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Original Article

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

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ABSTRACT

Objectives: We aimed to provide a consensus statement by the International Rapid Eye Movement Sleep Behavior Disorder Study Group (IRBD-SG) on devising controlled active treatment studies in rapid eye movement sleep behavior disorder (RBD) and devising studies of neuroprotection against Parkinson disease (PD) and related neurodegeneration in RBD.

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Methods: The consensus statement was generated during the fourth IRBD-SG symposium in Marburg, Germany in 2011. The IRBD-SG identified essential methodologic components for a randomized trial in RBD, including potential screening and diagnostic criteria, inclusion and exclusion criteria, primary and secondary outcomes for symptomatic therapy trials (particularly for melatonin and clonazepam), and potential primary and secondary outcomes for eventual trials with disease-modifying and neuroprotective agents. The latter trials are considered urgent, given the high conversion rate from idiopathic RBD (iRBD) to Parkinsonian disorders (i.e., PD, dementia with Lewy bodies [DLB], multiple system atrophy [MSA]).

Results: Six inclusion criteria were identified for symptomatic therapy and neuroprotective trials: (1) diagnosis of RBD needs to satisfy the International Classification of Sleep Disorders, second edition, (ICSD-2) criteria; (2) minimum frequency of RBD episodes should preferably be ≥ 2 times weekly to allow for assessment of change; (3) if the PD-RBD target population is included, it should be in the early stages of PD defined as Hoehn and Yahr stages 1–3 in Off (untreated); (4) iRBD patients with soft neurologic dysfunction and with operational criteria established by the consensus of study investigators; (5) patients with mild cognitive impairment (MCI); and (6) optimally treated comorbid OSA. Twenty-four exclusion criteria were identified. The primary outcome measure for RBD treatment trials was determined to be the Clinical Global Impression (CGI) efficacy index, consisting of a four-point scale with a four-point side-effect scale. Assessment of video-polysomnographic (vPSG) changes holds promise but is costly and needs further elaboration. Secondary outcome measures include sleep diaries; sleepiness scales; PD sleep scale 2 (PDSS-2); serial motor examinations; cognitive indices; mood and anxiety indices; assessment of frequency of falls, gait impairment, and apathy; fatigue severity scale; and actigraphy and customized bed alarm systems. Consensus also was established for evaluating the clinical and vPSG aspects of RBD. End points for neuroprotective trials in RBD, taking lessons from research in PD, should be focused on the ultimate goal of determining the performance of disease-modifying agents. To date no compound with convincing evidence of disease-modifying or neuroprotective efficacy has been identified in PD. Nevertheless, iRBD patients are considered ideal candidates for neuroprotective studies.

Conclusions: The IRBD-SG provides an important platform for developing multinational collaborative studies on RBD such as on environmental risk factors for iRBD, as recently reported in a peer-reviewed journal article, and on controlled active treatment studies for symptomatic and neuroprotective therapy that emerged during the 2011 consensus conference in Marburg, Germany, as described in our report.

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1. Introduction

Rapid eye movement sleep behavior disorder (RBD) is a complex multidimensional parasomnia that frequently is interlinked with other sleep disorders and their therapies (e.g., narcolepsy-cataplexy), a wide range of neurologic disorders, and the pharmacotherapy of psychiatric and medical disorders (e.g., antidepressants, β blockers) [1]. Experimental brainstem models of RBD in cats and rats [2–6] and a recently developed transgenic RBD mouse model with impaired gamma-aminobutyric acid and glycine transmission [7], have expanded knowledge on brain mechanisms subserving rapid eye movement (REM) atonia and REM sleep phasic motor activity and their dysfunction in RBD [8–12]. It is thus evident that RBD is situated at an active and strategic crossroad of the neurosciences and clinical (sleep) medicine. The literature on RBD has continued to grow exponentially, both in breadth and depth since the exponential growth of RBD publications was first quantified [13]. Two striking examples involve the strong link of RBD with narcolepsy [1,2] and the various strong associations of RBD with Parkinson disease (PD) and dementia with Lewy bodies (DLB), as comprehensively reviewed [14–16]. The notable finding that idiopathic RBD (iRBD) often heralds future parkinsonism/dementia (by more than 80% within 10–20 y after the diagnosis) has stimulated research on predictors of imminent parkinsonism in iRBD [17,18]. High-risk patients could be enrolled in therapeutic studies of promising neuroprotective (i.e., disease-modifying) agents that could prolong or ideally halt the progression of iRBD to clinical parkinsonism/dementia. To this end and for other compelling collaborative research goals, such as initiating and recently completing a case-control study of environmental risk factors for RBD [19], the International RBD Study Group (IRBD-SG) was founded.

2. The International RBD Study Group

The IRBD-SG was legally incorporated in Marburg, Germany in 2009, and it has since been recognized as a notable transnational network for accelerating movement disorders and RBD research [20]. The forerunner of the IRBD-SG was the RBD Task Force that held a World Association of Sleep Medicine–sponsored meeting on February 7, 2007 during the second World Association of Sleep Medicine congress in Bangkok, Thailand. In total, the IRBD-SG has held six symposia in Marburg (2007, 2008, and 2011), Montreal (2010), Otsu City, Japan (2011), and Paris (2012), and the seventh symposium is scheduled for Valencia (2013). The IRBD-SG is a network of leading basic science and clinical RBD researchers from North America, Europe, and Asia.

Objectives of the IRBD-SG are the promotion of international scientific research in the field of RBD and related fields and the optimization of medical care for patients by improving diagnostic and therapeutic measures. Given the relatively low number of patients with RBD identified at individual RBD research centers, a major focus of the IRBD-SG is to facilitate multicenter studies (i.e., the natural history and epidemiologic issues, including a search for risk factors [19], biomarkers, genetic studies, diagnostic procedures, and therapeutic interventions). Therefore, the IRBD-SG aims to strengthen the international scientific information and communication structures for RBD and to support the establishment of standardized patient documentation and respective databases. An overarching aim of the IRBD-SG is to enhance professional and public awareness of the field of RBD and associated fields and to foster cooperation among physicians, scientists, and patients and their family members as well as to utilize the media to serve as an educational public-awareness tool.

As the first example of such collaboration within the IRBD-SG, the recently published case-control study [19] of environmental risk factors in 316 iRBD patients (mainly older men) and 316 controls, who were evaluated at 11 centers in nine countries, found that prior head injury, prior occupational pesticide exposure, farming, welding, and smoking were significant risk factors.

We now wish to present a pertinent summary from the fourth IRBD-SG symposium held in Marburg, Germany (April 29, 2011–May 1, 2011) with proposed research protocols and their rationale based on the current state of knowledge. This symposium was sponsored by the National Parkinson Foundation, United States, and the German Parkinson Study Group. At this symposium, there was recognition that as the field of RBD advances, the essential next steps will include the development of treatment trials, either for symptomatic treatment of iRBD and other forms of RBD, or for neuroprotective therapy against α synuclein-mediated neurodegeneration. Such trials will entail complex issues related to establishing diagnostic criteria, defining valid parameters to quantify important dimensions of RBD, establishing primary and secondary therapy-sensitive efficacy parameters, and determining potential treatments, among others. This symposium became a consensus conference to identify essential methodologic components for a randomized trial in RBD, including potential screening and diagnostic criteria (e.g., automated vs visual scoring techniques of tonic or phasic electromyogram activity during REM sleep in RBD), inclusion and exclusion criteria, primary and secondary outcomes for symptomatic trials (particularly for melatonin and clonazepam), and potential primary and secondary outcomes of eventual neuroprotective trials. We believe that there is a high level of clinical and scientific importance inherent in these activities to justify broad dissemination.

3. Therapy of RBD: state of the art

There are three extensive reviews of the therapy for RBD [21–23]. Clonazepam and melatonin are the two most commonly used agents. However, there is only one published, double-blind, placebo-controlled trial of RBD that utilized melatonin in a fixed dose of 3 mg at bedtime in a crossover design with 4 weeks on either melatonin (3 mg) or placebo with a short washout phase of 5 days in between [24]. The coprimary outcome measures were change in the Clinical Global Impression (CGI) scale and change in % of REM sleep mini epochs without REM atonia. This was a small study ($n = 8$) of mild RBD in which the presenting concern was either nonrestorative sleep ($n = 6$) or narcolepsy-related symptoms ($n = 2$) but not specific RBD symptoms. Two patients had insomnia and one patient had PD. Four patients were described to have complete resolution of RBD, two had marked improvement, one had little improvement, and one remained unchanged with melatonin therapy. The authors acknowledged that the generalization of their findings could be questioned. Firstly, the group of included patients was small and not homogeneous, as at least one patient did not suffer from iRBD. Secondly, because melatonin has been reported to be effective in RBD at doses up to 15 mg at bedtime [23], the low-dose fixed-dose protocol in this study may have precluded further improvement. Furthermore, evidence from this study and from a prior case report by one of the authors [25], suggests that melatonin may induce a sustained benefit over time; therefore, a longer period of melatonin therapy in this study may have resulted in a greater response rate. However, this statement only relies on patient reports and is not supported by controlled data. Therefore, the study would need to be carefully documented. In the crossover study there was a modest, albeit significant, 12% reduction of the primary outcome measure, “REM sleep mini epochs without muscle atonia,” from 39% of total REM sleep before therapy to 27% after therapy. However, it is not clear to what extent the improvement in the coprimary outcome

measure “change in CGI ratings” with melatonin therapy reflected improvement of the presenting concern of nonrestorative sleep or of improvement of specific RBD symptoms. Details of RBD behaviors and problematic consequences were not provided. The outcome methods of this trial were insufficient to prove efficacy. Still this study does mark a start for formal RBD treatment studies.

4. Ethical and medical concerns

4.1. Ethical concerns

An issue to be considered is the ethics and medical-legal liability of placebo-controlled treatment trials of a typical sample of RBD patients, as these individuals commonly engage in recurrent sleep and dream-enacting behaviors that pose a risk for injury, including life-threatening injury [26], to oneself or his or her bed partner. Even the best attempts at maximizing the safety of the sleeping environment cannot guarantee that serious injury will not occur, either during the placebo- or active-treatment arm of the study. Therefore, appropriate strategies for presenting placebo-controlled treatment studies of RBD to institutional review boards across countries need to be carefully considered and discussed from the perspective of safety issues.

4.2. Discussion of the risk for future parkinsonism or dementia with iRBD patients and spouses

Another issue of growing clinical and research importance involves what to tell iRBD patients and their families about the probabilities and time course for developing a parkinsonian disorder or dementia. Additionally, they must be informed about group and individual findings from research studies that consistently show that brain structure, brain function, cognitive function, olfactory function, among others, in iRBD patients show pathologic changes that are similar to those found in patients with PD and DLB. Should the mechanism and extent of feedback of findings be incorporated in the patient information leaflet on research protocols, besides the scientific rationale for enrolling in the studies? Not addressing this issue could be highly problematic for several reasons, including the wide use of the Internet by the general public for obtaining medical and scientific information. However, this sensitive issue needs to be properly stated to the patients and family regarding an increased risk for future PD and DLB, but without guarantee of developing these diseases. Cultural, familial, religious, educational, and other factors need to be considered in this matter.

4.3. Medical concerns

Clonazepam has been shown to be efficacious in open-label clinical case series. There are well-known concerns of adverse effects, especially in the elderly (i.e., daytime sedation, increased risk for falls, etc.). However, in many elderly patients clonazepam can be well-tolerated, even when dementia or parkinsonism is already present. Therefore, a controlled trial with clonazepam will generate—for example, in comparison to melatonin—highly needed data on adverse events, development of tolerance, and withdrawal symptoms.

5. Proposed RBD treatment studies and their rationale: background

5.1. Selection of drugs for treatment studies

Lack of therapeutic trials according to evidence-based medicine criteria have stimulated the IRBD-SG to: (1) select a comparative

active treatment study of RBD as a proposal for a large multicenter trial, as this design has major safety advantages over a placebo-controlled treatment study; (2) select primary and secondary end points likely amenable to change under a symptomatic therapy in the absence of a convincing candidate for use in a neuroprotective trial; and (3) to choose the two medications already known to provide substantial benefit to RBD patients on a purely pragmatic level as active comparative agents (i.e., clonazepam, melatonin).

5.2. Selection of patient groups: iRBD and PD-RBD

Given the small prevalence of iRBD in the general population (estimated at 0.5% [27]), the substantially higher prevalence of RBD in the readily available group of patients with α -synucleinopathies (e.g., PD, multiple system atrophy [MSA], DLB) makes this population of added interest for therapeutic trials in RBD. However, the frequency of probable RBD (i.e., compelling clinical history of RBD in the absence of polysomnography [PSG]) based on two population-based studies in individuals aged ≥ 70 y is in the 6–9% range [28,29]. This prevalence suggests that recruitment and enrollment for longitudinal neuroprotective studies may be more feasible than previously considered, and a screening questionnaire for RBD would capture cases that may not present to any clinic.

6. Inclusion criteria for iRBD and PD-RBD treatment trials

The diagnosis of RBD needs to satisfy the ICSD-2 criteria [27].

(A) There should be at least two prior episodes of clinically reported or witnessed dream-enacting behavior supported by REM sleep without atonia recorded by PSG [30].

(B) To allow for assessment of change, the minimum frequency of RBD episodes should preferably be ≥ 2 times weekly (with complex movements, apart from any sleep talking) to the extent that reliable reporting is possible by a bed partner (especially for iRBD).

The frequency of reported RBD episodes depends on the level of awareness by the observer and also on the intensity and severity of the behaviors displayed by the patients. Night-to-night variability exists; however, RBD activity possibly occurs every night to a greater or lesser degree. Because the pathophysiology of iRBD and RBD in PD seems to be comparable, with similar motor-behavioral signs during REM and NREM sleep and with iRBD consistently occurring as an early sign or even as a preclinical marker for the major α -synucleinopathies (PD, DLB, MSA) as observed in many patient cohorts [14], then patients with iRBD and with PD-RBD can both be included in proposed treatment trials. A further reason to include PD patients with RBD is to extrapolate the benefit of the therapy to the PD population, as this has never been done in a PD-RBD cohort [31].

(C) iRBD Patients should preferably be naive to clonazepam and melatonin therapy as well as any dopaminergic therapy, as Fantini et al. [32] have reported some beneficial effects of the dopamine agonist pramipexole on RBD in an open label study.

In that study, eight patients with iRBD were treated with 0.78 ± 0.25 mg pramipexole for 1–9.5 months. Seven patients reported reduction in the frequency of RBD, but phasic electromyography (EMG) chin muscle activity in REM sleep did not change from baseline to treatment follow-up; however, videometry displayed a significant reduction of simple movements and insignificant reductions of complex movements. Ideally, de novo RBD patients should be selected.

(D) The PD-RBD target population should be in the early stages of PD, defined as Hoehn and Yahr stages 1–3.

Inclusion of PD-RBD patients would preferentially involve patients in the early stages of PD, both nontreated and treated, but the latter would need a stable treatment of 4 weeks with any

antiparkinsonian medication. All forms of dopaminergic medications would be allowed, including the monoamine oxidase inhibitors (MAO) B inhibitors, selegiline and rasagiline, with stratification analysis of outcome measures. Previously published data did not show a clinically significant influence of these medications on RBD in PD [31]. Inclusion of PD-RBD patients in the early stages of PD is both for safety reasons and because in the advanced stages of PD, there are more factors adversely influencing the quality of sleep, such as REM sleep duration, sleep fragmentation, and psychosis [31]. Additionally, one study of PD-RBD patients found no benefit from pramipexole therapy on either RBD clinical symptoms or on tonic/phasic EMG activity during REM sleep [33]. If possible de novo PD patients should be selected, as they may show the best treatment effects. Any effects of clonazepam on postural stability can be monitored by the Unified Parkinson Disease Rating Scale, part 3 (UPDRS-3), items 29 and 30, in PD patients with Hoehn and Yahr stages 1–3.

(E) iRBD patients with soft neurologic dysfunction.

There is a consensus that various iRBD patients display concurrent neurologic dysfunction, such as soft Parkinsonian signs, dysautonomia, mild cognitive deficits, abnormalities in olfactory function, ataxia and dysmetria, among others, thus raising the question of how stringent the inclusion criteria should be for iRBD. A consensus should be established for each study protocol in regard to how iRBD should be defined. Criteria should be developed for how iRBD patients are tested and how the results can influence entry into the study.

(F) RBD patients with mild cognitive impairment [34–36].

This inclusion is in line with the previous inclusion of RBD patients with soft neurologic dysfunction. Inclusion of mild cognitive impairment (MCI) patients will provide the opportunity to monitor possible negative effects of clonazepam on cognitive and motor performance. It might be preferable to include single-domain MCI, though more medical attention can be directed for potential adverse effects for those with multiple-domain MCI (who may be more at risk for dementia). However, as MCI associated with DLB pathology can run the full gamut from amnesic single-domain MCI, to nonamnesic single-domain MCI, to amnesic or nonamnesic multiple-domain MCI [29], it would be preferable not to be overly restrictive on which MCI subtypes to include or exclude. The diagnostic criteria and methods used for diagnosing MCI need to be specified, with a uniform battery of tests used at all centers. Proposed MCI criteria and cognitive tests in PD have recently been published [37], which can be considered as a starting point. However, these criteria have yet to be validated in PD and iRBD. Measures that are more sensitive to attention or executive episodic memory and visuospatial dysfunction should be considered for inclusion in the battery of tests.

(G) Optimally treated comorbid obstructive sleep apnea, with demonstrated apnea–hypopnea index (AHI) < 15 per hour following treatment with positive airway pressure therapy or with a non-positive airway pressure modality.

Exclusion of obstructive sleep apnea (OSA)-RBD patients would limit recruitment opportunities as well as the generalization of findings. Ongoing control of OSA and adequate compliance with positive airway pressure (PAP) therapy can be documented by PAP machine downloaded data and portable oximetry to minimize the confounding influence of OSA on the primary and secondary measures of RBD therapy. Treatment of comorbid OSA with optimal PAP settings or other measures improves sleep continuity and oxygenation and frequently improves daytime functioning. Additionally, optimal treatment of RBD may improve compliance with OSA treatment, especially with PAP by improving sleep continuity and reducing episodes of RBD activity displacing the PAP mask. Finally, RBD diminishes the severity of comorbid OSA [38].

7. Exclusion criteria for iRBD and PD-RBD treatment trials

(A) Known hypersensitivity to melatonin or clonazepam.

(B) Prior or current therapy of RBD (or other disorder) with melatonin or clonazepam.

The sample size may possibly be small with this exclusion. Alternatively, patients being treated with clonazepam could be included after a gradual washout period of at least 2 months to exclude a possible rebound effect, as previously described [39]. The same inclusion could apply for melatonin but with a shorter washout period.

(C) Current use of sedative-hypnotic medication (i.e., benzodiazepines, benzodiazepine receptor agonists, pregabalin, antipsychotics, etc.).

(D) Current use of antiepileptic medication or history of epilepsy.

While the older agents can stabilize sleep by reducing fragmentation and may increase slow-wave sleep, many of the newer agents have limited effects on sleep architecture. Additionally, these medications often are used in the management of nonepileptic conditions, such as pain management, mood disturbance, among others. Therefore, this exclusion criterion needs further deliberation.

(E) Alcoholism, recent interruption of alcohol consumption, or history of drug abuse.

(F) Previous serious injury or serious near-injury from RBD, or the clinical investigator determines that there is a substantial risk for serious injury if RBD is left untreated before enrollment in the study.

(G) For iRBD, lack of a bed partner/roommate/caretaker who sleeps in the same room.

Observers are necessary for assessment of the primary efficacy criteria, provided that they are reliable observers according to the investigator's opinion. This exclusion criterion may prove difficult for enrolling a sufficient number of PD patients, unless efficacy in this group is assessed by video-polysomnography (vPSG) studies.

(H) Serious medical disorders, particularly unstable medical disorders (e.g., malignant diseases, severe chronic obstructive pulmonary disease, unstable cardiac disorders, etc.).

(I) Patients with nocturnal confusional episodes and nocturnal falls.

(J) Pregnancy.

(K) PD patients with Hoehn and Yahr stages 4 and 5.

Any effects of clonazepam on postural stability will not be confounded by this exclusion criterion.

(L) Patients who start or change PD treatment during the study period (dropouts).

(M) Multiple system atrophy.

MSA-RBD may have a different disease progression from PD-RBD. MSA also has a distinctive EMG abnormality pattern that is characterized by persistent tonic muscle activity during REM sleep [40,41]. Additionally, screening out patients with ataxia and sleep-related stridor can further help to exclude MSA patients.

(N) Dementia (DLB, pervasive developmental disorders, etc.) and any cognitively impaired patient with significant functional impact.

How these patients are defined should be carefully considered. A substantial proportion of MCI and mild DLB patients score in the normal range on the mini-mental state examination (MMSE) and the Montreal Cognitive Assessment (MoCA). A cutoff score of 21 on the MoCA or a cutoff score of 26 on the MMSE would most likely exclude dementia.

The criteria of the Movement Disorder Society for PDD [42] could be used. This exclusion is valid because of the risk for potential adverse effects from treatment with clonazepam (and possibly melatonin), including confusional states from benzodiazepine therapy in demented patients. A MMSE score <26 is proposed.

For older (≥ 80 y) or less educated (<10 y) participants, references to published normal ranges may be used [43,44]. Alternatively, a MoCA screening cutoff score <21 could be used, as this has recently been proposed and validated for PDD [45].

(O) Narcolepsy, which has a different pathophysiology from iRBD.

(P) Untreated or suboptimally treated obstructive sleep apnea (AHI > 15/h).

This exclusion is for safety reasons and also for the presence of "OSA pseudo-RBD" [46] that can make it difficult to differentiate behaviors emerging from REM sleep associated with apnea and hypopnea from true RBD behaviors. A further concern is differentiating the mentalis muscle EMG activity at the end of an apnea from REM sleep without atonia (RWA).

(Q) Bipolar disorder, psychosis, and major depression.

These conditions often are associated with changes in sleep architecture and with the use of antidepressant and mood-stabilizing medications that also can affect sleep architecture. In addition, concerns over safety justify this exclusion.

(R) Beck Depression Inventory (BDI) > 13–19 (for the BDI 21-item scale), depending on whether or not RBD patients with mild or moderate depressive symptoms are to be included in the study protocol.

With a cutoff >13, patients with mild depressive symptoms (scores, 14–19) would be excluded, which is frequent in iRBD (approximately 15%).

(S) Patients taking β blockers and antidepressants.

Selective serotonin reuptake inhibitors, venlafaxine, mirtazapine, tricyclic antidepressants, and mixed-type A and B MAO inhibitors can induce or aggravate RBD and reduce REM sleep%. Given the potential major medical and psychiatric risks associated with discontinuation of these agents, these patients should be excluded. Use of MAO-B inhibitors in the therapy of PD may not be an exclusion criterion, depending on the study protocol.

(T) For patients who had previously taken an antidepressant medication, the drug-free interval for eligibility to be enrolled in the study should be ≥ 3 months.

Nevertheless, it has not yet been established how long medication-induced RBD/RWA can persist after discontinuation of the (presumed) offending agent. Patients who have taken antidepressants for years might have a permanent upregulated noradrenergic or serotonergic system.

(U) Patients with other parasomnias (e.g., nonrapid eye movement [NREM] parasomnias including parasomnia overlap disorder, i.e. RBD-NREM parasomnia).

(V) Patients with sleep-related movement disorders, such as rhythmic movement disorders.

(W) Patients with clinically relevant restless legs syndrome (RLS) (with RLS rating scale score >15).

The presence of any periodic limb movements index should not be an exclusion criterion; otherwise, most PD and many iRBD patients would be excluded. The periodic limb movements arousal index could be monitored for therapy outcome.

(X) During the study, if there is a sleep-related injury, with the threshold severity of injury needing to be defined, the patient will drop out of the study. This situation also may apply to potentially serious events occurring during sleep. Patients should be promptly clinically evaluated, with a completed final CGI.

(Y) Patients with structural intracranial lesions potentially able to mimic PD or even trigger RBD.

To exclude these patients, a neuroimaging study is advisable (computed tomography scan or optimally, if feasible, a magnetic resonance imaging scan [MRI]) whenever there is a clinical suspicion of secondary RBD based on history and signs on neurologic examination.

In symptomatic treatment trials and disease-modifying trials, all enrolled patients should have a brain MRI to systematically

exclude any structural brain lesions that could affect the outcome data, which also carries medical-legal implications. It is important to ensure data quality for potential drug licensing procedures and to allow the opportunity for potential subanalysis of MRI data.

8. Primary end points For RBD treatment trials

(A) CGI efficacy index

The consensus at the Marburg symposium was to use the CGI efficacy index (four-point scale with a four-point side-effect scale) as the primary outcome measure. There currently are no validated RBD severity scales, and CGI efficacy is simple and is commonly utilized in many studies. Additionally, a global measure CGI efficacy can assess the overall impact of RBD symptoms as the patient or caregiver experiences them. Either joint or separate CGIs also should be completed by the spouse or caretaker. The degree of change with therapy needs to be viewed in light of the level of baseline severity of RBD, which can be assessed with CGI severity. However, treatment differences may not be large enough to detect any CGI difference.

(B) vPSG: Assessing change in REM atonia; quantitative EMG analysis (also refer to Section 10).

The use of vPSG analysis of change with therapy is promising, but it is costly and may be limited by the level of uncertainty of night-to-night variability [47]. This topic will be considered in a separate section below, as expert consensus has been achieved.

The use of quantifying changes in REM atonia and REM sleep phasic motor activity with therapy is highly desired, but it is limited by the considerable cost and also by the extent of uncertainty of night-to-night variability, particularly for phasic muscle activity, which appears more variable than tonic muscle activity [47]. This approach could form a separate arm of the study performed at specialized centers that have the experience and capability to perform detailed, quantitative PSG-EMG analyses. However, the larger the sample size, then the extent of night-to-night variability can be minimized. Additionally, night-to-night variability can be assessed with ambulatory monitoring for RWA.

(C) Outcome scales.

Other potential primary outcomes could include the 5-point scale (Boeve): 4 = controlled; 3 = markedly improved; 2 = initially improved but subsequently returned; 1 = no change; 0 = worsened [48].

Another option would be an adapted version of the RBD-Hong Kong (RBD-HK) questionnaire [49], which assesses the frequency of a variety of dream enactment behaviors ranging from mild to severe. The timeline of the RBD-HK (which is over 1 y) would need to be changed to the timeline of the treatment period. Use of the Japanese version of the RBD-HK has recently demonstrated the ability to measure treatment responsiveness in 45 RBD subjects after 1 y of treatment [50].

9. Secondary outcome measures for RBD treatment trials

9.1. There are two major considerations: efficacy and tolerability/safety

(A) Sleep diaries completed by patient and bed partner.

These diaries would assess sleep duration, sleep quality, frequency and severity of clinically evident movements, and dream enactment behavior.

(B) Epworth sleepiness scale, Pittsburgh Sleep Quality Index (PSQI), and Karolinska sleepiness scale.

These scales would assess potential somnolence side effects of medications, and should be measured at the baseline visit and repeated following steady-state treatment with clonazepam or

melatonin. These measures should be repeated once during titration as well as just after achieving steady state in case change occurs (i.e., development of tolerance) as a potentially interesting tolerability measure. The Epworth sleepiness scale and PSQI have both been endorsed as appropriate tools for the assessment of sleep impairment in PD [51]. The PSQI is a self-rated questionnaire that assesses sleep quality and disturbances over the last month [52]. The PSQI contains 19 items that generate seven subcomponent scores, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Sum scores for these seven components yields a single global score. A global PSQI score >5 suggests that the subject is a poor sleeper. However, the PSQI may be too nonspecific for this type of study. The Karolinska sleepiness scale is a semiquantitative standardized 10-point scale on which the subject rates sleepiness during the previous 10 min, and therefore could be used as a single time assessment of sleepiness. The scale has been well-validated by simultaneous electroencephalogram (EEG) and performance measures [53].

(C) PD Sleep Scale 2.

The original PD Sleep Scale 2 (PDSS-2) [54,55], updated with the newly validated PDSS-2 [56], is a simple bedside tool for the disease-specific assessment of symptoms associated with sleep disturbance in PD. The PDSS addresses 15 commonly reported sleep-related symptoms and shows excellent test-retest reliability. The recent version of the scale (PDSS-2) typically demonstrates higher scores with advancing parkinsonism and excellent discrimination between PD patients and healthy controls [56]. The PDSS-2 is a 5-point rating scale ranging from 0 to 4, with high values indicating more sleep disturbances. We plan to administer PDSS-2 at baseline and the terminal study visit in all patients with symptomatic RBD associated with PD.

(D) Serial motor exams: UPDRS part 3.

(E) Cognitive indices: MMSE [57] and MoCA [58].

Both scales take 5–10 min to administer and can be partially cross-scored with each other. Although the MMSE is a standard instrument for assessing dementia, it is likely to be insensitive for assessing moderate changes in cognition. Therefore, MoCA may be more advantageous for assessing potential cognitive adverse events of medication (particularly clonazepam). The MoCA has multiple versions, reducing the concern of test-retest bias. Alternative versions of the MoCA are in development in other languages. The MoCA but not the MMSE is sensitive for detecting MCI in iRBD [59]. The MoCA appears to be the preferred instrument for use in these studies and is available for free at <http://www.mocatest.org/>.

(F) Mood and anxiety indices: BDI [60] and Beck Anxiety Inventory [61].

The BDI and Beck Anxiety Inventory are well-validated instruments utilized in clinical and research populations to screen and follow-up for depressive and anxiety symptoms, including demonstrating reliability and validity in the PD population [62,63].

(G) Assessment of frequency of falls, gait impairment, and apathy.

This assessment is particularly important for patients receiving clonazepam. Although there can be concern with using clonazepam in the elderly, clonazepam often is well-tolerated in older patients with RBD, even when dementia or a Parkinson syndrome is already present. If minimal or no deleterious effects of clonazepam are demonstrated in a controlled trial, these findings could be considered as being as important, or even more important, as confirming efficacy of clonazepam, which is anticipated to be quite likely. For the PD-RBD group, items 29 and 30 of the UPDRS-3, and the UPDRS-1 can be used. However, apathy is much more difficult to assess, as valid and reliable apathy scales do not yet exist for detecting subtle changes with therapy.

(H) Fatigue Severity Scale [64].

The Fatigue Severity Scale (FSS) has been widely utilized to assess fatigue in medical and neurologic populations and was recently recommended as an appropriate instrument to screen for and assess severity of fatigue in patients with PD [65]. This scale can be used to assess the impact of treatment on fatigue. Other established and well-working scales include the Pichot Fatigue Scale and the World Health Organization-5 Quality of Life-Depression Scale.

(I) Actigraphic monitoring

This method would yield quantitative results and may possibly be an effective secondary outcome measure, as it is not costly and it can assess movements over 14–28 consecutive nights, which hopefully can be correlated with RBD events and perhaps lead to an automatic detection algorithm. A case of monitoring RBD with actigraphy has been reported [66]. However, actigraphy cannot be considered a valid tool for RBD research, given the information that is currently available.

(J) A customized, pressure-sensitive, bed-alarm system.

This newly developed system holds promise as another possible secondary outcome measure, as the number of RBD-related events can be recorded nightly over extended time periods, allowing for a quantitative comparison of the number of pretreatment vs with-treatment (major) RBD behavioral events [67]. However, this method of assessment is best suited for monitoring RBD patients who are prone to falling or jumping out of bed (i.e., the detection of major events); therefore, there might be other movements detected that are not related to REM sleep. A validation study should preferably be conducted first. Another similar system is the BEDDIT-method, which also should be validated before using.

10. Consensus for evaluating the clinical and video aspects of RBD

10.1. Clinical interview and questionnaires

(A) Interview.

The optimal interview should include the patient and spouse or other nocturnal caretaker. When a bed partner is not available, the

patient should be interviewed about any unusual events such as self-injury or falling out of bed or comments from nurses or any relatives about their sleep behaviors or vocalizations. RBD often manifests as an attempted enactment of distinctly altered, unpleasant, action-filled, and violent dreams. Typically, at the end of an episode, the individual awakens quickly and becomes rapidly alert and oriented. The eyes usually remain closed during an RBD episode, with the person attending to the dream action and not to the actual environment. The interview must involve someone sleeping with or caretaking the patient in the same room, as this is key to the witnessing of RBD behavioral events.

(B) Rating scales (Table 1)

Scales assessing RBD are scarce. We found two scales screening for RBD, one scale assessing an inventory of RBD symptoms [68] (validated in German and English and later in Japanese) [69], and one scale assessing the RBD severity and RBD monthly frequency [49]. There is also the recently validated Mayo Sleep Questionnaire for RBD screening in dementia patients and in the elderly [70]. The screening scales and inventories are mainly based on a history of abnormal behaviors and apparent acting out of dreams, while the latter aspect has been removed as a diagnostic criterion in ICSD-2 (compared to the original ICSD in 1990), because RBD nondreamers and patients with RBD who are not awakened after an RBD episode may not remember having dreamt. The first two screening tools are sensitive, but their specificity decreases when applied to populations with other nocturnal movements, including sleepwalkers and patients with nocturnal epileptic seizures; the specificity also decreases in psychiatric populations [49,68,69]. Of note, adults with sleepwalking or sleep terrors also may have apparent acting out of dreams, sometimes with associated dreamlike mental content [71]. We suggest adding a question on sleepwalking, as walking during an RBD episode is very unusual in patients with RBD. The RBDQ-HK has the advantage of providing an index of RBD severity and episode frequency and has no misleading questions [49]. The RBDQ-HK appears to be appropriate for evaluating the effect of medication on RBD clinical features (also refer to Section 8C).

Table 1
Scales used to assess rapid eye movement sleep behavior disorder.

Scales	Purpose	Characteristics	Properties	Validation	Remarks
RBD Screening questionnaire [68]	Screening tool, epidemiology	Self-administrated, 13 questions on dreams (items 1–3, 8), movements (items 4, 6.1–6.3), disturbances (item 5, 6.4, 7, 9), and neurologic disease (item 10), scored 0 or 1. German- and Japanese [69]-validated versions. Item 6.1 (in my dreams I speak, shout, swear, or laugh, loudly) is the most sensitive item, while item 5 (it happened that I [almost] hurt my bed partner or myself) is the most specific item.	Range, 0–13 A score > 5 is 96% sensitive for RBD and 56% specific vs German population with sleep disorders and 92% specific vs healthy controls. A score >4.5 is 88% sensitive and 89% specific vs Japanese OSAS men, and 91% specific vs healthy controls. Test–retest reliability is 87% in Japan.	Germany, 54 patients with PSG-confirmed RBD (score, 9.5 ± 3) 160 sleep controls (score 5 ± 3), 133 healthy subject (score 2 ± 2) Japan, 52 patients with PSG-confirmed iRBD (score, 7.5 ± 2.8), 55 patients with treated OSAS (1.9 ± 2.3), 65 healthy subjects (1.6 ± 1.2)	No spouse report. No index of severity. Question 6 (relative to behavior during dreams and not dream enactment) can be misunderstood. Frequent false positives in sleepwalkers and epileptic patients.
RBDQ-HK [49]	Screening, epidemiology, severity	Self-administrated, 13 questions on dreams (items 1–5, scored 0–1), vocalizations (items 6–7, scored 0 or 2), movements (item 8, scored 0 or 2), disturbances (items 9–11, 13, scored 0 or 2), and dream-behavior isomorphism (item 13, scored 0 or 1), scored as a lifetime occurrence and with a yearly frequency (from 0 to 5) English and Chinese validated versions.	Range: 0–100 A score > 18–19 is 82% sensitive and 87% specific vs healthy controls. A model with two factors (dream-related and behavior- or consequences-related) explains 59% of the variance.	107 patients with PSG-confirmed RBD (score: 32 ± 16), 107 controls (healthy and with sleep disorders; score, 9 ± 10) High internal consistency (90%) and test–retest (89%) reliability	The score is lower when completed alone (40 ± 21) than in the presence of relatives (55 ± 17). The scale also assesses the RBD severity.

Abbreviations: RBD, rapid eye movement sleep behavior disorder; RBD-HK, rapid eye movement sleep behavior disorder Hong Kong questionnaire; OSAS, obstructive sleep apnea syndrome; PSG, polysomnography.

10.2. Polysomnographic RBD evaluation—focus on EMG

(A) Recommendation for PSG evaluation of RBD

Standard PSG montage according to the American Academy of Sleep Medicine plus bilateral flexor digitorum superficialis muscles on the upper extremity is encouraged. It is important to consider the same filter settings and impedance measures; amplification has to be stated and is shown on the PSG machine. Sampling frequency should be indicated. European data format should be used for data provision.

Recording of muscle activity during sleep also is important in the process of ruling out, in tandem with the clinical history, the parasomnia overlap disorder [27,72], with features of muscle activity in REM sleep plus features of NREM parasomnias coming in stages N2 and N3.

Why is the mentalis EMG not sufficient? There is a pro of the mentalis muscle: if you lose a lead in the standard montage included, then you have two replacements. Mentalis muscle activity is only present in REM sleep when there is RBD or RWA without clinical RBD. In contrast, there also is a con: there are too many artifacts due to snoring, speaking, swallowing, bruxism, rhythmic masticatory activity, CPAP background noise, breathing, tonic activity; however, this also can be true for extremity muscles. Mentalis muscle activity often is independent of body movement (e.g., when there is no movement of extremities).

Peripheral muscles also have been recorded. The most current evidence-based data provide the following guidelines regarding objective measures for detecting RWA and guidelines for their interpretation supporting the diagnosis of RBD: (1) RWA is supported by the polysomnographic findings of either tonic chin EMG activity in $\geq 30\%$ of REM sleep, or phasic chin EMG activity in $\geq 15\%$ REM sleep scored in 20-s epochs [73]; (2) any (tonic/phasic) chin EMG activity combined with bilateral phasic activity of the flexor digitorum superficialis muscles in $\geq 32\%$ of 3-s mini epochs scored in REM sleep, or in $\geq 27\%$ of 30-s epochs scored in REM sleep [74]; and (3) automated quantification methods have been developed for generating the REM sleep atonia index with scores ranging from 0 (complete loss of REM atonia) to 1 (complete preservation of REM-atonia). The cutoff score for RWA is a REM sleep atonia index < 0.9 [41,75–77].

A range of automatic analyses of the EMG in REM sleep and RBD exists: Burns et al. [78], Ferri et al. [40,41,75,76], Mayer et al. [79], Kempfner et al. [80], and Knudsen et al. [81].

(B) Rationale: why PSG monitoring is required.

The ICSD-2 [27] requires objective vPSG documentation for the diagnosis of RBD, as other conditions can present with dream-enacting behaviors and because abnormal EMG findings during REM sleep are virtually present every night in RBD patients. Motor activity can be recorded by EMG and video. Data have been reported on night-to-night variability, which demonstrated that EMG activity is more stable across nights compared to behavioral manifestations on the video [82–84]. There are published findings on how RBD patients can be distinguished from controls on the basis of REM sleep EMG and videographic motor activity. Additionally there is a spectrum of RBD severity, as reflected in PSG measures with changes of reduced RBD frequency and severity induced by medication being detected by PSG measures. The vPSG findings can provide support for the EMG findings from PSG monitoring.

(C) Combined EMG and video analysis to better detect the motor and vocal manifestations occurring in RBD [85].

Furthermore, two other approaches for scoring EMG activity in REM sleep and RBD have been published: Eisensehr et al. [86] on short and long-lasting muscle activity, and Bliwise et al. [87–89] on phasic EMG metric.

(D) Unresolved issues

The following are a list of unresolved issues:

- (1) The terms *phasic* and *tonic* have to be clarified unless the EMG scoring method combines the two into a unitary EMG metric, as was recently done with the chin EMG [40,41,74]. Moreover, the statistical analysis of quantified chin EMG measurements does not seem to support the separation between phasic and tonic activities, as they seem to belong to the same statistical distribution [40,79].
- (2) Amplitude criterion: is it better to use a 2- or 4-fold increase of the background EMG? This may be an insurmountable issue to resolve, as it is impossible to establish an exact threshold for visually detected events based on the rapidly fluctuating nature of the signal. Also, the advent and further ongoing development of automated quantitative analysis, especially for eventual large-scale studies, will make this issue of visual scoring moot.
- (3) How is baseline muscle tone defined? According to existing data, mean baseline EMG activity is approximately $2 \mu\text{V}$ [40,41,75,76,79]. However, it may depend on the body position and its changes throughout the night.
- (4) We do not have a definition for onset or offset of EMG activity.
- (5) Is it better to use 3-s mini epochs every 30 s instead of 2-s mini epochs every 20 s due to the gold standard for sleep scoring (the current AASM criteria)? There may be technical difficulties, as some PSG machines cannot switch their screens to 3-s mini epochs. Automated scoring can bypass this issue.
- (6) Long-lasting EMG activity may be missed by scoring 50% of muscle activity during 2- or 3-s bins if there is activity that lasts longer than the one in a particular bin. This issue also can be bypassed by automated scoring.
- (7) Awakenings and arousals should be excluded from scoring.
- (8) How should fragmented REM sleep be incorporated into a REM sleep epoch? If REM sleep is disrupted, should it be scored as belonging to one cycle or to several cycles (e.g., if the fragmentation epochs are 5 min apart, then they should still belong to one cycle? Whereas, if they are 20 min apart, should they belong to the next cycle)?
- (9) Night-to-night variability: is one night really sufficiently representative? One study has found low night-to-night variability in RBD, indicating that one night of vPSG may be sufficient [83]. On the other hand, a published abstract showed high variability of mentalis muscle tone during REM sleep in RBD over six consecutive nights [90].

10.3. Video-analysis of RBD

Observing an overtly abnormal behavior during REM sleep (i.e., more than minimal twitching, limb jerking, sleep talking) is direct evidence for RBD and is sufficient for meeting the ICSD-2 criteria for RBD documented by vPSG in the absence of a clinical RBD history (e.g., patient lives alone). In some patients, the EEG may be obscured by muscle artifact, the EMG activity may only be visible in some muscles not captured by the standard EMG montage, or the EEG can be difficult to score as REM sleep, especially in demented patients. Hence there is a need for having direct access to record REM sleep behavioral abnormalities. In addition, viewing the exact behavior provides invaluable information on the motor and cognitive systems at work, which can help to understand REM sleep features. Time-synchronized vPSG recording with an infrared light source and excellent quality is required. A specific oral or written consent for video surveillance usually is required. The usefulness of vPSG recording may be limited in cases of patients sleeping completely under the sheets or pillow. There is not yet a formal consensus on how to analyze the movements on the video. The movements observed during video analysis of RBD have been

classified early on as simple vs complex events, with elemental behaviors later classified as myoclonic and simple (minor or major) events [82]. Emotions could be scored as apparently positive, negative, or neutral. In a drug trial of pramipexole, the elementary movements were reduced, while the complex movements were unchanged [32]. There also were attempts to classify the movements according to the segment of the body and to the type of movement, by analogy to the dyskinesia scoring. A simple scale for RBD assessment was recently published [91]. This scale is similar to the dyskinesia scales, differentiating between small distal movements, proximal movements, and violent behavior with axial and whole body movements with or without vocalization. A classification of RBD behaviors needs to be as simple as possible. A blind assessment of RBD behavioral changes induced by treatment which is documented by vPSG provides another objective measure of RBD improvement, together with an EMG analysis and the rating scales. This videographic analysis could be conducted at specialized centers on a subgroup of patients enrolled in the treatment studies.

10.4. Outline of a therapeutic trial

After a confirmatory vPSG study, potential subjects who may qualify for the study will be screened and offered enrollment in the study with written consent. Screenings should include questions on headache, hallucinations, morning sleepiness, cognitive slowing or impairment, gait impairment, and falls, at a minimum.

Side effects described by the manufacturers of clonazepam and melatonin, along with other side effects most commonly reported in the peer-reviewed literature, should be mentioned in the consent form concerning safety issues. Baseline period should be around 2–4 weeks and subjects and bed partners will be asked to complete the CGI. Subjects will be contacted by phone 3 weeks after the initiation of the study drug to review compliance and side effects.

On week 0, subjects will be randomly assigned to fixed-dose therapy with either melatonin 6 mg (or extended-release melatonin) or clonazepam 0.5 mg. Subjects will be instructed to take the medication 30 min before usual sleep time. Study drug will be dispensed for 6 weeks. Alternatively, a titration protocol could be developed (refer to previous discussion).

During the week six visit, outcome measures will be collected. Study drug will be dispensed for an additional 6 weeks. If RBD symptoms were not frequent enough during the first two weeks, baseline period will be extended for additional 2 weeks.

On the week 12 visit, subjects will return their CGIs from the previous 6 weeks, and another CGI will be distributed to be completed after another 2 weeks. Subjects will not take study drug after this visit. For safety reasons, the drug should be tapered. On week 14, this will be the final visit; during this visit subjects will return CGIs.

10.5. Primary outcome measure

CGI will reflect a change in frequency and severity of RBD from baseline to 12 weeks as assessed by the patient and bed partner.

10.6. Secondary outcome measures

10.6.1. Efficacy

The level of efficacy will reflect changes in the secondary outcome measures, as previously described, from baseline to 12 weeks.

10.6.2. Safety and tolerability

Safety and tolerability are measured by the number of subjects who complete their assigned dose of study drug and the subjects with adverse events (and classify the type and severity of events).

11. End points for neuroprotective (i.e., disease-modifying) trials in RBD

11.1. Lessons from PD

The ultimate goal of clinical studies in RBD is the performance of disease-modifying or neuroprotective trials. So far no compound with convincing evidence of a neuroprotective efficacy has been identified in PD, including dopamine agonists [92]. This failure may be partially due to the selection of primary end points or the respective study design. There are arguably three key studies in the field of disease modification of PD, including the DATATOP (Deprenyl and Tocopherol Antioxidative Therapy for Parkinson Disease) clinical trial, the ELLDOPA (Earlier vs Later Levodopa Therapy in Parkinson Disease) study, and the ADAGIO (Attenuation of Disease Progression with AZILECT® [rasagiline] Given Once-daily) study [93–95].

The primary end point in the DATATOP study was the time to administration of levodopa in de novo PD patients, which was considerably delayed in the selegiline arm. However, this study did not take the symptomatic efficacy of selegiline into account. The primary end point in the ELLDOPA study was the change in the total UPDRS score after a 2-week washout of levodopa. This study has been criticized because of the short washout phase of the study compound. The primary end points in the ADAGIO study also were based on the total UPDRS score. This trial employed a delayed-start design to prevent a bias according to the symptomatic efficacy of rasagiline. However, the results of this study were inconclusive, as all end points were met for the dosage of 1 mg but not for the dosage of 2 mg daily. It can be hypothesized that the study data were influenced by a wash-in effect due to a continuing increase in symptomatic efficacy of rasagiline after 12 weeks.

The majority of disease-modifying and neuroprotective trials in PD used clinical end points, namely the UPDRS score or the time to administration of levodopa. Several studies employed a surrogate marker (i.e., the tracer uptake in dopamine transporter imaging as primary end point). However, it has been argued that the investigated study compounds influenced the expression level of the dopamine transporter and that dopamine transporter imaging (DAT) therefore is not a valid surrogate marker for disease progression in PD. However, this statement does not refer to DATATOP, ADAGIO, or ELLDOPA but rather refers to studies using pramipexole or ropinirole. This topic was discussed by Wooten [92].

DAT scan can be used as a biomarker of neuroprotection in a study with iRBD patients, based on the findings of Iranzo et al. [17] on reduction of nigrostriatal content over time in iRBD patients not taking dopaminergic drugs. Predictors of imminent parkinsonism in newly diagnosed iRBD patients, as described in the aforementioned study [17] and in the other recent study by Postuma et al. [18], offer hope that the timeline of neuroprotective studies can be relatively short (i.e., 5 y) in tandem with the hope of identifying an effective neuroprotective agent. A main concern for any neuroprotection study involving iRBD patients is enrolling too many patients who either do not have an underlying neurodegenerative disorder, or who are too early in their disease that they will not show cognitive or motor signs for 10–20 years. Therefore, DAT scans should be used at screening so that any iRBD patients

with abnormal findings can be enrolled, as they are most likely to have an underlying disease and convert over a 5-year span. DAT scans should be repeated after 3–5 years to gain insights into rate of change.

The most obvious clinical end point for neuroprotective trials in RBD seems to be the time to conversion from RBD to more overt neurodegenerative disorders such as PD, DLB, or MSA. However, the development of MCI was far more common than PD in a recent study [29], so a good cognitive assessment battery needs to be utilized along with expertise in diagnosing MCI. Although patients with MCI are at risk for neurodegenerative disorders, MCI is not a neurodegenerative disorder. Additionally, to date the clinical evolution of iRBD patients with MCI is unknown. MCI has considerable variability, and there are no validated MCI criteria in iRBD. Therefore, the development of MCI should not be an end point in these studies, but rather the development of parkinsonism or dementia. In neuroprotective trials, the study design should allow for a sufficiently long washout phase to determine if the study compound could possibly exert a symptomatic effect on PD motor symptoms. The same process applies to the expression levels of surrogate markers such as the dopamine transporter if the time to conversion is to be replaced by a time-wise more pragmatic primary end point. Apart from that, it will be interesting to discuss if future study designs should integrate regression-based modeling approaches as recently proposed [96].

Currently, there are no reliable data regarding the percentage of PD with and without RBD, and we do not know if different subtypes of PD can be classified according to PSG results. Because prospective trials are not available to date, we are not able to say if RBD during the neurodegenerative process is a biomarker itself for neurodegeneration or if it is just a biomarker for a specific subtype of PD. Alternatively, there could be subtypes of PD with RBD and without RBD that will not reflect the amount of neurodegeneration. Also, some PD patients and their spouses report improvements of RBD during the course of PD, but this has not yet been objectively verified due to a lack of systematic prospective serial PSG studies.

In regard to biomarkers, critical aspects of any neuroprotective study, as mandated by the Food and Drug Administration in the United States, include: (1) global improvement or stability in regards to Activities of Daily Living, cognition, motor, and other functions; and (2) one or more biomarkers being steady or more slowly evolving in treated vs untreated subjects. The most appealing imaging biomarkers thus far include DaTscan, MRI-diffusion tensor imaging, magnetic resonance spectroscopy, transcranial sonography, and others. These imaging biomarkers are critical not only to identify those patients at short-term risk for conversion to MCI or parkinsonism, but also for monitoring patients over time.

Conflict of Interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <http://dx.doi.org/10.1016/j.sleep.2013.02.016>.

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Notes added in proof

- 1) In late 2013 the American Academy of Sleep Medicine will publish the third edition of the International Classification of Sleep Disorders (ICSD-3), which will contain updated diagnostic criteria for RBD that can be utilized in the studies proposed in this manuscript.
- 2) Another study by the IRBD-SG has recently been published [97].
- 3) A pertinent study on clonazepam and melatonin therapy of RBD has recently been published [98].
- 4) A pertinent study on the REM atonia index has recently been published [99].

References

- [1] Mahowald MW, Schenck CH. REM sleep parasomnias. In: Kryger MH, Roth T, Dement WC, editors. Principles and Practice of Sleep Medicine. Philadelphia (PA): Elsevier Saunders; 2010. p. 1083–97.
- [2] Schenck CH, Mahowald MW. REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in SLEEP. *Sleep* 2002;25:120–38.
- [3] Mirmiran M. Oneiric behavior during active sleep induced by bilateral prefrontal lesions in juvenile rats. In: Koella W, editor. *Sleep 1982*. Basel (Switzerland): Karger; 1982.
- [4] 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(Pt 11):2770–88.
- [5] Schenck CH, Boeve BF. The strong presence of REM sleep behavior disorder in PD: clinical and research implications. *Neurology* 2011;77:1030–2 [editorial].
- [6] Krenzer M, Anaclet C, Vetrivelan R, Wang N, Vong L, Lowell BB, et al. Brainstem and spinal cord circuitry regulating REM sleep and muscle atonia. *PLoS One* 2011;6:e24998 [published online ahead of print October 17, 2011].
- [7] Brooks PL, Peever JH. Impaired GABA and glycine transmission triggers cardinal features of rapid eye movement sleep behavior disorder in mice. *J Neurosci* 2011;31:7111–21 [Published correction appears in *J Neurosci* 2011;31:9440].
- [8] Vetrivelan R, Fuller PM, Tong Q, Lu J. Medullary circuitry regulating rapid eye movement sleep and motor atonia. *J Neurosci* 2009;29:9361–9.
- [9] Anaclet C, Pedersen NP, Fuller PM, Lu J. Brainstem circuitry regulating phasic motor activation of trigeminal motoneurons during REM sleep. *PLoS One* 2010;5:e8788.
- [10] Luppi PH, Clement O, Sapin E, Gervasoni D, Peyron C, Leger L, et al. The neuronal network responsible for paradoxical sleep and its dysfunctions causing narcolepsy and rapid eye movement (REM) sleep behavior disorder. *Sleep Med Rev* 2011;15:153–63.
- [11] Clement O, Sapin E, Berod A, Fort P, Luppi PH. Evidence that neurons of the sublaterodorsal tegmental nucleus triggering paradoxical (REM) sleep are glutamatergic. *Sleep* 2011;34:419–23.
- [12] Iranzo A, Lu J. Pathophysiology of REM sleep behavior disorder, including its relationship with neurodegenerative diseases, evolving concepts and controversies. In: Chokroverty S, editor. *Sleep and movement disorders*, 2nd ed. Boston (MA): Butterworth-Heinemann; 2013 [in press].
- [13] Turek FW, Dugovic C. RBD—an emerging clue to neurodegenerative disorders. *Sleep* 2005;28:920–1.
- [14] 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.
- [15] Boeve BF. REM sleep behavior disorder: updated review of the core features, the REM sleep behavior disorder–neurodegenerative disease association, evolving concepts, controversies, and future directions. *Ann N Y Acad Sci* 2010;1184:15–54.
- [16] Postuma RB, Gagnon JF, Montplaisir JY. REM sleep behavior disorder: from dreams to neurodegeneration. *Neurobiol Dis* 2011;46:553–8 [published online ahead of print October 14, 2011].
- [17] Iranzo A, Lomena F, Stockner H, Valldeoriola F, Vilaseca I, Salameo M, et al. Decreased striatal dopamine transporter uptake and substantia nigra hyperechogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study. *Lancet Neurol* 2010;9:1070–7 [published correction in *Lancet Neurol* 2010;9:1045, published online ahead of print September 16, 2010].
- [18] Postuma RB, Gagnon JF, Vendette M, Desjardins C, Montplaisir J. Olfaction and color vision identify impending neurodegeneration in idiopathic REM sleep behavior disorder. *Ann Neurol* 2011;69:811–8.
- [19] Postuma RB, Montplaisir JY, Pelletier A, Dauvilliers Y, Oertel W, Iranzo A, et al. Environmental risk factors for REM sleep behavior disorder—a multicenter case-control study. *Neurology* 2012;79:428–34 [published online ahead of print June 27, 2012].
- [20] Movement disorders research: a new decade of cooperation. *Lancet Neurol* 2009;8:1073 [no authors listed].

- [21] Gagnon J-F, Postuma RB, Montplaisir J. Update on the pharmacology of REM sleep behavior disorder. *Neurology* 2006;67:742–7.
- [22] Guggler JJ, Wagner ML. Rapid eye movement sleep behavior disorder. *Ann Pharmacother* 2007;41:1833–41.
- [23] Schenck CH, Mahowald MW. REM sleep parasomnias in adults: REM sleep behavior disorder (RBD), isolated sleep paralysis and nightmare disorder. In: Barkoukij TJ, Matheson JK, Ferber RF, Doghramji K, editors. *Therapy in sleep medicine*. Philadelphia (PA): Elsevier Press; 2011. p. 549–58.
- [24] Kunz D, Mahlberg R. A two-part, double-blind, placebo-controlled trial of exogenous melatonin in REM sleep behaviour disorder. *J Sleep Res* 2010;19:591–6.
- [25] Kunz D, Bes F. Melatonin effects in a patient with severe REM sleep behavior disorder: case report and theoretical considerations. *Neuropsychobiology* 1997;36:211–4.
- [26] Schenck CH, Lee SA, Bornemann MA, Mahowald MW. Potentially lethal behaviors associated with rapid eye movement sleep behavior disorder: review of the literature and forensic implications. *J Forensic Sci* 2009;54:1475–84.
- [27] American Academy of Sleep Medicine. *International classification of sleep disorders: diagnostic and coding manual*. 2nd ed. Westchester (IL): American Academy of Sleep Medicine; 2005.
- [28] Molano J, Boeve B, Roberts R. Frequency of sleep disorders in the community-dwelling elderly: The Mayo Clinic Study of Aging. *Neurology* 2009;72(Suppl. 3):A107.
- [29] 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.
- [30] McCarter SJ, St Louis EK, Boeve BF. REM sleep behavior disorder and REM sleep without atonia as an early manifestation of degenerative neurological disease. *Curr Neurol Neurosci Rep* 2012;12:182–92.
- [31] TE Sixel-Döring F, Mollenhauer B, Trenkwalder C. Associated factors for REM sleep behavior disorder in Parkinson disease. *Neurology* 2011;77:1048–54.
- [32] Fantini ML, Gagnon JF, Filipini D, Montplaisir J. The effects of pramipexole in REM sleep behavior disorder. *Neurology* 2003;61:1418–20.
- [33] Kumru H, Iranzo A, Carrasco E, Valldeoriola F, Martí MJ, Santamaria J, et al. Lack of effects of pramipexole on REM sleep behavior disorder in Parkinson disease. *Sleep* 2008;31:1418–21.
- [34] Gagnon JF, Vendette M, Postuma RB, Desjardins C, Massicotte-Marquez J, Pannisset M, et al. Mild cognitive impairment in rapid eye movement sleep behavior disorder and Parkinson's disease. *Ann Neurol* 2009;66:39–47.
- [35] Boeve BF. Mild cognitive impairment associated with underlying Alzheimer's disease versus Lewy body disease. *Parkinsonism Relat Disord* 2012;18(Suppl. 1):S41–4.
- [36] Gagnon JF, Bertrand J-A, Génier Marchand D. Cognition in rapid eye movement sleep behavior disorder. *Front Neurol* 2012;3:82 [published online ahead of print May 17, 2012].
- [37] Litvan I, Goldman JG, Tröster AI, Schmand BA, Weintraub D, Petersen RC, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord* 2012;27:349–56 [published online ahead of print January 24, 2012].
- [38] Huang J, Zhang J, Lam SP, Li SX, Ho CK, Lam V, et al. Amelioration of obstructive sleep apnea in REM sleep behavior disorder: implication for the neuromuscular control of OSA. *Sleep* 2011;34:900–15.
- [39] Iranzo A, Ratti PL, Casanova-Molla J, Serradell M, Vilaseca I, Santamaria J. Excessive muscle activity increases over time in idiopathic REM sleep behavior disorder. *Sleep* 2009;32:1149–53.
- [40] Ferri R, Manconi M, Plazzi G, Bruni O, Vandi S, Montagna P, et al. A quantitative statistical analysis of the submental muscle EMG amplitude during sleep in normal controls and patients with REM sleep behavior disorder. *J Sleep Res* 2008;17:89–100.
- [41] 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.
- [42] Dubois B, Burn D, Goetz C, Aarsland D, Brown RG, Broe GA, et al. Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. *Mov Disord* 2007;22:2314–24.
- [43] Crum RM, Anthony JC, Bassett SS, Folstein MF. Population based norms for the Mini-Mental State Examination by age and educational level. *JAMA* 1993;269:2386–91.
- [44] Dufouil C, Clayton D, Brayne C, Chi LY, Denning TR, Paykel ES, et al. Population norms for the MMSE in the very old: estimates based on longitudinal data. *Neurology* 2000;55:1609–13.
- [45] Dalrymple-Alford JC, MacAskill MR, Nakas CT, Livingston L, Graham C, Crucian GP, et al. The MoCA: well suited screen for cognitive impairment in Parkinson disease. *Neurology* 2010;75:1717–25.
- [46] Iranzo A, Santamaria J. Severe obstructive sleep apnea/hypopnea mimicking REM sleep behavior disorder. *Sleep* 2005;28:203–6.
- [47] Cygan F, Oudiette D, Leclair-Visonneau L, Leu-Semenescu S, Arnulf I. Night-to-night variability in muscle tone, movements, and vocalizations in patients with REM sleep behavior disorder. *J Clin Sleep Med* 2010;6:551–5.
- [48] Boeve BF. Melatonin for treatment of REM sleep behavior disorder: response in 8 patients. *Sleep* 2001;24(suppl):A35.
- [49] Li SX, Wing YK, Lam SP, Zhang J, Yu MW, Ho CK, et al. Validation of a new REM sleep behavior disorder questionnaire (RBDQ-HK). *Sleep Med* 2010;11:43–8.
- [50] Sasai T, Matsuura M, Wing YK, Yuichi I. Validation of the Japanese version of the REM sleep behavior disorder questionnaire (RBDQ-JP). *Sleep Med* 2012;13:913–8.
- [51] Högl B, Arnulf I, Comella C, Ferreira J, Iranzo A, Tilley B, et al. Scales to assess sleep impairment in Parkinson's disease: critique and recommendations. *Mov Disord* 2010;25:2704–16.
- [52] Buysse DJ, Reynolds 3rd CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
- [53] Kaida K, Takahashi M, Akerstedt T, Nakata A, Otsuka Y, Haratani T, et al. Validation of the Karolinska sleepiness scale against performance and EEG variables. *Clin Neurophysiol* 2006;117:1574–81.
- [54] Chaudhuri KR, Pal S, DiMarco A, Whately-Smith C, Bridgman K, Mathew R, et al. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2002;73:629–35.
- [55] Chaudhuri KR, Martinez-Martin P. Clinical assessment of nocturnal disability in Parkinson's disease: the Parkinson's Disease Sleep Scale. *Neurology* 2004;63(8 (suppl 3)):S17–20.
- [56] Trenkwalder C, Kohlen R, Hogl B, Metta V, Sixel-Döring F, Frauscher B, et al. Parkinson's disease sleep scale-validation of the revised version PDSS-2. *Mov Disord* 2011;26:644–52.
- [57] Folstein MF, Folstein S, McHugh P. Mini-Mental State: a practical method for grading the cognitive state of patients for clinicians. *J Psychiatr Res* 1975;12:189–98.
- [58] Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695–9.
- [59] Gagnon JF, Postuma RB, Joncas S, Desjardins C, Latreille V. The Montreal Cognitive Assessment: a screening tool for mild cognitive impairment in REM sleep behavior disorder. *Mov Disord* 2010;25:936–40.
- [60] Beck AT, Steer RA, Brown G, editors. *Beck depression inventory*. San Antonio (TX): The Psychological Corporation; 1996.
- [61] Becker AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consulting Clin Psychol* 1988;56:893–7.
- [62] Schrag A, Barone P, Brown RG, Leentjens AF, McDonald WM, Starkstein S, et al. Depression rating scales in Parkinson's disease: critique and recommendations. *Mov Disord* 2007;22:1077–92.
- [63] Leentjens AF, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, Starkstein SE, et al. Anxiety rating scales in Parkinson's disease: critique and recommendations. *Mov Disord* 2008;23:2015–25.
- [64] Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46:1121–3.
- [65] Friedman JH, Alves G, Hagell P, Marinus J, Marsh L, Martinez-Martin P, et al. Fatigue rating scales critique and recommendations by the Movement Disorders Society task force on rating scales for Parkinson's disease. *Mov Disord* 2010;25:805–22.
- [66] Hurwitz TA, Ettinger MG, Mahowald MW, Espinosa AM. Actigraphic representation of REM-sleep behavior disorder. *Sleep Res* 1994;23:266.
- [67] Howell M, Arneson P, Schenck CH. A novel therapy for REM sleep behavior disorder (RBD). *J Clin Sleep Med* 2011;15:639–644A.
- [68] Stiasny-Kolster K, Mayer G, Schafer S, Moller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire—a new diagnostic instrument. *Mov Disord* 2007;22:2386–93.
- [69] Miyamoto T, Miyamoto M, Iwanami M, Kobayashi M, Nakamura M, Inoue Y, et al. The REM sleep behavior disorder screening questionnaire: validation study of a Japanese version. *Sleep Med* 2009;10:1151–4.
- [70] Boeve BF, Molano JR, Ferman TJ, Smith GE, Lin SC, Bieniek K, et al. Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in an aging and dementia cohort. *Sleep Med* 2011;12:445–53.
- [71] Oudiette D, Leu S, Pottier M, Buzarre M-A, Brion A, Arnulf I. Dreamlike mentations during sleepwalking and sleep terrors in adults. *Sleep* 2009;32:1621–7.
- [72] Schenck CH, Boyd JL, Mahowald MW. A parasomnia overlap disorder involving sleepwalking, sleep terrors, and REM sleep behavior disorder in 33 polysomnographically confirmed cases. *Sleep* 1997;20:972–81.
- [73] 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.
- [74] 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.
- [75] Ferri R, Bruni O, Fulda S, Zucconi M, Plazzi G. A quantitative analysis of the submental muscle electromyographic amplitude during rapid eye movement sleep across the lifespan. *J Sleep Res* 2012;21:257–63.
- [76] Ferri R, Fulda S, Cosentino FI, Pizze F, Plazzi G. A preliminary quantitative analysis of REM sleep chin EMG in Parkinson's disease with or without REM sleep behaviour disorder. *Sleep Med* 2012;13:707–13.
- [77] Fulda S, Plazzi G, Ferri R. Scoring atonia during normal and pathological rapid eye movement sleep: visual and automatic quantification methods. *Sleep Biol Rhythms* 2013;11(Suppl. 1):40–51.
- [78] 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.

- [79] 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.
- [80] Kempfner J, Sorensen G, Zoetmulder M, Jennum P, Sorensen HB. REM behaviour disorder detection associated with neurodegenerative diseases. *Conf Proc IEEE Eng Med Biol Soc* 2010;1:5093–6.
- [81] 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(Pt 2):568–79 [published online ahead of print February 3, 2010].
- [82] Frauscher B, Gschliesser V, Brandauer E, Ulmer H, Peralta CM, Muller J, et al. Video analysis of motor events in REM sleep behavior disorder. *Mov Disord* 2007;22:1464–70.
- [83] Zhang J, Lam SP, Ho CK, Li AM, Tsoh J, Mok V, et al. Diagnosis of REM sleep behavior disorder by video-polysomnographic study: is one night enough? *Sleep* 2008;31:1179–85.
- [84] Cygan F, Oudiette D, Leclair-Visonneau L, Leu-Semenescu S, Arnulf I. Night-to-night variability of muscle tone, movements, and vocalizations in patients with REM sleep behavior disorder. *J Clin Sleep Med* 2010;6:551–5.
- [85] Iranzo A, Frauscher B, Santos H, Gschliesser V, Ratti L, Falkenstetter T, et al. Usefulness of the SINBAR electromyographic montage to detect the motor and vocal manifestations occurring in REM sleep behavior disorder. *Sleep Med* 2011;12:284–8.
- [86] Eiseensehr 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.
- [87] Bliwise DL, He L, Pour Ansari F, Rye DB. Quantification of electromyographic activity during sleep: a phasic electromyographic metric. *J Clin Neurophysiol* 2006;23:59–67.
- [88] Bliwise DL, Rye DB. Elevated PEM (phasic electromyographic metric) rates identify rapid eye movement behavior disorder patients on nights without behavioral abnormalities. *Sleep* 2008;31:853–7.
- [89] Bliwise DL, Trotti LM, Greer SA, Juncos JJ, Rye DB. Phasic muscle activity in sleep and clinical features of Parkinson disease. *Ann Neurol* 2010;68:353–9.
- [90] Mayer G, Kesper K, Oertel W. Variation of muscle activity in REM sleep in patients with REM sleep behaviour disorder (RBD) and controls during 6 consecutive nights. *Mov Disord* 2010;25:S408.
- [91] 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.
- [92] Wooten GF. Agonists vs levodopa in PD: the thrill of witha. *Neurology* 2003;60:360–2.
- [93] Effects of tocopherol and deprenyl on the progression of disability in Parkinson's disease. *N Engl J Med* 1993;328:176–83 [no authors listed].
- [94] Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, Lang A, et al. Levodopa and the progression of Parkinson's disease. *N Engl J Med* 2004;351:2498–508.
- [95] Olanow CW, Rascol O, Hauser R, Feigin PD, Jankovic J, Lang A, et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med* 2009;361:1268–78.
- [96] Holford NH, Nutt JG. Interpreting the results of Parkinson's disease clinical trials: time for a change. *Mov Disord* 2011;26:569–77.
- [97] Dauvilliers Y, Postuma RB, Ferini-Strambi L, et al. Family history of idiopathic REM behavior disorder: a multicenter case-control study. *Neurology* 2013;80:2233–5.
- [98] McCarter SJ, Boswell CL, St Louis EK, et al. Treatment outcomes in REM sleep behavior disorder. *Sleep Med* 2013;14:237–42.
- [99] Ferri R, Marelli S, Cosentino FII, et al. Night-to-night variability of automatic quantitative parameters of the chin EMG amplitude (atonia index) in REM sleep behavior disorder. *J Clin Sleep Med* 2013;9:253–8.