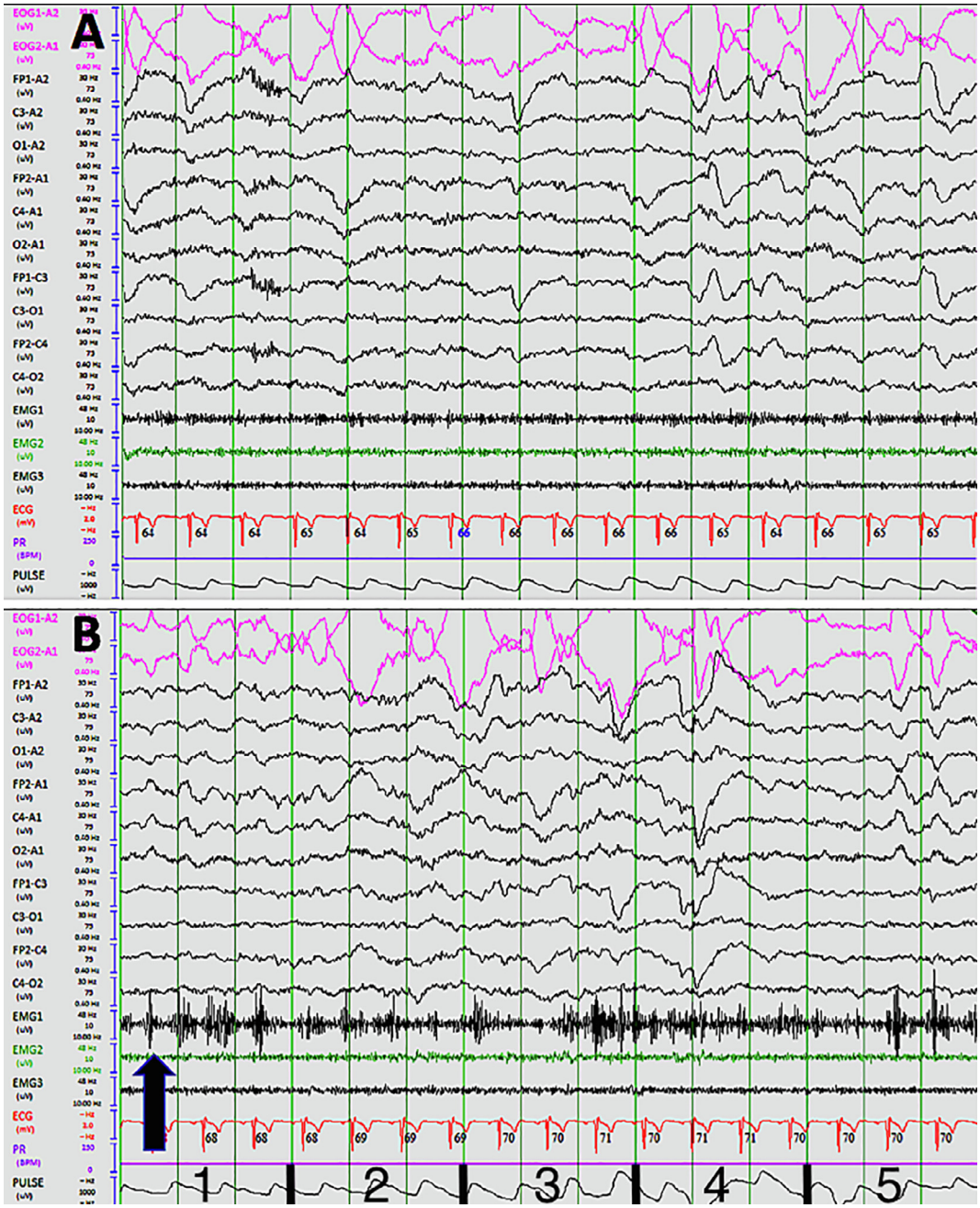

Fig. 1. RSWA on polysomnography. A 15-s epoch (5 mini epochs) with 2 electrooculography (EOG) channels, several electroencephalography (EEG) channels, a chin (submetalis muscle) electromyography (EMG 1) channel, 2 leg (tibialis anterior muscle) EMG channels (EMG 2 and 3), an electrocardiography (ECG) channel and a pulse oximetry channel (other breathing-related channels not shown). Figure A. shows normal REM sleep with typical Rapid-Eye-Movements on both EOG channels and total muscle atonia on all EMG channels. Figure B. shows REM sleep without atonia (arrow) with tonic EMG activity (an increase of >50% in baseline EMG amplitude) on the chin with superimposed phasic activity (burst that exceed 4 times the background EMG in all mini epochs). There is atonia on the leg channels.

Computed Tomography (Eisensehr et al., 2003; Barone et al., 2015; Stefani et al., 2016).

Other factors, however, have also been described to increase REM sleep tonus, including obstructive sleep apnea (OSA) (Petrenko and Gupta, 2016; Goyal et al., 2018), medication use (especially antidepressants) (McCarter et al., 2015a; Lee et al., 2016), narcolepsy (Dauvilliers et al., 2013), and brainstem lesions (McCarter et al., 2015b) resulting in either RSWA or RBD. Distinguishing isolated from secondary forms of RSWA can be important in the context of possible progression to neurodegenerative disorders, especially regarding therapeutic options, and patient selection for neuroprotective trials (Schenck et al., 2013; Högl et al., 2018). Furthermore, isolated RSWA patients may suffer from other prodromal parkinsonian non-motor symptoms (Berg et al., 2015), and some, such as excessive daytime sleepiness (EDS), autonomic dysfunction and depressive symptoms, may be the primary indication for polysomnography. However, the clinical profile of RSWA patients without the context of RBD, is less studied.

To gain more insight in the frequency of RSWA and described associated conditions, we investigated the occurrence of RSWA during 18 months in consecutively admitted adult patients in the sleep clinic of a general hospital. In iRSWA patients without known comorbidities, we have listed the clinical indication to perform a polysomnography for each patient and we have assessed the

presence of two sleep-related symptoms of prodromal PD (EDS and depressive symptoms) (Berg et al., 2015).

2. Materials and methods

2.1. Participants and clinical evaluation

We performed a prospective frequency study of patients with RSWA in the sleep department of the Sint Dimpna Hospital, Geel, Belgium. All patients that underwent a polysomnography from September 2016 until February 2018 were included in the study. All data were collected as part of the routine sleep lab assessment and included age, gender, medical history, medication use, body mass index (BMI) and the clinical indication for polysomnography. Primary indications for PSG were categorized into 6 categories: 1. excessive daytime sleepiness and/or tiredness, 2. sleep-related breathing disorders, 3. disturbances in initiating and/maintaining sleep, 4. sleep-related movement disorders, 5. a combination of 2 or more previous categories and 6. others. The presence of EDS was assessed with the Epworth Sleepiness Scale (ESS) (Johns, 1991) and presence of depressive symptoms with the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996). Subjects with unknown clinical history were excluded from analysis.

2.2. Video polysomnography

A classic full night video PSG was performed (Brainnet-Morpheus, MEDATEC, Fig. 1) with 2 electro-oculogram channels, 3 EMG channels (submentalis muscle and bilateral tibialis anterior muscle), electroencephalogram channels (bilateral prefrontal, central and occipital leads with a reference lead to mastoids), 2 nasal airflow channels, 2 respiratory effort channels, 1 oximetry channel, 1 snoring detector channel, 1 electrocardiography channel and 1 pulse transit time channel, a position and light detector, all with American Academy of Sleep Medicine (AASM) (Berry et al., 2017) recommended setup specifications. All PSGs were visually analyzed by a neurologist, specialized in sleep disorders. Positive PSG studies were subsequently analyzed by a researcher (FD). Sleep stage classification, arousals, periodic limb movements, presence of restless legs and respiratory events were scored according to the AASM manual (Berry et al., 2017). DEB was scored according to the RBD severity scale (Sixel-Döring et al., 2011) on video analyses. Subjects with complex motor behaviors or vocalizations were scored as DEB positive.

2.3. RSWA scoring

We only included subjects with >5 min of REM sleep. RSWA was scored in the submentalis muscle and bilateral tibialis anterior muscle. RSWA was visually scored in 30 s epochs, according to the AASM manual (Berry et al., 2017): either increased tonic activity, defined as an increase of >50% in baseline EMG amplitude (measured during nonREM sleep) or >10 μV during >50 percent of a REM epoch, or increased phasic activity, defined as all muscle activity during 0, 1–5 s that exceeded 4 times the background EMG activity in >50% of 3 s mini-epochs within a 30 s REM epoch. All EMG activity due to respiratory events, snoring, arousals or periodic limb movements was excluded from analysis. Patients with indefinable REM tonus due to severe artefacts on EMG channels, were excluded from analysis as well (Fig. 2). Total RSWA, tonic RSWA and phasic RSWA percentage was calculated as the percentage of REM epochs that show (tonic or phasic) RSWA.

We performed an interobserver analysis on 10 PSG studies (RSWA vs. no RSWA) which resulted in an interobserver agreement of 90% (Kappa coefficient 0.8: good agreement). When there was a disagreement on the presence of RSWA in the remaining PSGs during the study, the PSG was discussed again between the 2 observers.

2.4. Subjects with RSWA

Subjects with RSWA were categorized according to known etiology: REM sleep behavior disorder according to the ISCD-3 criteria (AASM, 2014), synucleinopathies, use of antidepressants (present or in the last 3 months), narcolepsy, moderate to severe OSA (Apnea-Hypopnea Index [AHI] $\geq$ 15/h) and iRSWA. All subjects with other central nervous system comorbidities or under treatment with psychotropic medication that theoretically could have influenced REM sleep atonia, were labeled as "other". To investigate if the frequency of moderate to severe OSA and use of antidepressants in the RSWA group differed from the group with total REM atonia, we performed a post hoc comparison between the RSWA group and 100 age and gender-matched subjects with total REM atonia (that underwent a PSG during the study period).

2.5. Subjects with iRSWA (case-control study)

Subjects with iRSWA, defined as subjects without any known etiology to cause RSWA, were further analyzed for prodromal PD symptoms. We performed a case-control study, comparing EDS and depressive symptoms between groups. The control group consisted of subjects with a total REM atonia during polysomnography. Possible secondary RSWA patients were excluded from this analysis, according to the following exclusion criteria: present or past <3 months use of antidepressants or antipsychotics, moderate or severe OSA (AHI $\geq$ 15/h), narcolepsy, central nervous system or psychiatric disorders, known synucleinopathy or RBD (with DEB on polysomnography or a history of DEB). Both groups were matched for age and gender. The same exclusion criteria were used for the control group as for the iRSWA group.

2.6. Ethical approval

This study used data collected for clinical purposes and no additional interventions (for research purposes) were performed. All subjects provided written informed consent for using their clinical data for scientific research. The Medical Ethics Committee of the St. Dimpna hospital approved the study.

2.7. Statistical analysis

Frequency of RSWA was calculated as the percentage of RSWA-positive PSG studies in total sample and frequency of different etiologies was calculated as percentage within the RSWA-positive group, both with upper and lower 95% confidence intervals. Frequencies of OSA and antidepressant use were calculated for the total group, the RSWA group and after excluding other causes of secondary RSWA. Differences in moderate to severe OSA and use of antidepressants frequency between subjects with RSWA and subjects with total REM atonia were calculated using a chi square test.

For the case-control study of iRSWA subjects, differences in BDI-II and ESS scores between iRSWA subjects and controls were calculated, using a univariate general linear model, adjusted for age and gender, and with a Bonferroni correction for multiple comparisons (significance level is set at $p = 0.050/2 = 0.025$). Furthermore, differences between groups in indication for PSG were analyzed with a Fisher's exact test and subsequently 6 post-hoc Fisher's exact tests to specify which indication differed between groups. Again, a post hoc Bonferroni correction for multiple comparisons was applied (significance level is set at $p = 0.050/6 = 0.008$). To explore

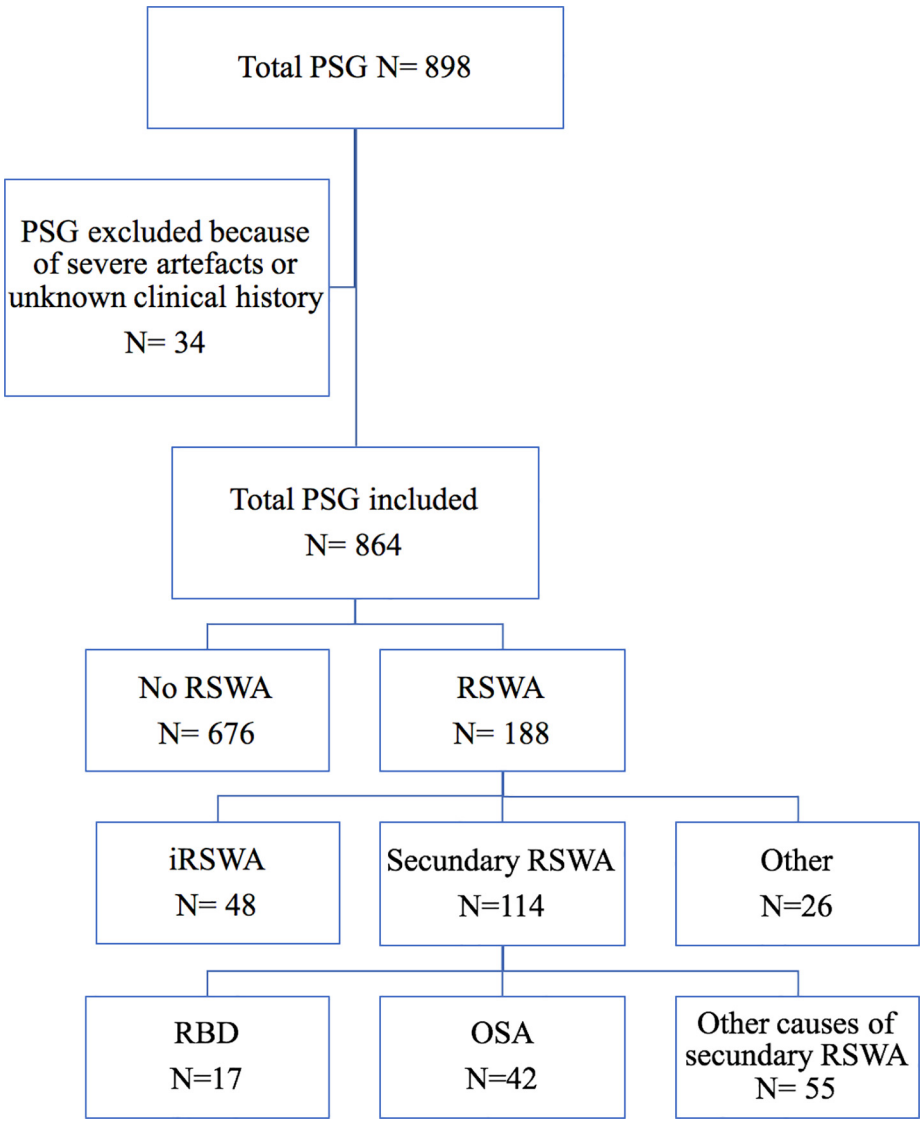

Fig. 2. Frequency of RSWA flowchart. PSG: polysomnography; RSWA: REM sleep without atonia; iRSWA: isolated RSWA; RBD: REM sleep behavior disorder; secondary RSWA: RSWA due to a cause known in literature; other: all other central nervous system disorders and major psychiatric disorders which may have influenced REM atonia. RBD: REM sleep behavior disorder. OSA: moderate to severe obstructive sleep apnea as single co-morbidity.

differences in other PSG parameters between the iRSWA and control group that might have influenced BDI-II and ESS score, a univariate general linear model, adjusted for age and gender, was used for continuous variables. Fisher's exact test was used for the presence of restless legs syndrome (with Bonferroni correction, significance level is set at $p = 0.050/12 = 0.004$). Post hoc, a correlation analysis was performed between RSWA percentage and ESS score as well as between the PSG parameters that showed a significant difference between groups and ESS score. Pearson's correlation coefficient was used, adjusted for age and gender.

The interobserver reliability on visual RSWA scoring was measured with an interobserver agreement percentage and Cohen's kappa statistic.

3. Results

3.1. RSWA group

Of the 864 included PSG (Fig. 2), 188 were positive for RSWA (frequency 21.8% [95% CI 19.1–24.6]). Table 1 describes the frequency of different etiologies within the RSWA group, confirming the presence of RSWA in patients with RBD, synucleinopathies and narcolepsy.

Within the RSWA group, 13.8% (95% CI 9.6–19.5) of the patients suffered from other psychiatric or central nervous system diseases: history of stroke, multiple sclerosis, epilepsy, metabolic encephalopathy on renal failure, recent psychosis (and/or use of antipsychotics), Alzheimer's disease, subarachnoidal bleeding, probable Creutzfeldt-Jakob disease.

There was a RBD frequency of 9.0% (95% CI 5.7–11.4, $n = 17/188$) in the RSWA group and of 2,0% (95% CI 1.2–3.1, $n = 17/864$) in the total study population.

There was a frequency of moderate to severe OSA of 39.4% (95% CI: 32.7–46.5; $n = 74/188$) in the total RSWA group. After excluding other causes of secondary RSWA, 46.0% of the RSWA patients had moderate to severe OSA as single comorbidity (95% CI 36.7–56.7, $n = 42/90$). There was a frequency of 49.0% (95% CI 39.4–58.7, $n = 49/100$) of moderate to severe OSA in the control group, with no significant difference between RSWA and total REM atonia subjects ($p = 0.115$). Antidepressant use was noted in 25.5% of the total RSWA group (95% CI 19.8–32.2, $n = 48/188$). After excluding other causes of secondary RSWA, we observed antidepressant use as sin-

Table 1
The frequency of isolated RSWA and secondary RSWA.

RSWA	Frequency in RSWA group (n = 188)	Frequency in total sample (n = 864)
Isolated RSWA (*n* = 48)	25.5% (19.8–32.2)	5.6% (4.2–7.3)
Secondary RSWA		
Severe OSA (*n* = 42)	22.3% (17.0–28.8)	4.9% (3.6–6.5)
Use of antidepressants (*n* = 22)	11.7% (7.9–17.1)	2.5% (1.7–3.8)
Severe OSA and use of AD (*n* = 19)	10.1% (6.6–15.2)	2.2% (1.4–3.4)
Isolated RBD (*n* = 6)	3.2% (1.5–6.8)	0.7% (0.3–1.5)
RBD and severe OSA (*n* = 6)	3.2% (1.5–6.8)	0.7% (0.3–1.5)
RBD and use of AD (*n* = 1)	0.5% (0.0–3.0)	0.2% (0.0–0.7)
RBD, severe OSA and use of AD (*n* = 4)	2.1% (0.8–5.3)	0.5% (0.2–1.2)
Narcolepsy (*n* = 6)	3.2% (1.5–6.8)	0.7% (0.3–1.5)
Narcolepsy and AD (*n* = 2)	1.1% (0.3–3.8)	0.2% (0.00–0.8)
Parkinson's disease (*n* = 3)	1.6% (0.5–4.6)	0.3% (0.1–1.0)
Parkinson's disease and OSA (*n* = 3)	1.6% (0.5–4.6)	0.3% (0.1–1.0)
Other (*n* = 26)*	13.8% (9.6–19.5)	3.0% (2.1–4.4)

Frequency is given as a percentage (95% lower-upper confidence interval). N: number of subjects. Severe OSA: obstructive sleep apnea with either a total or REM Apnea/hypopnea index ≥15/h. AD: anti-depressants. RBD: REM sleep behavior disorder.
*Other: includes all other central nervous system disorders and major psychiatric disorders which may have influenced REM atonia.

Table 2
The frequency of isolated RSWA and secondary RSWA without considering OSA as an etiological factor.

RSWA	Frequency in RSWA group (*n* = 188)	Frequency in total sample (*n* = 864)
isolated RSWA (*n* = 90)	47.8% (40.9–55.0)	10.4% (8.5–12.6)
Secondary RSWA		
Use of antidepressants (*n* = 41)	21.8% (16.5–28.2)	4.8% (3.5–6.4)
Isolated RBD (*n* = 12)	6.4% (3.7–10.8)	1.4% (0.0–2.4)
RBD and use of AD (*n* = 5)	2.6% (0.1–6.1)	0.6% (0.0–1.4)
Narcolepsy (*n* = 6)	3.2% (1.5–6.8)	0.7% (0.3–1.5)
Narcolepsy and AD (*n* = 2)	1.1% (0.3–3.8)	0.2% (0.0–0.8)
Parkinson's disease (*n* = 6)	3.2% (1.5–6.8)	0.7% (0.3–1.5)
Other (*n* = 26)*	13.8% (9.6–19.5)	3.0% (2.1–4.4)

This table shows frequencies of the RSWA and different etiologies without moderate to severe OSA as an etiology. Frequency is given as a percentage (95% lower-upper confidence interval). N: number of subjects. AD: anti-depressants. RBD: REM sleep behavior disorder.
* Other: includes all other central nervous system disorders and major psychiatric disorders which may have influenced REM atonia.

gle comorbidity in 31.4% of the RSWA patients (95% CI 21.2–43.0, *n* = 22/70). There was a frequency of 14.0% (95% CI 8.5–22.1, *n* = 14/100) of use of antidepressants in the control group, with a significant difference between RSWA and total REM atonia subjects ($p = 0.021$).

Since our results on moderate to severe OSA are inconclusive (a high OSA frequency in RSWA subjects, but also a high frequency in subjects with total REM atonia), we added an additional table (Table 2), indicating the frequencies of different etiologies without moderate to severe OSA as an etiology.

3.2. iRSWA group

The group of iRSWA patients consisted of 48 subjects, corresponding to a frequency of 5.6% [CI 4.2–7.3] (10.4% [CI 8.5–12.6] without regarding moderate to severe OSA as a cause of RSWA) in the total sample and to a frequency of 25.5% [CI 19.8–32.2] in the RSWA group (Fig. 2, Table 1). iRSWA subjects had a mean age of 43.7 (±13.0) years and 67% [95% CI 53.0–78.0] were male (Table 3).

Table 4 describes the different clinical indications for the PSG in iRSWA and control subjects. There was a significant difference in the PSG clinical indication between groups ($p = 0.006$) and EDS was more often the primary indication for the PSG in the iRSWA group (18 vs. 4, $p = 0.006$), whereas control subjects underwent a PSG more often for a combination (≥2) of different indications (3 vs. 11, $p = 0.007$). Mean ESS scores were 9.8 ± 4.8 for the iRSWA subjects and 7.5 ± 4.9 for the controls ($p = 0.014$). Mean BDI-II scores were 11.3 ± 7.9 for the iRSWA subjects and 9.5 ± 8.4 for the controls ($p = 0.229$). Table 5 describes the RSWA metrics of the iRSWA group.

Table 3
Clinical and polysomnographic parameters.

	iRSWA group (*n* = 48)	Control group (*n* = 38)	P value
Age (years)	43.6 (±13.0)	44.7 (±10.9)	0.699 (matched)
Gender (M/F)*	32/16	22/16	0.501 (matched)
Total sleep time (min)	411.9 (±85.0)	375.2 (±88.0)	0.054
N1 (%)	2.6 (±2.1)	3.5 (±3.9)	0.221
N2 (%)	44.2 (±17.2)	41.3 (±13.6)	0.391
N3 (%)	32.9 (±14.2)	38.6 (±16.7)	0.096
REM sleep (%)	23.9 (±12.7)	19.7 (±6.9)	0.070
Total AHI (N/h)	4.1 (±3.3)	6.3 (±3.7)	**0.003**
AHI during REM (N/h)	4.4 (±4.2)	8.4 (±4.57)	**0.001**
Total PLM index (N/h)	20.3 (±15.2)	15.8 (±15.6)	0.186
PLM during REM (N/h)	26.0 (±13.8)	16.5 (±13.0)	**0.004**
RLS (no/yes)*	38/10	34/4	0.248
BMI (kg/m^2)	27.8 (±5.4)	27.4 (±5.4)	0.401
Arousal index (N/h)	24.3 (±7.9)	21.4 (±6.8)	0.080

Clinical and polysomnographic parameters of iRSWA and control group. Means are given (±standard deviations). *Gender and RLS are given in numbers. RSWA: REM sleep without atonia. AHI: apnea/hypopnea index. PLM: periodic limb movement. RLS: restless legs. BMI:body mass index. P values are shown, with a significance level set at $P < 0.004$. Significant P values are shown in bold. The control group shows a higher total and REM AHI index, while the iRSWA group shows a borderline significantly higher PLM index during REM sleep.

Table 4
Indication for polysomnography.

Indication	iRSWA group (n = 48)	Control group (n = 38)	P value
Excessive daytime sleepiness and/or tiredness	*n* = 18 (37.5%)	*n* = 4 (10.5%)	**0.006**
Sleep-related breathing disorders	*n* = 22 (48.9%)	*n* = 19 (50.0%)	0.828
Disturbances in initiating and/or maintaining sleep	*n* = 2 (4.5%)	*n* = 2 (5.2%)	1.000
Sleep-related movement disorder	*n* = 1 (2.2%)	*n* = 0 (0.0%)	1.000
Combination of 2 or more of above	*n* = 3 (6.7%	*n* = 11 (28.9%)	**0.007**
Other*	*n* = 2 (4.5%)	*n* = 2 (5.3%)	1.000

Differences in PSG indication between the iRSWA and control group. Test: Fisher's exact test, significance level $P < 0.008$. Significant P values are shown in bold.
* Other: suspicion narcolepsy, screening before lung transplant, suspicion parasomnia, screening cardiac arrhythmia.

Table 5
RSWA metrics of iRSWA subjects.

Type of epochs	30 s epochs	3 s mini epochs
Total epochs included (N)	180.2 (±61.4)	1767,6 (±600.2)
Total RSWA (%)	11,0 (±12.1)	13,2 (±9.6)
Tonic RSWA (%)	3,7 (±8.1)	3,6 (±6.8)
Total phasic RSWA (%)	10,4 (±12.1)	12,8 (±10.2)
Mentalis phasic RSWA (%)	3,9 (±9.1)	4,0 (±6.8)
Tibialis anterior phasic RSWA (%)	7,0 (±7.0)	8,8 (±6.9)
PLM (N)	0 (±0)	9,5 (±11.9)
Artefact (N)	4,5 (±3.1)	75,1 (±45.6)

This table shows a detailed description of RSWA percentages in iRSWA subjects. Means are given (±standard deviations). % = percentage of included epochs for analysis. *n* = number of epochs. PLM = periodic limb movement. Artefact = All EMG activity due to respiratory events, snoring and arousals. Epochs with artefacts or PLMs were excluded from analysis.

No significant correlations were found between ESS score and total RSWA percentage ($r = 0.098$, $p = 0.389$), tonic RSWA percentage ($r = 0.034$, $p = 0.962$) or phasic RSWA percentage ($r = 0.094$, $p = 0.405$). No significant correlations were found between ESS score and PLM index during REM sleep ($r = 0.050$, $p = 0.709$) or AHI index ($r = 0.116$, $p = 0.320$).

4. Discussion

Our study describes the frequency of RSWA in a patient population, which was referred to a sleep clinic. We have observed an overall frequency of RSWA in 21.8% of the patients that underwent a PSG, suggesting that RSWA is a frequent PSG finding. Subsequently, our study highlights the different etiologies of RSWA and focuses on the clinical profile of iRSWA.

We found a total frequency of RSWA of 21,8% in our study. Few other studies have reported the frequency of RSWA with percentages between 2,1 and 15% (Kang et al., 2013; Sasai-Sakuma et al., 2014; McCarter et al., 2015a). The discrepancy between these results may be due to different study populations (a general versus a sleep lab population, demographic differences), different in/exclusion criteria regarding secondary RSWA and different methods of RSWA diagnosis (retrospective chart reviews versus prospective RSWA scoring of video polysomnographic studies, different muscle combinations and different cut-off values for the percentage of RSWA necessary for RSWA diagnosis). We prospectively investigated RSWA in a patient population, which was referred to a sleep clinic and used only few exclusion criteria, to give a complete overview of a clinical population. Since until now, no cut-off has been defined to differentiate pathological from physiological RSWA outside the context of RBD (Högl et al., 2018), we have included patients with one or more 30 s epochs of RSWA. This might explain the relatively high frequency of RSWA in our study. In some of these subjects, however, RSWA might be due to physiological variation rather than a pathological etiology. The discrepancy of RSWA frequency between studies emphasizes the need for an universal standardized RSWA scoring method and possible cut-off percentages for pathological RWSA.

Our findings confirm the presence of RSWA in established synucleinopathies (RBD, Parkinson's disease) and narcolepsy. Furthermore, 13.8% of the RSWA patients suffered from diseases of the central nervous system and/or psychiatric diseases. As all these concomitant diseases can, at least in theory, provoke central nervous system lesions or dysfunctions interrupting REM-sleep atonia pathways (Boeve et al., 2007), they might have affected REM tonus. Finally, we found a high frequency of OSA with RSWA, antidepressant-related RSWA, RBD and iRSWA, which will be discussed in the next paragraphs.

4.1. RSWA and antidepressants

In our study, we found antidepressant use as comorbidity in 25,5% of the RSWA patients, which is close to the percentage reported in RBD (23.8%) and higher than in our subjects with total atonia (14%) and a previously reported RBD negative sleeplab population (5.5%) (Haba-Rubio et al., 2018). Previous studies confirmed that antidepressants can increase REM tonus with or without RBD (McCarter et al., 2015a; Lee et al., 2016). However, several studies showed that patients with antidepressant (AD)-induced RBD were positive for other prodromal PD biomarkers and developed a synucleinopathy with a longer conversion time than AD-negative RBD patients (Postuma et al., 2013). These findings suggest that antidepressants trigger RBD in patients with an underlying neurodegeneration rather than cause a purely pharmacologic effect (Postuma et al., 2013). This overrepresentation of use of antidepressants may also be due to the fact that a clinical depression is a possible prodromal non-motor symptom of PD and related diseases (Berg et al., 2015).

Whether antidepressants cause or trigger RSWA is unclear. To explore a possible association between RSWA and depression, we investigated depressive symptoms in iRSWA subjects, which were not taking any antidepressant medication. Although we observed a higher mean BDI-II score in our iRSWA group than in the general (European) population (11.3 vs 3.7) (Schulte-van Maaren et al., 2013), we found no significant difference in mean BDI-II score between our iRSWA group and control group (11.3 vs 9.5, $p = 0.229$). This may suggest that BDI-II scores are increased in the sleeplab population in general, rather than specific in iRSWA patients. Furthermore, the mean BDI-II score of 11 is beneath the cut-off for clinical depression (>14) (Beck et al., 1996). These findings combined, may suggest an association between RSWA and antidepressant medication, but not with depression itself. Longitudinal studies investigating the persistence of RSWA after discontinuation of antidepressant medication and possible conversion to a synucleinopathy are therefore needed.

4.2. RSWA and REM sleep behavior disorder

In our RSWA group, only 9% (CI-5.7–11.4) of the patients had RBD. These results confirm that RSWA and DEB are not always associated. This may be of clinical relevance because the ICSD-3 criteria (AASM, 2014) allow RBD diagnosis when the polysomnography only shows RSWA and there is a history of DEB. This may lead to false positive RBD diagnoses, which has a clinical consequence, as isolated RBD is a very strong indicator of synucleinopathy and the clinical significance of isolated RSWA is still unknown. Repeating the polysomnographic study, to visualize both RSWA and DEB might be preferred for RBD diagnosis.

We found an overall frequency of 2.0% (CI 1.2–3.1) of RBD in our study, which is slightly higher than the RBD prevalence in the general population [1% (Haba-Rubio et al., 2018)]. The study group of Innsbruck reported a RBD frequency of 4.8 (CI 3.3–6.6) in their sleep clinic specialized in RBD and movement disorders (Frauscher et al., 2010), which was higher than in our general hospital sleep clinic population. Both studies, however, show that RBD is not rare in patients undergoing a clinical polysomnography. Sleep clinicians should be aware of the possible presence of RBD during PSG interpretation, since these patients are reported to be specially at risk of developing Lewy body disease (Iranzo et al., 2016).

4.3. RSWA and moderate to severe OSA

In our study, despite excluding muscle activity after respiratory events, we found moderate to severe OSA (AHI $\geq$ 15/h) as single comorbidity in 46.0% of the RSWA patients and a total frequency of 39.4%. Although this is higher than the reported prevalence in the general population (10% in 30–49 year-old male and 3% in female individuals) (Peppard et al., 2013), we found no significant difference in moderate to severe OSA frequency between patient with RSWA and subjects with total REM atonia. In comparison, the OSA prevalence in RBD patients is 67% (McCarter et al., 2013), but the relationship between OSA and RBD is still unclear. OSA can mimic RBD, indicated as "pseudo-RBD", causing DEB without RSWA (Iranzo and Santamaría, 2005). Several case reports, however, have described that OSA can induce RSWA with RBD, which can disappear after treatment of OSA with continuous positive airway pressure (CPAP) therapy (Petrenko and Gupta, 2016; Goyal et al., 2018). These findings suggest that OSA may cause RSWA. One study, however, could not confirm an effect of CPAP therapy on RSWA in OSA patients with RBD (McCarter et al.,

2014). Furthermore, physiologically increased REM sleep muscle activity due to respiratory artefacts in untreated OSA is sometimes difficult to distinguish from RSWA during PSG analysis. Since our results are inconclusive (a high OSA frequency in RSWA subjects, but also a high frequency in subjects with total REM atonia), follow-up studies on isolated RSWA patients with OSA after sufficient treatment with CPAP therapy are still needed to further explore this possible causality and to elucidate the effects of OSA in RSWA interpretation.

4.4. Isolated RSWA (iRSWA)

Of the RSWA subjects 25.5% did not have any known RSWA comorbidities, other central nervous system diseases nor were taking any medication that might have influenced REM tonus. This so-called iRSWA group had a frequency of 5.6% in our total sample (10.4% without regarding moderate to severe OSA as a cause of RSWA).

Compared to the control group, EDS was more often the primary indication for the PSG (37.5% vs 10.5%, $p = 0.006$) and the mean ESS score was significantly higher (9.8 vs 7.5, $p = 0.014$). These findings may suggest that RSWA is not just a coincidental finding, but related to EDS. Excessive sleepiness during daytime is a common non-motor symptom of PD, (Hobson et al., 2002) that sometimes occurs in the prodromal stage (Berg et al., 2015). This highlights the importance of RSWA analysis in polysomnographic studies of patients with unexplained EDS and is in line with the hypothesis of iRSWA as a prodromal sign of Lewy Body Disease (Högl et al., 2018). The exact mechanism causing EDS in PD seems multifactorial, with nocturnal sleep-related, psychological, pharmacologic and neurochemical factors. Previous studies reported hypothalamic dysfunction with orexin and melatonin disturbances (Al-Qassabi et al., 2017) and dysfunction of the arousal system, influenced by dopaminergic, cholinergic, serotonergic and noradrenergic pathways (Al-Qassabi et al., 2017), which all are driven by the brainstem, as are the main brain circuits responsible for REM sleep atonia (Högl et al., 2018). Therefore, we can hypothesize that iRSWA and EDS share overlapping neuroanatomical and/or physiological mechanisms. In RBD, however, previous studies showed inconsistent results on the presence of EDS (Arnulf et al., 2015; Iranzo et al., 2017; Postuma et al., 2017), which might be due to population and selection differences (Postuma et al., 2017). As has been mentioned before, further prospective studies are needed to investigate prodromal PD symptoms and biomarkers in relation to iRSWA and possible conversion to a synucleinopathy.

4.5. Strengths and limitations

Our study has several strengths, most importantly that the results reflect direct clinical practice in a sleep clinic population. The data were collected for clinical purposes and the methods used (PSG, questionnaires) are widely available and can be easily implanted in clinical practice in most hospitals.

Our study also has several limitations. First of all, DEB can be paroxysmal and although iRSWA patients in our study did not show DEB on the video polysomnography and had no history of DEB, we cannot exclude that paroxysmal DEB might be present without the patient's awareness and hence, that iRSWA is not truly 'isolated'. However, this limitation has little clinical relevance, since RBD will not be diagnosed without PSG-confirmed DEB or a history of DEB.

Secondly, previous studies showed higher specificity for phasic RSWA when measured on both m. flexor digitorum superficialis instead of the m. tibialis anterior. In case of suspicion of RBD a PSG with arm EMG recordings is recommended (Frauscher et al., 2012). As iRSWA is usually a co-incidental finding, we could not predict in which patients additional arm electrodes were needed. As a consequence, a classical polysomnography with only tibialis anterior recordings was performed in all patients. As a consequence, we may have missed a small percentage of phasic RSWA (Högl et al., 2018). Furthermore, we cannot exclude a small percentage of false positive phasic RSWA, on the tibialis muscle, due to the presence of fragmentary myoclonus, which criteria (Berry et al., 2017) overlap with RSWA. Since most sleep labs do not use arm electrodes on a routine video PSG, the tibialis anterior recordings in our study reflect findings in common clinical practice.

Thirdly, different automatic (Burns et al., 2007; Mayer et al., 2008; Ferri et al., 2010; Frauscher et al., 2014) and visual (Lapierre and Montplaisir, 1992; Bliwise et al., 2006; Montplaisir et al., 2010; Frauscher et al., 2012; McCarter et al., 2014; Berry et al., 2017) scoring methods for RSWA are available. Until now, there is no consensus on the best scoring method and no cut off has been defined to differentiate pathological from physiological RSWA outside the context of RBD (Högl et al., 2018). We used the AASM manual criteria, but as discussed earlier, other scoring methods can lead to different results in RSWA frequency.

Fourthly, when comparing other sleep parameters between the iRSWA and control group, the control group showed a significant higher AHI index (total and during REM) while the iRSWA group showed a borderline significant higher PLM index during REM sleep (not total PLM index). Both can cause EDS, but we did not find any correlation between both variables and the ESS score. We, however, cannot exclude that the borderline higher REM PLM index in the iRSWA group might have contributed to EDS.

4.6. Conclusions

RSWA is a frequent polysomnographic finding and occurs regularly in the context of sleep apnea, use of antidepressants or synucleinopathies. The frequency of iRSWA in our population is 5.6%. iRSWA subjects reported increased daytime sleepiness and had more often EDS as primary indication for the PSG. These findings highlight the importance of RSWA analysis on PSG in patients with EDS. Longitudinal studies are required to investigate the clinical relevance and possible conversion of iRSWA to a synucleinopathy.

Acknowledgments

We would like to thank all employees of the Laboratory for Sleep disorders, St Dimpna Regional Hospital, for their help with the data collection.

Disclosure statement

All authors: financial disclosures: none; non-financial disclosures: none.

References

Al-Qassabi A, Fereshtehnejad S-M, Postuma RB. Sleep disturbances in the prodromal stage of Parkinson disease. Curr Treat Options Neurol. 2017;19:22.
American Academy of Sleep Medicine. International classification of sleep disorders, 3rd ed. Darien, IL; 2014.
Arnulf I, Neutel D, Herlin B, Golmard J-L, Leu-Semenescu S, Cochen de Cock V, et al. Sleepiness in idiopathic REM sleep behavior disorder and Parkinson disease. Sleep 2015;38:1529–35.
Barone DA, Ebben MR, Samie A, Mortara D, Krieger AC. Autonomic dysfunction in isolated rapid eye movement sleep without atonia. Clin Neurophysiol. 2015;126:731–5.
Beck AT, Steer R, Borwn G. Manual for the beck depression inventory-II. San Antonio (TX): Psychol Corporation; 1996.
Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, et al. MDS research criteria for prodromal Parkinson's disease. Mov Disord 2015;30:1600–11.
Berry RB, Brooks R, Gamaldo CE, et al. for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: Rules,

Terminology and Technical Specifications. Darien, IL: American Academy of Sleep Medicine; 2017 [Version 2.4.].
Bliwise DL, He L, Ansari FP, Rye DB. Quantification of electromyographic activity during sleep: a phasic electromyographic metric. J Clin Neurophysiol 2006;23:59–67.
Boeve BF, Silber MH, Saper CB, Ferman TJ, Dickson DW, Parisi JE, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain 2007;130:2770–88.
Burns JW, Consens FB, Little RJ, Angell KJ, Gilman S, Chervin RD. EMG variance during polysomnography as an assessment for REM sleep behavior disorder. Sleep 2007;30:1771–8.
Dauvilliers Y, Jennum P, Plazzi G. Rapid eye movement sleep behavior disorder and rapid eye movement sleep without atonia in narcolepsy. Sleep Med 2013;14:775–81.
Eisensehr I, Linke R, Tatsch K, Kharraz B, Gildehaus JF, Wetter CT, et al. Increased muscle activity during rapid eye movement sleep correlates with decrease of striatal presynaptic dopamine transporters. IPT and IBZM SPECT imaging in subclinical and clinically manifest idiopathic REM sleep behavior disorder, Parkinson's disease, and controls. Sleep 2003;26:507–12.
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;11:947–9.
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.
Frauscher B, Gschliesser V, Brandauer E, Marti I, Furtner MT, Ulmer H, et al. REM sleep behavior disorder in 703 sleep-disorder patients: the importance of eliciting a comprehensive sleep history. Sleep Med 2010;11:167–71.
Frauscher B, Iranzo A, Gaig C, Gschliesser V, Guaita M, Raffelseder V, et al. Normative EMG values during REM sleep for the diagnosis of REM sleep behavior disorder. Sleep 2012;35:835–47.
Goyal A, Pawar KS, Khurana A, Kumar S. A case of Pseudo-RBD with OSA. Sleep Vigil 2018;2:87–9.
Haba-Rubio J, Frauscher B, Marques-Vidal P, Toriel J, Tobback N, Andries D, et al. Prevalence and determinants of rapid eye movement sleep behavior disorder in the general population. Sleep 2018;41:1–8.
Hobson DE, Lang AE, Martin WRW, Razmy A, Rivest J, Fleming J. Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian Movement Disorders Group. JAMA 2002;287:455–63.
Högl B, Stefani A, Videnovic A. Idiopathic REM sleep behaviour disorder and neurodegeneration - an update. Nat Rev Neurol 2018;14:40–55.
Iranzo A, Santamaría J. Severe obstructive sleep apnea/hypopnea mimicking REM sleep behavior disorder. Sleep 2005;28:203–6.
Iranzo A, Santamaria J, Tolosa E. Idiopathic rapid eye movement sleep behaviour disorder: diagnosis, management, and the need for neuroprotective interventions. Lancet Neurol 2016;15:405–19.
Iranzo A, Serradell M, Santamaria J. Excessive daytime sleepiness does not predict neurodegeneration in idiopathic REM sleep behavior disorder. Sleep 2017;40:12.
Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540–5.
Kang S-H, Yoon I-Y, Lee SD, Han JW, Kim TH, Kim KW. REM sleep behavior disorder in the Korean elderly population: prevalence and clinical characteristics. Sleep 2013;36:1147–52.
Lapierre O, Montplaisir J. Polysomnographic features of REM sleep behavior disorder: development of a scoring method. Neurology 1992;42:1371–4.
Lee K, Baron K, Soca R, Attarian H. The prevalence and characteristics of REM sleep without atonia (RSWA) in patients taking antidepressants. J Clin Sleep Med 2016;12:351–5.
Mayer G, Kesper K, Ploch T, Canisius S, Penzel T, Oertel W, et al. Quantification of tonic and phasic muscle activity in REM sleep behavior disorder. J Clin Neurophysiol 2008;25:48–55.
McCarter SJ, Boswell CL, St Louis EK, Dueffert LG, Slocumb N, Boeve BF, et al. Treatment outcomes in REM sleep behavior disorder. Sleep Med 2013;14:237–42.
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.
McCarter SJ, St. Louis EK, Sandness DJ, Arndt KA, Erickson MK, Tabatabai GM, et al. Antidepressants increase REM sleep muscle tone in patients with and without REM sleep behavior disorder. Sleep 2015a;38:907–17.
McCarter SJ, Tippmann-Peikert M, Sandness DJ, Flanagan EP, Kantarci K, Boeve BF, et al. Neuroimaging-evident lesional pathology associated with REM sleep behavior disorder. Sleep Med. 2015b;16:1502–10.
Montplaisir J, Gagnon J-F, Fantini ML, Postuma RB, Dauvilliers Y, Desautels A, et al. Polysomnographic diagnosis of idiopathic REM sleep behavior disorder. Mov Disord 2010;25:2044–51.
Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol 2013;177:1006–14.
Petrenko I, Gupta D. Can REM without atonia (RWA) be present in pseudo-REM sleep behavior disorder (pseudo-RBD) due to obstructive sleep apnea (OSA)? Neurology 2016;86(Supplement).
Postuma RB, Gagnon J-F, Pelletier A, Montplaisir JY. Insomnia and somnolence in idiopathic RBD: a prospective cohort study. NPJ Park Dis 2017;3:9.
Postuma RB, Gagnon J-F, Tuineaig M, Bertrand J-A, Latreille V, Desjardins C, et al. Antidepressants and REM sleep behavior disorder: isolated side effect or neurodegenerative signal? Sleep 2013;36:1579–85.
Sasai-Sakuma T, Frauscher B, Mitterling T, Ehrmann L, Gabelia D, Brandauer E, et al. Quantitative assessment of isolated rapid eye movement (REM) sleep without atonia without clinical REM sleep behavior disorder: clinical and research implications. Sleep Med 2014;15:1009–15.
Schenck CH, Montplaisir JY, Frauscher B, Hogl B, Gagnon J-F, 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.
Schulte-van Maaren YWM, Carlier IVE, Zitman FG, van Hemert AM, de Waal MWM, van der Does AJW, et al. Reference values for major depression questionnaires: the Leiden Routine Outcome Monitoring Study. J Affect Disord 2013;149:342–9.
Sixel-Döring F, Schweitzer M, Mollenhauer B, Trenkwalder C. Intraindividual variability of REM Sleep behavior disorder in Parkinson's disease: a comparative assessment using a new REM sleep behavior disorder severity scale (RBDSS) for clinical routine. J Clin Sleep Med 2011;7:75–80.
Stefani A, Gabelia D, Högl B, Mitterling T, Mahlknecht P, Stockner H, et al. Long-term follow-up investigation of isolated rapid eye movement sleep without atonia without rapid eye movement sleep behavior disorder: a pilot study. J Clin Sleep Med 2016;11:1273–9.