Neuroprotective Trials in REM Sleep Behavior Disorder
The Way Forward Becomes Clearer

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Abstract

As neuroprotective therapies continue to be advanced against neurodegenerative synucleino-pathies, such as Parkinson disease (PD), dementia with Lewy bodies (DLBs), and multiple system atrophy, increasing attention is turning to the prodromal stages of disease. Treatments at the prodromal stage have the compelling advantages of being applied early enough to make a meaningful difference and can be tested without confounding by symptomatic therapies used for clinical PD/DLB. As it currently stands, patients with idiopathic/isolated REM sleep behavior disorder (iRBD) represent the only large existing cohort of untreated prodromal PD/DLB that would be ready to start a clinical trial now. Several thousand patients with RBD are currently being followed in research-based clinics, and more than 80% of them will develop a full neurodegenerative synucleinopathy. Research into RBD phenoconversion rates and predictors has advanced considerably, and we are now able to generate increasingly precise estimates of progression rates, can select stratification markers to enrich trials, and are able to understand the progression and sample size implications of different primary outcome measures. This review will outline the potential for neuroprotective trials in iRBD, including the pathophysiologic mechanisms with the most promise to target in iRBD, selection criteria for inclusion, and the optimal primary trial outcome measures to choose.

Glossary

DAT = dopamine transporter; **DLB** = dementia with Lewy body; **GBA** = glucocerebrosidase A; **HR** = hazard ratio; **iRBD** = isolated RBD; **IRBDSG** = International REM Sleep Behavior Study Group; **LRRK-2** = leucine-rich repeat kinase 2; **MCI** = mild cognitive impairment; **MDS-UPDRS** = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; **MoCA** = Montreal Cognitive Assessment; **MSA** = multiple system atrophy; **PARS** = Parkinson at-risk study; **PD** = Parkinson disease; **RBD** = REM sleep behavior disorder.

The neurodegenerative synucleinopathies, namely, Parkinson disease (PD), dementia with Lewy bodies (DLBs), and multiple system atrophy (MSA), all have a prodromal interval. During this period, subtle symptoms and signs are present, but clinical diseases (e.g., parkinsonism, dementia, and cerebellar ataxia) are not yet fully manifest.[1] As neuroprotective therapies are being developed, interest is turning to prodromal stages to test and eventually use these therapies, while there is still time to prevent irreversible degeneration.

REM sleep behavior disorder (RBD) refers to a sleep disorder in which the normal systems that maintain REM atonia/paralysis are lost, resulting in apparent acting out of dreams.[2] RBD has been associated with brainstem lesions, pharmacologic triggers (most notably antidepressants), autoimmune diseases, etc. However, in most cases, it is related to an underlying neurodegenerative synucleinopathy. RBD and its hallmark on a polysomnogram (i.e., loss of REM atonia) are common in all synucleinopathies, occurring in 30%–70% of patients with PD, 70%–80% of DLB, and 70%–90% of MSA. In many cases, the RBD precedes other manifestations of disease, during which time, it is termed idiopathic/isolated RBD (iRBD). This review will summarize the potential for the use of patients with iRBD in the development of neuroprotective therapy, with a focus on practical issues for clinical trials.

Why Focus on iRBD?

Moving into a prodromal population such as RBD has some disadvantages. First, although there are many potential patients available (perhaps 1% of the general population), the majority are unaware of their prodromal PD status. The known participant pool is therefore much smaller than for clinical PD. Second, from a regulatory standpoint, there is no clear path to licensing of a product for prodromal PD. (The degree to which this is a true limitation is unclear because regulators are unlikely to ignore any truly compelling study showing neuroprotective effects. Moreover, aducanumab has been provisionally licensed for Alzheimer disease based on studies conducted entirely in a population that can be, by PD definition, considered as prodromal [i.e., "mild cognitive impairment (MCI) due to Alzheimer disease" is akin to "mild motor/sleep/autonomic impairment due to PD"].) Third, a small proportion of patients with iRBD may have nonsynucleinopathy causes (undiagnosed narcolepsy,[3] autoimmune conditions,[4] posttraumatic stress,[5] etc). Therefore,

further diagnostic procedures to ensure underlying synucleinopathy may be useful (see Stratification section). Finally, patients with prodromal PD generally feel well and often do not consider themselves as having a disease; therefore, medication side effects and dosing convenience become especially important in this population.

Despite these disadvantages, there are compelling reasons to select patients with RBD for neuroprotective therapy in PD/DLB, namely, (1) the long prodromal time window, (2) the absence of symptomatic therapeutic confounds, and especially (3) the extreme predictive power/high disease risk.

Time Window

Any neuroprotective therapy against a progressive neurodegenerative disease should be applied as early as possible in the disease course. In most series, the interval between development/diagnosis of RBD and defined neurodegenerative disease averages 10–15 years. Hence, RBD offers an opportunity to intervene very early. Analyses of the time course of prodromal symptoms suggest that only olfaction (20 years) and autonomic dysfunction (10–25 years) offer similarly long prodromal intervals.[6] By contrast, motor and cognitive abnormalities have prodromal intervals of 5–8 years. Moreover, these motor/cognitive variables progress slowly initially, followed more rapid loss soon before phenoconversion,[7] so testing only has sufficient specificity in the 2–3 years before diagnosis. By contrast, the 10–15-year interval offered by iRBD provides a notable window of opportunity to intervene before neurodegeneration advances. Used at RBD onset, a neuroprotective agent that slows disease by one-third could result in 3–5 years of additional life without clinical PD or dementia and 6–10 total extra years without severe disability.

No Symptomatic Confound

A second advantage, especially compelling for trial design, is that patients with iRBD are not taking symptomatic motor or cognitive treatments. The use of effective symptomatic therapy is among the biggest challenges in trial design, especially in PD. Any patient starting or substantially changing doses of symptomatic medication can experience benefits that far outweigh anything measurable in the underlying progression. For example, in the Earlier versus Later Levodopa Therapy in Parkinson Disease study of early PD, the primary outcome (Unified Parkinson's Disease Rating Scale [UPDRS], Part III) progressed approximately 9 points per year in the placebo group.[8] The group randomized to 200 mg 3 times a day of

levodopa was 12 points better at the study end. Hence, with initiation of levodopa, 1.3 years of apparent progression would "wash away." This issue is becoming especially acute because there is a broad shift toward the earlier use of symptomatic therapy; it is now uncommon to see patients with PD left untreated for more than 1–2 years.

Conversion Rate

Given that it is of extreme interest to provide treatment early in the course of PD, and before symptomatic treatments, are patients with iRBD the best choice? As it stands, there is no single clinical marker that has been shown to have the predictive value of iRBD. In numerous cohort studies, patients with iRBD (without any further stratification) will phenoconvert to parkinsonism or dementia at a rate of 6%–8% per year. For diagnostic test utility, this corresponds to a positive likelihood ratio of more than 100.[9] By contrast, easily measured clinical variables, such as olfactory loss, clinical autonomic dysfunction, motor testing, and subtle cognitive abnormalities, are associated with likelihood ratios between 2 and 10. Moreover, no biomarkers used as "stand alone" markers have had such high specificity; the highest is dopaminergic transporter imaging, with a likelihood ratio of 40. The phenoconversion rate of RBD is such that even a person with a genetic alteration conferring 100% PD risk would have a lower phenoconversion rate (i.e., a disease-free 50-year old with 100% penetrance by age 80 years has a rate of only 3% per year). Given that the primary gene targets (glucocerebrosidase A [GBA] and leucine-rich repeat kinase 2 [LRRK-2]) have <30% lifetime prevalence, the phenoconversion rate will undoubtedly be lower still. Perhaps the only other clinical condition with a specificity that may approach RBD is laboratory-diagnosed pure autonomic failure for which short-term studies have found up to 10% annual phenoconversion rates[10,11]; as these studies are confirmed, patients with pure autonomic failure could potentially be combined with patients with iRBD to have a larger, more generalizable cohort.

Beyond single markers, another way to find patients with high conversion rates is to undergo multiple-stage screening, in which a large population is screened with inexpensive low-specificity tests, followed by more specific secondary screens. Another prominent example is the Parkinson at-risk study (PARS), which screened olfaction then followed hyposmics with a dopamine transporter (DAT) scan. This 2-stage procedure was able to detect patients with prodromal PD with 67% phenoconversion after 6 years of follow-up.[12] Whereas staged stepwise population screening approaches may offer advantages in generalizability, the major challenge is the number of people needing to be screened, for example, PARS screened 10,139 participants to recruit 21 participants with hyposmia and DAT deficit.[13] So far, all large-scale general population screens ultimately obtain small numbers of patients with de novo PD (generally 10–30). By contrast, the 2019 multicenter analysis of iRBD described 352 de novo PD/DLB/MSA cases. Moreover, this study involved only half of the centers currently in the International REM Sleep Behavior Study Group (IRBDSG) (and only half of the patients currently in the participating centers were recruited); therefore, the IRBDSG now has >4,000 patients with iRBD currently in an active follow-up. Note also that a 2-stage screening approach has already been used in RBD, in which simple screening questionnaires for RBD were placed in newspapers and then followed up with a polysomnogram for screen positives.[14,15] By adapting this method, a large proportion of patients with RBD could likely be generated for potential trials. Practically speaking, therefore, patients with RBD likely represent the only large existing cohort of untreated prodromal PD/DLB that would be ready to start a clinical trial now.

How Can Trials Be Performed?

Although many details of trial design depend on the specifics of a trial, there are 3 critical questions which will need to be answered before a trial begins: which agent to try, which patient with RBD to select, and what primary outcome measure to pick. Thankfully, research is advancing, and we are starting to get clearer answers to these critical questions.

Which Agent?

From the array of potential neuroprotective therapies in development, many would be appropriate for a trial in RBD. Still, some agents might better suit iRBD specifically. In selecting an agent, 3 key points should be considered. First, patients with iRBD are early in their disease process. Second, RBD leads to multiple phenotypic outcomes (i.e., both dementia and parkinsonism), indicating a broad degeneration. Third, RBD marks a subtype within PD and DLB, which may mark differences in pathophysiology.

Early

If iRBD is early, then any potential agent must target a pathophysiology that is present early in the disease process, before substantial neurodegeneration occurs. Hence, therapies focused on replacing neurons that are lost (e.g., implanted stem-cell therapies) have no particular advantage in RBD; given the logistical challenges, one could simply choose to apply these to persons with already-established PD. Therapies that target end stages of neurodegeneration (e.g., restorative therapies) may also have less utility.

Not Just PD

If RBD predicts multiple Lewy body diseases, potential therapies must target a pathophysiologic process common across Lewy body diseases (or even better, across all synucleinopathies, including MSA). This would rule out amyloid-focused therapies (which might target DLB but not PD) or any therapy that focuses on specifically protecting brainstem neurons (e.g., calcium-channel blockade targeting L-type pacemaker activity).

Subtypes

Within both PD and DLB, RBD identifies a subtype of disease. In DLB, RBD occurs in the majority and is associated with a

higher prevalence of parkinsonism, more hallucinations, more cognitive fluctuations, and higher mortality[16] (more like synuclein/PD, less like amyloid/Alzheimer disease). In PD, approximately half have clinical RBD and within PD, RBD is strongly associated with cognitive impairment, autonomic dysfunction, and gait dysfunction (i.e., more like DLB than non-RBD subtypes).[17] In prospective studies, RBD in PD has been associated with faster development of dependency, death, and dementia.[18,19] The presence of RBD within PD is associated with more synuclein deposition at autopsy, suggesting that RBD marks a "synuclein-driven" pathophysiology.[20]

Of note, certain PD genes are not generally linked to RBD, most notably parkin, PINK-1, and LRRK-2. This generally argues against focusing on therapies targeting mitochondrial molecules in the parkin/PINK-1 pathway or using LRRK-2 inhibitors in iRBD. However, there are clear links between RBD and synuclein on a genetic basis. These links suggest the 2 prime targets.

Synuclein

Synuclein is an obvious choice for a target in RBD, for the compelling reason that every patient with idiopathic RBD in multicenter cohort studies has gone on to develop a clinical neurodegenerative synucleinopathy. Genetic studies find a role for synuclein polymorphisms in PD.[21] Fine mapping studies have suggested that synuclein polymorphisms in the 5′ region are most associated with RBD (this is the same region associated with DLB but is less associated with PD, in which polymorphisms cluster on the 3′ end[21]). Autopsy studies of the few patients with idiopathic RBD who died in their still-idiopathic stage all found synucleinopathy, generally in an earlier stage than is seen in established PD.

Current synuclein-based approaches include passive immunotherapy, active immunization, small molecule aggregation inhibitors, and antisense therapy to reduce synuclein synthesis. In the idiopathic RBD stage, when patients are generally free of substantial neurologic symptoms, burden of treatment itself also needs to be considered. Therefore, synuclein-based therapies should not only have an excellent safety profile but should ideally be easy to administer. Therefore, "one-shot" therapies such as active immunization or oral agents are particularly attractive. Concerns regarding potential adverse effects of synuclein manipulation are also of particular importance at this phase (i.e., the balance between potential beneficial functions of normal synuclein vs adverse effects of abnormal synuclein aggregation might be different in very early disease stages than in advanced PD).

Lysosome and Glucocerebrosidase A

In addition to synuclein, genetics of iRBD point to therapies targeting GBA specifically and to the lysosome more generally. There is a strong relationship between iRBD and GBA. GBA mutations are a strong risk factor for both PD and DLB

(although MSA links are less clear). Multicenter studies also find GBA mutations in approximately 10% of patients with iRBD, a proportion that exceeds that of PD.[22] The classic GBA-PD subtype of worse prognosis and earlier cognitive impairment is similar to the RBD subtype within PD.[23-26] Within iRBD stages, GBA mutations are uncorrelated with any clinical features (i.e., GBA-associated iRBD is extremely similar to iRBD as a whole).[27] On the other hand, GBA is associated with faster phenoconversion from iRBD to PD and DLB. This suggests that GBA mutations might act as an accelerant of the same pathophysiologic process seen in RBD as a whole.[27] Although the recent announcement of the failure of a trial of substrate-reduction therapy with venglustat is disappointing, other therapies targeting GBA are in development, and many more therapies (e.g., ambroxol) target the lysosome more broadly. Many are orally available, and some have relatively well-established safety profiles, suggesting good potential for GBA-based/lysosomal-based therapies.

These are not the only early options for treatment because many other pathophysiologic processes (inflammation, mitophagy, and oxidation) underlie PD. Regardless, as new avenues are evaluated, it is essential to keep the 3 essential features in mind; choose an agent that targets early pathophysiology, that can target at least PD and DLB (and perhaps MSA as well), and which matches the clinical/genetic/pathophysiologic profile seen in RBD.

Which Patient?

Although the advantage of long time intervals will be considerable once a therapy is developed, this can create a challenge for trial design; no neuroprotective trial can practically be planned for 15 years of duration. Therefore, it is prudent to perform simple additional selection measures to enrich the trial population for a higher phenoconversion rate. These can include measures to confirm the presence of prodromal synucleinopathy (e.g., olfactory testing and biopsy confirmation) and to identify more advanced stages (which helps to ensure that patients have sufficient disease burden to detect meaningful change over time). Any selection measure should be made with the important caveat that selection criteria reduce both the number of patients eligible for a trial and its potential generalizability outside the trial population. Based on research so far, some of the leading selection parameters are included.

Age

Age is the most important risk factor for neurodegenerative disease in general. In iRBD, age increases phenoconversion rates by approximately 50%–70% per decade.[28,29] Stratification to age >55 years has shown modest reduction in sample size estimates. Moreover, it is likely that the very young (i.e., <40 years) are relatively more likely to have non-synucleinopathy causes of their RBD, including unrecognized narcolepsy, PTSD, pharmacologic-triggered RBD, and possible autoimmune causes. Therefore, it seems prudent to add a minimum cutoff age, perhaps in the range of 45–55 years. It is unclear whether a maximum age range is scientifically valid;

however, for practical considerations (adverse events, competing morbidity/mortality, etc), many trials exclude those with very advanced age (e.g., age >85–90 years).

Clinical Markers of Degeneration

Based on multicenter analyses, many clinical markers can identify patients at higher risk. Olfactory loss is observed in more than 60% of patients with iRBD and is strongly associated with higher phenoconversion rates (hazard ratio [HR] = 2-5-3).[28] Olfaction is lost early in the course of iRBD with a predicted prodromal window of >20 years; therefore, it would be less sensitive to the stage of disease. For an agent unable to target MSA pathophysiology, selecting on olfactory loss will have the advantage of excluding most patients with prodromal MSA, who have normal olfaction.[28,30] Another clear selection candidate is subtle motor abnormality, whether measured by clinical scales (e.g., Movement Disorder Society-Sponsored Revision of the UPDRS [MDS-UPDRS]) or quantitative motor testing. In multicenter studies, these were strongly associated with phenoconversion rates (HR >3, with annual phenoconversion rates up to 15%, cutting sample size estimates in half).[28,29] Of note, motor abnormalities predict both dementia and parkinsonism-first conversions.[28] Motor abnormalities generally identify those proximate to phenoconversion and are therefore usually less generalizable (only 30%–40% of iRBD candidates would be eligible). Combining cognition and motor function as "either/or," measures can slightly expand the eligible pool, albeit with slightly reduced conversion rates than seen with motor testing alone.[28]

Biomarkers/Neuroimaging Markers

In general, nonclinical markers have not been found to have a predictive value better than clinical markers. However, they have the advantage of independence of the major clinical trial outcomes (i.e., selecting patients based on MDS-UPDRS, then using the same MDS-UPDRS as an outcome measure introduces biases from regression to the mean, potential collider bias, etc). Biomarkers can also serve as an independent "second opinion" in the presence of or stage of synucleinopathy. Biopsy measures confirming synucleinopathy may serve this purpose; several studies have now clearly documented abnormal deposition in skin and submandibular tissue in iRBD.[31-34] Skin biopsies are particularly easy to obtain and have been positive in 58%–82% of patients with iRBD (vs 0%–5% of controls). Synuclein-seeding assays (e.g., RT_QUIC and PMCA assays) from CSF or skin are also very promising, and early CSF studies find abnormal synuclein seeds in up to 90% of patients with iRBD.[35]

Arguably, the most promising neuroimaging marker for patient selection is dopamine functional imaging (e.g., DAT scan). Imaging the dopaminergic system serves 2 purposes; it both confirms the presence of neurodegeneration and identifies the subject as being relatively advanced in their disease process. Approximately 40% of patients with RBD have abnormal dopaminergic imaging, and several studies have now documented a predictive value of DAT scanning for both PD and DLB-first phenoconversion.[36-38] A recent multicenter study of the IRBDSG found a HR of 4.35 for patients with abnormal uptake in the putamen, with an annual phenoconversion rate of 15%.[38] Given the need for most studies to add biomarker readouts, DAT is currently the imaging marker with the most established potential in clinical trials.

Combining Measures

Prodromal Criteria

The MDS prodromal criteria were designed to estimate the probability that any individual is in the state of prodromal PD.[9,39] They use a mathematical Bayesian method to combine markers together in likelihood ratios. The criteria have been validated both in general population studies and in patients with idiopathic RBD.[40-42] They have the important advantage of being agnostic as to the pathway in which a patient gets to a diagnosis; hence, a study could combine patients with RBD who have olfactory loss, and/or subtle motor findings, and/or abnormal DAT scans. In multicenter studies, the annual phenoconversion risk of those who meet MDS criteria is 8.2%, compared with 6.3% for iRBD as a whole, suggesting moderate reduction in sample size. Moreover, 75%–80% of PSG-proven iRBD patients meet MDS prodromal criteria, suggesting excellent generalizability.[28]

MDS prodromal PD criteria could be potentially combined with the recently published prodromal DLB criteria.[43] The DLB criteria are conceptually different in that they focus on MCI; they aim to distinguish which patients with MCI have underlying Lewy body disease (this makes their role in iRBD less clear because essentially all iRBD patients with cognitive impairment already are known to have Lewy body disease). However, combination of MDS criteria with DLB criteria in an "either/or" fashion might potentially improve generalizability further. So far, this approach has not been tested in iRBD cohorts.

Therefore, there are numerous options to stratify patients for neuroprotective trials. It is impossible to nominate a clear favorite that applies to all scenarios. Rather, it may be better to choose selection parameters depending on the specifics of the trial, considering factors such as the required study duration, the specific agent being tested, and the primary outcome.

Which Primary Outcome?

In considering a primary outcome for clinical trials, several factors are critical.

1. Any primary outcome must measure a construct important in quality of life (i.e., surrogate markers and biomarkers can be useful in early proof-of-concept stages but are not sufficient as primary outcomes for definitive studies).
2. Variables must be reproducible and consistently measured across sites.

3. Categorical variables must have clearly defined boundaries and be standardizable.
4. Continuous variables must have a low signal-to-noise ratio and change consistently over time.

Based on these considerations, there are 2 top considerations for a primary outcome, namely, phenoconversion from RBD to defined neurodegenerative disease (or standard motor/cognitive rating scales). Both have differing advantages and disadvantages.

Phenoconversion

This is the most obvious candidate because it is a clear "hard" outcome that is meaningful for patients. Prevention of parkinsonism or dementia is a clearly important endpoint. Such an endpoint would be analyzed as a categorical variable (likely a time-to-event analysis) and nominated as an "either-or" of parkinsonism, dementia, and perhaps cerebellar ataxia (i.e., MSA-C). There are standard criteria for each of these, for example, the Movement Disorders Society criteria for PD[44] and the consensus criteria for dementia with Lewy bodies[45] (noting that standard criteria for cerebellar ataxia are lacking).

The primary disadvantage of phenoconversion is that even with standard criteria, boundaries between normal and abnormal can be difficult to define. For example, when can one define "true" bradykinesia vs equivocal slowing? Does rigidity observable only with activation maneuvers suffice? How does one define dementia for patients who have limited awareness of deficits or very low lifestyle demands on their activities of daily living? A second, more conceptual concern is that "phenoconversion" implies a fundamental difference between prodromal and established disease. Perhaps all disease exists on a spectrum, and prodromal PD/DLB *is* PD/DLB (just at an earlier stage); if so, why not use the scales of established disease to measure change?

Clinical Scales

In most trials of clinical PD, the clinical scale of choice is the MDS-UPDRS, which tracks change well over time, has a highly standardized means of assessment, and has benchmarks of minimal clinically significant change. A similar unitary DLB scale does not exist, although many standard cognitive measures are available for testing. Continuous variables can have the potential for increased statistical power (resulting in lower sample size), provided that they have a good signal-to-noise ratio.

One disadvantage of clinical rating scales is the possibility of floor effects and nonlinearity, for example, many patients with iRBD have completely normal UPDRS scores for several years, followed by a rapid increase closer to phenoconversion.[6] If there is little true deficit to measure, then random variations in measurements can reduce power. Cognitive variables have similar concerns, with the additional concern of practise effects (true progression is missed because participants improve on the tests with practise).

We recently conducted an analysis of potential clinical measures over time in patients with iRBD, followed annually with the same protocol, allowing tracking of change over time.[46] We found generally similar sample size estimates between a categorical time-to-event analysis of phenoconversion and continuous analysis of MDS-UPDRS or simple quantitative motor tests. However, a hybrid approach, using a time-to-event analysis of a clinically meaningful decline in clinical scales (either a 4-point decline in MDS-UPDRS or a 4-point decline in the Montreal Cognitive Assessment [MoCA] was the most efficient), reducing sample size by almost 50%. Given the anchor in a clinically meaningful change plus a lower sample size, this may be the leading candidate as a primary outcome.

What Trial Duration?

One notable advantage of using patients with RBD is the ability to perform longer-duration trials. However, there is no fixed minimum trial duration. To illustrate, in a categorical time-to-event analysis (e.g., phenoconversion and milestone of decline) with a 50% effective agent, 65 "events" are required to have sufficient trial power. A trial's sample size/duration can then be planned to obtain the number of events required; the shorter the trial, the larger the sample size. For example, our prior analysis found that with the abovementioned 4-point MDS-UPDRS/MoCA outcome, 126 patients per group would be required in a 2-year trial for 80% power.[46] If a 1-year trial is desired, sample size must be approximately doubled (n = 232, assuming proportional hazards). If one wanted a 4-year trial, sample size would be approximately halved (n = 73).

It should be noted, however, that almost all preventative agents would have some mechanistic lag time between dosing and measurable protective effect. This lag time would be especially long in agents that work very early in disease pathophysiology (e.g., passive immunotherapy preventing cell-to-cell transmission of synuclein). For these agents, longer trials may be essential for success. These mechanistic benefits of long-duration must be balanced against critical practical concerns, such as patient retention, patent life, and consistency of trial execution. Overall, trial durations of 2–3 years might strike the best balance between the chance of successful prevention and practical feasibility concerns.

Conclusion

As it currently stands, patients with idiopathic/isolated RBD represent the only trial-ready large cohort of patients with prodromal PD currently in existence. With rapid advances in our understanding of prodromal PD and DLB, we now have the essential knowledge required to start a neuroprotective trial against neurodegeneration in PD. Any successful trial in prodromal PD will be a landmark for the field and a major advance in patient care; the time to start is now.

Appendix Author

Name	Location	Contribution
Ronald B. Postuma, MD, MSc	Department of Neurology, McGill University, Montreal, Quebec, Canada	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design

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