

## REM sleep behaviour disorder

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**Abstract** | Rapid eye movement (REM) sleep behaviour disorder (RBD) is a parasomnia that is characterized by loss of muscle atonia during REM sleep (known as REM sleep without atonia, or RSWA) and abnormal behaviours occurring during REM sleep, often as dream enactments that can cause injury. RBD is categorized as either idiopathic RBD or symptomatic (also known as secondary) RBD; the latter is associated with antidepressant use or with neurological diseases, especially  $\alpha$ -synucleinopathies (such as Parkinson disease, dementia with Lewy bodies and multiple system atrophy) but also narcolepsy type 1. A clinical history of dream enactment or complex motor behaviours together with the presence of muscle activity during REM sleep confirmed by video polysomnography are mandatory for a definite RBD diagnosis. Management involves clonazepam and/or melatonin and counselling and aims to suppress unpleasant dreams and behaviours and improve bedpartner quality of life. RSWA and RBD are now recognized as manifestations of an  $\alpha$ -synucleinopathy; most older adults with idiopathic RBD will eventually develop an overt neurodegenerative syndrome. In the future, studies will likely evaluate neuroprotective therapies in patients with idiopathic RBD to prevent or delay  $\alpha$ -synucleinopathy-related motor and cognitive decline.

Normal sleep involves cycles of rapid eye movement (REM) sleep and non-REM (NREM) sleep, with the latter being subdivided into phases N1, N2 and N3 sleep. REM sleep is typically characterized by generalized muscle atonia, REMs, activated electroencephalogram and dreaming. Conversely, during NREM sleep, muscle atonia is not present, and dreaming is absent or diminished (BOX 1). REM sleep behaviour disorder (RBD) is characterized by abnormal behaviours, usually dream enactments, and an excess of muscle tone and/or phasic muscle twitching during REM sleep<sup>1–3</sup>. Excessive muscle tone during REM sleep, referred to as REM sleep without atonia (RSWA), is the core objective finding in RBD<sup>1–3</sup>. Sleep-related injury to the self and/or the bedpartner is frequent in patients with RBD and is related to repeated dream enactment behaviours that usually start >2 hours after sleep onset and predominantly occur in the second part of the night (that is, the time of the longest REM sleep episodes). Most motor events during RBD episodes are simple elementary movements, even in patients with severe RBD, and violent behaviours are rarely observed; however, when present, violent behaviours occur most frequently during phasic REM sleep epochs<sup>4,5</sup>. Examples of reported violent dreams and associated behaviours include the patient being attacked or chased by unfamiliar people or animals, leading to grabbing, punching, biting, kicking or leaping from the bed, and examples of non-violent behaviours include laughing, gesturing,

crying or singing<sup>6–10</sup>. RBD has a highly variable presentation across nights and across patients in terms of the frequency, duration and type of behaviours. During episodes, the patient's eyes are closed, precluding attention to the environment (posing a major risk of injury), although unlike NREM parasomnias<sup>11</sup>, patients often awaken rapidly at the end of an episode, are typically alert, coherent and oriented and recall the dream content<sup>1</sup>. During an episode, walking, running and leaving the bedroom are very unusual.

RBD has been categorized into idiopathic RBD (iRBD) and symptomatic (or secondary RBD) forms, for which the latter is mainly associated with  $\alpha$ -synucleinopathy neurodegenerative diseases (especially Parkinson disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA)) but can also be associated with other neurological disorders, especially narcolepsy type 1 (which frequently has a milder severity than iRBD and RBD associated with an  $\alpha$ -synucleinopathy), or may be triggered by antidepressant medications<sup>6,7</sup>. With RBD associated with narcolepsy type 1 and at times with other forms of RBD, RBD might not be the presenting complaint or even the major symptom. In most cases, patients with iRBD, especially men >50 years of age, will convert to an  $\alpha$ -synucleinopathy, with a mean interval for conversion from time of RBD onset of ~10 years<sup>8,10,12</sup>. This important finding is the basis for iRBD also being referred to as 'cryptogenic RBD' and 'isolated RBD'.

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Furthermore, in a retrospective study of patients with identified  $\alpha$ -synucleinopathies and RBD, the presumed onset of RBD dated as far back as 50 years before the emergence of overt neurodegeneration, suggesting that  $\alpha$ -synuclein pathology can be present in the nervous system long before neurological symptoms emerge, with RBD being a very early herald of the future neurodegeneration<sup>13</sup>.

This Primer focuses on the epidemiology, mechanisms and pathophysiology, diagnosis and management of RBD, including the risk factors for RBD and for progression to  $\alpha$ -synucleinopathy. This Primer also discusses the quality of life (QOL) issues faced by patients and their bedpartners, and touches upon future directions and unanswered clinical and research questions.

### Epidemiology

Only limited data on the prevalence of iRBD are available because the correct diagnosis requires video polysomnography (vPSG, BOX 1), which is expensive, time-consuming and is not available in all clinical centres. Epidemiological studies that use screening tools for dream enactment behaviours, without confirmation by vPSG, produce the highest estimates of iRBD prevalence, which ranges from 3% to 10% globally<sup>14–18</sup>. However, most RBD screening tools likely detect other conditions, such as somnambulism (also known as sleepwalking), other NREM parasomnias, confusional arousals secondary to obstructive sleep apnoea syndrome (OSAS) and periodic limb movement disorder. In addition, many patients are not aware of their dream-enacting behaviours and, accordingly, can screen negative for RBD despite the presence of symptoms (see Diagnosis, screening and prevention).

The most reliable estimates of prevalence come from community-based studies. The first study demonstrated a prevalence of 1.15% for PSG-demonstrated iRBD and a prevalence of 5% for asymptomatic RSWA in individuals >60 years of age in South Korea<sup>19</sup>. This study confirmed iRBD by initial vPSG to identify abnormal muscle tone and then telephoned those with RSWA to screen for dream enactment behaviours<sup>19</sup>. The population-based HypnoLaus study reported a similar prevalence of 1.06% for RBD determined using standardized screening

questions and ambulatory PSG. Of interest, no clear difference was demonstrated in the rate of RBD in men and women, suggesting that the strong male predominance that is observed in sleep clinics reflects a selection bias related to RBD in males being more aggressive and violent and therefore more clinically consequential than RBD in females<sup>20</sup>. In Spain, the prevalence of iRBD was 0.74% in individuals >60 years of age in primary care centres<sup>21</sup>. In this study, RBD was determined using a two-stage approach: a single screening question followed by neurological assessment and vPSG when screening tests were positive. However, in the Spanish study, 12 patients who refused PSG or had no REM sleep during PSG were considered RBD-negative, which might have led to underestimates in prevalence<sup>21</sup>. The HypnoLaus study and the Spanish study included screening questions that relied upon patients recognizing the symptoms of dream enactment; however, as previously mentioned, many patients do not recognize these symptoms. Accordingly, the prevalence of patients with RBD who are not aware of their dream-enacting behaviours and therefore screen negative for RBD is unknown; identifying those patients would increase the overall prevalence of RBD, although it remains unclear by how much. Moreover, some patients with mild RSWA who were classified as RBD-negative might evolve to clinical RBD. Regardless of these limitations, the results are consistent between the highest quality studies; patients with iRBD who have complaints of dream-enacting behaviours comprise ~1% of the population >60 years of age.

The prevalence of secondary RBD varies depending on the primary disorder. Overall, between 30% and 50% of patients with PD have RBD, compared with >70% of patients with DLB or MSA<sup>7,10</sup>. Up to 50% of patients with narcolepsy have RBD or RSWA<sup>22,23</sup>.

### Risk factors

The strongest risk factors for iRBD are increased age and male sex. iRBD starts in the fifth or sixth decade of life; however, some patients with secondary RBD have reported a younger age at onset, particularly individuals with narcolepsy type 1 and autoimmune or brain disorders<sup>24,25</sup>. The presence of RBD in younger individuals might also be more likely to be related to depression or anxiety, partially owing to antidepressant-associated RBD<sup>24,25</sup>. In individuals <50 years of age, the prevalence of RBD is similar in men and women, whereas above this age, a male preponderance has been reported<sup>24</sup>. However, the effect of sex on prevalence might be related to bias in presentation (for example, men are less likely to sleep alone and might display more violent behaviours than women), as the most recent epidemiological data did not find any sex predilection<sup>15,19,20,26</sup>.

Despite several studies evaluating the risk factors for iRBD, a large set of comprehensive studies by 12 centres of the International RBD Study Group has evaluated the risk factors for PSG-confirmed iRBD<sup>26–29</sup>. Some of the identified risk factors were similar to the risk factors for  $\alpha$ -synucleinopathies; for example, pesticide exposure (and farming) and head injury were more common in patients with iRBD than individuals without RBD (that is, healthy controls and sleep centre controls)<sup>26</sup>. However,

other risk factors differed; smoking was more common in patients with iRBD than individuals without RBD<sup>26</sup>, which is the opposite of the relationship in PD<sup>30</sup>. This finding was also confirmed in the HypnoLaus study<sup>20</sup>, although increased smoking in patients with RBD might be confounded by educational attainment and income<sup>15</sup>. Patients with iRBD have lower levels of educational attainment than sleep centre controls, although the reasons for this observation are unclear. Patients with iRBD have a higher prevalence of ischaemic heart disease (although the reason for this finding is unclear and might be related to smoking and other confounding risk factors), chronic obstructive pulmonary disease (perhaps related to smoking) and depression (perhaps owing to both antidepressant use and/or sleep disturbance related to post-traumatic stress or anxiety)<sup>28</sup>. Larger-scale studies from the general population using only screening tools without PSG confirmation have found largely similar results to the study using individuals with PSG-confirmed iRBD<sup>15–17</sup>.

Patients with iRBD have a higher frequency of a proxy-reported family history of dream enactment behaviours than patients without RBD but not of neurodegenerative disorders (such as  $\alpha$ -synucleinopathies and dementia)<sup>29</sup>. A positive family history of dream

enactment behaviours was demonstrated in 13.8% of patients with iRBD compared with 4.8% of controls<sup>29</sup>; however, the degree to which this finding could be confounded by ascertainment bias (awareness of one's dream enactment might trigger questioning of family members) is uncertain. However, in any case, these data suggest a genetic contribution to iRBD. Indeed, polymorphisms in *GBA* (encoding glucosylceramidase), *LRRK2* (encoding leucine-rich repeat serine/threonine-protein kinase 2) and *SNCA* (encoding  $\alpha$ -synuclein) are genetic risk factors for iRBD<sup>31–33</sup>, although one study failed to demonstrate an association between *LRRK2* mutations and iRBD<sup>34</sup>. These genes have also been implicated in  $\alpha$ -synucleinopathies (all three genes are considered genetic risk factors for PD), and accordingly, at least part of the genetic component of PD is similar to RBD. Whether there are other genetic risk factors for RBD that have not been identified in patients with PD or DLB remains to be determined<sup>32,35</sup>.

### Risk of $\alpha$ -synucleinopathy

RBD is by far the strongest prodromal marker of  $\alpha$ -synucleinopathies. In the first patient cohort, 38% of patients with RBD developed PD or dementia at a mean interval of ~4 years after the diagnosis of RBD and at a mean interval of ~13 years after the onset of RBD<sup>36</sup>, which rose to 81% after a mean interval of ~14 years from the onset of iRBD<sup>37</sup>. This finding was confirmed 10 years later by a study in Barcelona, in which 45% of patients developed either defined neurodegeneration or mild cognitive impairment 5 years after RBD diagnosis and 11 years from the reported onset of RBD<sup>38</sup>; this value increased to 91% >14 years after diagnosis<sup>39</sup> (FIG. 1). Moreover, another study from Barcelona has documented at least one neurodegenerative marker in all remaining patients<sup>40</sup>. The elevated risk of neurodegeneration in patients with iRBD has now been confirmed by many centres<sup>12,41–45</sup>. Data from 12 sleep centres were combined in a study by the International RBD Study Group and demonstrated, on average, an 8% annual risk of neurodegeneration, which was consistent with the largest single-centre studies<sup>46</sup>. Thus, the large majority of patients (at least those >50 years of age) with vPSG-confirmed iRBD have prodromal neurodegeneration.

### Mechanisms/pathophysiology

Multiple studies have been carried out to identify the neuronal systems responsible for the genesis of REM sleep, and have led to the identification of a complex but comprehensive neuronal network (FIG. 2). Such a description opened the path to the identification of the pathophysiology of RBD and RSWA. An animal model of RBD was described 21 years before the formal description of RBD in humans; cats with bilateral electrolytic lesions of the dorsal pontine tegmentum (including noradrenergic neurons in the locus coeruleus (LC) and cholinergic neurons of the laterodorsal tegmental nucleus (LDT)<sup>47,48</sup>) had a state of (paradoxical) REM sleep that was characterized by cortical activation, REMs and violent behaviours<sup>49</sup>. Different types of 'oneiric behaviours' in the cats were characterized by highly coordinated movements that mimicked grooming, fight and flight.

#### Box 1 | Key terms

**Dream mentation.** The mental content associated with dreamlike states.

**Hypersomnia.** Excessive night-time sleep or excessive daytime sleepiness.

**Non-rapid eye movement (NREM) sleep.** The sleep phase that cycles with rapid eye movement (REM) sleep during the nocturnal sleep period. NREM sleep is characterized by electroencephalogram slowing (theta and delta), sleep spindles, K-complexes, muscle tone and diminished or absent dreaming.

**Parasomnias.** Sleep disorders that manifest with recurrent, abnormal behavioural, experiential and autonomic nervous system events during any stage of REM or NREM sleep or during wake–sleep and sleep–wake transitional states.

**REM sleep.** The sleep phase that cycles with NREM during the nocturnal sleep period. REM sleep is characterized by generalized skeletal muscle atonia, activated electroencephalogram, REMs and dreaming.

**Rhythmic movement disorder.** A sleep disorder characterized by repeated complex movements that occur immediately before sleep and/or persist into sleep or emerge during sleep.

**Sexsomnia.** A parasomnia characterized by the patient engaging in sexual acts during sleep, spanning sexual vocalization, masturbation, fondling and attempted or completed intercourse with a bedpartner. There is usually complete amnesia for the sexual behaviour.

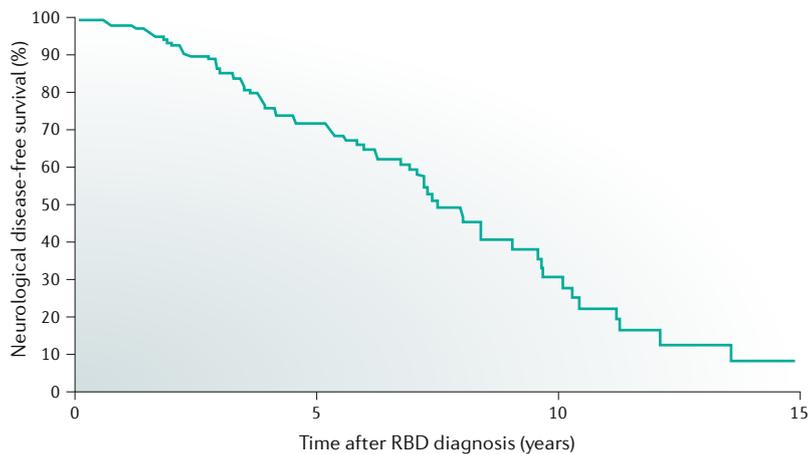
**Slow wave sleep.** A deep phase (1–4 Hz) of non-REM sleep.

**Somnambulism.** Episodes of abnormal sleep-related complex movements and behaviours that derive from incomplete arousals out of NREM sleep (mainly slow wave sleep) and that usually occur during the first third of the major sleep period. Also known as sleepwalking.

**Status dissociatus.** A state of dissociation characterized by the asynchronous occurrence of the various components of the different REM and non-REM sleep and wake states that prevents the recognition of any state of being.

**Synucleinopathy.** A neurodegenerative disease characterized by the accumulation of  $\alpha$ -synuclein. This class of disorders includes Parkinson disease, dementia with Lewy bodies and multiple system atrophy.

**Video polysomnography.** A diagnostic test used to evaluate sleep cycles and any related behaviour. This test includes synchronized video, electroencephalography, electrocardiography, electrooculography and electromyography.



**Fig. 1 | Conversion of RBD to synucleinopathy.** In 174 patients diagnosed with video polysomnography-confirmed rapid eye movement (REM) sleep behaviour disorder (RBD), the estimated risk of a neurodegenerative syndrome was 33.1% 5 years after the diagnosis of idiopathic RBD, 75.7% after 10 years and 90.9% after 14 years. Adapted with permission from Iranzo A, et al. (2014) Neurodegenerative Disorder Risk in Idiopathic REM Sleep Behavior Disorder: Study in 174 Patients. *PLOS ONE* 9(2): e89741. <https://doi.org/10.1371/journal.pone.0089741>, CC-BY-4.0 (REF.<sup>39</sup>).

Thus, lesions within the pontine system (which is responsible for generating muscle atonia during REM sleep) were initially speculated to underlie RBD<sup>50</sup>. However, unit recordings in animals demonstrated the activation and inactivation of LC noradrenergic neurons during waking and REM sleep, respectively, and the activation of LDT cholinergic neurons during both wake and REM sleep<sup>51,52</sup>. Furthermore, selective lesions of either the LDT cholinergic neurons or LC noradrenergic neurons in rats did not induce RSWA, indicating that these areas are not involved in the pathophysiology of RBD<sup>53</sup>.

#### Brainstem nuclei

Neurons in the sublateralodorsal tegmental nucleus (SLD) were subsequently demonstrated to have a role in the generation of muscle atonia in REM sleep. These neurons were identified using *in situ* hybridization of *SLC17A6* (encoding vesicular glutamate transporter 2 (vGLUT2), which has a role in transporting glutamate into synaptic vesicles and is, therefore, required for glutamatergic neurotransmission) and immunohistochemistry for c-Fos (a nuclear protein that is expressed in activated neurons) in rats with REM sleep hypersomnia<sup>53,54</sup>. SLD neurons express vGLUT2, and unit recordings of these neurons confirmed that they are selectively active during REM sleep. In addition, inactivation of vGLUT2 in SLD neurons induces RSWA and RBD and leads to a 30% decrease in REM sleep quantities in rats and mice<sup>55,56</sup>. These data, coupled with the finding of reduced signal intensity in the LC and SLD in patients with RBD using neuromelanin-sensitive imaging<sup>57</sup>, suggested that RBD is induced by neurodegeneration of SLD glutamatergic neurons. However, neuromelanin is contained within noradrenergic LC neurons and is not found within glutamatergic SLD neurons, and patients with RBD do not have a decrease in REM sleep quantities, suggesting that another system downstream of the glutamatergic SLD neurons degenerates in RBD<sup>55,58</sup>.

SLD neurons have direct efferent projections to  $\gamma$ -aminobutyric acid (GABA) and glycine-containing neurons of the ventral medulla, such as those localized in the nucleus raphe magnus (RMg) and the ventral gigantocellular (GiV), alpha gigantocellular (GiA) and lateral paragigantocellular (LPGi) reticular nuclei<sup>55,59</sup>. These neurons directly project to spinal motor neurons<sup>60</sup>, express c-Fos after the induction of REM sleep by bicuculline injection in the SLD in rats<sup>59</sup> or during REM sleep hypersomnia in rats<sup>60</sup>, and are likely to induce the hyperpolarization of motor neurons by GABA and glycine during REM sleep and by this means induce muscle atonia<sup>61,62</sup>. In agreement with this hypothesis, lesions of the ventral medulla in cats induce RSWA<sup>63</sup>, and genetic inactivation in rats with the vesicular inhibitory amino acid transporter (vGAT, which is responsible for transporting GABA and glycine in synaptic vesicles and, therefore, is required for their transmission), specifically in ventral medullary GABAergic and/or glycinergic neurons in rats, led to RSWA and RBD, with a small decrease in REM sleep bout duration but not a significant decrease in REM sleep quantities<sup>64</sup>. Interestingly, RBD has been observed in patients with inflammatory lesions of the ventral medulla<sup>64</sup>, and functional neuroimaging and post-mortem studies demonstrated Lewy bodies and neuronal loss in the same area<sup>65–67</sup>. Accordingly, it seems likely that RBD results from specific neurodegeneration of GABAergic or glycinergic ventral medullary neurons.

#### Other brain regions

Whether other neurons aside from those in the SLD and ventral medulla might trigger RBD is still under study. Structures that activate the SLD glutamatergic neurons might degenerate in RBD, such as the GABAergic neurons of the ventrolateral periaqueductal grey (VLPAG) or the melanin-concentrating hormone hypothalamic neurons (FIG. 2); however, manipulation of the activity of these neurons affects the occurrence of REM sleep rather than muscle atonia, suggesting that these neurons are not involved<sup>68</sup>.

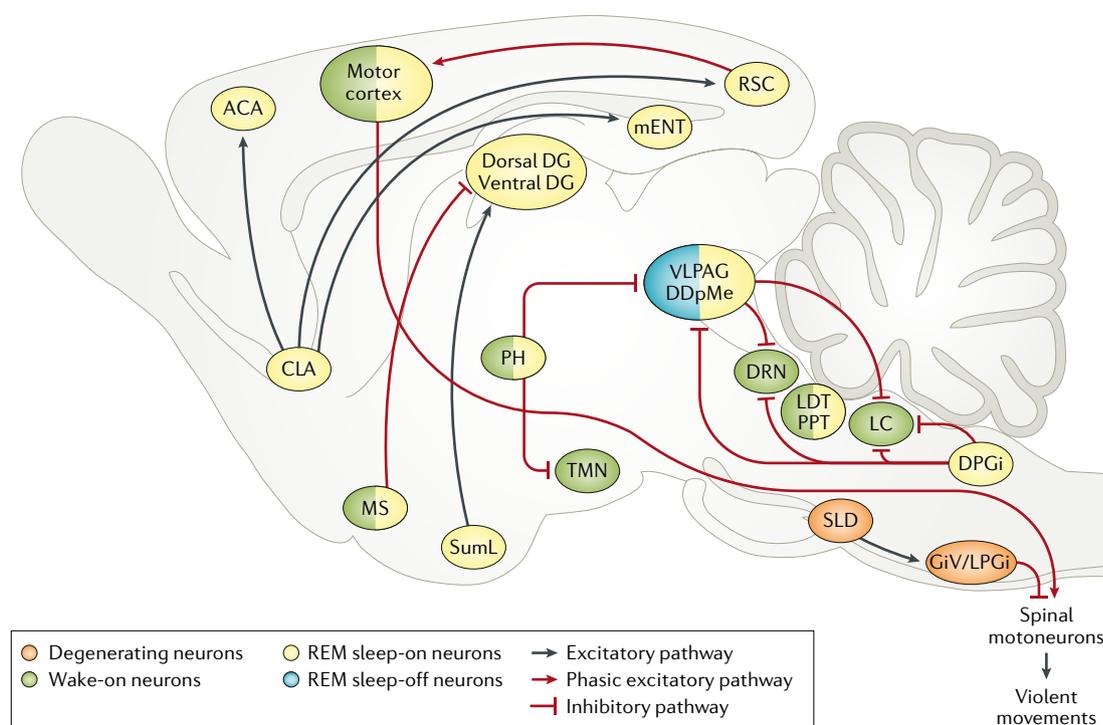
The origin of the violent movements that occur during RBD episodes is also still under study. During REM sleep, in addition to the strong GABAergic and glycinergic inhibition from the GiA, GiV, LPGi and RMg, motor neurons are phasically excited by glutamate<sup>69</sup>. Thus, all types of movements in patients with RBD are likely due to phasic excitation of motor neurons in the absence of tonic inhibition. The precise timing of voluntary movements, rhythmic movements, afferent reflexes and other motor acts is mediated primarily by a combination of excitatory and inhibitory phasic synaptic drive to motor neurons that rely on glutamatergic, GABAergic and glycinergic neurotransmission<sup>70</sup>. Although most GABAergic, glycinergic and glutamatergic premotor neurons are spinal interneurons located in the close vicinity of motor neurons, some premotor neurons are also located in the pontomedullary reticular nuclei and the red nucleus<sup>70</sup> and receive projections from the glutamatergic pyramidal neurons in the motor cortex to induce voluntary movements during waking<sup>70</sup>. We hypothesize that this motor network is also

activated during REM sleep and is responsible for RBD in the absence of GABAergic or glycinergic inhibition. However, additional experiments are needed to confirm the involvement of this network, although some evidence indicates that the motor cortex is involved (see below). For simplification, only the direct pathway from the motor cortex to motor neurons is shown in FIG. 2.

Supporting the role of the motor cortex in RBD, patients can display purposeful, prolonged, elaborate and complex motor behaviours, including singing and long speeches<sup>71</sup>. Furthermore, a pattern of electroencephalographic activation during REM sleep that is similar to the pattern observed during the performance of a voluntary movement during wakefulness was observed in the motor cortex in patients with epilepsy<sup>72</sup>. Accordingly, a common motor pathway of RBD was demonstrated using ictal

single-photon emission computed tomography (SPECT) during RBD episodes in patients with iRBD or RBD with PD, MSA or narcolepsy, and the motor generator responsible for dream-enacting behaviours was localized to the supplementary motor area — bypassing the basal ganglia<sup>73,74</sup>. This finding confirms a major functional role of high-order motor cortical areas in generating movements during dream-enacted behaviour in RBD, where tonic inhibition of motor neurons is no longer efficient<sup>75</sup>.

The cortical limbic system, which has a role in controlling emotion, might also be involved in RBD, as the behaviours observed in patients are violent and the recalled dreams are unpleasant and fearful. Supporting this hypothesis, cortical activation during REM sleep is restricted to a few limbic regions, including the retrosplenial cortex, medial entorhinal cortex, anterior



**Fig. 2 | Neuronal network generating REM sleep and inducing REM sleep without atonia and RBD.** In rats and mice, rapid eye movement (REM) sleep is induced by the activation of REM-on  $\gamma$ -aminobutyric acid (GABA)ergic neurons located in the posterior lateral hypothalamus (PH), the dorsal paragigantocellular reticular nucleus (DPGi) and the ventrolateral periaqueductal grey (VLPAG). These neurons inactivate REM-off GABAergic neurons in the VLPAG and the monoaminergic neurons in the tuberomammillary nucleus (TMN), locus coeruleus (LC) and the dorsal raphe nucleus (DRN). In addition, neurons of the VLPAG and the dorsal deep mesencephalic nuclei (DDpMe) project to the sublateralodorsal tegmental nucleus (SLD, not shown); in healthy individuals, the disinhibited descending SLD REM-on neurons induce muscle atonia via their excitatory projections to glycinergic premotor neurons in the ventral alpha, raphe magnus (RMg) and lateral gigantocellular reticular nuclei (ventral gigantocellular (GiV), alpha gigantocellular (GiA) and lateral paragigantocellular (LPGi) reticular nuclei). The cortical activation during REM sleep is restricted to a few limbic structures, including the retrosplenial cortex (RSC), medial entorhinal cortex (mENT) and anterior cingulate cortex (ACA) and the dentate gyrus (DG). The RSC and ACA are activated by glutamatergic neurons of the claustrum (CLA), whereas DG granule cells are activated by GABAergic and glutamatergic neurons from the lateral supramammillary nucleus (SumL). The projection from GABAergic neurons of the medial septum (MS) induces theta activity in the hippocampus, the electroencephalogram (EEG) signature of REM sleep. Activation of these limbic cortices (in particular the RSC) produces dream scenarios and activates the motor cortex, which in turn activates spinal motor neurons. However, in healthy individuals, motor neuronal activation is overridden by inhibition from the GiV, GiA, RMg and LPGi. In patients with REM sleep behaviour disorder (RBD), excitation induces violent movements. In patients with RBD, glutamatergic neurons in the SLD and/or glycinergic or GABAergic neurons from the GiV, GiA, RMg and LPGi degenerate, thereby removing the inhibition from spinal motor neurons and preventing the induction of muscle atonia. LDT, laterodorsal tegmental nucleus; PPT, pedunculopontine tegmental nucleus.

**Box 2 | ICSD-3 diagnostic criteria for RBD**

To obtain a diagnosis of rapid eye movement (REM) sleep behaviour disorder (RBD), the following criteria must all be met.

- Repeated episodes of sleep-related vocalization and/or complex motor behaviours.
- These behaviours are documented by polysomnography to occur during REM sleep or, based on a clinical history of dream enactment, are presumed to occur during REM sleep.
- Polysomnography demonstrates REM sleep without atonia.
- The disturbance is not better explained by another sleep disorder, mental disorder, medication or substance abuse.

ICSD-3, International Classification of Sleep Disorders, Third Edition.

cingulate cortex and the dentate gyrus. One possibility is that the activation of these structures produces dream scenarios and excites glutamatergic pyramidal neurons in the motor cortex, which in turn excites spinal motor neurons (FIG. 2). However, in newborn rats, glutamatergic neurons in the reticular formation and the red nucleus and not the motor cortex are responsible for activating motor neurons during REM sleep<sup>76,77</sup>. This might be because the cortex is not yet functional at early stages of development. Another possibility is that movements that occur during RBD are due to the activation of both brainstem generators and the motor cortex.

**Secondary RBD**

As previously mentioned, patients with narcolepsy type 1 also often present with RSWA, excessive twitching in REM sleep and clinical episodes of RBD<sup>23,78–80</sup>. Narcolepsy type 1 is caused by the loss of hypocretin (also known as orexin) neurons in the hypothalamus, leading to hypocretin deficiency. Hypocretin neurons are fairly inactive in quiet waking and have moderate and approximately equal levels of activity during grooming and eating and maximal activity during exploratory behaviour. Hypocretin cells are silent in NREM sleep and tonic periods of REM sleep, with occasional burst discharge in phasic REM<sup>81</sup>. Thus, hypocretin neurons inhibit REM sleep and increase, rather than decrease, muscle tone<sup>81</sup>. In addition, no lesion has been observed in patients with narcolepsy in the brainstem structures responsible for muscle atonia. Thus, the occurrence of RBD in patients with narcolepsy is difficult to explain, and no consensus is available for the mechanisms involved.

On the basis of the Braak hypothesis of pathological staging of the spread of Lewy body pathology in PD, neurodegeneration might start in the enteric nervous system and be transmitted by a trans-synaptic propagation of misfolded  $\alpha$ -synuclein protein in the medulla and the pons, inducing RSWA and RBD<sup>82–84</sup>. The temporal sequence of evolution with Lewy bodies and associated neurodegeneration in either the substantia nigra or the cortex might explain the motor symptoms of PD and the cognitive symptoms of DLB, respectively. However, not all patients with DLB or PD present first with RBD, and

RBD commonly occurs in patients with DLB or PD after the onset of motor or cognitive symptoms. Altogether, such findings suggest a complex and highly heterogeneous location and progression of the pathological process across patients.

**Diagnosis, screening and prevention**

The diagnosis of RBD is based on the International Classification of Sleep Disorders, Third Edition (ICSD-3), which includes a history of repeated dream enactment with complex motor behaviours, as determined during clinical history taking or observed during vPSG. The core objective finding necessary for the RBD diagnosis is loss of skeletal muscle atonia during REM sleep<sup>1</sup> (BOX 2). The diagnosis of iRBD is made in the absence of other conditions that cause symptomatic or secondary RBD (BOX 3).

**Clinical diagnosis**

Dream enactment behaviours observed in patients with RBD can range from excessive body and limb jerking to complex, seemingly goal-directed behaviour, such as gesturing, punching, kicking, sitting up, leaping from bed and (rarely) running<sup>1</sup>. A large spectrum of non-violent behaviours, such as laughing, singing, dancing and smoking a fictive cigarette, has been observed in patients with RBD<sup>85</sup>. Dream mentation and behaviour are often those of self-defence or defence of others against attacks by unfamiliar people and animals. Indeed, most patients describe the dream content as nightmares, with people and animals attacking them or their loved ones, and such content is unpleasant. Aggressive, action-filled dream mentation and violent behaviours are frequently reported in patients with iRBD<sup>86–88</sup> but are less common in patients with RBD associated with PD<sup>89</sup>. Violent behaviours during sleep can produce injuries such as bruises, lacerations, fractures, broken bones or subdural haematomas and can potentially be lethal behaviours, including defenestration and diving from bed<sup>90</sup>. Indeed, injuries to the self and/or bedpartners are well documented in patients and are the main reason for patients with RBD to seek clinical consultation<sup>1</sup>. Some patients or their bedpartners report that the screams and swearing awaken themselves or others, including guests in the home or neighbours. This matter can be particularly embarrassing when patients sleep outside of the usual home environment. Patients usually have no history of aggressive or violent behaviour during the daytime, and by contrast, patients with iRBD are often described as passive or apathic during the daytime.

Clinically, eliciting a clear history of dream enactment behaviour is often difficult, as almost half of patients might not be aware of the behaviours, remember the associated dream content or have cognitive impairment that precludes the report of a positive history. Thus, obtaining information from bedpartners is important. A typical history of dream enactment behaviours can provide a probable RBD diagnosis that needs further confirmation using vPSG for definitive diagnosis. Using clinical criteria only for the diagnosis of RBD has several limitations, as RBD can be difficult to distinguish

from other motor behaviours that occur during sleep, such as NREM sleep parasomnias, nocturnal seizures or movements associated with resumption of breathing in patients with OSAS.

### Sleep laboratory diagnosis

The definitive diagnosis of RBD requires a vPSG assessment that documents the presence of electromyography (EMG) abnormalities during REM sleep as defined by the ICSD-3 (BOX 2). Features essential for the RBD diagnosis include an excess of muscle tone and/or an excess of phasic EMG twitch activity during REM sleep<sup>1</sup>. RSWA has a high night-to-night stability<sup>91</sup>; accordingly, a single night of vPSG is usually adequate for the diagnosis of RBD, provided that sufficient REM sleep is present during the recording.

One of the difficulties in scoring PSG recordings of patients with RBD is identifying REM sleep, as the presence of mentalis muscle atonia is an essential feature of normal REM sleep. Accordingly, a validated and universally accepted visual analysis method for scoring REM sleep in patients with RBD was developed based on electroencephalography (EEG) and electroculography findings only<sup>92,93</sup>. Initially, abnormal muscle activity during REM sleep was quantified only in the mentalis muscle<sup>92,93</sup>, which is routinely recorded as part of a standard PSG. Subsequently, the Sleep Innsbruck Barcelona (SINBAR) group used EMG to assess several upper limb and lower limb muscles in

individuals with RBD or controls and demonstrated excessive phasic activity in several muscles of the limbs, especially in the flexor digitorum superficialis (FDS) muscles (FIG. 3). The SINBAR group recommended the use of a vPSG montage including EMG of the mentalis and FDS muscles for RBD diagnosis<sup>5</sup>. Tonic and phasic motor activity in these muscles can be quantified separately, but the quantification of tonic, phasic or both types of activity is recommended for diagnosis in the mentalis muscle and the quantification of phasic activity is recommended in the FDS (no tonic activity occurs in FDS during sleep and waking; BOX 4). For the mentalis and FDS muscles, a cut-off value of 32% best discriminated individuals with iRBD or RBD associated with PD from controls<sup>5</sup>. However, multicentre controlled studies are needed to further validate this method for the diagnosis of RBD. Scoring tonic and phasic activities separately might provide additional and important information, as they most likely rely on different pathophysiology processes and have different responses to melatonin treatment<sup>94</sup>.

Using visual analysis to identify motor activities in the chin and arm muscles on EMG traces is time-consuming, and interscorer reliability might vary among investigators with different expertise or working at different sites; thus, automatic analysis methods have been developed<sup>95–97</sup>. These automatic scoring methods were tested against the gold-standard visual analysis and were as effective and specific for the differentiation of iRBD or RBD associated with neurodegenerative diseases from controls<sup>97–102</sup>. However, these automated techniques remain to be implemented in all sleep laboratories for use in routine clinical practice.

Interestingly, individuals can show RSWA without any history or vPSG-recorded behavioural manifestations of RBD<sup>103</sup>. RSWA without abnormal behaviour is more frequent among elderly individuals and patients with PD<sup>6,10</sup> and might represent an early stage of RBD, and accordingly, is a risk factor for neurodegenerative diseases. In one study of 14 individuals with RSWA, one progressed to RBD, and ten were positive for at least one biomarker of neurodegeneration after a mean follow-up of 8.6 years<sup>104</sup>. Conversely, RBD events can be observed without the presence of RSWA on PSG recordings. This phenomenon occurs more frequently in patients with *de novo* PD than in healthy controls and might be an early sign of neurodegeneration and precede RBD<sup>105</sup>.

In contrast to the excessive motor activities observed during REM sleep in patients with RBD, all other features of REM sleep, including REM latency, REM percentage, REM density, number of REM periods and REM to NREM cycling, are usually preserved<sup>10,93</sup>. However, periodic leg movements in sleep (PLMS) are present in up to 75% of patients with RBD<sup>106</sup>. PLMS in patients with RBD show major differences from those observed in patients with restless legs syndrome (also known as Willis–Ekbom disease) or in the general elderly population<sup>107</sup>. In individuals with RBD, PLMS are not truly periodic, as they occur preferentially during REM sleep<sup>106,107</sup>, and are less likely to be associated with microarousals or autonomic activation<sup>106</sup>.

### Box 3 | Secondary RBD

Symptomatic rapid eye movement (REM) sleep behaviour disorder (RBD) (also known as secondary RBD) might be related to various neurological disorders, such as neurodegenerative diseases (mostly  $\alpha$ -synucleinopathies), narcolepsy type 1, Guillain-Barré syndrome, spinocerebellar ataxia type 3, brainstem tumours, stroke, multiple sclerosis or paraneoplastic or autoimmune disorders. Symptomatic RBD can also be induced acutely by withdrawal from alcohol and sedative agents or by medication intake (such as antidepressants)<sup>7,8,126</sup>.

RBD in patients with narcolepsy has a different phenotype than idiopathic RBD (iRBD) and is characterized by an absence of sex predominance, earlier age at onset, lower frequency of movements and fewer occurrences of complex and violent behaviours<sup>79,80</sup>. RBD is strongly associated with narcolepsy type 1 (also known as narcolepsy with cataplexy) and hypocretin deficiency<sup>78,204</sup>. RBD might be triggered or aggravated by the treatment of cataplexy (for example, with antidepressants) but can be improved with sodium oxybate therapy<sup>205,206</sup>. RBD in children is also often associated with narcolepsy type 1 (REF.<sup>207</sup>) and might be an initial symptom of narcolepsy type 1 (REF.<sup>208</sup>).

As previously mentioned, RBD and REM sleep without atonia (RSWA) are strongly associated with neurodegenerative diseases, especially  $\alpha$ -synucleinopathies<sup>7–10</sup>. Using video polysomnography, RBD is found in ~50% of patients with Parkinson disease<sup>209</sup>, >80% of patients with dementia with Lewy bodies and up to 90% of patients with multiple system atrophy<sup>210</sup>.

RBD might also occur due to the long-term use of various medications, particularly antidepressants. Numerous studies have demonstrated dream enactment behaviour and/or RSWA with use of antidepressants<sup>20,24,25,28,134,211,212</sup>, mainly serotonin reuptake and serotonin and noradrenaline reuptake inhibitors<sup>211</sup>. Frequent antidepressant use was reported in association with early-onset RBD, an effect that was larger than the association with depression alone<sup>213</sup>. In a prospective study<sup>179</sup>, patients with RBD using antidepressants during a 4–5-year follow-up period had a lower risk of neurodegenerative disease than patients without antidepressant use, although markers of prodromal neurodegeneration were present at baseline assessment<sup>179</sup>. One explanation is that antidepressants might unmask latent RBD with pre-existing RSWA as a marker of  $\alpha$ -synucleinopathy. However, future longitudinal studies for this subpopulation are currently required.

### Differential diagnosis

Overnight vPSG should rule out other sleep conditions with RBD-like features, such as OSAS<sup>108</sup>, PLMS<sup>109</sup>, NREM parasomnias (such as sleepwalking, sleep terrors and confusional arousals<sup>11</sup>, nightmares and sleep-related seizures (mainly sleep-related hypermotor epilepsy)<sup>1,110</sup>). These diagnoses are screened for during the clinical evaluation but are more formally ruled out during night-time vPSG.

As RBD is more prevalent in men >50 years of age, a high percentage of patients with RBD have sleep-disordered breathing (for example OSAS) and have frequent respiratory events during REM sleep. In some patients with OSAS, respiratory effort and/or resumption of breathing are associated with motor events and vocalization, particularly during REM sleep, which can be misinterpreted as RBD<sup>111</sup>. In these cases, restudying the patient after the treatment of OSAS before making a reliable diagnosis of RBD is recommended.

Other mimics of RBD include sleepwalking and night terrors. In contrast to RBD, these conditions are characterized by complex behaviours that are usually initiated during arousals from slow wave sleep (the deep phase of NREM sleep)<sup>112,113</sup>. Episodes of sleepwalking or night terrors usually start in childhood and occur during the first part of the night and even during the first hour of sleep. In contrast to RBD, patients with sleepwalking or

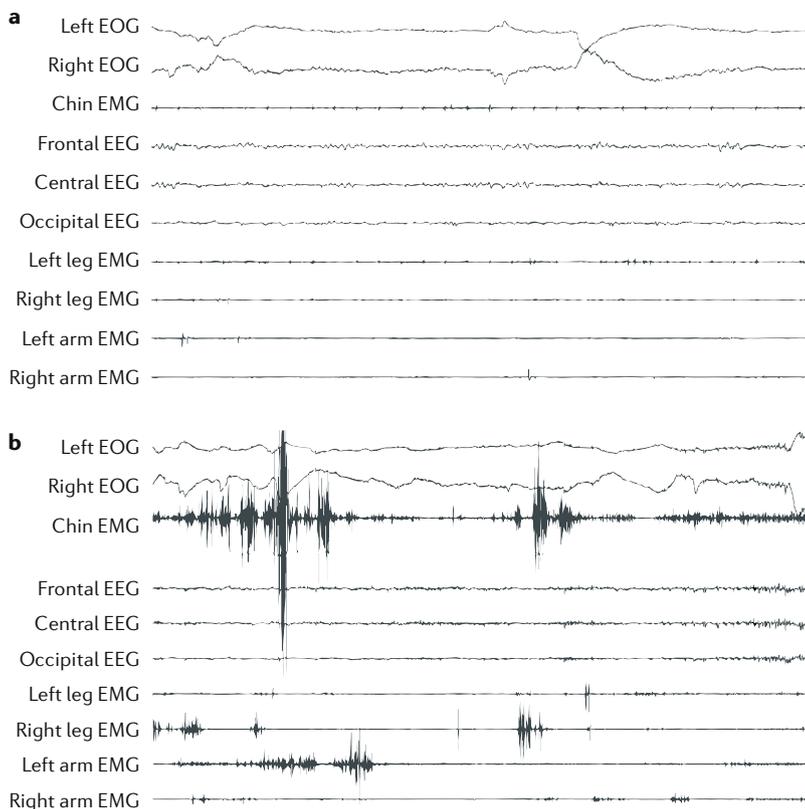
night terrors are generally confused upon arousal and do not remember elaborate dream content (although fragmentary dreams are not uncommon in adults with NREM parasomnias<sup>11,114</sup>). In addition, in contrast to sleepwalkers, patients with RBD very rarely walk or leave the bedroom during nocturnal events. However, one condition called parasomnia overlap disorder is characterized by both RBD and either a disorder of arousal, sleep-related eating disorder, sexsomnia or rhythmic movement disorder and is considered a clinical subtype of RBD<sup>1</sup>. Parasomnia overlap disorder often begins during childhood or adolescence and can be idiopathic or secondary to neurological disorders (such as narcolepsy, brain trauma, brain tumour or multiple sclerosis) or to substance abuse or withdrawal states<sup>1</sup>. Parasomnia overlap disorder is a rare condition that requires a careful diagnosis based on both clinical history and vPSG results.

Status dissociatus is also considered a subtype of RBD<sup>1</sup> and is due to the intrusion of features typical of a different sleep–wake state into an ongoing sleep–wake state<sup>115</sup>. The expression of state dissociation is characterized by the asynchronous occurrence of the various components of the different states that prevents the recognition of any state of being. Status dissociatus can manifest clinically as dream-related behaviours that mimic RBD with a mix of different stages (that is, wake, REM and NREM sleep) into an ongoing state of being unidentifiable using conventional sleep scoring<sup>115</sup>. An underlying neurological condition such as narcolepsy type 1 and autoimmune encephalopathies is often associated with status dissociatus.

Dream enactment can also be associated with post-traumatic stress disorder. However, studies evaluating this association are limited, and therefore whether this counts as true RBD related to RSWA or is reflective of a general sleep disruption, with nightmares of such severity to overcome otherwise normal REM sleep muscle paralysis, is unknown and requires further study<sup>116</sup>.

### Screening questionnaires

Several validated questionnaires have been developed to help screen or diagnose patients with probable RBD when PSG is not accessible or for use in large-scale epidemiological studies, despite the limitations of this technique<sup>117</sup> (see Epidemiology). Despite the availability and validation of these questionnaires, critical appraisal of the results obtained using these tools is required for several reasons. For example, in practice, most patients who have completed these questionnaires are already diagnosed with RBD, some patients are unable to complete the questionnaires, and some patients live alone and are not aware of their parasomnias. Moreover, symptomatic RBD is relatively uncommon; thus, even with a questionnaire of high specificity, the majority of patients who screen positive will not have true RBD. For example, assuming an optimal sensitivity and specificity of 90%, only 10% of patients screening positive will actually have RBD. Accordingly, despite the availability of these tools, formal diagnosis of RBD requires both clinical assessment and PSG, and the sole use of these tools should not be relied on for the diagnosis of RBD.



**Fig. 3 | PSG recording of REM sleep. a** | Polysomnography (PSG) recording from a control individual. **b** | PSG recording from a patient with rapid eye movement (REM) sleep behaviour disorder (RBD). Note the electromyogram (EMG) activity in the chin EMG and left arm EMG. The leg EMG recording was obtained from the left and right anterior tibialis muscles, and the arm EMG recording was obtained from the left and right flexor digitorum superficialis muscles. EEG, electroencephalogram; EOG, electrooculogram.

**Box 4 | Phasic, tonic and any EMG activity during REM sleep<sup>a</sup>**

**Phasic activity:** a short burst of electromyography (EMG) activity lasting 0.1–5.0 s that is more than twice as high as the background EMG amplitude. Can be measured in 3 s mini-epochs or 30 s epochs.

**Tonic activity:** EMG activity increased by at least a factor of two or four compared with baseline in more than half of the epoch. Can be measured in 3 s mini-epochs or 30 s epochs.

**Any activity:** either phasic or tonic EMG activity. In addition, tonic and phasic muscle activity lasting between 5 and 15 s can be scored and can be measured in 3 s mini-epochs or 30 s epochs. Cut-off values for any EMG-increased activities during REM sleep were as follows: 18% for the chin 3 s mini-epochs, 32% for the combination of chin and flexor digitorum superficialis based on entire rapid eye movement (REM) sleep for the 3 s mini-epochs and 27% for 30 s epochs as recommended by the International Classification of Sleep Disorders, Third Edition (ICSD-3)<sup>1,2</sup>.

<sup>a</sup>According to the Sleep Innsbruck Barcelona (SINBAR) criteria.

The RBD Screening Questionnaire (RBDSQ)<sup>118</sup> is the most widely used tool over the past decade and includes 13 yes-or-no questions regarding the presence of movements and dream-enacting behaviours during sleep. The RBDSQ has high sensitivity (91%) and acceptable specificity (77%), although the specificity was the lowest specificity among RBD questionnaires reported in one meta-analysis<sup>119</sup>. Moreover, the RBDSQ has poor sensitivity and specificity in individuals with PD<sup>120</sup>. The Hong Kong Questionnaire (RBD-HK) includes 12 questions with two frequency assessments for each question (lifetime and 1-year frequency)<sup>121</sup> and has a sensitivity of 82% and a specificity of 87%<sup>121</sup>. A five-item questionnaire called the Innsbruck RBD inventory has also been developed<sup>122</sup> and has a high sensitivity (91%) and specificity (86%), with the correct diagnosis of patients with RBD in >85% of instances.

As RBD symptoms can be described relatively simply in individuals aware of the symptoms, two single-question tools have been developed accordingly. The RBD Single Question Screen (RBD1Q) consists of a single yes-or-no question of “Have you ever been told, or suspected yourself, that you seem to ‘act out your dreams’ while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?”<sup>123</sup>. The RBD1Q was validated in a multicentre case–control study in which all participants underwent PSG to formally diagnose RBD and demonstrated a sensitivity of 93.8% and a specificity of 87.2% for RBD diagnosis<sup>123</sup>. The specificity remained high in mimics of RBD, such as OSAS (although patients with NREM parasomnia were not included). Similar results were obtained after the exclusion of participants using antidepressants or patients treated with clonazepam and/or melatonin. Another tool, the Mayo Sleep Questionnaire (MSQ), is a 16-question tool with one question validated for screening for RBD in older patients with or without cognitive impairment<sup>124</sup>. The MSQ includes follow-up questions for individuals who screen positive that assess duration, injury and relationship to dream content. In a validation study, the MSQ had a sensitivity of 98% and specificity of 74%. Finally, a single summary question from the Innsbruck questionnaire found moderate sensitivity (74%) but

high specificity (93%) for RBD, suggesting potential as a screening tool<sup>122</sup>.

**Management**

The fact that patients often endure RBD for many years before seeking diagnosis and treatment and that some patients never will seek diagnosis is striking. Most patients with de novo PD with comorbid RBD do not seek medical advice for RBD features before the diagnosis of PD. Some patients with RBD are not overly bothered by the features of the disorder, and some are not aware of their dream enactment behaviours and/or do not recall their dreams. However, those with clinically meaningful RBD do require intervention; the primary goals of managing RBD are to minimize dream enactment behaviours, associated injuries and unpleasant dreams, and to improve bedpartner QOL<sup>6,8,10,125–129</sup>.

**Education or counselling**

After diagnosis of RBD, all patients and their bedpartners should be counselled on simple steps to minimize injury<sup>8,10,125,126</sup>. These steps include moving sharp and rigid objects away from the bed and placing pillows or other soft items between the patient and structures (such as the headboard or nightstand). For patients with the potential for falling or jumping out of bed, placing a mattress on the floor adjacent to the bed and/or using padded bedside rails are useful. Although these safety measures reduce the chance of injury to the patient and their bedpartners, they do not tend to have a major effect on vocalizations or nightmares. Patients with RBD are often ingenious in finding measures to reduce injury, and readers might be interested in reviewing excellent and entertaining sources on the various means with which this ingenuity is exemplified<sup>10,130</sup>. Patients should be advised to avoid alcohol intake, as this can trigger or aggravate RBD.

**Non-pharmacological therapies**

Hypnotherapy has demonstrated some efficacy in the treatment of parasomnias, including RBD; however, it could not be recommended as it is not an evidence-based treatment<sup>131</sup>. Incidentally, a pressurized bed alarm customized with a familiar voice to deliver a calming message during vigorous dream enactment behaviour was shown to be effective in one small series, but this tool remains rarely used in clinical practice<sup>132</sup>. Comorbid OSAS should be treated with nasal continuous positive airway pressure to improve RBD-like behaviours and to allow clonazepam prescription (which can worsen OSAS symptoms; see Pharmacotherapies).

**Pharmacotherapies**

When safety measures have not been sufficiently effective and the non-pharmacological modes of management (if attempted) have also been inadequate, pharmacotherapy often remains warranted in iRBD. Before starting pharmacotherapy, clinicians should first consider discontinuing any agents that have been implicated in precipitating or aggravating RBD. However, this topic is controversial, and whether such agents are ‘causing’ or ‘unmasking’ RBD in individuals who might

already have altered REM sleep (such as an early and otherwise clinically silent  $\alpha$ -synucleinopathy) is debated. Regardless, discontinuing the most well-known RBD aggravators is prudent, including selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs) and tricyclic antidepressants such as clomipramine<sup>24,25,133,134</sup>. In patients with depression who require pharmacotherapy, other forms of antidepressants that have not been associated with increased RBD features should be considered, such as bupropion. Lipophilic  $\beta$ -blockers (such as bisoprolol) have also been described to induce RBD<sup>135</sup>, which is intriguing because these medications interact with melatonin metabolism.

No large double-blind placebo-controlled trials focusing on RBD symptomatology have been carried out. However, ample clinical experience supporting the use of clonazepam and melatonin is available, and clinicians should consider one or both drugs if pharmacotherapy is deemed necessary<sup>125,127,136–139</sup>. However, neither drug is approved by the US FDA or the European Medicines Agency (EMA) for this indication. Most patients are managed effectively and have few or no nightmares, vocalizations or dream enactment behaviours for years or decades with nightly administration of low-dose clonazepam<sup>136</sup>, but the abrupt withdrawal of clonazepam can result in RBD rebound. Patients developing tolerance to and dependence on clonazepam with escalating doses over time are very rare. Why clonazepam is effective for the treatment of RBD whereas other benzodiazepine GABA<sub>A</sub> receptor agonists (such as diazepam or lorazepam) are not effective is unknown. Adverse effects of clonazepam are common, are often dose-related and include somnolence, enuresis, gait impairment, altered cognition and dizziness<sup>136,137</sup>.

Melatonin administration at night is also effective for the treatment of RBD<sup>94,140–142</sup>. One approach to melatonin treatment (which can be purchased over the counter in many countries) is to start at a low dose for 5–7 days, increasing the dose every 5–7 days to a maximum dose of 12 mg/night. Melatonin has very few adverse effects, although rare adverse effects can include headache and somnolence. Little or no information is available regarding the effect of long-acting forms of melatonin and melatonin agonists in patients with RBD.

No studies have directly compared the effects of clonazepam and melatonin on RBD symptoms. Clonazepam taken at bedtime is the drug of choice in individuals without substantial cognitive impairment, gait impairment or untreated OSAS<sup>138,142</sup>. Some clinicians use melatonin as a first-line therapy for many patients, particularly those with cognitive impairment, parkinsonism or untreated OSAS, given the better safety profile of melatonin compared with clonazepam. If melatonin is not effective, then either clonazepam can be added or melatonin can be abruptly discontinued and clonazepam commenced. Indeed, in some patients, combination therapy using melatonin plus clonazepam is more effective than using either drug alone<sup>139,141</sup>. The bottom line is that the vast majority of patients with RBD are effectively treated using a combination of education and counselling and melatonin and/or clonazepam.

Why clonazepam and melatonin improve RBD is not clear. One study suggested that clonazepam reduces phasic activity during REM sleep<sup>92</sup>, but RSWA and mildly abnormal behaviours might still be present in those who undergo PSG. Melatonin reduces tonic activity during REM sleep and decreases the number of stage shifts in REM sleep, suggesting that it has a more direct mode of action to restore REM sleep modulation<sup>140</sup>. Other hypotheses posit that melatonin potentiates the action of GABA on GABA<sub>A</sub> receptors on the spinal motor neurons that leads to reduced muscle atonia in RBD or that melatonin decreases calmodulin, which affects cytoskeletal structure and the nicotinic acetylcholine receptors in skeletal muscle cells<sup>94</sup>.

Some individuals have continued RBD despite education or counselling and clonazepam plus melatonin use. For some of these individuals, RBD is secondary to antidepressant use, and these medications cannot be changed or discontinued. No consensus of optimal third-line therapies is available, and a trial and error approach must be used after considering experiences with other agents and particular patient circumstances. Other drugs that have been reported to improve RBD in single case reports or small series include dopamine agonists (pramipexole<sup>143</sup> and rotigotine<sup>144</sup>), cholinesterase inhibitors (donepezil<sup>145</sup> and rivastigmine<sup>146,147</sup>), anticonvulsants (carbamazepine<sup>148</sup>, benzodiazepines (triazolam<sup>7</sup>) and others<sup>125</sup>), antipsychotics (clozapine<sup>7</sup> and quetiapine<sup>6</sup>), levodopa<sup>139</sup>, sodium oxybate<sup>149</sup> and ramelteon<sup>150</sup>. A reasonable approach is to consider selecting an agent to potentially improve RBD and another problematic clinical issue. For example, quetiapine or clozapine might be reasonable choices in a patient with DLB and severe RBD refractory to melatonin and clonazepam who also has problematic visual hallucinations. Some patients with RBD and comorbid OSAS report that continuous positive airway pressure improves but does not resolve their symptoms of RBD<sup>9</sup>.

### Quality of life

RBD can be associated with a major QOL burden. Repeated injuries to the self and to the bedpartner are common, including potentially lethal behaviours<sup>7,9,90,126</sup> that have forensic implications<sup>151,152</sup>. Patients with RBD might have marital burdens<sup>153–155</sup> and single patients might avoid meeting potential partners owing to embarrassment or fear of causing injury. Patients with PD with comorbid RBD have worse symptoms and QOL than patients with PD without RBD<sup>156–158</sup>.

### Risk of injury

As previously mentioned, chronic RBD typically involves middle-aged or older men and manifests as aggressive dream-enacting behaviours that cause repeated injury to themselves and/or their bedpartners<sup>7,9,126</sup>. Reported injuries due to sleep violence and jumping out of bed include ecchymoses, subdural haematomas, lacerations (of, for example, arteries, nerves or tendons), fractures (including fractures of high cervical vertebrae, such as C2), dislocations, abrasions or rug burns, tooth chipping and hair pulling<sup>7,9,90,126,159–161</sup>. Potentially lethal behaviours include

choking or headlock, diving from bed, defenestration or near-defenestration and punching a pregnant bedpartner<sup>90</sup>. Not surprisingly, violent RBD behaviours carry an increased forensic risk, including parasomnia pseudo-suicide and inadvertent homicide<sup>151,152</sup>.

### **Bedpartner or spousal QOL**

Although some patients might be unaware of their abnormal behaviours at night, their bedpartners are aware of these behaviours and might be worried about the risk of injuries to their spouse and themselves, which can cause considerable negative psychosocial effects on patients and their partners<sup>155</sup>. In one cross-sectional study, almost all spouses of patients with iRBD reported disturbances from the nocturnal RBD behaviours of their bedpartners, and 62.5% of spouses reported a history of injury during sleep<sup>155</sup>. Spouses of patients with iRBD or those with OSAS reported a comparably high frequency of insomnia, anxiety and depressive symptoms<sup>155</sup>. However, spouses of patients with iRBD reported more impaired QOL and adverse effects on the marital relationship from RBD behaviours than spouses of patients with OSAS. The risk of injury and fragmented sleep in the bedpartner can lead to the bedpartner sleeping in a separate bedroom, resulting in diminished intimacy between partners. Individuals with RBD who are in a committed relationship can have concerns that they have unconscious resentment or anger towards the partner, as reflected by their aggressive sleep behaviours, when in fact this parasomnia is almost always due to an alteration in REM sleep physiology. The bedpartner might also have the same concerns about the individual with iRBD. Successful treatment of RBD often results in a more pleasant and satisfying relationship with the partner. As most patients with RBD have been married for decades, spouses know that aggressive behaviours do not reflect the patient's personality during wakefulness, which explains why divorce or marital discord due to RBD is rare<sup>153,154,162</sup>.

### **Patients with comorbid RBD**

QOL is negatively affected in patients with early PD and probable RBD compared with patients with early PD without probable RBD<sup>156</sup>. A case-control study demonstrated a higher rate of early morning dystonia, distressing hallucinations and higher scores on the Unified Parkinson Disease Rating Scale (UPDRS)-IV, Parkinson Disease Sleep Scale-2 total score and subscores (reflecting insomnia and distressing dreams) and the Parkinson Disease Questionnaire (PDQ-39) domain scores for cognition and emotional well-being in patients with PD and probable RBD than in patients with PD without probable RBD<sup>157</sup>. Another study confirmed the large effect of vPSG-confirmed RBD on multiple non-motor symptoms in patients with PD (especially on depression and fatigue)<sup>158</sup>. In addition, individuals with PD and RBD are more severely impaired across motor domains than patients without RBD. The increased motor impairment includes axial symptoms (such as postural instability with falls), freezing of gait and dysarthria<sup>163</sup>. In addition, RBD is associated with a worse prognosis in individuals with PD or DLB. In individuals with PD, RBD is associated

with a subtype with early dementia and faster motor and global progression<sup>164</sup>. In patients with DLB, RBD is associated with a shorter duration of dementia, earlier onset of parkinsonism, earlier onset of visual hallucinations and mortality<sup>163,165</sup>.

Given the frequent comorbidity of RBD with neurological disorders, QOL impairment reflects the effects of both RBD and comorbid disorders. Although, as previously mentioned, RBD is strongly associated with narcolepsy type 1 (REF<sup>78</sup>), no studies have assessed the specific effect of RBD on QOL in patients with narcolepsy type 1.

### **Outlook**

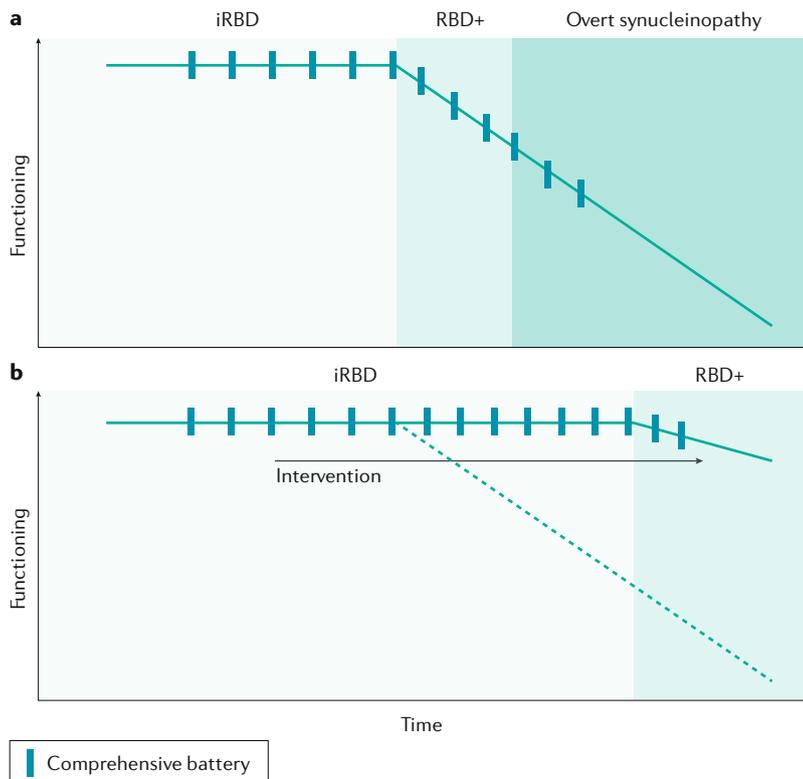
#### **Conversion to overt $\alpha$ -synucleinopathy**

The most important implication of RBD is its association with neurological disease, particularly neurodegenerative  $\alpha$ -synucleinopathies. PD, MSA and DLB represented up to 98% of all  $\alpha$ -synucleinopathies (referred to as overt  $\alpha$ -synucleinopathies, in contrast to RBD, which can be considered a prodromal  $\alpha$ -synucleinopathy in this context) associated with RBD in a large neuropathological study<sup>166</sup>. This finding makes the documentation of RBD one of the most effective diagnostic tests in neurology, particularly in diagnosing DLB. In the latest DLB diagnostic criteria, documenting RBD on the basis of history and vPSG in a patient with dementia, particularly when associated with another core feature of DLB, is sufficient to diagnose probable DLB<sup>167</sup>.

Although other prodromal markers of PD are known, they have a lower predictive power than the presence of iRBD; for example, in the Movement Disorders Society Prodromal Parkinson criteria, PSG-proven RBD has a positive likelihood ratio for PD of 130 compared with a ratio of 2–4 for other prodromal markers, such as depression, constipation and olfaction<sup>168</sup>. Recognition of the unique predictive value of iRBD for  $\alpha$ -synucleinopathy has led to numerous studies examining other prodromal disease markers. Accordingly, the recognition of biomarkers associated with the risk of neurodegenerative disease is key to identifying patients with iRBD who have a higher risk of phenoconversion. Moreover, biomarkers can be assessed (albeit imperfectly) in individuals without RBD to test whether these markers predict PD or other  $\alpha$ -synucleinopathies and how they change during the earliest disease stages. Knowledge gained from biomarker studies could be incorporated into clinical trials of neuroprotective compounds for PD and DLB (for example, by aiding in patient stratification) and could identify potential candidates for neuroprotective therapy when available. In addition, testing for other markers can help the individual counselling of patients, which can aid in life planning or help physicians predict imminent neurodegenerative signs in these patients.

#### **Clinical biomarkers for risk of overt $\alpha$ -synucleinopathies.**

Several easily measured clinical markers have been shown to predict the risk of conversion to  $\alpha$ -synucleinopathy in patients with iRBD. For example, olfactory loss is associated with a 2–3-fold increased risk of phenoconversion to PD and DLB<sup>13,169,170</sup>; patients with normal olfaction at the time of RBD diagnosis often still lose this sense before phenoconversion. Impaired colour vision



**Fig. 4 | Schematic framework of the natural history effects of neuroprotective therapies in iRBD.** **a** | As previously mentioned, many patients with idiopathic rapid eye movement (REM) sleep behaviour disorder (iRBD) will eventually develop a neurodegenerative disorder, of which  $\alpha$ -synucleinopathy (including Parkinson disease, dementia with Lewy bodies and multiple system atrophy) is common. Before these patients develop overt synucleinopathy, they may have an intermediate stage (RBD+), in which mild cognitive impairment, mild parkinsonism signs and mild autonomic disturbances might occur. **b** | Commencing neuroprotective therapy (when available) in individuals with iRBD might delay conversion to  $\alpha$ -synucleinopathy. Adapted with permission from REF.<sup>214</sup>, Elsevier.

(which occurs in ~50% of patients with iRBD) increased phenoconversion risk by approximately threefold in one study<sup>46,169</sup>. In terms of autonomic dysfunction, symptoms of autonomic dysfunction (evaluated using the SCOPA-AUT questionnaire) are associated with a higher risk of phenoconversion<sup>44</sup>, although in a study by the RBD study group, only cardiovascular autonomic symptoms increased this risk<sup>46</sup>. However, a study from the Montreal cohort demonstrated no predictive value of autonomic symptoms or electrocardiogram changes<sup>171,172</sup>, although an absent predictive value might be consistent with a very long prodromal interval, such that most patients already have autonomic loss at the time of RBD diagnosis. One study demonstrated a greater frequency of  $\alpha$ -synuclein pathology in the enteric nervous system without changes in intestinal permeability in patients with PD and RBD than in PD patients without RBD<sup>173</sup>.

Patients with iRBD with a UPDRS score of >3 at any timepoint have an approximately fourfold risk of phenoconversion over the next few years. The first daytime motor signs in iRBD appear to start 4–8 years before the onset of parkinsonism<sup>174</sup>. Other quantitative motor tests (Purdue Pegboard, alternate-tap and timed up-and-go) also identify phenoconversion risk; motor abnormalities predict the risk of DLB and PD equally,

illustrating the overlap in the phenotype of these disorders<sup>163,164,167</sup>. Mild cognitive impairment increases the risk of phenoconversion for 'dementia-first' DLB converters but not for 'parkinsonism-first' converters (such as PD and MSA)<sup>175</sup>. The reason for this is unclear but could be related to a relatively short prodromal interval for cognition alteration (such that patients only develop changes 2–4 years before dementia onset) or mean that having normal cognition with no comorbid pathology (such as without amyloid deposition) means that neurodegeneration will first affect brainstem structures.

Regarding other sleep disorders or psychiatric disorders, two studies have demonstrated a higher risk of conversion associated with daytime somnolence<sup>42,45</sup>, whereas two other studies did not report this finding<sup>176,177</sup>. One study demonstrated no effect of insomnia on the risk of phenoconversion<sup>177</sup>. The association between the severity of REM atonia loss and conversion risk remains unclear, although some studies demonstrate a small increase in risk in individuals with more severe loss of REM atonia<sup>38,178</sup>. Depression is a known risk factor for PD in the general population<sup>168</sup>, and patients with iRBD with comorbid depression are more likely to develop neurodegeneration than those without depression<sup>41</sup>. However, a lower risk of neurodegeneration was demonstrated in individuals with antidepressant use at baseline by one study<sup>179</sup>. The relationship between depression and risk of conversion might be confounded by antidepressant-triggered RBD, resulting in a biphasic complex relationship<sup>179</sup>.

**Other biomarkers for the risk of overt synucleinopathies.** Numerous putative markers of prodromal PD and/or DLB are abnormal in patients with iRBD and can predict the risk of conversion. Several brain imaging markers have been investigated<sup>180</sup>, of which SPECT of striatal dopamine transporters (DAT-SPECT) is the most extensively studied<sup>181–183</sup>. Dopamine PET and/or SPECT imaging is abnormal in ~40–50% of patients with iRBD, and several studies have demonstrated that abnormalities in DAT-SPECT identify patients at higher risk of phenoconversion<sup>44,184,185</sup>. Moreover, a reduction in striatal dopamine transporters was demonstrated in patients with iRBD, with a continuum of reduction from subclinical RBD to clinical iRBD and finally to PD<sup>185</sup>. Additionally, a significant correlation was found between the percentage of REM sleep muscle atonia and striatal dopaminergic transmission. In addition, metabolic patterns of glucose utilization detected using PET or SPECT associated with PD have been reported and can identify patients at higher risk of phenoconversion<sup>186</sup>. A more specific RBD metabolic network has been identified using fluorodeoxyglucose (FDG)-PET, which is a strong biomarker for patients at high risk of developing an overt neurodegenerative syndrome<sup>187</sup>. Specific tracer PET studies have also found widespread denervation of noradrenergic and cholinergic structures<sup>188,189</sup>, as well as activation of microglia in the brainstem and cortical areas<sup>190</sup>. A specific synuclein tracer for PET or SPECT has not been developed to date; this development would be a major advance in prodromal diagnosis.

Hippocampal hypoperfusion is observed in iRBD and early DLB and might identify a high likelihood of phenoconversion to DLB in patients with iRBD<sup>191</sup>.

Slow EEG activities (that is, high slow-to-fast power ratio via EEG spectral analysis), particularly detected by posterior EEG leads, which has been reported in PD and DLB, marks increased disease risk<sup>192,193</sup>. The role of substantia nigra ultrasonography in predicting the risk of conversion is less clear than other biomarkers; an early study suggested a predictive value of substantia nigra hyperechogenicity, which was not borne out on further follow-up<sup>194</sup>. Atrophy of the brainstem and cortical regions detected using MRI, abnormal functional connectivity on resting state MRI<sup>195</sup> and abnormalities in the substantia nigra on iron-sensitive sequences and diffusion tensor imaging (especially in the substantia nigra and locus ceruleus<sup>196</sup>) can be found in up to 80% of patients with iRBD, but more longitudinal studies are warranted to validate the risk of subsequent phenoconversion in these patients<sup>180</sup>. Some studies have suggested abnormalities in the microbiome of patients with PD, which might be present in RBD, although the importance of these findings is unclear. Biopsies have also documented abnormal  $\alpha$ -synuclein deposition in the colon<sup>173,197</sup>, skin<sup>198,199</sup> and submandibular glands<sup>200</sup> in the majority of patients with iRBD, potentially providing proof of  $\alpha$ -synucleinopathy. One study showed that patients with PD and RBD have a greater frequency of  $\alpha$ -synuclein pathology in the enteric nervous system without changes in intestinal permeability than patients with PD without RBD<sup>173</sup>.

**Prevention of overt  $\alpha$ -synucleinopathy.** All neurodegenerative diseases have a prodromal interval, during which symptoms have started but have not reached the threshold for diagnosis<sup>168</sup>. The prodromal interval can last for >10 years for PD<sup>201</sup>, but the duration of the prodromal interval for DLB is not known. Although risk factors for iRBD and conversion to  $\alpha$ -synucleinopathies have been identified, whether modifying environmental risk factors has a potential benefit during the prodromal stage needs further clarification<sup>202</sup>. To date, no neuroprotective therapies for PD or DLB have been developed, and studying patients with iRBD might be of major benefit for the development of neuroprotective therapy. In addition, patients with iRBD would be well poised to receive such therapies, as these patients are early enough in the neurodegeneration to intervene and are not receiving symptomatic PD treatments (eliminating a major confounding factor in neuroprotective studies) (FIG. 4). Advising patients to follow a healthy lifestyle and to take part in prospective cohort studies in anticipation of eventual neuroprotective trials has been suggested in one study<sup>203</sup>. However, when

and how best to advise patients about this risk remain controversial and unclear in clinical practice.

## RSWA

Several questions regarding the diagnosis, significance, natural history and prognosis of RSWA and phasic events in REM sleep remain answered and need to be resolved in the next decade. These questions include the minimum duration of REM sleep necessary to diagnose RSWA and phasic events; the pathological cut-off for altered REM sleep motor atonia, especially in the context of OSAS and antidepressant intake; the effect of age distribution on RSWA cut-off; and the physiological versus abnormal type of behaviours observed during REM sleep documented by vPSG. Individuals with isolated RSWA but without dream enactment are frequent in the general population, with evidence suggesting that some patients with RSWA will develop clinical RBD with longitudinal follow-up, and approximately half of the reported patients with iRBD are unaware of their parasomnias<sup>20</sup>. Thus, longitudinal studies on individuals with RSWA are required to clarify whether RSWA is a marker of  $\alpha$ -synucleinopathy, to propose symptomatic therapy to prevent injury caused by motor events during sleep and to establish an early diagnosis of parkinsonism or mild cognitive impairment to further improve the function and QOL of patients.

## Management

Prospective treatment studies are required to improve the knowledge on the short-term and long-term effectiveness of therapies on RSWA, REM phasic activity and clinical RBD. Although the prognosis of younger patients with iRBD and those with antidepressant-associated RBD remains unclear, up to 90% of patients with typical iRBD will develop an overt neurodegenerative disease during follow-up<sup>39</sup>. Thus, the RBD field is highly motivated to commence neuroprotective trials that could delay or prevent this process. For patient selection for these trials, patients with vPSG-proven RBD could undergo tissue biopsy to confirm pathological  $\alpha$ -synucleinopathy. Then, by stratifying using the above detailed biomarkers, subgroups with phenoconversion rates as high as 20% per year can be identified (allowing definitive preventive trials with as few as 100 patients per group). The next decade holds great optimism as the field moves forward from observational studies to protective treatment to prevent or delay  $\alpha$ -synucleinopathy-related motor and cognitive decline.

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#### Author contributions

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