clinical and translational neuroscience

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Review

Update on Rapid-Eye-Movement Sleep Behavior Disorder (RBD): Focus on Its Strong Association with α-Synucleinopathies

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Abstract: REM sleep behavior disorder (RBD) is a parasomnia in which the customary generalized skeletal muscle atonia of REM sleep, "REM-atonia", is compromised, allowing for the injurious acting-out of dreams. RBD can be idiopathic/isolated (iRBD) or symptomatic of neurological disorders, and can be triggered by most antidepressants. RBD mainly affects middle-aged and older adults, and is strongly linked with alpha-synucleinopathies, mainly Parkinson's disease (PD) and dementia with Lewy bodies (DLB). iRBD is now known to be the earliest and strongest predictor of future PD/DLB, which has stimulated a major international clinical and basic science research effort to enroll iRBD patients for upcoming neuroprotective/disease-modifying trials and to identify the most promising interventions to test in these cohorts. This review will provide the latest pertinent information on the rapidly expanding field of RBD. The methods included a PubMed literature search that included PubCrawlers, which utilizes the NCBI (National Center for Biotechnology Information) E-utils tools for publication retrieval, using the keywords "REM sleep behavior disorder" and "RBD". The results yielded the latest updates on iRBD as prodromal PD/DLB, with the most promising biomarkers for phenoconversion provided, along with a presentation of three clinical research consortiums that are systematically gathering patients in preparation for enrollment in upcoming clinical trials: (i) The International RBD Study Group; (ii) The North American Prodromal Synucleinopathy (NAPS and NAPS2) Consortium; and (iii) The FARPRESTO Italian multicenter RBD research consortium. In addition, updates on the Parasomnia Overlap Disorder (RBD + NREM parasomnia) and on narcolepsy-RBD are provided, along with new epidemiologic data, the latest RBD management guidelines, and updates on animal models of RBD. Emerging areas of critical RBD research are also highlighted. In conclusion, RBD is a notable example of clinical and translational neuroscience research.

Keywords: REM sleep behavior disorder; RBD; alpha-synucleinopathy; Parkinson's disease; dementia with Lewy bodies; narcolepsy; parasomnia overlap disorder; sleepwalking; major depression; antidepressant medication

Citation: Schenck, C.H. Update on Rapid-Eye-Movement Sleep Behavior Disorder (RBD): Focus on Its Strong Association with α-Synucleinopathies. *Clin. Transl. Neurosci.* **2023**, *7*, 19. https://doi.org/10.3390/ctn7030019

Academic Editor: Claudio Bassetti

Received: 9 June 2023
Revised: 30 June 2023
Accepted: 25 July 2023
Published: 28 July 2023

1. Introduction

RBD is classified as a parasomnia, viz. a sleep-related behavioral, experiential, and autonomic nervous system disorder, during REM sleep that features the essential objective diagnostic finding of a loss of the customary mammalian atonia of REM sleep [1], due to damage or dysfunction in two key brainstem centers (and their linked pathways) that generate REM-atonia. These neuronal groups were identified by elegant basic studies in rats by the Lyon group, and consist of the glutamate sublateral dorsal nucleus in the pontine tegmentum and the GABAergic and glycinergic ventromedial medulla inhibitory neurons [2,3]. This topic has been further discussed in a recent review of RBD [4].

The diagnostic criteria of RBD are as follows [1].

Criteria A–D must be met:

A. Repeated episodes of sleep-related vocalization or complex motor behaviors.

B. These behaviors are documented by video-polysomnography to occur during REM sleep or, based on a clinical history of dream enactment, are presumed to occur during REM sleep.

C. PSG recording demonstrates REM sleep without atonia (RWA).

D. The disturbance is not better explained by another current sleep disorder or mental disorder.

A broad range of behaviors, including aggressive and violent behaviors, can emerge with RBD, as documented during video-polysomnography and/or as reported by the spouse. These behaviors often represent the enactment of unpleasant, action-filled, or violent dreams in which the individual is being confronted, attacked, or chased by unfamiliar people, animals, or insects. Typically, the individual awakens quickly, becomes rapidly alert (as is typical of REM sleep awakenings), and when questioned immediately at the end of an episode will report a dream with a coherent story. The dream action corresponds closely to the observed sleep behaviors, which is termed "isomorphism". The eyes usually remain closed during an RBD episode (as the dreamer attends to the dream environment), in contrast to sleepwalking, a non-REM sleep parasomnia in which the eyes are open.

RBD was formally described in humans by our group in 1986 and named in 1987 [5–7], 21 years after Jouvet and Delorme in Lyon reported on the first experimental animal model of RBD induced by pontine tegmental lesions in cats [8]. Subsequently, various aspects of RBD in humans were identified in the United States, Japan, and Europe from 1966 to 1985, as reviewed in [7]. RBD can present as an idiopathic/isolated condition (iRBD) or as a symptomatic condition. The first textbook on RBD, published in 2018, comprehensively covers the range of RBD-related conditions [9]. This current update on RBD will primarily focus on its strong association with the α-synucleinopathies, particularly Parkinson's disease (PD) and dementia with Lewy bodies (DLB). This is the predominant field of clinical and basic research in RBD.

Schematic diagram depicting how on the left side, the pons, the site for generating REM sleep, simultaneously sends ascending activating signals (in red) to the motor cortex, and descending inhibitory signals (in blue) to the spinal cord alpha-motoneurons via the medulla, to result in REM-atonia, with brief, benign twitches in REM sleep. The right side depicts the range of clinical insults (including presumed neurodevelopmental priming in some cases) that can cause REM without atonia, increased twitching in REM sleep, and RBD, with disinhibition of the REM-atonia pathway indicated by the red color replacing the blue color on the left side.

2. Historical Perspectives on RBD, PD, and DLB

Case VI from the original text written by James Parkinson in his Essay On the Shaking Palsy from 1817 contains this excerpt: ""His attendants observed, that of late the trembling would sometimes begin in his sleep, and increase until it awakened him: when he always was in a state of agitation and alarm. . .when exhausted nature seizures a small portion of sleep, the motion becomes so violent as not only to shake the bed- hangings, but even the floor and sashes of the room. . ." Therefore, James Parkinson, in his description of the original cases of the disease that bears his name, also identified RBD in a patient with PD. RBD was formally identified 169 years later [5]. Also, RBD was first described in world literature in 1605 by Cervantes in *Don Quixote*, chapter 35 "Adventure with the Wine Skins", in which there was a fight with a giant during dream enactment while Don Quixote was actually stabbing filled wine skins. There is evidence indicating that Don Quixote had DLB, with visual hallucinations, associated with his RBD [10].

3. RBD and Its Strong Association with Alpha-Synuclein Neurodegeneration

iRBD is now known to be the earliest and strongest predictor of future PD and DLB [11–14] due to the early α-synuclein damage to the REM-atonia generators [2,3], following the proposed Braak rostral–caudal staging for α-synucleinopathy progression [15]. As such, RBD can be viewed as the earliest "sentinel node" indicating the presence of an α-synucleinopathy, a clinical sign of synuclein attack on the REM-atonia-generating nuclei and pathways in the brainstem [2,3], and not just a "prodrome" [16].

In fact, the Movement Disorders Society, in a consensus statement, concluded that iRBD (proven by video-polysomnography) has the highest likelihood ratio (LR) for PD phenoconversion (LR = 130), and also has the highest predictive value (>10×) for PD heno-conversion, compared to any other clinical marker (e.g., LR = 4 for olfaction; LR = 10 for abnormal motor exam), and a predictive value > 3× higher than any biomarker (e.g., dopaminergic Positron Emission Tomography/Single-Photon Emission Computed Tomography, LR = 40) [14].

Longitudinal studies on iRBD have found that over 90% of patients will eventually phenoconvert to an overt α-synucleinopathy [13,17]. In a meta-analysis examining the conversion from iRBD to future PD and DLB, the conversion rates were 33%, 82%, and 97% of cases at 5 year, 10.5 year, and 14 year follow-ups, respectively [13]. Therefore, it is not a matter of "if" but "when" patients with iRBD will phenoconvert. There have been two published postmortem studies on iRBD patients, and both showed Lewy body disease with α-synuclein deposits in the brainstem [18,19]. The first case involved an 86-year-old man with a 22-year history of iRBD, video-polysomnography-confirmed, without any clinical evidence of parkinsonism during serial neurologic examinations. He died of pneumonia. Postmortem histopathology revealed Lewy body disease in the locus coeruleus and substantia nigra [18]. The second case involved a 72-year-old man with a 15-year history of iRBD, video-polysomnography-confirmed, who also died of pneumonia [19]. Postmortem histopathology detected α-synuclein pathology in the ventromedial medulla inhibitory neurons in the medullary reticular formation—the exact site for generating REM-atonia identified in rats by the Lyon group [3]. Recently, α-synuclein has been detected in another area of the Central Nervous System (CNS) in iRBD patients, viz. the cerebrospinal fluid [20–22].

Furthermore, studies of the peripheral nervous system in iRBD patients have detected α-synuclein deposits (by antemortem histopathology, i.e., biopsy) in the following five regions studied [23,24]: (i) gut (enteric)—colon and stool; (ii) skin; (iii) submandibular gland; (iv) labial salivary gland; and (v) parotid gland.

Therefore, a bona fide case of "idiopathic" RBD still awaits postmortem histopathologic confirmation—which would not be expected. This is a prime reason for why the term "isolated RBD" has been proposed [25], and increasingly utilized and accepted in the medical literature, as it anticipates the eventual transition to overt synucleinopathy. This is an important reconceptualization, as emphasized by the authors [25].

The genetic underpinnings of iRBD represent another notable area of current research in relation to α-synucleinopathies. A recent genome-wide association study by the IRBDSG aimed to identify genetic risk loci associated with RBD across the genome [26]. A meta-analysis was performed for 2843 cases and 139,636 controls comprising a case–control GWAS of 1,061 iRBD cases and 8,386 controls, and also a case–control GWAS from "23andMe, Inc." using PD patients with probable RBD (PD + pRBD) and controls without PD or RBD (N cases = 1782, N controls = 131,250). Five RBD risk loci were identified, including INPP5F and SCARB2, along with replications of known RBD associations near SNCA9, TMEM1750, and two GBA variants. These genetic findings suggest that RBD-associated synucleinopathy may only have a partially overlapping genetic background with PD and DLB, and are in line with clinical research indicating that RBD-PD is a distinct—and more malignant—variant of PD. The prodromal presence of iRBD is a marker of future increased global morbidity in PD with greater motor, cognitive, autonomic, and psychiatric

dysfunction, and greater disease burden (to self and caretaker), compared to PD without RBD [27].

A group of experts in Lewy body disease and iRBD as prodromal PD has just published a comprehensive literature review that "demonstrates numerous cellular and molecular neuropathological changes occurring prior to the appearance of Lewy Bodies in dopamine neurons" [28]. This review offered to provide a pertinent overview of early pathological events in PD that could assist in the development of novel disease-modifying strategies and interventions. In a related development, attention has been called to the circadian rhythm perspective in α-synucleinopathies and disease modification [29].

4. RBD Clinical Research Cohorts

Multi-center iRBD patient cohorts are being gathered in preparation for testing promising neuroprotective/disease-modifying agents to slow down or halt the progression from iRBD to overt PD/DLB. To that end, the International RBD Study Group (IRBDSG) was formed in 2007, comprised of clinical and basic scientists, with yearly research symposia, collaborative projects, and peer-reviewed publications. For example, there was a recent report on the biomarkers of phenoconversion, ranked in descending order of strength for predicting phenoconversion, with the extent of RWA being the strongest predictor [30] as listed in Table 1. Another recent publication by the IRBDSG reported on the progression of clinical biomarkers in prodromal PD and DLB [31]. An important practical aspect of this study was the calculation of sample size requirements for demonstrating a slowing of the progression of neurodegenerative measures under different anticipated neuroprotective treatment effects. A total of 1,160 iRBD patients were followed for more than a mean of 3 years. Of all the clinical variables that were assessed, motor variables progressed the fastest and required the lowest sample sizes, i.e., 151–560 per group at 50% drug efficacy and 2-year trial duration. In contrast, cognitive, olfactory, and autonomic variables showed more modest progression and higher variability, resulting in larger sample sizes. Moreover, the most efficient design was a time-to-event analysis that used combined milestones of motor and cognitive decline, with an estimated sample size of 117 per group at the same 50% drug efficacy and 2-year trial duration. Also, although phenoconverters from iRBD showed overall greater conversion than non-converters across the multiple domains tested, the only robust difference in progression between PD and DLB phenoconverters was in cognitive testing. As the authors concluded, "these findings provide optimized clinical endpoints and sample size estimates to inform future neuroprotective trials." In this context, the challenges in the study of patients at risk for PD need to be considered [32]. A group from the IRBDSG has just published a focused summary of the clinical and research implications of iRBD [33].

Another research consortium was formed with National Institutes of Health funding, viz. the North American Prodromal Synucleinopathy Consortium (NAPS) in 2018 and NAPS2 in 2021 (5 yr Udall grant), which includes nine centers, including our group at the University of Minnesota. The NIH-funded study is entitled "Neuroprotective treatment trial planning in RBD (isolated RBD as prodromal synucleinopathy)." The goal is to prepare for clinical trials of the neuroprotective treatments currently in development. A registry of iRBD patients (300+) is being established; quantitative biological and functional measures of synucleinopathy burden are being developed; and a formal process to evaluate candidate neuroprotective agents is being established. Functional assessments span the cognitive, neuropsychiatric, motor, sensory, autonomic, and sleep domains. Fluid biomarkers are being collected, and serial quantitative RWA assessments are performed to help determine the optimal predictor or cluster of predictors of imminent phenoconversion, preferably in the 1-3+ year range. The baseline characteristics of the NAPS cohort have recently been published [34]. Additionally, the multi-center FARPRESTO consortium in Italy will be studying the predictive risk factors for phenoconversion in iRBD, along with identifying RBD phenotypes, and the impact of RBD on quality of life and sleep [35].

Table 1. Biomarker Candidates in Isolated RBD.

1. Neurophysiology	REM-without-atonia *, EEG Evoked Potentials Transcranial Magnetic Stimulation Other biomarkers
2. Motor Function	Gait Speech Alternate tap test Eye movements Other biomarkers
3. Cognition:	Mild cognitive impairment: intermediate stage before dementia
4. Hyposmia	Present in two-thirds of isolated RBD patients
5.Color vision discrimination	
6. Autonomic function:	Mild/moderate impairment in isolated RBD
7. Biofluids:	Serum, plasma Cerebrospinal fluid
8. Tissue Biopsy:	Phosphorylated-alpha-synuclein (pSyn) deposits: peripheral autonomic nerves, enteric mucosa, salivary glands
9. Nigro-striatal dopaminergic impairment:	Nigro-striatal dopaminergic impairment: consistently found by PET and SPECT imaging
10. Genetic Markers	Partial overlap of iRBD with PD/DLB genetic markers GBA variants robustly present. **
11. Other:	Complex (Combination) Biomarkers

Adapted (with modification) from reference [30]. In decreasing order of strength for predicting phenoconversion to overt parkinsonism. * The strongest identified biomarker for predicting phenoconversion. ** The GBA gene encodes for the lysosomal enzyme glucocerebrosidase (GCase). Mutations in the GBA gene, as found in GBA variants, may lead to loss of GCase activity and lysosomal dysfunction, which may impair α-synuclein degradation and promote α-synuclein accumulation and spreading.

Other prognostic biomarkers for iRBD phenoconversion include DAT (dopamine transporter) binding and RWA [36]; Montreal Cognitive Assessment abnormality combined with reduced Metaiodobenzylguanidine scintigraphy [37]; Fluorodeoxyglucose-Positron Emission Tomography findings combined with learning vector quantization that allows for the classification of neurodegenerative diseases and the trajectory of iRBD [38]; brain metabolism related to mild cognitive impairment and phenoconversion risk [39]; and severity of RWA being correlated with measures of cognitive impairment and depressive symptoms in iRBD [40]—the same group of investigators also found that RWA correlates with abnormal vestibular-evoked myogenic potentials (another brainstem marker) in iRBD [41].

5. Depression, RBD, Synucleinopathy

A novel RBD research area involves the prevalence and correlates of RBD in psychiatric outpatients with major depressive disorder (MDD) [42]. The first study, conducted by the Hong Kong group, screened for RBD, and the prevalence of vPSG-verified RBD was 9% in a predominantly middle-aged MDD population, with associated olfactory and color vision deficits serving as α-synucleinopathy biomarkers. Therefore, patients with RBD and MDD may represent an MDD subtype with an underlying α-synuclein neurodegenerative disorder. This insight was reinforced in a just-accepted study by the same Hong Kong group entitled "Familial α-synucleinopathy spectrum features in patients with psychiatric REM sleep behavior disorder" [43]. In this case–control family study, a familial coaggregation of α-synucleinopathy spectrum features was found in the patients with vPSG-documented psy-RBD (mainly MDD), but not in the psychiatric or healthy controls,

suggesting an underlying α-synucleinopathy in psy-RBD as a neurodegeneration-related subtype of psychiatric disorder. Significant findings in familial first-degree relatives (FDRs) included possible/provisional RBD, definite RBD (vPSG-confirmed), increased phasic RWA, depression, clinical diagnosis of PD/dementia risk, prodromal PD, as compared with healthy control FDRs. When compared with psy control FDRs, psy-RBD-FDRs had a higher risk for definite RBD, RWA, diagnosis of PD/dementia, and risk of prodromal PD. In contrast, psychiatric controls only presented with a familial aggregation of depression. These results emphasize the need to systematically search for RBD in the middle-aged and older MDD population. Also, RBD in MDD calls attention to a subgroup of MDD patients with vulnerability to future neurodegeneration. These patients should be identified for enrollment in future neuroprotective studies, as a new category of "precision psychiatry."

6. RBD in PD, DLB, and MSA

Besides iRBD being recognized as prodromal synucleinopathy (at least in middle-aged and older adults), RBD has a strong presence in patients already diagnosed with PD, DLB, and Multiple System Atrophy (MSA). For PD, the largest clinical and vPSG series to date studied an unselected cohort of 457 sleep-disturbed patients with PD. RBD was confirmed in 46% of these PD patients [44]. Significant findings included no preferred PD subtype for RBD, no gender preference, and RBD was associated with older age. Also, PD patients with RBD, compared to PD patients without RBD, had significantly longer disease duration, higher Hoehn and Yahr stages, more falls, more fluctuations, more psychiatric comorbidity, a higher dose of levodopa, and more periodic leg movements during sleep. For DLB, in the latest diagnostic criteria established by the DLB Consortium in 2017 [45], RBD is the first of the four core features listed for clinically probable DLB due to its presence in 75% of published DLB case series, as reviewed in [45]. Finally, RBD has been documented by vPSG to be present in 90% of patients with MSA [46]. Prognostic counseling and ethical issues regarding RBD as prodromal parkinsonism have been addressed in several recent publications, with expert input from medical ethicists [47–52].

7. Parasomnia Overlap Disorder and Its Comorbidity with PD

When RBD emerges together with an NREM parasomnia, it is designated as the "Parasomnia Overlap Disorder" (POD) that was formally described and named by our center in 1997 with a series of 33 cases of RBD combined with a disorder of NREM arousal (confusional arousals, sleepwalking, and sleep terrors) that emerged either idiopathically (iPOD) or symptomatically with neurological and other disorders [53]. The mean age at presentation was 34 + (SD) 14 yrs, and the mean age of parasomnia onset was 15 + 16 yrs (range 1–66); 70% were males. Although POD is classified as a subtype of RBD in the ICSD-3 [1], diagnostic criteria for both RBD and a NREM parasomnia must be met in order to diagnose POD [1].

Since 1997, the literature on POD has grown to more than 150 published cases [54,55], and now includes appetitive NREM sleep parasomnias (sexsomnia and sleep-related eating disorder [1]) and Rhythmic Movement Disorder [1]. Additional types and CNS locations of symptomatic cases have been identified. Also, the mid- to late-life onset of SW is now known to be associated with PD, as described below, and when there is also coexisting RBD, then POD is present in PD. In this context, a series of three studies by the Bassetti group in Bern will be described. The first was a retrospective study that found de novo sleepwalking in 3.6% (6/165) of consecutive patients with PD [56]. Four of these six patients with sleepwalking and PD also had video-polysomnography-confirmed RBD, and thus POD. The second was a prospective questionnaire study of sleepwalking in PD that found that 9% (36/417) of PD patients reported sleepwalking—including 5% (22/417) with adult-onset sleepwalking [57]. Moreover, 72% of these 36 patients also had presumed RBD, and thus presumed POD. The third study [58] performed video-polysomnography in 30 PD patients from the previous questionnaire study: N=10 (PD + sleepwalking), N = 10 (PD + presumed RBD), and N=10 (PD + no parasomnia history). Of the 10 PD

patients with sleepwalking, 8/10 also had RBD, and thus POD. Therefore, PD carries an increased risk for generalized motor dyscontrol across NREM and REM sleep manifesting as POD. Finally, an epidemiologic cross-sectional study of 25,694 men from the Health Professionals Follow-up Study, a population-based cohort of male health professionals in the United States, searched for probable sleepwalking (prob-Sleepwalking) and probable RBD (pRBD) using the Mayo Sleep Questionnaire [59]. Significant findings were that 0.9% had prob-Sleepwalking, 10.6% had pRBD, and 1.0% had PD. After adjusting for potential confounders, prob-Sleepwalking, pRBD, and combined prob-Sleepwalking/pRBD had higher odds of PD, with an Odds Ratio (OR) of 4.80 for prob-Sleepwalking; 6.36 for pRBD; and 8.44 for combined prob-Sleepwalking/pRBD.

8. Antidepressant-Induced RBD: A Neurodegenerative Signal?

Most antidepressants, especially Serotonin-Specific Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors, and also mirtazapine, tricyclic antidepressants, and monoamine oxidase inhibitors, can trigger RWA/RBD [60–67]—but not bupropion, a dopaminergic/noradrenergic agonist. Therefore, unless otherwise contraindicated, bupropion should be the treatment of choice for an RBD patient with clinical depression. In a provocative study entitled "Antidepressants and REM sleep behavior disorder: isolated side effect or neurodegenerative signal?" [68], 100 iRBD patients and 45 matched controls were studied; 27/100 iRBD patients were taking antidepressants and when they were compared to the controls for the presence of neurodegenerative biomarkers, significant abnormalities were found in 12/14 of these biomarkers, such as olfaction, color vision, Unified Parkinson's Disease Rating Scale II/III score, alternate tap test, systolic blood pressure drop, mild cognitive impairment, constipation, etc. Presumably, antidepressant use in these depressed patients already predisposed to RBD and parkinsonism (as indicated by the robust presence of neurodegeneration markers) accelerated the emergence of RBD. This calls to mind the pertinent study on RBD-Major Depressive Disorder by the Hong Kong group described above [42].

9. RBD and Narcolepsy

RBD is present in up to 60% of Narcolepsy type 1 (hypocretin-deficient) patients, and represents a distinct phenotype of RBD, with gender parity, earlier age of onset than with iRBD, lower frequency of RBD episodes, less-complex movements during REM sleep, less-aggressive and -violent RBD behaviors, and a more even distribution of RBD episodes across all REM epochs compared to iRBD [69]. However, a full understanding of the RBD-Narcolepsy phenotype is still lacking, as some patients have normal cerebrospinal fluid hypocretin levels, and also RBD may be found in Narcolepsy type 2 (without cataplexy) patients [69]. There is no evidence to date that patients with RBD-Narcolepsy are at increased risk for future neurodegeneration. A biomarker study comparing 17 Narcolepsy type 1-RBD patients and 30 iRBD patients found that 87% of iRBD patients had positive skin biopsies for phosphorylated α-synuclein deposits, whereas 0% of Narcolepsy type 1-RBD patients had positive skin biopsies [70]. Therefore, clinicians managing patients with RBD-Narcolepsy can be confident about the lack of identified risk for these patients to develop future neurodegeneration.

Furthermore, a vPSG study, with quantitated RWA, explored the psychobehavioral profile of Narcolepsy type 1 patients with and without RBD compared with healthy controls [71]. The one significant difference found between patients with Narcolepsy type 1 with and without RBD was impaired objective attention in patients with Narcolepsy type 1-RBD. Also, in patients with Narcolepsy type 1-RBD, RWA was positively correlated with depression.

10. Treatment of RBD and RBD Differential Diagnosis

The American Academy of Sleep Medicine recently published updated clinical practice guidelines for the management of RBD [72]. First, a safe sleeping environment must be

maintained to prevent potentially injurious nocturnal behaviors. Next, recommended pharmacotherapy for adults with iRBD or with secondary RBD due to a medical condition includes, as recommended treatments, clonazepam, melatonin (immediate-release), and pramipexole (for iRBD). The American Academy of Sleep Medicine stated that "these are "conditional" recommendations and that the clinician should use his/her "clinical knowledge and experience, and to strongly consider the patient's values and preferences, to determine the best course of action".

The differential diagnosis of RBD (with dream-enacting behaviors) primarily includes NREM parasomnias, Obstructive Sleep Apnea Pseudo-RBD, Sleep-Related Periodic Limb Movement Disorder pseudo-RBD, and nocturnal seizures. Further discussion on this important topic is beyond the scope of this review, but has been comprehensively addressed [7,73]. Obstructive Sleep Apnea-Pseudo RBD, along with Obstructive Sleep Apnea comorbidity with RBD and treatment outcomes [74], is currently considered to be "a hot topic" [75].

11. Recent Epidemiologic Data

Two community-based polysomnographic studies, conducted in Switzerland and Japan, found prevalence rates for iRBD of 1.06% and 1.23%, respectively, in middle-aged and older adults [76,77]. Furthermore, the Swiss study found an equal gender ratio [76], in contrast to sleep-clinic-based studies that found male predominance. Therefore, the literature on RBD being a male-predominant disorder has reflected a sleep clinic gender bias for middle-aged and older males who had more aggressive and injurious RBD behaviors that prompted clinical referral, as demonstrated in two large series [78,79].

Epidemiologic studies of RBD from four additional countries deserve mention. A community-based Korean study of 348 subjects > 60 years old who underwent video-polysomnography and clinical assessments found a prevalence estimate of 2.01% for total RBD and a prevalence estimate of 1.34% for iRBD [80]. A community-based primary care Spanish study of patients > 60 years old who were screened for RBD and who then underwent video-polysomnography found an estimated prevalence of 0.74% for iRBD [81]. Another community-based study of elderly subjects in Arizona, USA, utilizing RBD screening surveys, without video-polysomnography, found an estimated prevalence of 1.7% for probable RBD [82]. And a population-based study of patients attending primary care clinics in Catania, Italy, involving screening instruments followed by clinical interviews and video-polysomnography, found an estimated prevalence of 3.48% for probable RBD and an estimated prevalence of 1.18% for definite RBD [83].

12. Concluding Remarks

A number of RBD topics that were not covered in this review due to space limitations have recently been reported and reviewed [9,75,84]. Some of these topics include RBD in children, adolescents, and adults under 50 years old; acute RBD; stress disorders and RBD; gut microbiome dysbiosis in RBD [85]; abnormal activation of motor cortical network during phasic REM sleep in iRBD [86]; NREM sleep EEG oscillations in iRBD [87]; altered resting-state thalamo-occipital functional connectivity in iRBD [88]; quantitative actigraphic assessment of treatment response in RBD [89]; digital biomarkers in RBD [90–92]; machine learning research in RBD [93,94]; and animal models of RBD [95–98]. In conclusion, RBD is situated at an important and ever-expanding crossroads of clinical (sleep) medicine, neurology, and neuroscience.

Funding: This research received no external funding.

Acknowledgments: Michael J. Howell, my sleep medicine colleague at the University of Minnesota, brought to my attention Case VI on PD-RBD written by James Parkinson in his Essay On the Shaking Palsy.

Conflicts of Interest: The author declares no conflict of interest.

References

1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*, 3rd ed.; American Academy of Sleep Medicine: Darien, IL, USA, 2023.
2. Valencia Garcia, S.; Libourel, P.-A.; Lazarus, M.; Grassi, D.; Luppi, P.-H.; Fort, P. Genetic inactivation of glutamate sublaterodorsal nucleus recapitulates REM sleep behaviour disorder. *Brain* **2017**, *140*, 414–420. [CrossRef] [PubMed]
3. Valencia Garcia, S.; Brischoux, F.; Clémen, O.; Libourel, P.A.; Arthaud, S.; Lazarus, M.; Luppi, P.H.; Fort, P. Ventromedial medulla inhibitory neuron inactivation induces REM sleep without atonia and REM sleep behavior disorder. *Nat. Commun.* **2018**, *9*, 504. [CrossRef] [PubMed]
4. Dauvilliers, Y.; Schenck, C.H.; Postuma, R.B.; Iranzo, A.; Luppi, P.H.; Plazzi, G.; Montplaisir, J.; Boeve, B. REM sleep behaviour disorder. *Nat. Rev. Dis. Primers* **2018**, *4*, 19. [CrossRef] [PubMed]
5. Schenck, C.H.; Bundlie, S.R.; Ettinger, M.G.; Mahowald, M.W. Chronic behavioral disorders of human REM sleep: A new category of parasomnia. *Sleep* **1986**, *9*, 293–308. [CrossRef]
6. Schenck, C.H.; Bundlie, S.R.; Patterson, A.L.; Mahowald, M.W. Rapid eye movement sleep behavior disorder. A treatable parasomnia affecting older adults. *JAMA* **1987**, *257*, 1786–1789. [CrossRef]
7. Schenck, C.H.; Mahowald, M.W. REM sleep behavior disorder: Clinical, developmental, and neuroscience perspectives 16 years after its formal identification in *SLEEP*. *Sleep* **2002**, *25*, 120–138. [CrossRef]
8. Jouvet, M.; Delorme, F. Locus coeruleus et sommeil paradoxal. *C. R. Seances Soc. Biol. Ses Fil.* **1965**, *159*, 895–899.
9. Schenck, C.H.; Högl, B.; Videnovic, A. (Eds.) *Rapid-Eye-Movement Sleep Behavior Disorder*; Springer Nature: Cham, Switzerland, 2018; ISBN 978-3-319-90151-0. [CrossRef]
10. García Ruiz, P.J.; Gulliksen, L. Did Don Quixote have Lewy body disease? *J. R. Soc. Med.* **1999**, *92*, 200–201. [CrossRef]
11. Schenck, C.H.; Boeve, B.F.; Mahowald, M.W. Delayed emergence of a parkinsonian disorder or dementia in 81% of older males initially diagnosed with idiopathic REM sleep behavior disorder (RBD): 16 year update on a previously reported series. *Sleep Med.* **2013**, *14*, 744–748. [CrossRef]
12. Iranzo, A.; Tolosa, E.; Gelpi, E.; Molinuevo, J.L.; Valldeoriola, F.; Serradell, M.; Sanchez-Valle, R.; Vilaseca, I.; Lomeña, F.; Vilas, D.; et al. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: An observational cohort study. *Lancet Neurol.* **2013**, *12*, 443–453.
13. Galbiati, A.; Verga, L.; Giora, E.; Zucconi, M.; Ferini-Strambi, L. The risk of neurodegeneration in REM sleep behavior disorder: A systematic review and meta-analysis of longitudinal studies. *Sleep Med. Rev.* **2019**, *43*, 37–46. [CrossRef] [PubMed]
14. Berg, D.; Postuma, R.B.; Adler, C.H.; Bloem, B.R.; Chan, P.; Dubois, B.; Gasser, T.; Goetz, C.G.; Halliday, G.; Joseph, L.; et al. MDS research criteria for prodromal Parkinson's disease. *Mov. Disord.* **2015**, *30*, 1600–1611. [CrossRef] [PubMed]
15. Braak, H.; Del Tredici, K.; Rüb, U.; De Vos, R.A.I.; Jansen Steur, E.N.H.; Braak, E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol. Aging* **2003**, *24*, 197–211. [CrossRef]
16. Mahowald, M.W.; Schenck, C.H. The "when" and "where" of α-synucleinopathies: Insights from REM sleep behavior disorder. *Neurology* **2018**, *91*, 435–436. [CrossRef] [PubMed]
17. Iranzo, A.; Fernández-Arcos, A.; Tolosa, E.; Serradell, M.; Molinuevo, J.L.; Valldeoriola, F.; Gelpi, E.; Vilaseca, I.; Sánchez-Valle, R.; Lladó, A.; et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: Study in 174 patients. *PLoS ONE* **2014**, *9*, e89741. [CrossRef]
18. Uchiyama, M.; Isse, K.; Tanaka, K.; Yokota, N.; Hamamoto, M.; Aida, S.; Ito, Y.; Yoshimura, M.; Okawa, M. Incidental Lewy body disease in a patient with REM sleep behavior disorder. *Neurology* **1995**, *45*, 709–712. [CrossRef]
19. Boeve, B.F.; Dickson, D.W.; Olson, E.J.; Shepard, J.W.; Silber, M.H.; Ferman, T.J.; Ahlskog, J.E.; Benarroch, E.E. Insights into REM sleep behavior disorder pathophysiology in brainstem-predominant Lewy body disease. *Sleep Med.* **2007**, *8*, 60–64. [CrossRef]
20. Iranzo, A.; Fairfoul, G.; Ayudhaya, A.C.N.; Serradell, M.; Gelpi, E.; Vilaseca, I.; Sanchez-Valle, R.; Gaig, C.; Santamaria, J.; Tolosa, E.; et al. Detection of α-synuclein in CSF by RT-QuIC in patients with isolated rapid-eye-movement sleep behaviour disorder: A longitudinal observational study. *Lancet Neurol.* **2021**, *20*, 203–212. [CrossRef]
21. Poggiolini, I.; Gupta, V.; Lawton, M.; Lee, S.; El-Turabi, A.; Querejeta-Coma, A.; Trenkwalder, C.; Sixel-Döring, F.; Foubert-Samier, A.; Pavy-Le Traon, A.; et al. Diagnostic value of cerebrospinal fluid alpha-synuclein seed quantification in synucleinopathies. *Brain* **2022**, *145*, 584–595. [CrossRef]
22. Concha-Marambio, L.; Weber, S.; Farris, C.M.; Dakna, M.; Lang, E.; Wicke, T.; Ma, Y.; Starke, M.; Ebentheuer, J.; Sixel-Döring, F.; et al. Accurate detection of α-synuclein seeds in cerebrospinal fluid from isolated rapid eye movement sleep behavior disorder and patients with Parkinson's disease in the DeNovo Parkinson (DeNoPa) cohort. *Mov. Disord.* **2023**, *38*, 567–578. [CrossRef]
23. Schenck, C.H. Neuropathology of RBD. In *Rapid-Eye-Movement Sleep Behavior Disorder*; Schenck, C.H., Högl, B., Videnovic, A., Eds.; Springer Nature: Cham, Switzerland, 2018; pp. 579–587. ISBN 978-3-319-90151-0. [CrossRef]
24. Schaffrath, A.; Schleyken, S.; Seger, A.; Jergas, H.; Özdüzenciler, P.; Pils, M.; Blömeke, L.; Cousin, A.; Willbold, J.; Bujnicki, T.; et al. Patients with isolated REM-sleep behavior disorder have elevated levels of alpha-synuclein aggregates in stool. *NPJ Parkinson's Dis.* **2023**, *9*, 14. [CrossRef] [PubMed]
25. Högl, B.; Stefani, A.; Videnovic, A. Idiopathic REM sleep behaviour disorder and neurodegeneration—An update. *Nat. Rev. Neurol.* **2018**, *14*, 40–55. [CrossRef] [PubMed]

26. Krohn, L.; Heilbron, K.; Blauwendraat, C.; Reynolds, R.H.; Yu, E.; Senkevich, K.; Rudakou, U.; Estiar, M.A.; Gustavsson, E.K.; Brolin, K.; et al. Genome-wide association study of REM sleep behavior disorder identifies polygenic risk and brain expression effects. *Nat. Commun.* **2022**, *13*, 7496. [CrossRef] [PubMed]
27. Bohnen, N.I.; Hu, M. Sleep disturbance as potential risk and progression factor for Parkinson's disease. *J. Parkinson's Dis.* **2019**, *9*, 603–614. [CrossRef]
28. Koeglsperger, T.; Rumpf, S.L.; Schließer, P.; Struebing, F.L.; Brendel, M.; Levin, J.; Trenkwalder, C.; Höglinger, G.U.; Herms, J. Neuropathology of incidental Lewy body & prodromal Parkinson's disease. *Mol. Neurodegener.* **2023**, *18*, 32. [CrossRef]
29. Kunz, D.; Oster, H.; Rawashdeh, O.; Neumann, W.J.; Münte, T.; Berg, D. Sleep and circadian rhythms in α-synucleinopathies—Perspectives for disease modification. *Acta Physiol.* **2023**, *238*, e13966. [CrossRef]
30. Miglis, M.G.; Adler, C.H.; Antelmi, E.; Arnaldi, D.; Baldelli, L.; Boeve, B.F.; Cesari, M.; Dall'Antonia, I.; Diederich, N.J.; Doppler, K.; et al. Biomarkers of conversion to α-synucleinopathy in isolated rapid-eye-movement sleep behaviour disorder. *Lancet Neurol.* **2021**, *20*, 671–684. [CrossRef]
31. Joza, S.; Hu, M.T.; Jung, K.Y.; Kunz, D.; Stefani, A.; Dušek, P.; Terzaghi, M.; Arnaldi, D.; Videnovic, A.; Schiess, M.C.; et al. International REM Sleep Behavior Disorder Study Group. Progression of clinical markers in prodromal Parkinson's disease and dementia with Lewy bodies: A multicentre study. *Brain* **2023**, awad072, *online ahead of print*. [CrossRef]
32. Marras, C.; Alcalay, R.N.; Siderowf, A.; Postuma, R.B. Challenges in the study of individuals at risk for Parkinson disease. *Handb. Clin. Neurol.* **2023**, *192*, 219–229.
33. Stefani, A.; Trenkwalder, C.; Arnulf, I.; Bliwise, D.L.; Boeve, B.F.; Inoue, Y.; Iranzo, A.; Lewis, S.J.; Provini, F.; Schenck, C.; et al. Isolated rapid eye movement sleep behaviour disorder: Clinical and research implications. *J. Neurol. Neurosurg. Psychiatry* **2023**, *94*, 581–582. [CrossRef]
34. Elliott, J.E.; Lim, M.M.; Keil, A.T.; Postuma, R.B.; Pelletier, A.; Gagnon, J.F.; St Louis, E.K.; Forsberg, L.K.; Fields, J.A.; Huddleston, D.E.; et al. North American Prodromal Synucleinopathy (NAPS) Consortium. Baseline characteristics of the North American prodromal Synucleinopathy cohort. *Ann. Clin. Transl. Neurol.* **2023**, *10*, 520–535. [CrossRef] [PubMed]
35. Puligheddu, M.; Figorilli, M.; Antelmi, E.; FARPRESTO Consortium. Predictive risk factors of phenoconversion in idiopathic REM sleep behavior disorder: The Italian study "FARPRESTO". *Neurol. Sci.* **2022**, *43*, 6919–6928. [CrossRef]
36. Kunz, D.; Stotz, S.; de Zeeuw, J.; Papakonstantinou, A.; Dümchen, S.; Haberecht, M.; Plotkin, M.; Bes, F. Prognostic biomarkers in prodromal α-synucleinopathies: DAT binding and REM sleep without atonia. *J. Neurol. Neurosurg. Psychiatry* **2023**, *94*, 532–540. [CrossRef] [PubMed]
37. Miyamoto, M.; Miyamoto, T. Montreal Cognitive Assessment Predicts the Short-Term Risk of Lewy Body Disease in Isolated REM Sleep Behavior Disorder with Reduced MIBG Scintigraphy. *Mov. Disord. Clin. Pract.* **2022**, *10*, 32–41. [CrossRef] [PubMed]
38. Van Veen, R.; Meles, S.K.; Renken, R.J.; Reesink, F.E.; Oertel, W.H.; Janzen, A.; de Vries, G.J.; Leenders, K.L.; Biehl, M. FDG-PET combined with learning vector quantization allows classification of neurodegenerative diseases and reveals the trajectory of idiopathic REM sleep behavior disorder. *Comput. Methods Programs Biomed.* **2022**, *225*, 107042. [CrossRef]
39. Yoon, E.J.; Lee, J.Y.; Kim, H.; Yoo, D.; Shin, J.H.; Nam, H.; Jeon, B.; Kim, Y.K. Brain metabolism related to mild cognitive impairment and phenoconversion in patients with isolated REM sleep behavior disorder. *Neurology* **2022**, *98*, e2413–e2424. [CrossRef]
40. Figorilli, M.; Meloni, F.; Lecca, R.; Tamburrino, L.; Mascia, M.G.; Cocco, V.; Meloni, M.; Marques, A.R.; Vidal, T.; Congiu, P.; et al. Severity of REM sleep without atonia correlates with measures of cognitive impairment and depressive symptoms in REM sleep behaviour disorder. *J. Sleep Res.* **2023**, e13880, *online ahead of print*. [CrossRef]
41. Puligheddu, M.; Figorilli, M.; Serra, A.; Laccu, I.; Congiu, P.; Tamburrino, L.; de Natale, E.R.; Ginatempo, F.; Deriu, F.; Loi, G.; et al. REM Sleep without Atonia Correlates with Abnormal Vestibular Evoked Myogenic Potentials in Isolated REM Sleep Behavior Disorder. *Sleep* **2019**, *42*, zsz128. [CrossRef]
42. Wang, J.; Chau, S.W.H.; Lam, S.P.; Liu, Y.; Zhang, J.; Chan, N.Y.; Cheung, M.M.S.; Yu, M.W.M.; Tsang, J.C.T.; Chan, J.W.Y.; et al. Prevalence and correlates of REM sleep behaviour disorder in patients with major depressive disorder: A two-phase study. *J. Neurol. Neurosurg. Psychiatry* **2022**, *93*, 1010–1017. [CrossRef]
43. Jing Wang, J.; Lam, S.P.; Huang, B.; Liu, Y.; Zhang, J.; Yu, M.W.M.; Tsang, J.C.C.; Zhou, L.; Chau, S.W.H.; Chan, N.Y.; et al. Familial α-Synucleinopathy spectrum features in patients with psychiatric REM sleep behavior disorder. *J. Neurol. Neurosurg. Psychiatry* **2023**. *online ahead of print*. [CrossRef]
44. Sixel-Döring, F.; Trautmann, E.; Mollenhauer, B.; Trenkwalder, C. Associated factors for REM sleep behavior disorder in Parkinson disease. *Neurology* **2011**, *77*, 1048–1054. [CrossRef] [PubMed]
45. McKeith, I.G.; Boeve, B.F.; Dickson, D.W.; Halliday, G.; Taylor, J.P.; Weintraub, D.; Aarsland, D.; Galvin, J.; Attems, J.; Ballard, C.G.; et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* **2017**, *89*, 88–100. [CrossRef] [PubMed]
46. Plazzi, G.; Corsini, R.; Provini, F.; Pierangeli, G.; Martinelli, P.; Montagna, P.; Lugaresi, E.; Cortelli, P. REM sleep behavior disorders in multiple system atrophy. *Neurology* **1997**, *48*, 1094–1097. [CrossRef]
47. Arnaldi, D.; Antelmi, E.; St Louis, E.K.; Postuma, R.B.; Arnulf, I. Idiopathic REM sleep behavior disorder and neurodegenerative risk: To tell or not to tell to the patient? How to minimize the risk? *Sleep Med. Rev.* **2017**, *36*, 82–95. [CrossRef] [PubMed]

48. St Louis, E.K. Prognostic counseling for patients with idiopathic/isolated REM sleep behavior disorder: Should we tell them what's coming? Yes. *Mov. Disord. Clin. Pract.* **2019**, *6*, 667–668. [CrossRef]
49. Malkani, R.G.; Wenger, N.S. REM sleep behavior disorder as a pathway to dementia: If, when, how, what, and why should physicians disclose the diagnosis and risk for dementia. *Curr. Sleep Med. Rep.* **2021**, *24*, 57–64. [CrossRef]
50. Feinstein, M.A.; Sharp, R.R.; Sandness, D.J.; Feemster, J.C.; Junna, M.; Kotagal, S.; Lipford, M.C.; Tippmann-Peikert, M.; Boeve, B.F.; Silber, M.H.; et al. Physician and patient determinants of prognostic counseling in idiopathic REM sleep-behavior disorder. *Sleep Med.* **2019**, *62*, 80–85. [CrossRef]
51. Teigen, L.N.; Sharp, R.R.; Hirsch, J.R.; Campbell, E.; Timm, P.C.; Sandness, D.J.; Feemster, J.C.; Gossard, T.R.; Faber, S.M.; Steele, T.A.; et al. Specialist approaches to prognostic counseling in isolated REM sleep behavior disorder. *Sleep Med.* **2021**, *79*, 107–112. [CrossRef]
52. Stefani, A.; Mozersky, J.; Kotagal, V.; Högl, B.; Ingravallo, F.; Ju, Y.S.; Avidan, A.; Sharp, R.; Videnovic, A.; Schenck, C.H.; et al. Ethical aspects of prodromal synucleinopathy prognostic counseling. *Semin. Neurol.* **2023**, *43*, 166–177. [CrossRef]
53. Schenck, C.H.; Boyd, J.L.; Mahowald, M.W. A parasomnia overlap disorder involving sleepwalking, sleep terrors, and REM sleep behavior disorder in 33 polysomnographically confirmed cases. *Sleep* **1997**, *20*, 972–981. [CrossRef]
54. Schenck, C.H.; Howell, M.J. Spectrum of rapid eye movement sleep behavior disorder (overlap between rapid eye movement sleep behavior disorder and other parasomnias). *Sleep Biol. Rhythm* **2013**, *11* (Suppl. 1), 27–34. [CrossRef]
55. Schenck, C.H.; Howell, M.J. Parasomnia overlap disorder: RBD and NREM Parasomnias. In *Rapid-Eye-Movement Sleep Behavior Disorder*; Schenck, C.H., Hogl, B., Videnovic, A., Eds.; Springer Nature: Cham, Switzerland, 2018; pp. 359–369. [CrossRef]
56. Poryazova, R.; Waldvogel, D.; Bassetti, C.L. Sleepwalking in patients with Parkinson disease. *Arch. Neurol.* **2007**, *64*, 1524–1527. [CrossRef] [PubMed]
57. Oberholzer, M.; Poryazova, R.; Bassetti, C.L. Sleepwalking in Parkinson's disease: A questionnaire-based survey. *J. Neurol.* **2011**, *258*, 1261–1267. [CrossRef]
58. Di Fabio, N.; Poryazova, R.; Oberholzer, M.; Baumann, C.R.; Bassetti, C.L. Sleepwalking, REM sleep behaviour disorder and overlap parasomnia in patients with Parkinson's disease. *Eur. Neurol.* **2013**, *70*, 297–303. [CrossRef]
59. Zhang, X.; Molsberry, S.A.; Pavlova, M.; Schwarzschild, M.A.; Ascherio, A.; Gao, X. Association of Sleepwalking and REM Sleep Behavior Disorder with Parkinson Disease in Men. *JAMA Network Open* **2021**, *4*, e215713. [CrossRef] [PubMed]
60. Schenck, C.H.; Mahowald, M.W.; Kim, S.W.; O'Connor, K.A.; Hurwitz, T.D. Prominent eye movements during NREM sleep and REM sleep behavior disorder associated with fluoxetine treatment of depression and obsessive-compulsive disorder. *Sleep* **1992**, *15*, 226–235. [CrossRef] [PubMed]
61. Winkelman, J.W.; James, L. Serotonergic antidepressants are associated with REM sleep without atonia. *Sleep* **2004**, *27*, 317–321. [CrossRef] [PubMed]
62. Parish, J.M. Violent dreaming and antidepressant drugs: Or how paroxetine made me dream that I was fighting Saddam Hussein. *J. Clin. Sleep Med.* **2007**, *3*, 529–531. [CrossRef]
63. Applebee, G.A.; Attarian, H.P.; Schenck, C.H. An angry bed partner. *J. Clin. Sleep Med.* **2009**, *5*, 477–479. [CrossRef]
64. Hoque, R.; Chesson, A.L., Jr. Pharmacologically induced/exacerbated restless legs syndrome, periodic limb movements of sleep, and REM behavior disorder/REM sleep without atonia: Literature review, qualitative scoring, and comparative analysis. *J. Clin. Sleep Med.* **2010**, *6*, 79–83. [CrossRef]
65. Sheyner, I.; Khan, S.; Stewart, J.T. A case of selective serotonin reuptake inhibitor-induced rapid eye movement behavior disorder. *J. Am. Geriatr. Soc.* **2010**, *58*, 1421–1422. [CrossRef]
66. 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*, 351–355. [CrossRef] [PubMed]
67. Tan, L.; Zhou, J.; Yang, L.; Ren, R.; Zhang, Y.; Li, T.; Tang, X. Duloxetine-induced rapid eye movement sleep behavior disorder: A case report. *BMC Psychiatry* **2017**, *17*, 372. [CrossRef] [PubMed]
68. Postuma, R.B.; Gagnon, J.F.; Tuineaig, M.; Bertrand, J.A.; Latreille, V.; Desjardins, C.; Montplaisir, J.Y. Antidepressants and REM sleep behavior disorder: Isolated side effect or neurodegenerative signal? *Sleep* **2013**, *36*, 1579–1585. [CrossRef] [PubMed]
69. Antelmi, E.; Pizza, F.; Franceschini, C.; Ferri, R.; Plazzi, G. REM sleep behavior disorder in narcolepsy: A secondary form or an intrinsic feature? *Sleep Med. Rev.* **2020**, *50*, 101254. [CrossRef] [PubMed]
70. Antelmi, E.; Pizza, F.; Donadio, V.; Filardi, M.; Sosero, Y.L.; Incensi, A.; Vandi, S.; Moresco, M.; Ferri, R.; Marelli, S.; et al. Biomarkers for REM sleep behavior disorder in idiopathic and narcoleptic patients. *Ann. Clin. Transl. Neurol.* **2019**, *6*, 1872–1876. [CrossRef] [PubMed]
71. Mombelli, S.; Ricordeau, F.; Gillard, L.; Lecca, R.; Vidal, T.; Pereira, B.; Beudin, P.; Vitello, N.; Bastuji, H.; Peter-Derex, L.; et al. Psychobehavioural profile in narcolepsy type 1 with and without REM sleep behaviour disorder. *J. Sleep Res.* **2023**, e13925, *online ahead of print*. [CrossRef]
72. Howell, M.; Avidan, A.Y.; Foldvary-Schaefer, N.; Malkani, R.G.; During, E.H.; Roland, J.P.; McCarter, S.J.; Zak, R.S.; Carandang, G.; Kazmi, U.; et al. Management of REM sleep behavior disorder: An American Academy of Sleep Medicine clinical practice guideline. *J. Clin. Sleep Med.* **2022**, *19*, 759–768. [CrossRef]
73. Antelmi, E.; Lippolis, M.; Biscarini, F.; Tinazzi, M.; Plazzi, G. REM sleep behavior disorder: Mimics and variants. *Sleep Med. Rev.* **2021**, *60*, 101515. [CrossRef]

74. Lee, W.J.; Sunwoo, J.S.; Byun, J.I.; Kim, H.J.; Lee, S.T.; Jung, K.H.; Park, K.I.; Chu, K.; Kim, M.; Lee, S.K.; et al. Isolated rapid eye movement sleep behavior disorder combined with obstructive sleep apnea: Response to treatment and its associated factors. *Sleep Med.* **2022**, *91*, 75–83. [CrossRef]
75. Schenck, C.H. RBD, sexsomnia, sleepwalking and sleep paralysis comorbidities: Relevance to pulmonary, dental, and behavioral sleep medicine. *Sleep Sci.* **2021**, *14*, 87–91. [PubMed]
76. Haba-Rubio, J.; Frauscher, B.; Marques-Vidal, P.; Toriel, J.; Tobback, N.; Andries, D.; Preisig, M.; Vollenweider, P.; Postuma, R.; Heinzer, R. Prevalence and determinants of REM sleep behavior disorder in the General Population. *Sleep* **2018**, *41*, zsx197. [CrossRef] [PubMed]
77. Sasai-Sakuma, T.; Takeuchi, N.; Asai, Y.; Inoue, Y.; Inoue, Y. Prevalence and clinical characteristics of REM sleep behavior disorder in Japanese elderly people. *Sleep* **2020**, *43*, zsaa024. [CrossRef] [PubMed]
78. Schenck, C.H.; Hurwitz, T.D.; Mahowald, M.W. Symposium: Normal and abnormal REM sleep regulation: REM sleep behaviour disorder: An update on a series of 96 patients and a review of the world literature. *J. Sleep Res.* **1993**, *2*, 224–231. [PubMed]
79. Olson, E.J.; Boeve, B.F.; Silber, M.H. Rapid eye movement sleep behaviour disorder: Demographic, clinical and laboratory findings in 93 cases. *Brain* **2000**, *123 Pt 2*, 331–339. [CrossRef]
80. Kang, S.H.; Yoon, I.Y.; Lee, S.D.; Han, J.W.; Kim, T.H.; Kim, K.W. REM sleep behavior disorder in the Korean elderly population: Prevalence and clinical characteristics. *Sleep* **2013**, *36*, 1147–1152. [CrossRef]
81. Pujol, M.; Pujol, J.; Alonso, T.; Fuentes, A.; Pallerola, M.; Freixenet, J.; Barbé, F.; Salamero, M.; Santamaría, J.; Iranzo, A. Idiopathic REM sleep behavior disorder in the elderly Spanish community: A primary care center study with a two-stage design using video-polysomnography. *Sleep Med.* **2017**, *40*, 116–121. [CrossRef]
82. Shprecher, D.R.; Serrano, G.E.; Zhang, N.; Intorcia, A.; Davis, K.J.; Glass, M.; Curry, J.; Walker, J.; Cutler, B.; Callan, M.; et al. Prevalence of REM sleep behavior disorder in Sun City, Arizona. *Heliyon* **2020**, *6*, e03140. [CrossRef]
83. Cicero, C.E.; Giuliano, L.; Sgroi, R.; Squillaci, R.; Terravecchia, C.; Vancheri, E.; Todaro, V.; Reitano, P.; Rizzo, S.; Luca, A.; et al. Italian Society of General Medicine of Catania Study Group. Prevalence of isolated RBD in the city of Catania, Italy: A population-based study. *J. Clin. Sleep Med.* **2021**, *17*, 2241–2248. [CrossRef]
84. Schenck, C.H. REM sleep behavior disorder as a complex condition with heterogeneous underlying disorders: Clinical management and prognostic implications. *Sleep Breath.* **2022**, *26*, 1289–1298. [CrossRef]
85. Huang, B.; Chau, S.W.H.; Liu, Y.; Chan, J.W.Y.; Wang, J.; Ma, S.L.; Zhang, J.; Chan, P.K.S.; Yeoh, Y.K.; Chen, Z.; et al. Gut microbiome dysbiosis across early Parkinson's disease, REM sleep behavior disorder and their first-degree relatives. *Nat. Commun.* **2023**, *14*, 2501. [CrossRef] [PubMed]
86. Sunwoo, J.-S.; Cha, K.S.; Byun, J.-I.; Kim, T.J.; Jun, J.S.; Lim, J.A.; Lee, S.T.; Jung, K.H.; Park, K.I.; Chu, K.; et al. Abnormal activation of motor cortical network during phasic REM sleep in idiopathic REM sleep behavior disorder. *Sleep* **2019**, *42*, zsy227. [CrossRef] [PubMed]
87. Sunwoo, J.-S.; Cha, K.S.; Byun, J.-I.; Jun, J.S.; Kim, T.J.; Shin, J.W.; Lee, S.T.; Jung, K.H.; Park, K.I.; Chu, K.; et al. Nonrapid Eye Movement Sleep EEG Oscillations in Idiopathic REM Sleep Behavior Disorder: A Study of Sleep Spindles and Slow Oscillations. *Sleep* **2021**, *44*, zsaa160. [CrossRef] [PubMed]
88. Byun, J.-I.; Kim, H.-W.; Kang, H.; Cha, K.S.; Sunwoo, J.S.; Shin, J.W.; Moon, J.; Lee, S.T.; Jung, K.H.; Chu, K.; et al. Altered resting-state thalamo-occipital functional connectivity is associated with cognition in isolated rapid eye movement sleep behavior disorder. *Sleep Med.* **2020**, *69*, 198–203. [CrossRef]
89. Park, K.; Shin, Y.W.; Hwang, S.; Jeong, E.; Kim, T.J.; Jun, J.S.; Shin, J.W.; Byun, J.I.; Sunwoo, J.S.; Kim, H.J.; et al. Quantitative measurement of motor activity during sleep in isolated REM sleep behavior disorder patients using actigraphy before and after treatment with clonazepam. *Sleep* **2023**, zsad132, *online ahead of print*. [CrossRef]
90. Arora, S.; Baig, F.; Lo, C.; Barber, T.R.; Lawton, M.A.; Zhan, A.; Rolinski, M.; Ruffmann, C.; Klein, J.C.; Rumbold, J.; et al. Smartphone motor testing to distinguish idiopathic REM sleep behavior disorder, controls, and PD. *Neurology* **2018**, *91*, e1528–e1538. [CrossRef]
91. Gnarra, O.; Wulf, M.; Schäfer, C.; Nef, T.; Bassetti, C. REM sleep behaviour disorder, a narrative review from a technological perspective. *Sleep* **2023**, *46*, zsad030. [CrossRef]
92. Stefani, A.; Cesari, M. Digital health technologies and digital biomarkers in RBD: Need for order out of chaos. *Sleep* **2023**, *46*, zsad109. [CrossRef]
93. Kim, H.; Seo, P.; Byun, J.I.; Jung, K.Y.; Kim, K.H. Spatiotemporal characteristics of cortical activities of REM sleep behavior disorder revealed by explainable machine learning using 3D convolutional neural network. *Sci. Rep.* **2023**, *13*, 8221. [CrossRef]
94. Kim, H.; Seo, P.; Kim, M.J.; Huh, J.I.; Sunwoo, J.S.; Cha, K.S.; Jeong, E.; Kim, H.J.; Jung, K.Y.; Kim, K.H.; et al. Characterization of attentional event-related potential from REM sleep behavior disorder patients based on explainable machine learning. *Comput. Methods Programs Biomed.* **2023**, *234*, 107496. [CrossRef]
95. Lai, Y.-Y.; Hsieh, K.-C.; Siegel, J.M. Animal models of REM sleep behavior disorder. In *Rapid-Eye-Movement Sleep Behavior Disorder*; Schenck, C.H., Högl, B., Videnovic, A., Eds.; Springer Nature: Cham, Switzerland, 2018; pp. 611–623; ISBN 978-3-319-90151-0. [CrossRef]

96. Vetrivelan, R.; Lu, J. Neural circuitry regulating REM sleep and its implication in REM sleep behavior disorder. In *Rapid-Eye-Movement Sleep Behavior Disorder*; Schenck, C.H., Högl, B., Videnovic, A., Eds.; Springer Nature: Cham, Switzerland, 2018; pp. 559–577; ISBN 978-3-319-90151-0. [CrossRef]
97. McKenna, D.; Peever, J. REM sleep behavior disorder: The link between synucleinopathies and REM sleep circuits. In *Rapid-Eye-Movement Sleep Behavior Disorder*; Schenck, C.H., Högl, B., Videnovic, A., Eds.; Springer Nature: Cham, Switzerland, 2018; pp. 625–637; ISBN 978-3-319-90151-0. [CrossRef]
98. Kam, K.; Vetter, K.; Tejiram, R.A.; Pettibone, W.D.; Shim, K.; Audrain, M.; Yu, L.; Daehn, I.S.; Ehrlich, M.E.; Varga, A.W. Effect of aging and a dual orexin receptor antagonist on sleep architecture and NREM oscillations including a REM behavior disorder phenotype in the PS19 mouse model of tauopathy. *J. Neurosci.* **2023**, *43*, 4738–4749. [CrossRef] [PubMed]