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Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients[☆]

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Abstract

Objective: To describe the treatment response with melatonin for rapid eye movement (REM) sleep behavior disorder (RBD) associated with other neurologic disorders.

Background: Clonazepam has been considered the treatment of choice for RBD. However, an alternative treatment is desirable for those with RBD refractory to clonazepam, for those who experience intolerable side-effects with clonazepam, and for those in whom clonazepam precipitates or aggravates obstructive sleep apnea (OSA). To date, there is minimal published data and limited follow-up regarding the use of melatonin for patients with RBD associated with other neurologic syndromes and disorders.

Design/methods: The response to melatonin treatment for RBD was reviewed on consecutive patients the investigators treated with this agent at Mayo Clinic Rochester from January 2000 to June 2001. The coexisting neurologic disorders, reasons for using melatonin, effective doses, side-effects, and duration of follow-up were also reviewed on all patients.

Results: Fourteen patients were commenced on melatonin over the specified time period (13 male, median RBD onset age 56 years, range 20–77 years). The coexisting neurologic findings/disorders were dementia with Lewy bodies ($n = 7$), mild cognitive impairment with mild parkinsonism ($n = 2$), multiple system atrophy ($n = 2$), narcolepsy ($n = 2$), and Parkinson's disease ($n = 1$). The reasons for using melatonin in these cases were incomplete response of RBD to clonazepam in six patients, existing cognitive impairment in five, intolerable side-effects with clonazepam in two, and presence of severe obstructive sleep apnea and narcolepsy in one. With seven patients continuing to use clonazepam at 0.5–1.0 mg/night, RBD was controlled in six patients, significantly improved in four, and initially improved but subsequently returned in two; no improvement occurred in one patient and increased RBD frequency/severity occurred in one patient. The effective melatonin doses were 3 mg in two cases, 6 mg in seven cases, 9 mg in one case, and 12 mg in two cases. Five patients reported side-effects, which included morning headaches (2), morning sleepiness (2), and delusions/hallucinations (1); these symptoms resolved with decreased dosage. The mean duration of follow-up was 14 months (range 9–25 months), with eight patients experiencing continued benefit with melatonin beyond 12 months of therapy.

Conclusions: In this series, persistent benefit with melatonin beyond 1 year of therapy occurred in most but not all patients. Melatonin can be considered as a possible sole or add-on therapy in select patients with RBD. Prospective, long-term, controlled trials with melatonin are warranted in a larger number of patients with RBD associated with a variety of neurologic symptoms and disorders.

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1. Introduction

Rapid eye movement sleep behavior disorder (RBD) is characterized by loss of normal skeletal muscle atonia during rapid eye movement (REM) sleep with prominent motor activity and disturbed dreaming. Clonazepam has been the treatment of choice for RBD [1–4]. However, an

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alternative treatment is desirable is certain clinical situations – when RBD is refractory to clonazepam, when significant side-effects occur with clonazepam, and when clonazepam precipitates or aggravates obstructive sleep apnea (OSA).

Several other agents have been attempted for treatment of RBD and success has been variable. In an open label trial of melatonin (3 mg/night) in RBD, Kunz and Bes reported significant improvement of RBD in five out of six patients over a 6-week period of administration [5]. Amelioration of RBD symptomatology with 3–9 mg of nightly melatonin was subsequently reported in 13 out of 15 patients, although the duration of treatment was not specified [6]. With the exception of one patient with Parkinson's disease and one patient with 'sympathetic dysautonomia' in the Kunz and Bes report, all other patients in these articles had no other reported neurologic symptoms or disorders and thus had idiopathic RBD.

In this report, we present our updated experience with melatonin for RBD associated with several neurologic conditions [7].

2. Methods

The response to melatonin treatment for RBD was reviewed by the investigators on consecutive patients treated with this agent at Mayo Clinic Rochester from January 2000 to June 2001. All patients met minimal criteria for the diagnosis of RBD [8]. All patients were experiencing dream enactment behavior one or more nights per week, and some form of treatment was considered clinically necessary as potentially injurious behavior was occurring. A titration protocol was determined a priori, in which over-the-counter melatonin was recommended at 3 mg/night and increased in 3 mg increments every five to seven nights as necessary and tolerated to a maximum of 12 mg/night.

In May 2002, the clinical records were reviewed on all patients who had been commenced on melatonin by the investigators. The following data were collected and analyzed: demographic information, onset ages of RBD and neurologic disorders, coexisting neurologic disorders, reasons for initiating melatonin, response to melatonin, effective doses, adverse effects, and duration of follow-up. Based on both the patient's and bed partner's report on follow-up evaluations, the response to melatonin was categorized as one of the following: RBD controlled, RBD markedly improved but not eliminated, RBD initially improved but subsequently returned, RBD not significantly changed, or RBD worsened.

This analysis was reviewed and approved by the Mayo Foundation Institutional Review Board (IRB). Seven patients are also participating in one of the Mayo IRB-approved longitudinal studies on aging and dementia.

3. Results

There were 15 consecutive patients treated with melatonin over the specified time period. Due to a state statute, in which records cannot be reviewed on patients who have not authorized our institution to allow review of their medical records for research purposes, one patient was excluded from this analysis. The demographic and clinical information on the remaining 14 patients are shown in Table 1. All but one patient are male. RBD preceded the onset of the neurologic disorder in 11 (73%) of the patients.

The coexisting neurologic findings/disorders were dementia with Lewy bodies ($n = 7$), mild cognitive impairment with mild parkinsonism ($n = 2$), multiple system atrophy ($n = 2$), narcolepsy ($n = 2$), and Parkinson's disease ($n = 1$). The preponderance of patients with cognitive impairment reflects our clinical and research interests [9–12]. All patients with the diagnosis of dementia with Lewy bodies (DLB) met published criteria for clinically probable DLB [13,14]. The patients with mild cognitive impairment (MCI) and mild parkinsonism were diagnosed as such due to the presence of (a) clinically significant impairment in one cognitive domain (primarily memory) but absence of frank dementia [15], (b) presence of extrapyramidal signs (e.g. masked facies, stooped posture, reduced armswing, hypokinetic dysarthria, rigidity, resting tremor, bradykinesia, or postural instability), and (c) parkinsonism of insufficient severity to warrant levodopa therapy. Thus, these patients had features that were qualitatively different than those of amnesic MCI [16]. The two patients diagnosed with multiple system atrophy (MSA) met published criteria for this disorder [17]. The two diagnosed with narcolepsy met criteria for definite narcolepsy [18]. The one patient with Parkinson's disease had over a 10-year history of all of the cardinal signs of PD which were clearly levodopa-responsive.

The reasons for administering melatonin in these patients included significant dementia (all DLB patients) and thus

Table 1
Demographic and clinical data in 14 patients treated with melatonin for REM sleep behavior disorder

Feature	Result
Male gender	13 patients
Polysomnography performed	13 patients
RBD confirmed (RSWA present)	12 patients
Age of onset of RBD:	
Median (years)	56
Range (years)	20–77
Age of onset of neurologic disorder ^a	
Median (years)	65
Range (years)	40–76

RBD, REM sleep behavior disorder, RSWA, REM sleep without atonia.

^a RBD preceded neurologic disorder in 11 patients by a median of 6 years, range 1–37 years.

reluctance to potentially aggravate dementia with clonazepam (five cases), incomplete response to clonazepam monotherapy (four cases), incomplete response to clonazepam and greater cognitive impairment with increased dosing of clonazepam (two cases), severe OSA and narcolepsy (one case), daytime sleepiness with clonazepam (one case), and impotence with clonazepam (one case). Follow-up data regarding response was available for all patients since initiation of melatonin. The mean duration of follow-up was 14 months (range 9–25 months); six patients had used melatonin less than 12 months, six had used it for 12–18 months, and two for more than 18 months. The response to melatonin therapy is shown in Table 2. Eight patients (57%) found melatonin therapy effective for 12 months or more. Two patients with initial complete response discontinued melatonin after 9 months, when effectiveness seemed to wane. One patient with complete resolution of RBD discontinued melatonin 8 months after initiation and RBD has not returned. One patient with no improvement in RBD after 2 months and sleepiness above 6 mg/night discontinued melatonin, one patient with increased frequency of RBD after 5 months discontinued melatonin, and one patient who experienced improvement in RBD died from lymphoma 4 months after commencing melatonin. Ten (71%) experienced marked improvement to complete control in RBD symptomatology, of whom five were also using 0.5–1.0 mg of clonazepam nightly. Thus, five patients experienced significant improvement in RBD features on melatonin monotherapy. In all cases, improvement in nightmares tended to correlate with the improvement in dream enactment behavior. Melatonin was ineffective in two patients, one of whom perceived an increase in frequency and severity of events. The effective doses of melatonin were 3 mg/night in two cases, 6 mg/night in seven patients (with clonazepam coadministered at 0.5 mg/night in four patients and 1 mg/night in one patient), 9 mg/night in one case, and 12 mg/night in two patients (both also used clonazepam 0.5 mg/night). As shown in Table 3, only five (36%) patients experienced side-effects, and these symptoms resolved with decreased dosing. Only one patient discontinued melatonin due to side-effects

Table 2
Response to melatonin in 14 patients with REM sleep behavior disorder

Response	N	Clonazepam coadministered
Controlled RBD	6	0.5 mg for 1 patient, 1 mg for 1 patient
Markedly improved but not controlled	4	0.5 mg for 3 patients
Initial complete response, then RBD returned	2	0.5 mg for both patients
No significant improvement	1	
RBD frequency and/or severity worsened	1	

Pt, patient; RBD, REM sleep behavior disorder.

Table 3

Adverse effects in 14 patients treated with melatonin for REM sleep behavior disorder

Adverse effects	N	Clonazepam coadministered
Delusions and hallucinations (12 mg) ^a	1	1 mg
Headache (12 mg) ^a	2	0.5 mg in 1 patient
Morning sleepiness (9 mg) ^b	2	0.5 mg in 1 patient

^a Symptoms resolved at 6–9 mg/night.

^b One patient discontinued due to this symptom.

(sleepiness); this patient also did not improve with treatment at lower doses.

All patients were using other psychoactive medications (donepezil in nine patients, a selective serotonin reuptake inhibitor in five patients, carbidopa/levodopa in four, a psychostimulant in two), but no significant improvement in RBD frequency or severity was temporally associated with initiation of any of these drugs.

4. Discussion

The management of REM sleep behavior disorder can be a challenging clinical problem in patients with underlying neurodegenerative disorders. While clonazepam appears to be the most effective treatment for RBD, this agent is not devoid of side effects. Treatments that do not significantly affect daytime cognition and alertness nor complicate the management of OSA are highly desirable. In this series, persistent benefit with melatonin (with or without concomitant low-dose clonazepam) beyond 1 year of therapy occurred in most (57%) but not all patients. Side effects were infrequent, dose-related, and resolved with lowering the dose or discontinuation. No prospective, double-blind, placebo-controlled trials have been performed for any therapy of RBD, and confirmation of the benefit of melatonin must await such a trial.

While these data appear to substantiate the effectiveness of melatonin for the treatment of the majority of patients with RBD, the mechanism by which this occurs remains unclear. Kunz and Bes [5] have suggested that melatonin restores RBD-related desynchronization of the circadian rhythms. Polysomnographic studies have shown partial restoration of REM sleep atonia with melatonin [5,6], whereas suppression of increased phasic EMG activity in REM sleep was detected with clonazepam [19]. Perhaps the efficacy of combined melatonin and clonazepam in some patients reflects their differing but additive effects on RBD pathophysiology.

None of the patients who were administered donepezil noted any significant change in frequency or severity of RBD symptoms. This observation appears to contradict the findings in one report, in which three patients experienced improvement in RBD symptoms with donepezil [20]. In our experience with over 50 patients with DLB and RBD who

have been treated with donepezil, no patient has experienced significant improvement in RBD symptoms (B. Boeve and M. Silber, unpublished data).

We acknowledge the limitations in this report. The study was open label and uncontrolled. We instructed all patients to use over-the-counter melatonin, and since the formulation of each brand may vary, the response and side effects could be due in part to the particular brands used. The response to treatment was based on patient and bed partner reports and thus not objectively measured. Furthermore, the frequency and severity of RBD spontaneously fluctuates in many patients, and gradually declines in some patients with neurodegenerative disorders [3,11]. The improvement over time could be related to this phenomenon, but this would not account for the abrupt cessation of RBD features shortly after initiation of melatonin. We did not control for other psychoactive medication use, but no patient experienced any apparent change in RBD frequency or severity with donepezil, carbidopa/levodopa, selective serotonin reuptake inhibitors, or psychostimulants. Also, since few females were included in this and other reports, it is not yet known if melatonin is similar in efficacy and side-effect profile in females as in males. Despite these limitations, the data suggest that melatonin can be considered as a possible sole or add-on therapy in select patients with RBD. Prospective, long-term, controlled trials using melatonin are warranted in a larger number of patients with RBD associated with a variety of neurologic symptoms and disorders.

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