REVIEW

Clinical trials in REM sleep behavioural disorder: challenges and opportunities

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ABSTRACT

The rapid eye movement sleep behavioural disorder (RBD) population is an ideal study population for testing disease-modifying treatments for synucleinopathies, since RBD represents an early prodromal stage of synucleinopathy when neuropathology may be more responsive to treatment. While clonazepam and melatonin are most commonly used as symptomatic treatments for RBD, clinical trials of symptomatic treatments are also needed to identify evidence-based treatments. A comprehensive framework for both disease-modifying and symptomatic treatment trials in RBD is described, including potential treatments in the pipeline, cost-effective participant recruitment and selection, study design, outcomes and dissemination of results. For disease-modifying treatment clinical trials, the recommended primary outcome is phenoconversion to an overt synucleinopathy, and stratification features should be used to select a study population at high risk of phenoconversion, to enable more rapid clinical trials. For symptomatic treatment clinical trials, objective polysomnogram-based measurement of RBD-related movements and vocalisations should be the primary outcome measure, rather than subjective scales or diaries. Mobile technology to enable objective measurement of RBD episodes in the ambulatory setting, and advances in imaging, biofluid, tissue, and neurophysiological biomarkers of synucleinopathies, will enable more efficient clinical trials but are still in development. Increasing awareness of RBD among the general public and medical community coupled with timely diagnosis of these diseases will facilitate progress in the development of therapeutics for RBD and associated neurodegenerative disorders.

INTRODUCTION

Rapid eye movement sleep behavioural disorder (RBD) is characterised by 'acting out' of dreams and is diagnosed by video polysomnography (vPSG) demonstrating a loss of muscle atonia that normally accompanies REM sleep. Isolated RBD (iRBD) is the most reliable clinical marker of prodromal synucleinopathies, a group of neurodegenerative disorders including Parkinson's disease (PD), dementia with Lewy bodies (DLBs) and multiple system atrophy (MSA).[1] The vast majority of individuals with iRBD are diagnosed with any synucleinopathy within 20 years of onset of iRBD.[2] Therefore, the iRBD population can serve as an ideal study group for testing agents that may modify synuclein-specific neurodegeneration, that is, disease-modifying treatments to delay or prevent phenoconversion to an overt synucleinopathy. Furthermore, since the symptoms of RBD may cause sleep disruption and injury, and existing treatments are not always effective, there is also a need for clinical trials of new symptomatic treatments for RBD.

In 2013, the International RBD Study Group (IRBDSG) published a consensus statement on devising symptomatic and disease-modifying clinical trials in RBD.[3] Since then, scientific progress regarding the pathophysiology and biomarkers of synucleinopathies has provided an exciting and timely platform for clinical trials. In this manuscript, we update the current knowledge on RBD treatments and discuss pivotal considerations for both symptomatic and disease-modifying clinical trials in RBD.

CURRENT APPROACHES TO RBD TREATMENT

Disease-modifying treatments

There are currently no disease-modifying treatments for RBD. Regular surveillance for symptoms of an overt synucleinopathy, including parkinsonism, cognitive decline and autonomic dysfunction is recommended, so that they can be addressed promptly.[4] However, there is an obvious need for clinical trials for disease-modifying treatments, and if feasible, patients should be referred to registries of patients with RBD and resources where they can obtain up-to-date information on any clinical trials that arise (table 1).

Symptomatic treatments for RBD

Symptomatic treatment is required when the symptoms of RBD cause potential injury or sleep disruption to the patient or bed partner. All individuals with RBD must take environmental precautions, such as removing weapons from the bedroom, removing or moving sharp furniture/objects, lowering bed height, padding the floor next to the bed and other changes to minimise the chance of injury during an RBD episode. Medications known to exacerbate RBD, including serotonin reuptake inhibitors, serotonin-norepinephrine reuptake

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Table 1 RBD registries and resources for RBD clinical investigations

Name	Website	Description
International RBD Study Group	IRBDSG.com	Organisation of RBD researchers representing registries of patients with RBD across the world.
North American Prodromal Synucleinopathy Consortium (NAPS Consortium)	naps-rbd.org	Research participant registry at 10 sites in the USA and Canada, with the goal of forming a trial-ready cohort for disease-modifying clinical trials in RBD.
Parkinson's Progression Markers Initiative (PPMI)	ppmi-info.org	PD biomarkers study which previously enrolled participants with iRBD; currently closed to enrolment. Next phase (PPMI2) to start in 2020.
ClinicalTrials.gov	clinicaltrials.gov	Database of privately and publicly funded clinical studies conducted around the world, a resource provided by the US National Library of Medicine.
Fox Trial Finder from the Michael J Fox Foundation	foxtrialfinder.michaeljfox.org	Database of PD-related clinical trials that matches potential participants to actively enrolling studies.

iRBD, isolated rapid eye movement sleep behavioural disorder; PD, Parkinson's disease; RBD, rapid eye movement sleep behavioural disorder.

inhibitors and tricyclic antidepressants should be discontinued or avoided if possible.[5] Heavy alcohol use may also increase RBD episodes[6] and should be limited in individuals who have exhibited correlations between alcohol use and RBD episodes.

Clonazepam and melatonin are most frequently used for symptomatic treatment of RBD, largely based on case series, and a smattering of other medications has also been reported to be effective. Clonazepam reduces the frequency of unpleasant dreams and violent dream enactment behaviour,[7 8] with complete resolution of symptoms observed in more than half of patients in large case series.[9–11] Data on dose increases of clonazepam or treatment failure over long-term follow-up are conflicting.[8 12] Side effects (morning sedation, confusion, dizziness and falls) may limit clonazepam utility, especially among older adults and/or in RBD coexistent with overt neurodegenerative disorders.[13] Unfortunately, a recent placebo-controlled trial in RBD occurring with PD was negative, with only a trend of RBD symptom improvement with clonazepam compared with placebo, as measured by clinical global impression of change (CGI).[14]

Melatonin, for its more favourable side effect profile, is frequently preferred as initial therapy for RBD.[15 16] In higher doses (6 to 18 mg at bedtime) melatonin improved frequency and severity of RBD symptoms in up to 70% of patients, as documented in several observational studies.[15 17] Lower doses (2 mg slow release and 3 mg immediate release) in conjunction with a '30 min prior to bedtime, always at the same clock time' dosing regimen showed improvement in over 90% of patients with iRBD in open-label trials.[18 19] Unfortunately, a recent placebo-controlled trial using extended-release melatonin was also negative.[20] The mechanism of action of melatonin in RBD is unclear, but the persistent effect after melatonin discontinuation is hypothesised to be due to action on the circadian system.[18] Clinical synucleinopathies are mostly accompanied by a substantial dysfunction of the circadian system.[21 22] Considering that endogenous melatonin signalling is dampened in synucleinopathies, one can hypothesise that melatonin may improve RBD via a restructuring and resynchronisation of circadian rhythmicity,[23] a hypothesis that needs to be further studied.

Other medications for RBD are used less frequently, typically if melatonin and clonazepam have failed to adequately symptoms or have intolerable side effects. Randomised, placebo-controlled, double-blind studies showed that rivastigmine reduced reported number of RBD episodes in the setting of mild cognitive impairment[24] or PD[25] resistant to clonazepam and melatonin, and that memantine reduced subjective physical activity during sleep in individuals with probable RBD in the setting of DLB or PD with dementia.[26] Scattered case reports indicate that some individuals with RBD have symptomatic benefit from donepezil (although some cases did not have vPSG-confirmed RBD),[27] levodopa, dopaminergic medications, imipramine, carbamazepine, sodium oxybate, triazolam, zopiclone, quetiapine and clozapine.[7 13 28–31]

In summary, there are no symptomatic treatments with a high level of supporting clinical trial evidence for RBD, particularly iRBD. Clonazepam and melatonin are most commonly used for symptomatic treatment of RBD based on large case series; however, recent placebo-controlled trials were negative.[20] An important note of discussion is whether these trials used the best endpoints for evaluating RBD severity. The CGI, although recommended by the IRBDSG previously,[3] is highly subjective and dependent on the patient and/or bed partner, neither of whom may be aware of or recall all RBD episodes.[14] Sleep logs or event diaries face similar problems.[20] For RBD occurring with overt neurodegenerative diseases, placebo-controlled studies have shown that rivastigmine and memantine are effective, although outcome measures were not optimal in these studies also. All other RBD symptomatic treatments are based on open-label studies or case reports. Clearly, clinical trials that can overcome factors that have hampered development[32] of better symptomatic RBD treatments are needed, and we outline recommendations for such trials in the following sections.

STUDY POPULATIONS FOR RBD CLINICAL TRIALS

Study participants for clinical trials in RBD should have RBD based on the criteria established by the International Classification of Sleep Disorders,[33] the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition[34] or the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events.[35] Critically, RBD diagnosis requires confirmation by vPSG, as there are many mimics.

Study populations for disease-modifying treatment trials

Selection of the study population for disease-modifying clinical trials in RBD should align with the following general principles: (1) defining a group for which there is a greater chance of detecting a possible difference between the compared interventions, (2) isolating a homogeneous group to reduce the variability of response and potential confounders, (3) obtaining a representative sample of the disease to be able to extrapolate results, (4) defining realistic recruitment goals (sample size, time and cost) and (5) maintaining ethical standards by choosing patients who are likely to benefit.

Ideally, individuals with iRBD would be the 'most pure' study cohort for trials of disease-modifying treatments. This, however, needs to be placed in the context of feasibility of such an approach. Individuals with iRBD may take up to 10 years before the phenoconversion takes place, which would make trial duration too long. In contrast, at the time of RBD manifestation,

Table 2 Potential features to select study populations at high risk for phenoconversion, for disease-modifying clinical trials in RBD

Age	Equal or older than 65 years; or consider range between 55 and 75 years old[36 37]
RBD features	Longer disease duration[38] iRBD (ie, not due to narcolepsy, not due to brainstem lesion, not due to other known brain pathology) RBD not occurring in temporal association with antidepressant medications
Olfaction	Dysfunction measured by the cross-cultural 12-item test[37 39 40]
Cognitive	Abnormal performance assessed by neuropsychological testing[41 42]
Motor	Subtle motor dysfunction: parkinsonism, ataxia and/or dysmetria measured by the part III of the Unified Parkinson's Disease Rating Scale[37 43 44] Abnormal motor performance assessed by objective testing (eg, Purdue Pegboard)
Colour vision	Abnormal colour vision assessed by FM-100
Autonomic	Autonomic dysfunction: constipation, urinary symptoms, erectile dysfunction, orthostatic hypotension[36 45 46]
Dopamine imaging	DaT SPECT: reduced nigrostriatal dopaminergic binding in the putamen and striatum[47 48]
Genetic	GBA mutation[49] or other genotype that increases phenoconversion risk
Other	See section of Outcome Measures for Symptomatic Trials below or symptomatic trials section for discussion of imaging, biofluid and other potential selection biomarkers in development

DaT, Dopamine transporter SPECT; FM-100, the Farnsworth Munsell 100 HueColor Vision Test; GBA, glucocerebrosidase ; iRBD, isolated rapid eye movement sleep behavioural disorder; RBD, rapid eye movement sleep behavioural disorder; SPECT, single-photon emission CT.

the aggregated alpha-synuclein has likely already reached the brainstem and the 'phenoconversion' process has began.

For disease-modifying clinical trials, it would be critical to select a study population at appropriate risk of phenoconversion to overt synucleinopathy, to enable smaller and more rapid clinical trials. We will need to strike the right balance of enrolling individuals with RBD and coexistent reasonable presence of other markers of neurodegenerative process. In a multicentre study through the IRBDSG, clinical or demographic features such as older age, family history of dementia, motor symptoms, autonomic symptoms, pesticide exposure, olfactory function and others increased the risk of phenoconversion.[36] Table 2 [36–49] summarises potential criteria to select an RBD study population with highest risk of phenoconversion. Rapidly accumulating research on RBD and particularly biomarkers will refine these criteria in coming years. For example, genetic risk variance may be an important element for balancing clinical trial arms.[50] Additionally, any clinical trial will need to balance the opposing forces of requiring a study population at high risk of phenoconversion and the overall low prevalence of RBD.

Study populations for symptomatic treatment trials

For symptomatic treatment trials, study participant selection need not be as stringent as for disease-modifying trials. Individuals with RBD and a clinical need for improvement of RBD episode severity or frequency could be enrolled in symptomatic treatment trials. There are still some considerations to ensure efficient symptomatic treatment trials. Study participants should demonstrate sufficient severity of RBD prior to treatment, such that a clinically meaningful improvement can be detected. Ideally, study populations should be tailored to match the putative mechanism of action of a study drug. Individuals with untreated or suboptimally treated obstructive sleep apnoea (OSA) or other sleep disorders should be excluded, because arousals related to other sleep disorders may increase the perceived severity of RBD symptoms. In individuals with coexistent RBD and OSA, the employment of continuous positive airway pressure may be considered to minimise the confounding effect of OSA on arousal instability and phasic and tonic increases of muscle tone. If subjective report will be part of the outcome measure of RBD severity, then the presence of a bed partner should be mandatory or used as a stratification feature. Optimally, the study group should be homogeneous in RBD aetiology and subtype, such as iRBD, RBD associated with narcolepsy or RBD associated with a specific synucleinopathy. Considering that treatment with antidepressants may worsen or provoke RBD symptoms, clinical studies that allow for withdrawal of these medications, when possible, would provide additional insight into the relationship between medications' use and RBD.

Screening and recruitment for RBD clinical trials

Recruiting participants for clinical trials for RBD faces several fundamental methodological issues. While RBD is present in ~1% of middle-aged and older adults with no differences of frequency in the sexes, only a small proportion of people with RBD, mostly male, come to clinical attention.[51] Individuals with more severe or injurious RBD episodes are more likely to come to clinical attention and are unlikely to be representative of the whole RBD population. Furthermore, since vPSG is required for RBD diagnosis, access to sleep subspecialty expertise is required, and additionally hampers potential recruitment for clinical trials.

Given the relatively low prevalence of RBD, screening and recruitment methods for RBD clinical trials must be carefully planned. Effective screening methods with excellent accuracy will be a critical step in disease-modifying trials targeting the RBD population. Several structured screening questionnaires for RBD are available.[52–56] However, there are no screening tools for RBD that have been validated in community-dwelling subjects unselected for sleep complaints. The Mayo Sleep Questionnaire yields very high sensitivity and good specificity in discriminating RBD from other sleep disorders in the community-based[54] and in ageing and dementia populations.[57] However, as it relies on bed partner's report, its use is limited to individuals not sleeping alone. Note that current RBD questionnaires (eg, RBD Single Question Screen[56] and REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ)[52]) do not reliably differentiate RBD from non-REM parasomnias and other mimics such as excessive periodic limb movements,[58] hence additional information on ambulation, history of the parasomnia and other clinical features must be collected for improved accuracy. The Innsbruck RBD Inventory has the highest sensitivity (85%–91%) and good specificity (84%–86%)[53] in patients referred to sleep clinics and does not rely on bed partner's information, but is not yet validated in a community setting. Evidence about the usefulness of other questionnaires as screening tools for RBD in de novo PD is conflicting[59 60] and insufficient for other patient populations. A questionnaire that bed partners use to rate the severity of RBD was developed and used in the development of the RBD Polysomnographic Score among individuals affected by synucleinopathies.[61]

Potential participants with positive screens will need to undergo vPSG to determine if they fulfil criteria for RBD. Due to the low prevalence of RBD compared with the relatively high

prevalence of periodic limb movement disorder, OSA and other sleep disorders causing 'pseudo-RBD', a substantial number of RBD-screen-positive individuals will be false positives, meaning they do not have RBD. Since vPSG is costly, additional steps to narrow the pool of potential trial participants may be necessary to make a clinical trial feasible. For example, for a disease-modifying trial, a multistep approach that combines a screening questionnaire, clinical interview and clinical testing for features of higher risk of phenoconversion to synucleinopathies (as in table 2), followed by vPSG, would be more efficient. In contrast, for a symptomatic clinical trial, individuals with PD, or other diagnoses in which the prevalence of RBD is high, could directly undergo vPSG if a screening questionnaire is positive. Development of more reliable devices in the home environment, such as actigraphy[62 63] or home sleep recordings, would further facilitate recruitment by narrowing the potential participant pool to those at highest likelihood of true RBD.

CLINICAL TRIAL DESIGN

Several trial designs have been employed in disease-modifying trials in PD, including washout design, delayed-start design, futility designs, as well as designs that assess either time to an event or a change in rating scale over time as endpoints.[64] Each of these designs had advantages but also disadvantages that resulted in difficulties with the interpretation of study findings. A majority of trials in PD used clinical end points and/or surrogate markers, and choice of these outcome metrics may have influenced negative trial results. Several PD trials employed surrogate imaging markers of the nigrostriatal system, specifically positron emission tomography (PET) imaging as a measure of dopa decarboxylation, and single-photon emission CT (SPECT) imaging of the dopamine transporter.[65 66] While initially promising, dopaminergic medications interacted with imaging radioligands thus affecting the interpretation of results. Novel techniques such as clinical trial simulation and disease modelling may be applicable to RBD trials.[67]

An important issue to consider is how to distinguish a potential symptomatic effect (on the outcome measure, such as motor function) from a disease-modifying effect, if the agent has any symptomatic effect. Three designs have been proposed to address this concern: (1) delayed-start trial designs, (2) longitudinal studies with repeated assessments to perform meaningful slope analysis and (3) trials measuring outcomes following a washout period. Currently, there is no evidence for any agent causing a symptomatic effect (on neurological function) in RBD; therefore this discussion is a theoretical one.

Overall, the recommended design for a disease-modifying clinical trial in RBD is a prospective, randomised, parallel-group, double-blinded, placebo-controlled trial.[68] An adaptive trial design may be considered to reduce number of participants or study duration. A washout period or other design feature to account for the possibility of a neurological symptomatic effect should be considered also. For trials centred on symptomatic treatments of RBD, randomised, double-blind, placebo-controlled, parallel-arm or cross-over trail designs should be considered.

CLINICAL TRIAL DURATION

It is quite challenging to predict the ideal duration of a disease modifying trial in RBD. This concept continues to evolve as we work to improve dynamic biomarkers of neurodegeneration progression. Based on the current understanding of RBD progression, it is reasonable to propose the time range up to 2 years. Most published disease-modification efficacy trials in PD also have an at least 6–10 months of placebo-controlled phase or delayed start phase, followed by a 1.5 to 2 years open-label phase. Regardless of the duration of the primary clinical trial, a long-term open-label phase is recommended, to collect safety and efficacy data.

On the other hand, for a symptomatic treatment, clinical trial duration can be quite short (weeks). However, a longer open-label phase is recommended to collect safety and efficacy data long term, since most patients with RBD will take symptomatic treatments for years.

AGENT SELECTION FOR CLINICAL TRIALS IN RBD

Disease-modifying treatment

Disease-modifying treatments in RBD should ideally halt or slow formation and spread of abnormal synuclein deposits, prevent neuronal death and/or diminish subsequent circuit-level deficits. There are multiple treatments in the pipeline for early PD or DLB that could be considered for neuroprotective trials in RBD. While all disease-modifying treatments in PD have failed in clinical trials thus far, it is possible that one of these treatments may be effective in iRBD, which represents a much earlier and potentially reversible stage of neuropathology. Additionally, some 'symptomatic' treatments for RBD may have possible neuroprotective effects.[19 69] Furthermore, it may be worthwhile to assess any disease-modifying benefit of behavioural or lifestyle changes that have been reported to be associated with decreased PD, DLB or MSA risk. Table 3[18 70–99] summarises possible existing disease-modifying treatments and interventions, although we anticipate new potential therapies to emerge in coming years.

Symptomatic treatment

The available symptomatic treatments for RBD lack clear high-quality evidence for use or disuse, particularly in iRBD. There are no additional agents that we are aware of that are promising for symptomatic benefit in RBD. Therefore, we recommend symptomatic treatment trials with medications such as clonazepam, melatonin/melatonin agonists with careful planning to overcome some of the obstacles that have hampered symptomatic clinical trials in RBD thus far.[32]

OUTCOME MEASURES FOR DISEASE-MODIFYING TRIALS

Phenoconversion, or progression to overt synucleinopathy, should be the primary outcome measure in a trial. A major challenge is the rate of phenoconversion in the iRBD population as a whole, estimated at 41% by 5 years[36] and at 50% at 8 years,[2] which translates to a prohibitively long and expensive clinical trial. This may even be an overestimate, as only the most violent or injury-prone phenotypes of iRBD are likely to come to clinical attention at academic sleep centres with large RBD cohorts. Therefore, markers that can serve as either (1) a selection marker for a subpopulation of patients with RBD at highest risk of phenoconversion or (2) a dynamic marker that tracks reliably with synuclein pathology during the prodromal phase and can be used as a surrogate outcome measure, would allow for more rapid clinical trials.

There is evidence for the presynaptic dopamine imaging, particularly ^{123}I-Ioflupane (^{123}I-FP-CIT or DaTScan) SPECT as a reliable biomarker. In the largest study with 87 subjects showing iRBD, abnormal ^{123}I-Ioflupane binding predicted symptomatic phenoconversion by 3 and 5 years.[100] Thus, dopamine transporter imaging could be used as a selection marker. As for whether dopamine imaging alone can be used as a dynamic marker, there

Table 3 Potential approaches for disease modification in PD and iRBD

Mechanisms	Agents	Comments
Immunisation	Monoclonal antibodies directed toward the toxic conformations of synuclein	Several ongoing phase I and II trials of passive and active immunisation (*RO7046015*, *PASADENA* trial; *BIIB054*, *SPARK* trial)[70]
	Blockers of synuclein misfolding or aggregation	*NPT088*, glycerol phenylbutyrate, squalamine,[71] nilotinib, selective c-Abl inhibitors,[72] epigallocatechin gallate[73]
Neuroinflammation modifiers		
Anti-inflammatory	Ibuprofen	Lower PD risk in people receiving non-steroidal anti-inflammatory agents[74]; alpha-synuclein increases inflammation
	AZD3241 (selective, irreversible myeloperoxidase inhibitor)[75]	*Benefit on microglia brain imaging in a short-term trial in PD*[75]
Antibiotics	Doxycycline, tetracycline	Protective in PD animal models[76]; Rosacea is associated with higher PD risk, treatment with doxycycline reduces this risk[77]
Oxidative stress	Melatonin (antioxidant)	**Symptomatic effect in RBD**[18] Neuroprotective in various animal PD models[78]
	Glutathione (antioxidant)	N-acetylcysteine (glutathione precursor) trial[79] *Troloxamide-quinone trial (NCT02462603)*
	Apamin (from bee venom)	Protective in a PD mouse model[80]
Iron	Deferiprone (iron chelator)	FAIRPARKI: small randomised double-blind delayed start trial in treated patients with PD[81] SKY and FAIRPARKII ongoing trials
Adrenergic system	Beta-2 adrenergic receptor (B2R) agonist	B2R agonists: lower PD risk[71]; B2R regulates the alpha-synuclein gene[82]
	Modafinil: common and safe stimulant in narcolepsy	Neuroprotective in MPTP parkinsonism marmosets and cats[83] **Some patients with RBD are sleepy**[84]
Glucagon-like peptide-1	Exenatide (antidiabetics)	May reduce DA neurons apoptosis[85]
Glucocerebrosidase activity (GBA mutation)	Glucosylceramide synthase inhibitors; GBA-modifying drugs (ambroxol)	Tailored treatment in GBA mutation carriers or in sporadic PD with low GBA activity (*NCT0294182*) **GBA mutations in 10% of patients with iRBD**[86]
Reduce α-synuclein fibrillation and decrease parthenatos cell-death pathway	Poly(adenosine 5′-diphosphate-ribose) polymerase 1 (PARP1) inhibitors	Olaparib, rucaparib, niraparib, talazoparib are all FDA approved for certain cancers
Increasing DA activity	Nicotine	Lower PD risk in smokers[87] **But higher RBD risk in smokers**[88] *Trial NIC-PD, n=160: ongoing*
Lifestyle modifiers		
Diet: selective increased consumption	Caffeine (black tea, coffee)	Lower PD risk in heavy coffee drinkers[89] **No lower RBD risk**[88]
Diet: selective increased consumption	Eating edible solanaceae (tomatoes, peppers, potatoes) containing nicotine	Epidemiological evidence for lower PD risk when eating these foods[90]
Diet: selective increased consumption	Eating more omega 3 polyunsaturated fatty acids	But no neuroprotection in mild cognitive impairment (MAPT study)[91]
Diet: selective decreased consumption	Reducing milk consumption	Increased PD risk when drinking fresh milk[92]
Diet: selective decreased consumption	Avoid eating tropical fruits/food containing annonacin (soursop)	Associated with atypical PD[93] **RBD in up to 55% of patients with parkinsonism of French West Indies**[94]
Diet: selective increased consumption	Yerba mate tea	Inverse association between yerba mate consumption and PD in South America[95 96]
Lifestyle: decreasing exposure (food, air)	Avoid exposure to pesticides	**RBD is more frequent in workers using pesticides**[88] PD is more frequent in workers using pesticides
Exercise and physical activity	Exercise and physical therapy	Anti-inflammatory, antioxidant, promitochondrial, trophic and anti-synuclein effects[97–99]

In italics: human trials in PD; in bold: data in iRBD. Most details can be found in a recent review.[142] As for lifestyle changes, details can be obtained from a recent review on RBD risk factors.[4]

c-Abl, Abelson non-receptor tyrosine kinase ; DA, dopamine; FDA, Food and Drug Administration; GBA, glucocerebrosidase ; iRBD, isolated rapid eye movement sleep behavioural disorder; MAPT, microtubule-associated protein tau; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's disease; RBD, rapid eye movement sleep behavioural disorder.

are insufficient data. A longitudinal study of n=20 patients with iRBD and 20 control participants found that patients with iRBD had decreased ^{123}I-FP-CIT binding at baseline and that mean values decreased at 1.5 years and 3 years.[48] The three patients with lowest putamenal ^{123}I-FP-CIT binding at baseline developed PD; however, the rate of change in binding was no different between patients starting with normal or abnormal binding levels, therefore predicting phenoconversion may still be difficult according to these data. A meta-analysis combining data from ^{123}I-Ioflupane SPECT, iodine-123 labelled N-(3-iodopropen-2-yl)-2beta-carbomethoxy-3beta-(chlorophenyl) tropane PET (^{123}I-IPT PET), [11C]dihydrotetrabenazine and 18F-DOPA L-6-[18F] fluoro-3,4-dihydroxyphenylalnine PET found that tracer uptake was decreased in RBD compared with controls and further decreased in PD.[101] Therefore, it might be assumed that dopamine binding would decrease within an individual from prodromal to overt symptomatic synucleinopathy. However, there are insufficient data regarding rate of change,

particularly regarding the subgroups of RBD that are on trajectories toward DLB or MSA, to recommend use of dopamine imaging as a dynamic marker at this time.

Other potential selection markers include REM sleep without atonia (RSWA) and some clinical features. RSWA, quantified during PSG, is associated with clinical severity measures such as gait freezing and cognitive impairment in PD,[102 103] and RSWA increases or progresses over time, with high RSWA amounts shown to be a risk factor for developing a symptomatic synucleinopathy.[104] Multiple methods for quantifying RSWA by manual visual scoring have been developed, with varying combinations of metrics, such as electromyography signal from different muscles; 'tonic', 'phasic' or 'any' RSWA quantification; cut-off values; inclusion or exclusion of RSWA associated with apnoeas; and other factors.[105–109] Additionally, automated methods have been developed and tested against visual methods[62 110–113] and substantially reduced processing time. Recent developments in ambulatory sleep monitoring devices and signal analysis methods may allow for measurement of RSWA at home over multiple nights or longitudinally.[114] There is no clearly superior method of RSWA quantification,[115] but consistent application of a single method—particularly one with multicentre comparisons and validations—would be required to use RSWA as an outcome marker.

Poor olfaction, impaired colour vision and subtle motor dysfunction, particularly in combination, also predict faster phenoconversion.[36 116] Sequential biomarker assessment can identify prodromal PD efficiently, and by adding male sex and constipation, the percentage of a positive prediction of DaTScan can be significantly increased.[117] On the other hand, there are currently insufficient data to support using any clinical markers or RSWA as dynamic markers. Of note, other cognitive and neurological functions may not be useful: a clinical battery—which did not include olfaction or autonomic function—was not predictive of abnormal dopamine transporter imaging in RBD.[118]

There are no reliable fluid biomarkers for distinguishing RBD from controls. Tissue biomarkers such as α-synuclein deposits in skin,[119 120] submandibular glands,[121] enteric nervous system via colonic biopsies,[122] particularly phosphorylated α-synuclein are promising, but these markers require validation against clinical diagnosis and progression, and especially no data as dynamic markers are currently available.

Various imaging modalities have demonstrated abnormalities in iRBD. MRI studies in RBD have shown an abnormal susceptibility weighted imaging signal in the substantia nigra,[123] but correlative clinical data are lacking. Transcranial sonography shows substantia nigra hyperechogenicity in RBD as a group, and this trait predicts risk of phenoconversion, but with poor sensitivity and specificity, and does not change over time.[124] Metabolic imaging with ^{18}F-fluorodeoxyglucose PET has shown a 'PD motor-related pattern' in RBD, with correlation with RBD disease duration, but there are insufficient clinical staging and prognostic data.[125 126] Cardiac ^{123}I-meta-iodobenzylguanidine (^{123}I-MIBG) scans show decreased sympathetic activity in RBD[127]; however, there are no correlated clinical prognostic data, this marker has a non-linear trajectory and there are significant differences between MSA and PD. There are limited or conflicting data regarding RBD and postsynaptic dopaminergic imaging, cerebral blood flow imaging, structural MRI, diffusion tensor imaging by MRI, resting state functional MRI and magnetic resonance spectroscopy (for review see[128]). There are currently insufficient data to support using any of these imaging modalities as selection or even dynamic biomarkers of synucleinopathy in RBD.

There are emerging techniques and new biomarkers that may be applicable to RBD treatment trials in the future. For example, different conformations of α-synuclein can now be quantified. A recent study found that CSF total α-synuclein was decreased in DLB and PD compared with Alzheimer's disease (AD), but oligomeric α-synuclein was higher.[129] Real-time quaking-induced conversion, which assesses the rate of synuclein aggregation rather than absolute levels, can distinguish PD and DLB from AD, other tauopathies and controls,[130] but still does not predict phenoconversion. A combination of biomarkers may be more effective. A recent study showed that CSF amyloid-β-42, which is decreased in AD, was decreased in early PD patients with RBD and was associated with cognitive decline.[131] Therefore, AD biomarkers such as tau, amyloid-β and others may be useful alone or in combination with biomarkers specific to synucleinopathies. Recent data show that serum neurofilament light chain NFLE may be a progression marker in PD and may be useful in RBD. Other techniques such as α-synuclein quantification in plasma exosomes,[132] isolating brain-derived extracellular vesicles from blood[133] and proteonomic approaches are all in development in synucleinopathies and may be useful markers in the future.

In summary, the primary outcome measure for a trial should be phenoconversion using clinical diagnostic criteria of PD, MSA or DLB, as there are no validated dynamic biomarkers. Presynaptic dopamine transporter imaging should be used as a selection marker to enrich the population at risk for phenoconversion, following an initial preselection based on less costly markers such as poor olfaction, constipation or RSWA severity, as described above and in table 2. At this time, there are insufficient data to support using any biomarkers as dynamic outcome markers for synucleinopathy.

Outcome measures for symptomatic trials

In the prior consensus statement,[3] the CGI was recommended as a primary outcome measure, for a clinician to estimate a holistic change in RBD severity. However, RBD symptom severity reporting is highly subjective, with violent movements more likely to be recalled and reported by patients and bed partners. Furthermore, other factors unrelated to RBD, such as frailty, anticoagulation medication, potential for injury, bed partner's presence, bed partner's quality of sleep, patient's/bed partner's ability to perceive and recall RBD-related behaviours, environment and other factors unrelated to RBD will affect any subjective outcome measures, including the CGI.

Repeated assessment of symptoms severity according to bed partners is another possible outcome measure. However, we would not recommend this method alone, as it relies on the presence of a bed partner and, once present, is also influenced by external factors such as arousal threshold of the bed partner, sleeping in separate bedrooms and so on. A questionnaire that bed partners use to rate the severity of RBD was developed and used in the development of the RBD Polysomnographic Score among individuals affected by synucleinopathies,[61] yet it has not been employed so far to our knowledge for symptom monitoring in ecological settings in clinical trials.

In contrast, RBD severity may be objectively quantified by vPSG. Although it is difficult to quantify the high complexity of motor activities and vocalisations in RBD, the RBD Severity Scale (RBDSS) is a validated method to assess both frequency and severity of motor and vocalisation events during REM sleep.[134] Due to high night-to-night variation in RBD symptom severity,[134] however, two or more nights of vPSG are recommended to

reduce variance and therefore improve effect size and therefore reduces the practical application of this measure. The major challenges of using objective vPSG-based severity measures are the cost of vPSG as well as any effect of sleeping in unfamiliar surroundings on RBD behaviours. However, cost of vPSG is not prohibitively high, as demonstrated by clinical trials that have assessed RBDSS before and during drug treatment.[135–137] It is also possible to exclude the first night's data as an adaptation night.[136]

Portable, home-based methods to quantify RBD events such as home video analysis, home vPSG or activity sensors such as actigraphy[63 138] are under development or have already been shown to be useful to detect or at least screen for RBD, but sensitivity to treatment has not been demonstrated in any of these tools.[63] These types of methods will allow for lower cost as well as improve feasibility of multiple nights (even daily) of data collection. It will be critical to validate any such methods against vPSG as a gold standard.

RSWA could also be considered as an outcome measure for RBD severity. However, the degree of change in disruptive RBD behaviours may not necessarily correlate with change in RSWA. For example, clonazepam does not seem to significantly decrease RSWA, even while decreasing phasic movements.[135] However, for potential symptomatic treatments whose mechanism of action is to affect skeletal muscle control during REM sleep, RSWA would be a key objective symptomatic outcome measure, particularly if RSWA can be monitored in the ambulatory setting.

Additionally, a 'clinically meaningful' level of change needs to be determined. For instance, a small change in small movements or vocalisations imperceptible to the patient or bed partner is not clinically meaningful. Therefore, we recommend the addition of measures of number of events, falls, injuries, sleep disruption and daytime functioning as secondary outcomes along with vPSG-based measures, such that we have data to define a minimum clinically meaningful change objectively.

INCREASING AWARENESS OF RBD

The association between RBD and synucleinopathy has been increasingly disseminated. However, there is still substantial work needed to increase the awareness of RBD both in the general population and healthcare professionals. General medical practitioners and geriatric specialists, who are most likely to encounter individuals with RBD symptoms, may not be aware of the neurological implications of RBD or the importance of screening for RBD. Moreover, since sleep medicine specialists have primary specialisation in a variety of fields, such as pulmonology, psychiatry, otolaryngology, internal medicine and others, not all individuals with RBD being assessed by sleep medicine physicians may be evaluated or treated for RBD, since vPSG may not be routinely performed or vPSG may not be scored for RBD. RBD currently lacks a patient advocacy group, and organised research efforts (such as IRBDSG or NAPS Consortium) are based on existing RBD cohorts followed at subspecialty centres. Coordinated multidisciplinary efforts among sleep experts, neurologists and healthcare professionals will be required to educate the public and medical professionals about RBD. Ethical considerations should be emphasised in all dissemination campaigns, given the neurological implications of RBD and the current lack of disease-modifying treatments; therefore, personalised counselling should be the first priority when diagnosing RBD, and resources (such as in table 1) to promote RBD clinical trials should be emphasised.[139–141] Based on the rapid pace of ongoing RBD research, we anticipate in the very near future to engage a larger group of experts, patients, industry leaders and stakeholders who will enable highly impactful clinical trials to advance the field of RBD therapeutics and synucleinopathies.

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