

# Treatment of isolated REM sleep behavior disorder using melatonin as a chronobiotic

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## Abstract

Melatonin is recommended as a first-line treatment in isolated REM sleep behavior disorder (iRBD), although no large patient group has been reported. To assess effects, time course and confounding factors in the treatment of patients with iRBD using melatonin, 209 consecutive patients were included in this single-center, observational cohort study. A total of 171 patients had taken melatonin according to our chronobiotic protocol (2 mg,  $\geq 6$  months, *always-at-the-same-clock time*, 10-11pm, corrected for chronotype), 13 had applied melatonin for about 1-3 months, and 25 underwent mixed treatments. In total, 1529 clinical evaluations were performed, including Clinical Global Impression (CGI) and a newly developed RBD symptom severity scale (Ikelos-RS), analyzed using linear mixed models. Validation of Ikelos-RS showed excellent inter-rater reliability ( $\rho = 0.9$ ,  $P < .001$ ), test-retest reliability ( $\rho = 0.9$ ,  $P < .001$ ) and convergent validity ( $\rho = 0.9$ ,  $P < .001$ ). With melatonin, RBD symptom severity gradually improved over the first 4 weeks of treatment (Ikelos-RS: 6.1 vs. 2.5; CGI Severity: 5.7 vs. 3.2) and remained stably improved (mean follow-up  $4.2 \pm 3.1$  years; range: 0.6-21.7 years). Initial response was slowed to up to 3 months with melatonin-suppressing (betablockers) or REM sleep spoiling co-medication (antidepressants) and failed with inadequately timed melatonin intake. When melatonin was discontinued after 6 months, symptoms remained stably improved (mean follow-up after discontinuation of  $4.9 \pm 2.5$  years; range: 0.6-9.2). When administered only 1-3 months, RBD symptoms gradually returned. Without any melatonin, RBD symptoms persisted and did not wear off over time. Clock-timed, low-dose, long-term melatonin treatment in patients with iRBD appears to be associated with the improvement of symptoms. The outlasting improvement over years questions a pure symptomatic effect. Clock-time dependency challenges existing prescription guidelines for melatonin.

## KEYWORDS

chronobiotic, dementia, disease modification, melatonin, neurodegeneration, parkinsonism, RBD, synucleinopathy

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## 1 | INTRODUCTION

In patients with isolated rapid eye movement sleep behavior disorder (iRBD), the characteristic atonia of voluntary muscles in REM sleep is impaired, leading to acting out of dreams. Initially, patients start to vocalize, speak and move complexly. As the disorder progresses, patients may yell, fight or jump out of bed, often injuring themselves or their sleeping partner.<sup>1</sup> Recently, iRBD was recognized as the most reliable prodromal biomarker of synucleinopathies such as Lewy body dementia and Parkinson's disease.<sup>2-4</sup> As such, iRBD offers an early window for insights into the pathophysiologic process as well as for disease-modifying treatments.

The mainstay of the treatment in RBD is the prevention of injuries by modifying a patients' sleep environment and suppressing motor activity during sleep with benzodiazepines, usually clonazepam.<sup>5,6</sup> Being reluctant to initiate a long-term benzodiazepine treatment, we introduced the use of melatonin as a therapy for patients with RBD 25 years ago.<sup>7,8</sup> Since then, melatonin has developed into one of the two most recommended level B treatment options in RBD,<sup>9</sup> although reports on the effects of melatonin in RBD were relatively rare.<sup>10</sup> Moreover, in contrast to our own randomized controlled trial (RCT),<sup>11</sup> two recent RCTs failed to show any effect of melatonin on RBD, questioning the effect in general.<sup>12,13</sup> Mechanisms of melatonin are cited as poorly understood, comprised in the statement that "most experts are frankly puzzled why melatonin has any effect on RBD".<sup>14</sup>

Already in our first patient of 1995, effects with melatonin treatment were unusual: gradually developing reduction of RBD symptom's frequency and severity over weeks, accompanied by a substantial improvement in cognitive performance and an outlasting effect months after discontinuation.<sup>7</sup>

Inspired by our first patient and questioning the possible mode of action, we experimentally treated three groups of patients using melatonin: patients with (1) RBD; (2) REM sleep deficit; and (3) periodic limb movement disorder during sleep (PLMD, as a well-defined motor disturbance within sleep). Interestingly, melatonin improved primary outcome parameters in all three groups of patients.<sup>15,16</sup> The conclusion we made was that the effect might be not specific to a disorder, but to a basic sleep mechanism. The combination of four common observations found in the three patient populations pointed us to the assumption that the circadian clock is involved: (1) a positive response occurred only when melatonin was administered within a narrow time span between 10 and 11PM; (2) responders and nonresponders were best differentiated by a stable clock time of administration, as opposed to flexible administration due to regular prescription guidelines (eg, "at bedtime", "1-2 hours before bedtime" or "after meal"); (3) a gradual response over weeks; (4) a persisting effect after discontinuation of treatment. Based on these observations, we have developed a "chronobiotic protocol" for

the use of melatonin treatment,<sup>17</sup> which we validated in two small sampled RCTs.<sup>11,16</sup>

The aim of the present evaluation was to assess effects, time course and confounding factors of melatonin treatment on RBD symptoms severity in a large group of patients with iRBD.

## 2 | METHODS

### 2.1 | Patients

The present evaluation was performed in the framework of a larger project documenting the outcome of melatonin treatment in patients with iRBD (in part preprinted in medRxiv, doi.org/10.1101/2020.11.05.20224592). Since 2016, we started to systematically recontact all our patients diagnosed with iRBD and ever since perform a yearly staging of the individual pathological progression. Data presented here include the time course and factors influencing the effects of melatonin treatment on RBD-specific behavior.

Until December 2020, we have diagnosed RBD in 290 consecutive patients according to the International Classification of Sleep Disorders (ICSD-3). Patients passed through a three night's video-polysomnography (vPSG), with standard montages enlarged for parasomnias. Sleep stages were manually scored, with the modification of the criteria on atonia to allow increased EMG activity during REM sleep.<sup>18</sup> REM sleep without atonia was automatically scored with a method based on the original description given by Lapierre and Montplaisir, adapted and validated by Consens et al.<sup>19,20</sup> Isolated RBD was present in 209 patients of whom 171 were long-term ( $\geq 6$  months) treated with melatonin according to our chronobiotic protocol, and 38 were treated with the usual mixture of treatments (Table 1). In total, 14 of 209 patients converted to clinical synucleinopathy. Observational period ended at time of conversion.

In our clinic, most patients are referred by a neurologist. Patients are diagnosed and redirected with a therapeutic recommendation. In patients with RBD, we usually initiate treatment while advising to take low-dose (2 mg) melatonin, long-term, according to our chronobiotic protocol. Even though this had been recommended to all of our patients with iRBD, 38 had not been treated with melatonin for 6 or more months ("mixed treatment" group). Some had improved with melatonin, discontinued and concluded that "they were cured" because RBD symptoms did not reoccur ( $n = 13$ , "short-term melatonin" in Figure 1). The remaining 25 patients ("various" in Figure 1) experienced an initial worsening or treatment failure (melatonin stopped after 1-7 nights;  $n = 13$ ) and were hesitant to take melatonin, or their treating physicians were reluctant to prescribe it (melatonin was stopped within 4 weeks;  $n = 12$ ). In those 25 patients,

**TABLE 1** Demographic and Clinical Data

Video-PSG-confirmed RBD		N = 290	
a) Secondary RBD		64	
RSWA only during apnea		23	
RBD only during antidepressant treatment		2	
Converted at baseline		39	
b) iRBD		226	
Recent patients (<6 mo of follow-up)		17	
Current iRBD sample		209	
Average follow-up		4.0 ± 3.0 yrs (0.5-21.7)	
<i>Group Specifics</i>			
Male		160/209 (76.6%)	
Age at estimated RBD onset		63.3 ± 9.3 yrs (23-84)	
Age at baseline/RBD diagnosis		68.1 ± 8.9 yrs (30-86)	
RBD severity	Ikelos-RS total score	6.0 ± 1.1	
	CGI severity	5.5 ± 1.0	
Excessive daytime sleepiness (ESS)		7.2 ± 4.0	
Betablockers		65/209 (31.1%)	
Antidepressants		43/209 (20.6%)	
<i>Biomarkers</i>			
DaT-SPECT abnormal		61/133 (45.9%)	
UPDRS-III (neuromotor)		2.2 ± 3.2 (177/210)	
MMSE (cognition)		29.0 ± 1.2 (171/210)	
Olfaction	hyposmia	144/150	79/150 (52.7%)
	abnormal	(96%)	65/150 (43.3%)
	anosmia		
SCOPA-AUT (constipation)		75/158 (47.5%)	

Note: Results given as means ± SD; classification “abnormal DaT-SPECT” defined as >2SD below the mean specific binding ratio in either posterior or anterior (left or right) putamen; olfaction determined using “Sniffing-Sticks” with scores <30 “hyposmia,” <15 “anosmia.”

Abbreviations: CGI, Clinical Global Impression; DaT-SPECT, Dopamine Transporter Single-Photon Emission Computed Tomography; ESS, Epworth Sleepiness Scale; Ikelos-RS, Ikelos rating scale; Irdb, Isolated REM sleep Behavior Disorder; MMSE, Mini Mental State Examination; PSG, Polysomnography; RSWA, REM sleep without atonia; SCOPA-AUT, Scales for Outcomes in Parkinson's disease-Autonomic; UPDRS-III, Unified Parkinson Disease Rating Scale-part III.

the usual mixture of therapies was applied by their neurologist (see below). Follow-up consultations were conducted in person or by telephone by the attending physician. Adverse events were not systematically studied. Long-term side effects (eg, after weeks and longer) of melatonin treatment were not reported by any of the treated patients.

All patients had provided written informed consent for anonymous analysis and publication of their clinical data. The ethics committee of Charité-Universitätsmedizin Berlin approved publication of the results of the post hoc data analysis.

## 2.2 | RBD symptom severity rating scale—Ikelos-RS

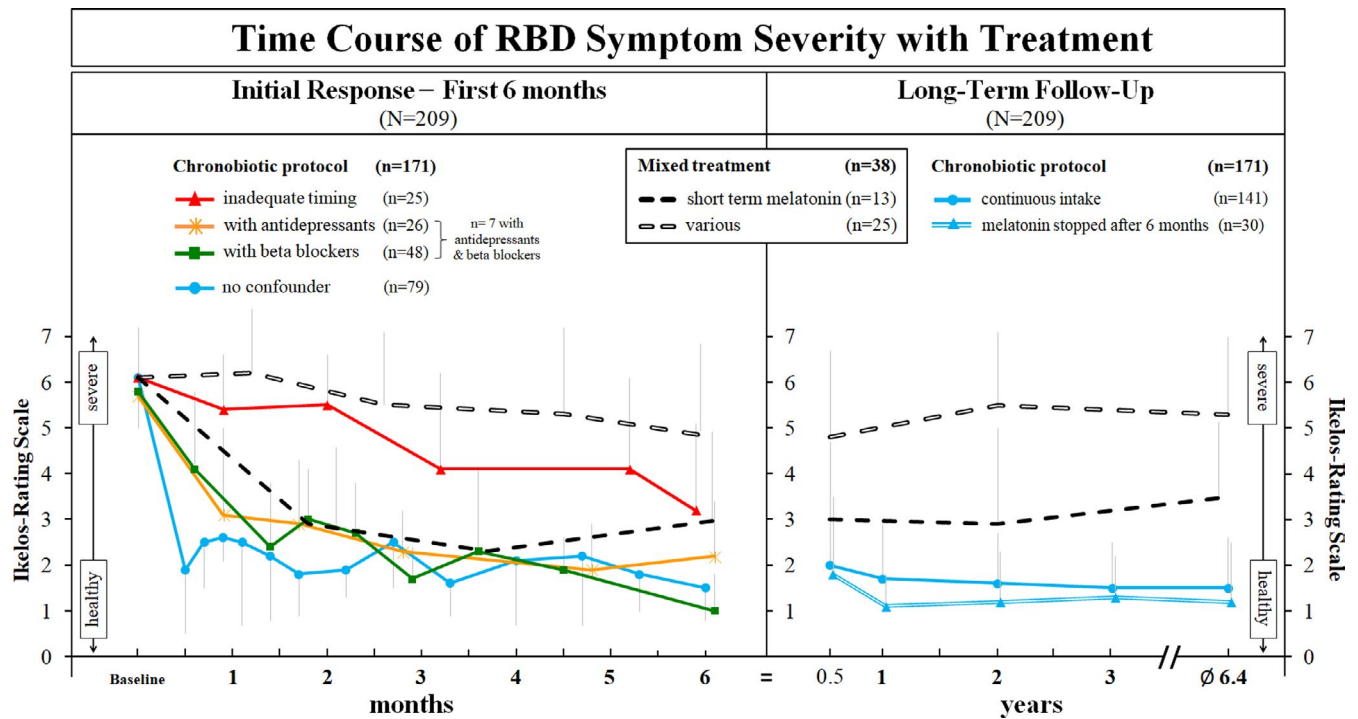
We specifically developed and validated an RBD symptom severity rating scale called Ikelos-RS, after the god of nightmares in the Greek mythology. The Ikelos-RS was rated by a clinician, based on interview with patient's bed partner only. Observational periods were either the last 6 months (default), or since the last interview if less than 6 months. If no regular bed partner was available (n = 8), reports of friends or relatives during periods of, for example, vacation or visits were taken with shorter observational periods. Additionally, RBD-relevant particularities, for example influencing co-medication (like beta blockers or antidepressants) or symptoms of synucleinopathies, were documented. The Ikelos-RS was filled out at baseline (approximately at the time of videopolysomnography) and at every follow-up.

Severity of RBD symptoms is evaluated on two dimensions: on the first scale “frequency,” occurrence of symptoms is estimated from never (=0) to ≤2 to 3 times a month (=1), 1 to 2 times a week (=2), 3 to 5 times a week (=3) or daily (=4). The second scale “expression” describes the form of the most severe manifestation of RBD symptoms from speech or slight distal movements (=0), to screaming or complex, nonaggressive movements (=1), complex movements with risk of injury (=2) or movements driving the patient out of bed (=3). Both ratings are added to a total score (range 0-7) and supplemented by two components of the Clinical Global Impression (CGI Severity Scale (CGI-S) and CGI-Improvement Scale (CGI-I)).

## 2.3 | Chronobiotic protocol

Prior to the third night of vPSG, we initiate long-term melatonin treatment according to a chronobiotic protocol, which implies one major instruction: to take melatonin “always-at-the-same-clock-time” once per day. This clock time should be established at 30 minutes prior to patient's *habitual* bedtime. Patients are instructed to skip melatonin intake if in incidental cases this fixed time cannot be kept, with the explanation that intake at an inappropriate clock time may exacerbate their RBD symptoms.

The rationale for this strict schedule is that since our initial pilot studies with RBD patients about 25 years ago, we repeatedly observed that responders and nonresponders were best distinguished by evaluating their sleep hygiene, that is, stable vs. varying bedtimes and times of melatonin intake (summarized in<sup>10,17</sup>). This clinical observation is in agreement with the fact that melatonin is known to feedback on the suprachiasmatic nucleus, the central pacemaker or master-clock.<sup>21-23</sup> As a consequence, exogenous melatonin should be administered consistently within a rather narrow time span in



**FIGURE 1** Time Course of RBD Symptom Severity with Treatment. Vertical gray lines represent standard deviations. Chronobiotic Protocol: 2 mg melatonin slow release,  $\geq 6$  mo, *always-at-the-same-clock-time*, between 10 and 11PM—corrected for chronotype, melatonin intake to be skipped in case impossible during this time span. Inadequate timing: initial administration with varying clock times (“before bedtime”) or too early (“after meal”); Mixed Treatment—short-term melatonin: melatonin according to chronobiotic protocol but stopped after 1-3 mo of treatment; Various: usual treatment of RBD at the advice of referring physician; Left panel: development of RBD symptom severity scores (Ikelos-RS) over the first 6 mo; Right panel: symptom severity shown over subsequent years; for the chronobiotic protocol, the former subgroups are combined and now subdivided into (a) one with continuous melatonin intake until last follow-up and (b) one in which patients stopped melatonin intake after 6 mo (patients felt “cured”)

order to gain optimal effects. Patients are informed that melatonin in RBD rarely exhibits effects during first days of treatment, rather effects occur within the first weeks. Sometimes symptoms even rapidly worsen over the first days, presumably because appointed time of administration induced a transient initial delay or advance of circadian phase.<sup>23</sup> In those patients, in whom melatonin does not show positive effects over the first 3 weeks of treatment, the time of administration is controlled referring to individual chronotype.

## 2.4 | Statistical analysis

Validation of the Ikelos-RS included evaluation of convergent validity within a bivariate correlation analysis (Spearman's rho) with Ikelos-RS and CGI-S. Spearman's rank correlation coefficient was also used to measure test-retest and interrater reliability.

To investigate initial time course and confounding factors of RBD symptom regression within the first 6 months of treatment, linear mixed models were performed (using the variables “group” and “time” as well as the interaction term

“group x time” as fixed factors), while subdividing the patients into six groups:

Under chronobiotic protocol:

- without the confounders below (n = 79)
- with inadequate timing of melatonin intake (n = 25), for example, too early (prescription “after a meal”) or with changing clock time (prescription “at bedtime”)
- with betablockers (n = 48): metoprolol (n = 21), bisoprolol (n = 21), and various (n = 6)
- with antidepressants (n = 26): citalopram (n = 6), escitalopram (n = 4), venlafaxine (n = 4), mirtazapine (n = 3), paroxetine (n = 2), duloxetine (n = 2), trimipramine (n = 2), agomelatine, amitriptyline, and doxepin (each n = 1)

Mixed therapies:

- short-term melatonin—up to 3 months (n=13)
- various medications (n=25) (eg, clonazepam, other benzodiazepines, zolpidem, dopaminergic agents, mirtazapine, trazodone, or no treatment)



The time course of RBD symptom expression of the group without confounders (=reference group) was compared with those of the other 5 groups (“model A”) one by one at different time points (at baseline; after 2, 4, and 6 weeks; and after 3, 4, and 6 months). Data of patients who took both betablockers and antidepressants ( $n = 7$ ) were excluded from this analysis.

To investigate differences after the initial period of 6 months, the patients of the long-term chronobiotic treatment group were re-classified in patients who (1) continued to take melatonin regularly ( $n = 141$ , “regularly” defined as daily intake at least 50% of the time between treatment initiation and last follow-up) and (2) stopped after about 6 months ( $n = 30$ ), thus including all 171 patients (compared in “model B1”). Grouping was based on the information provided by the patients during the regular medical consultations, in which the (dis-)continuation of melatonin was documented, as well as on completed RBD diaries, in which some of the patients daily recorded the occurrence of symptoms or a change in medication over several weeks. Additionally, the time courses of both subclassifications of the patients under mixed treatments were compared (“model B2”). In both models, groups were compared at 6, 12, 24, 36, and 48 months after initiation of melatonin treatment.

The Ikelos-RS total score is, strictly speaking, an ordinal measure. To allow robust statistical modeling and because higher Ikelos-RS values are associated with more pronounced symptoms, a linear mixed model was preferred over a cumulative link mixed model for ordinal data to test time and group effects. Since the analysis of ordinal-scaled data with parametric methods does not result in high type I error rates,<sup>24</sup> changes in RBD symptom severity and differences over time between the different groups were investigated within a random intercept model.

Significance was defined as P-values less than .05. Bonferroni post hoc test was used for multiple testing corrections in all executed mixed models. Analyses and modeling were implemented using IBM SPSS Statistics (version 23.0).

## 3 | RESULTS

### 3.1 | Patients

Table 1 gives demographics and clinical specifics of our patients. In 290 vPSG-confirmed patients, RBD was determined as being secondary ( $n = 64$ ) due to: (1) conversion to clinical synucleinopathy prior to vPSG ( $n = 39$ ) and (2) REM sleep without atonia (RSWA) and complex behavior during REM sleep occurring only after respiratory events ( $n = 23$ ), or RBD symptoms clearly starting after antidepressant use and absent after the cessation of antidepressant use ( $n = 2$ ). Thus, a total of 209 patients with iRBD were included in our

analysis with group specifics and biomarkers presented in Table 1.

### 3.2 | Validation of Ikelos-RS

To test convergent validity, the Ikelos-RS total score was correlated with the CGI-S in 1529 cases. For the evaluation of the interrater reliability, 45 Ikelos-RS were filled out by two independent physicians. 174 Ikelos-RS were filled out again by the same physician after at least six months. Overall, correlation analyses (using Spearman's rho) showed that the Ikelos-RS can be considered as a valid measuring instrument. Results provide evidence for excellent convergent validity ( $\rho = 0.9$ ,  $P < .001$ ), excellent interrater reliability ( $\rho = 0.9$ ,  $P < .001$ ), and excellent test-retest reliability ( $\rho = 0.9$ ,  $P < .001$ ).

### 3.3 | Changes in symptom severity

RBD symptom severity was evaluated with a total of 1529 Ikelos-RS and scored at the time of diagnosis and at each follow-up visit (usually at least three times per year since 2016). The average last follow-up was  $4.2 \pm 3.1$  years after diagnosis (range: 0.6-21.7 years) for the 171 patients under long-term chronobiotic treatment, and  $3.1 \pm 2.1$  years (range: 0.3-7.6 years) for the 38 patients under mixed treatments.

Figure 1 shows different time courses of RBD symptom severity depending on subgroup classification (model A:  $F_{5,1463} = 9.21$ ,  $P < .001$ ). Patients who took melatonin according to our chronobiotic protocol improved over the first 4-6 weeks of treatment (estimated mean Ikelos-RS at baseline: 5.24, after 6 weeks: 3.29) and remained stably improved (estimated mean Ikelos-RS after 6 months: 1.83). Changes in Ikelos-RS were paralleled by a reduction in CGI severity ( $\rho = 0.9$ ,  $P < .001$ ). In contrast, patients taking melatonin not always at the same clock time (group “inadequate timing,”  $n = 25$ ) initially failed to show improvements in RBD symptom severity, indicated by significantly higher values in the Ikelos-RS during the first 6 months of treatment as compared with the “no confounder” (estimate:  $-0.26$ , SE: 0.06,  $P < .001$ ). This group stuck to the prescription in the medication package leaflet to “take melatonin after a meal, 1-2 hours before bedtime.” Some ( $n = 11$ ) reported an initial worsening of RBD symptoms (eg. jumping out of bed 3 nights in a row) during the first few days up to one week after starting melatonin treatment around 6-8PM (prescription “after a meal”). The remaining patients in this category ( $n = 14$ ) varied their time of intake by several hours (prescription “before bedtime”), resulting in changing clock time of administration with changing bedtimes. After reinstruction on

proper timing, mostly after one or two months after treatment initiation, RBD symptoms improved in all of these patients.

Patients on concomitant betablocker or antidepressant therapy responded more slowly at the beginning of melatonin treatment, but generally showed similar expression of RBD symptoms compared to the no-confounder group after the first three months of therapy (betablockers—estimate:  $-0.01$ , SE:  $0.05$ ,  $P = .814$ ; antidepressants—estimate:  $-0.11$ , SE:  $0.06$ ,  $P = .078$ ). RBD symptoms leveled out at low Ikelos-RS values, with almost no patient reporting a complete disappearance of RBD symptoms. Of 171 patients on long-term treatment, 141 continued to take melatonin until last follow-up (mean follow-up:  $3.7 \pm 2.8$  yrs; range:  $0.5$ - $21.7$ ), and 30 discontinued after 6 months (mean follow-up after discontinuation  $4.9 \pm 2.5$  years; range:  $0.6$ - $9.2$ ). RBD symptoms did not worsen over time in any of these patients (Figure 1, right panel; model B1:  $F_{1,1370} = 1.77$ ,  $P = .183$ ).

In the group of patients on mixed treatments, short-term melatonin initially improved the symptom severity in 13 patients (similar to the reference group “no-confounders”), but stopping melatonin intake after 1-3 months resulted in partly return of symptoms (Figure 1; “short-term melatonin”; estimate:  $0.21$ , SE:  $0.10$ ,  $P = .048$ ). Those 25 patients without improvement (Figure 1, “various”) did not report changes in frequency or severity of RBD symptoms over time (eg, a “wearing-off”), with patients having received short-term melatonin still showing milder RBD symptoms in direct comparison even after years of discontinuation (model B2:  $F_{1,134} = 16.39$ ,  $P < .001$ ).

## 4 | DISCUSSION

Data reported here represent the largest single-center sample of patients with iRBD and almost triple the number of reported patients with iRBD being treated with melatonin.<sup>10</sup> Characteristics such as age, sex, age at RBD onset, comorbidity, and co-medication, and of severity of RBD-specific biomarkers like neuromotor and cognitive performance, olfaction, and dopamine-transporter density are similar to other large groups of iRBD patients.<sup>4,25</sup> Thus, our sample can be considered representative.

Data support the gradual and substantial improvement of iRBD symptoms when treated with melatonin according to our chronobiotic protocol.<sup>10,11</sup> For the first time, we report a systematic evaluation of factors confounding the melatonin treatment, such as using betablockers and antidepressants or the inadequate timing of melatonin, which may explain conflicting publications on melatonin effectiveness. Moreover, the outlasting stable improvement of iRBD symptoms in those 30 patients, who discontinued melatonin after 6 months treatment, questions a pure symptomatic nature of the effect.<sup>6,9</sup>

### 4.1 | Chronobiotic aspects

Besides having a myriad of other effects,<sup>26,27</sup> melatonin acts as a chronobiotic.<sup>22</sup> Exogenous melatonin shifts the internal circadian phase according to a phase response curve and may be used in jetlag or to adjust late chronotypes to social time schedules.<sup>23</sup> No phase shifting or sleep facilitating effects were reported when melatonin was administered in the early evening.<sup>23,28</sup> The preferred time for melatonin administration in our chronobiotic protocol is precisely in this time-period, around 10-11PM. This is not contradictory. Crucial in the context of RBD seems to be a second, yet under-appreciated chronobiotic effect of melatonin: its darkness promoting property.<sup>22,29</sup> When administered during its endogenous rise in the evening, melatonin does not shift phase, but strengthens the coordination of nightly circadian factors, with consequences such as promoting wake-related activities in nocturnal species and sleep-related activities in diurnal species. The sleep stage predominantly driven and modulated by the circadian timing system is that of REM sleep.<sup>30-32</sup> The timing of impulses to this system seems decisive and, once established, needs to be kept “*always-at-the-same-clock-time*.” In contrast, administering melatonin at any other time induces phase shifts resulting in desynchrony of internal rhythms.<sup>23,33,34</sup>

Based on our experience, using our chronobiotic protocol in patients with REM sleep deficit and iRBD, we had earlier shown in two RCTs that effects are grounded on resynchronization of circadian rhythms. The resynchronization results in a strengthened circadian amplitude of, for example, core body temperature and REM sleep polarity.<sup>11,16</sup>

Only recently, various reports suggested sleep and the circadian timing system to be causally involved in neurodegenerative mechanisms, including synucleinopathy.<sup>35-37</sup> Over the last decade, the previously unknown glymphatic system was described, elegantly explaining clearance of metabolic waste, including synuclein, from the brain during sleep.<sup>38-40</sup> Not surprising, data in mice show that glymphatic influx and clearance exhibit circadian rhythms.<sup>41</sup> Circadian abnormalities and flattening of circadian rhythms have repeatedly been proven in patients with Parkinson's disease.<sup>35,36</sup> Thus, the assumption that a synchronizing strengthening of circadian rhythms via light and melatonin—the hormone of darkness—may ameliorate neurodegenerative processes is tempting.<sup>36,37,42</sup>

### 4.2 | Confounding medication

Patients on concomitant betablocker or antidepressant therapy seemed to respond more slowly at the beginning of melatonin treatment, although they did not differ in general from the no-confounder group. Both antidepressants and betablockers

are known to induce secondary RBD as well as to increase RSWA in patients with iRBD.<sup>43,44</sup> Antidepressants are well known to influence REM sleep, with anticholinergic agents to suppress, but serotonergic and noradrenergic agents to spoil the quality of REM sleep.<sup>45</sup> As has been known for decades, lipophilic propranolol blocks melatonin secretion from the pineal gland via beta-receptors.<sup>46</sup> The suppression of melatonin with betablockers predominantly affects REM sleep, which can be reversed by exogenous melatonin.<sup>47</sup> Long-term medication with betablockers is likely to have changed melatonin receptor sensitivity, thus delaying response to initial melatonin.<sup>21,48</sup> The same negative effect could be attributed to recommended increasing dosage of melatonin. Because melatonin influences its own receptor, it is important to have a melatonin-free period over the day. Supraphysiologic melatonin doses, especially in slow metabolizers, prevent the absence of melatonin during the day and could induce insensitivity in melatonin receptors the next evening.<sup>49</sup>

### 4.3 | RBD severity/Ikelos—rating scale

All of our patients at baseline showed involuntary falling out of bed or had attacked their bedpartner in the months before video-PSG-based RBD diagnosis. These behaviors indicate highest severity of RBD symptoms and were for most patients the reason that they felt urged to contact a professional. Within 2 weeks after starting melatonin treatment, while bed partners still noticed complex behavior almost every night, aggressive behaviors in the group without confounders had almost disappeared, objectivated by substantial improvement in CGI and Ikelos-RS. Improvement seems to be indicated by reduction of first aggressiveness and later frequency. The initial high symptom severity at baseline could have resulted in a regression toward the mean effect in the symptom ratings later on. This does not seem very plausible though, as neither the “various treatments” group, nor the group with “inadequate timing of melatonin” showed changes that might be interpreted as such an effect.

Improvements in RBD symptoms persisted for years, even when melatonin was discontinued. This long-lasting improvement cannot be attributed to a spontaneous “wearing-off” of symptoms over time, since the “various treatments” group of patients showed no improvement over time. The treatment duration required for melatonin remains unclear and can only be estimated. Whereas patients who stopped melatonin administration after at least 6 months remained improved, patients who discontinued melatonin after 4–12 weeks worsened again with respect to RBD symptoms—though not to baseline levels.

The newly developed Ikelos-RS shows excellent results for inter-rater reliability, test-retest reliability, and convergent validity, although the latter will be positively biased by the

fact that both Ikelos and CGI are observer-dependent and retrospective ratings, underlying the same recollection error. Existing instruments for the evaluation of RBD severity such as the widely used RBD-SS<sup>50</sup> are polysomnography based, and rather used as screening tools to support diagnosis.<sup>51,52</sup> They may not be suitable for follow-up observations. The RBDQ-HK<sup>53</sup> used in both recent RCTs showing negative results of melatonin in RBD,<sup>12,13</sup> evaluates a broad spectrum of RBD-related symptoms including dream content, behavioral factors and frequency. The long list of thirteen questions may restrict its use to institutionalized patients rather than outpatient practice.<sup>54</sup>

We developed the Ikelos-RS for monitoring treatment response based on clinical interview. A reliable report can only be provided by bedpartners, since most patients notice dreaming and aggressive behavior only. The four categories in severity were developed after clinical experience of a step-like improvement during melatonin treatment. To determine frequency of acting out within and between single nights has not shown to be suitable. Periods of acting out differ, as bed partners sometimes report out-acting 10 days in a row followed by 3 weeks of absence, or sometimes 3–4 nights every week. Thus, longer periods of observation have proven to be more meaningful. For the evaluation of treatment with a more gradual response in the initial phase, our clinical experience suggests observational time periods of 2–4 weeks. Nevertheless, a systematic evaluation of daily vs. longer-term diaries is still needed.

Two strengths of our Ikelos scale are simplicity and the use of bed partner reports only, to be assessed, for example, in a phone-call. Validation beyond the analysis presented here, including RSWA and evaluation of videometric material of PSG, will be published elsewhere as part of the dissertation by one of the authors (SS).

### 4.4 | Limitations

This is an observational study and the validity of observer-dependent results might therefore be questioned. Possible unforeseen placebo effects should caution the interpretation, given the uncontrolled and unblinded design of the study. Although all RBD symptom severity ratings were performed unblinded, they were based on bed partner observation only and the changes were substantial. Symptoms such as frightening aggressiveness several times per week improved in almost all patients long-term treated with melatonin and were replaced by milder symptoms like speaking aloud and slight movements occurring every other week. Most bedpartners that had left the common bedroom because of violent behavior of their partners returned after treatment with melatonin.

The rate of improvement of RBD symptoms with melatonin in previously reported case series varies, and two recent

RCTs have shown no effect.<sup>12,13</sup> Unfortunately, melatonin has been sold worldwide for the past 25 years as a hypnotic to be administered in connection with clock time independent events (eg, “after a meal,” “at bedtime”). Most people who took melatonin—including those in the two recent RCTs with negative results—will therefore not have adhered to a schedule based strictly on clock time. As an example, in our Clinic for Sleep & Chronomedicine, we precisely explain the chronobiotic protocol but even though, still some patients stuck to the aberrant leaflet prescription. Our study indeed demonstrates that beneficial effects of melatonin can easily be disrupted with improper timing of intake, which may well explain lower response rates reported by other groups.<sup>9,12,13,25</sup> In those patients for whom we had a chance to reinstruct, melatonin improved RBD symptoms. On the other hand, melatonin should not be considered a harmless drug or being without side effects. Inadequate timing of melatonin seems likely not only to fail in improvement, but rather to worsen symptomatology due to desynchronization.

Possible other modes of action should be mentioned. The present co-first-line treatment for RBD, clonazepam, immediately improves RBD-related motor behavior.<sup>5,9,25</sup> In contrast, melatonin is not known to have any direct effects on motor behavior. Various other neuroprotective or scavenging effects via melatonin<sup>26,27</sup> and its receptors<sup>55</sup> are to be studied.

## 5 | CONCLUSION

This largest single-center study on iRBD suggests insights into mechanisms behind success and failure of melatonin treatment, which may be relevant beyond the treatment of RBD. Clock-timed, low-dose, long-term melatonin treatment in patients with iRBD appears to be associated with the improvement of symptoms. Initial response slows down with melatonin suppressing or REM sleep spoiling co-medication like betablockers or antidepressants. Positive response fails with inadequately timed melatonin intake. This clock time dependency challenges the existing prescription guidelines for melatonin. The outlasting improvement over years questions a pure symptomatic effect of melatonin in patients with iRBD.

## CONFLICT OF INTEREST

None.

## AUTHOR CONTRIBUTIONS

DK, SS, and FB designed the study, developed methods, collected, analyzed and interpreted the data, prepared, and approved the final version of the manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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**How to cite this article:** Kunz D, Stotz S, Bes F. Treatment of isolated REM sleep behavior disorder using melatonin as a chronobiotic. *J Pineal Res.* 2021;71:e12759. <https://doi.org/10.1111/jpi.12759>