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Original article

# Use of pramipexole in REM sleep behavior disorder: Results from a case series

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**Abstract**

*Background and purpose*: Rapid eye movement (REM) sleep behavior disorder (RBD) has a known association with other medical conditions, including narcolepsy and neurodegenerative diseases such as synuclienopathies. RBD is currently treated with clonazepam as a first-line therapy. Recent research suggests that the pathophysiology underlying RBD may involve a dopaminergic deficiency, given its association with Parkinson syndromes and restless legs syndrome (RLS). We report on the efficacy of pramipexole, a dopaminergic D2-3 receptor agonist, in the treatment of RBD.

*Patients and methods*: The first 10 consecutive patients presenting with a history and polysomnographically confirmed RBD were given pramipexole as either a single dose before bedtime or as a divided dose regimen with the first dose given in the early evening and the second dose at bedtime. Medication was titrated to control RBD symptoms and the clinical response was monitored through interviews with the patient, spouse, and close family members during the course of the study at regularly scheduled follow-up visits.

*Results*: The mean length of treatment was 13.1 months, and the average total evening dose of pramipexole at the end of the study was $0.89 \pm 0.31$ mg. A divided dose regimen of pramipexole was used in 56% of patients remaining on pramipexole. We found that 89% of patients experienced either a moderate reduction or complete resolution in the frequency of RBD symptoms throughout the duration of the study. Moreover, 67% reported at least a moderate reduction in the severity of remaining symptoms.

*Conclusions*: Pramipexole markedly reduced the frequency and severity of RBD symptoms and appeared to maintain efficacy for up to 25 months as assessed at follow-up visits. Clonazepam may have numerous unwanted side effects in the elderly or narcoleptics with RBD, such as prominent sedation and the potential exacerbation of underlying obstructive breathing in sleep. The potential role of pramipexole in improving RBD and its associated dopamine deficient syndromes warrants further research in the use of dopaminergic agonists as a potential first-line alternative therapy for RBD.



*Keywords:* REM behavior disorder; Pramipexole; Dopaminergic; Clonazepam; Restless leg syndrome; Periodic limb movements in sleep

## 1. Introduction

Rapid eve movement (REM) sleep behavior disorder (RBD) is a parasomnia caused by a loss of skeletal muscle atonia during REM sleep [1]. The resulting behavioral release and dream-enacting behavior of RBD is often violent in nature, with flailing of the arms or legs and may be a cause of bodily injury. The first case report with symptoms suggestive of RBD dates back to 1969, in a patient with a pontine tumor [2]. Although structural ponto-medullar lesions are now a known cause of RBD, a strong association has been found between RBD and neurodegenerative diseases such as synucleinopathies, including Parkinson's disease (PD), dementia with Lewy Bodies (DLB) and multiple system atrophy (MSA). Moreover, RBD may precede the onset of an associated neurodegenerative disease by 10 or more years. RBD has also been shown to have an association with other sleep disorders such as narcolepsy, restless legs syndrome (RLS), and periodic limb movement disorder (PLMD) [1,3,4].

The current standard of care for the treatment of RBD is based on two clinical studies [5,6]. The typical regimen uses clonazepam in doses ranging from 0.25 to 2.0 mg before sleep. The reported success in treatment with clonazepam is

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nearly 90%. Although generally well tolerated, clonazepam may cause undesirable side effects including excessive drowsiness that may be problematic in those with neurodegenerative illnesses. Furthermore, clonazepam may exacerbate underlying obstructive sleep apnea (OSA) or the excessive daytime sleepiness of narcolepsy [7]. Finally, some patients do not obtain adequate response from clonazepam. There is, therefore, a need for other options that may be equally effective in the treatment of RBD, yet have fewer adverse events.

The close association of RBD with parkinsonism, RLS and PLMD suggests a potential role of decreased dopaminergic neurotransmission in the expression of RBD. Albin et al. [8] confirm that in patients with idiopathic RBD there appears to be a loss of dopaminergic midbrain neurons. Other studies also support the hypothesis that a decrease in dopaminergic neurotransmission is associated with RBD with or without documented neurodegenerative diseases [9,10]. A recent study involving eight patients with idiopathic RBD found moderate success in treatment with pramipexole, a dopaminergic D2–3 receptor agonist [11]. We present new data supporting the use of pramipexole in RBD as demonstrated in this case series involving ten consecutive patients presenting with RBD.

## 2. Materials and methods

Ten consecutive patients presenting with RBD to the Ohio Sleep Medicine and Neuroscience Institute were placed on pramipexole as their first line of therapy for this disorder. This case series began when pramipexole was used in two consecutive patients with both RBD and RLS. When it was found that these patients reported a marked improvement or resolution of both RBD and RLS symptoms in the absence of adverse events, pramipexole was then offered as a treatment option for the next eight consecutive patients presenting with RBD. Four of these eight additional patients also had at least mild RLS symptoms or periodic limb movements in sleep (PLMS) prompting use of the dopaminergic agonist. The other four without RLS or PLMS had mild to moderate obstructive sleep apnea and were placed on pramipexole based on clinical judgment, initially on a trial basis, given the potential of clonazepam in exacerbating the obstructive breathing in sleep and the initial clinical success in improving RBD symptoms in the other patients with RBD. These four patients were informed that clonazepam is considered standard for the treatment of RBD and offered this medication as a potential treatment, but decided on a trial with pramipexole after a discussion of various treatment options, including observation with safety precautions. Following the clinical use of pramipexole in these ten consecutive patients presenting with RBD, a retrospective chart review was performed. Eight of the 10 patients continue to use pramipexole and are followed clinically in regular outpatient visits.

All patients included in this study presented with a clear clinical history of complex, and typically violent, behavioral activation during sleep consistently associated with dreaming and occurring at least on a weekly basis with symptoms for at least 1 year prior to the initial evaluation. All patients presented to the clinic over a 20-month period with follow-up at 2–6 month intervals. Prior to initiation of treatment, all patients underwent a complete history, physical exam, and diagnostic polysomnogram (PSG) in search of pre-existing neurodegenerative illnesses and/or sleep disorders, and to confirm the behavioral and/or electromyographic (EMG) activation characteristic of RBD. A detailed neurological exam was performed on all patients by a board certified neurologist (MHS) prior to beginning medication and with re-assessments at follow-up visits. Finally, 8 of 10 patients underwent a multiple sleep latency test (MSLT) following the diagnostic PSG.

PSG techniques and scoring were based on internationally accepted criteria as specified by Rechtschaffen and Kales [12]. Arousals in this study were scored based on an American Sleep Disorders Association (ASDA) [13] protocol and as modified by the Ohio Sleep Medicine and Neuroscience Institute [14]. This modification contains two important changes; first, arousals are scored in REM sleep even if no concurrent increases in submental EMG amplitude occur and second, K complexes and vertex sharp waves that directly precede an arousal are scored as part of the arousal. When arousals occurred during inspiration and were associated with snoring, they were scored as a respiratory arousal.

Pramipexole was used as the first-line treatment for RBD in all but one patient; one patient had previously been on clonazepam. Initiation doses began at 0.25–0.75 mg for a maximum total evening dose of 0.50–1.5 mg in either a single or divided dose regimen. Dose titration occurred at follow-up office visits, and doses were increased based on the patient's residual or persistent symptoms determined from an extensive interview with the patient and, in all but one case, with the patient's spouse or close family members. Those on the divided dose regimen received their first dose in the early evening and the second dose at bedtime. Those on the single dose regimen received pramipexole only before bedtime. Once patients were placed on either a single or divided dose regimen, the timing of these doses was not changed during the course of clinical follow-up.

Efficacy of treatment with pramipexole was evaluated at follow-up office visits. Response was gauged by both alterations in RBD frequency and intensity as observed by the patient, bed partner, and/or close family members. RBD frequency and intensity outcomes were measured as not changed (0), mildly reduced (+), moderately reduced (++), or resolved (+++). Adverse effects to pramipexole were also assessed at these follow-up visits.

## 3. Results

### 3.1. Patient demographics and polysomnographic data

A diagnostic PSG demonstrated prominent tonic and phasic EMG activation of the submentalis and anterior tibialis muscles in all patients during REM sleep. Moreover, seven patients also demonstrated complex behavioral activation during REM sleep, characterized by yelling and gross motor movements of the extremities. In the three patients who failed to demonstrate complex behavioral activation during the diagnostic PSG, all had a clinical history of at least weekly violent dream-enacting behavior, and all demonstrated the typical tonic and phasic EMG activation in REM sleep with associated simple arm and leg movements.

A total of 10 consecutive patients were enrolled in this case series after a clinical history and PSG-documented RBD. All but one patient remained on pramipexole as their sole treatment. As can be seen in Table 1, patient demographic data demonstrates that the study population was overwhelmingly male (90%) and elderly (mean age = 72.9 ± 1.9 years). Mild cognitive impairment was present in two patients, characterized by a mild decrease in short-term memory, but still performing all activities of daily living. One of these patients discontinued pramipexole secondary to hallucinations (see below) and experienced a rapid decline in cognitive function approximately 1 year after discontinuing pramipexole. Finally, two additional patients had a recent onset of Parkinsonism, demonstrating mild bradykinesia and increased muscle tone, but minimal gait impairment.

Concomitant sleep disorders were prevalent in this group (Table 1). Although 8 of 10 patients met criteria for OSA (apnea + hypopnea index (A + HI) ≥ 5) with four having an A + HI > 15, obstructive breathing in sleep was generally mild with only one patient demonstrating a pulse oxygen saturation (SpO2) nadir of less than 85% (Table 1). Of those with an A + HI < 10, inspiratory snore arousals were common, giving an average respiratory arousal index (RAI) of 23.3 events per hour of sleep.

Five patients had at least mild RLS symptoms and six patients had a PLMI > 5. The mean periodic limb movement index (PLMI) during sleep and periodic limb movement arousal index (PLMAI) were 24.5 and 6.5, respectively. Finally, two patients were given a presumptive diagnosis of narcolepsy following their clinical and PSG evaluation (patients no. 4 and 8 in Table 1). These two patients had a mean sleep onset latency (SOL) of 0.6 min or less on the MSLT and had at least one nap with unequivocal REM sleep (Table 1). Although neither had a history of cataplexy, both patients also had shortened REM latencies on the nocturnal PSG and had a clinical history of excessive daytime sleepiness dating back to young adulthood.

### 3.2. Dosage escalation and clinical effects

The average starting total evening dose of pramipexole was 0.35 mg with 70% of patients starting at 0.25 mg. Nine of 10 patients remained on pramipexole at study completion, with all requiring dose escalation for an average total evening dose of 0.89 mg. The maximum total evening dose of 1.5 mg was required in one individual. A split dose regimen was utilized in this study once it became apparent that many of the subjects continued to exhibit RBD symptoms primarily in the first 2 h of the night after initiation of pramipexole. Symptom control was improved after using a split dose regimen with the first dose administered in the early evening. Of the nine patients remaining on pramipexole at the end of the study, 5 (56%) were on the divided dose regimen, while the remaining 4 (44%) received a single dose at bedtime. The mean

Table 1
Patient demographic, polysomnogram (PSG) and multiple sleep latency test (MSLT) variables in 10 consecutive RBD patients prior to treatment with pramipexole

| PSG/MSLT variable | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Mean |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 77 | 72 | 76 | 76 | 65 | 70 | 75 | 78 | 80 | 60 | 72.9 |
| Sex | M | M | M | M | M | F | M | M | M | M | |
| BMI | 26.1 | 34.1 | 31.6 | 28.3 | 27.9 | 25 | 29.7 | 28.6 | 42.4 | 24.8 | 29.85 |
| Total sleep time (min.) | 379 | 314 | 139 | 326 | 357 | 360 | 192 | 309 | 319 | 365 | 306 |
| REM latency (min.) | 182 | 122 | 121 | 28 | 77 | 57 | 84 | 24.8 | 105 | 88 | 111 |
| % Stage 1 sleep | 31.1 | 32.8 | 26.3 | 65.8 | 30.2 | 19.6 | 32.4 | 45.1 | 50.9 | 45.2 | 37.9 |
| A + H Index | 9.3 | 33.0 | 23.7 | 18.6 | 6.6 | 3.2 | 21.3 | 9.9 | 10.7 | 3.8 | 14.0 |
| Lowest SpO2 (%) | 86 | 86 | 78 | 89 | 87 | 85 | 90 | 88 | 86 | 90 | 86.5 |
| PLM index | 71.2 | 13.8 | 34.5 | 61.0 | 3.4 | 1.5 | 8.1 | 51.3 | 0 | 0 | 24.5 |
| PLMA index | 18.4 | 2.1 | 4.7 | 21.4 | 0.8 | 0 | 4.4 | 13 | 0 | 0 | 6.5 |
| Average SOL during MSLT (min.) | Not done | 13.5 | 16.4 | 0.6 | 4.2 | Not done | 18.6 | 0.1 | 16.0 | 19.1 | 11.1 |
| No. Naps with REM during MSLT | Not done | 0 | 0 | 3 | 0 | Not done | 0 | 1 | 0 | 0 | NA |

Abbreviations: A + H, apnea + hypopnea; PLM, periodic limb movement; PLMA, periodic limb movement arousal; EMG, electromylogram; SOL, sleep onset latency.

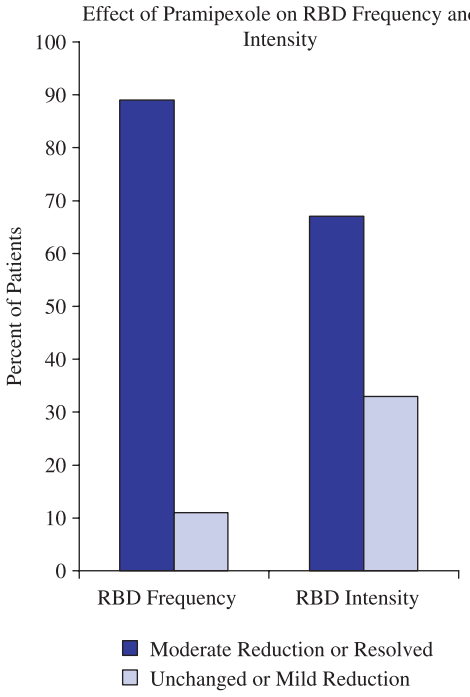


Fig. 1. Percentage of patients on pramipexole reporting at least a moderate reduction in REM sleep behavior disorder (RBD) symptom frequency or intensity with respect to those reporting either no or only mild reductions.

follow-up duration on treatment was 13.1 months with a range of 4–25 months.

Study patients experienced a marked reduction in their symptom frequency and intensity. Although one patient was discontinued from pramipexole secondary to hallucinations, eight of nine patients remaining in the study had either a moderate reduction or complete resolution regarding the frequency of their symptoms (see Fig. 1 and Table 2). With respect to the intensity of RBD symptoms remaining at the end of the study, six of the nine experienced either a moderate reduction or resolution in symptom intensity (Fig. 1). Whereas all subjects reported at least weekly complex motor activation such as thrashing of the limbs, yelling, or leaving the bed while dreaming prior to pramipexole, such gross motor movements and vocalizations were most consistently reduced in subjects who responded to pramipexole. When symptoms remained in patients reporting a moderate reduction in symptom intensity, these symptoms were reduced to minimal (subtle) limb movements or minor vocalizations during dream sleep. Thrashing, yelling or getting out of bed during dream sleep was essentially eliminated per report in this group.

Only one patient remaining in the study at completion experienced no change in either RBD frequency or intensity (patient no. 6, Tables 1 and 2). In addition, one patient who had previously responded to treatment with clonazepam for RBD also experienced a moderate reduction in both symptom frequency and intensity with a total evening dose of 1.0 mg of pramipexole administered in a divided dose regimen (0.5 mg at each dose).

### 3.3. Adverse effects

Adverse effects were uncommon and mainly limited to mild nausea. One patient experienced vivid hallucinations and thus resulted in the only medication withdrawal.

## 4. Discussion

This case series represents the largest study to date utilizing a dopaminergic agonist in the treatment of RBD and includes a long-term follow-up on pramipexole. These data suggest that pramipexole has at least a moderate efficacy in the treatment of RBD, perhaps paralleling that previously documented with clonazepam. We found that 89% of RBD patients on pramipexole (0.5–1.5 mg total evening dose) reported either a moderate reduction or complete resolution in the frequency of their RBD symptoms. Moreover, 67% of the patients on pramipexole at the end of this case series reported at least a moderate reduction in symptom intensity. Treatment efficacy appeared to be well maintained even after 25 months of follow-up. Although our RBD patient population represents a heterogeneous group given that patient selection was based on ten consecutive RBD patients presenting to our clinic, these data suggest that pramipexole may be efficacious in the treatment of RBD in spite of this heterogeneity.

There is considerable evidence to suggest that RBD may represent a dopaminergic deficiency disorder [15]. As noted earlier, RBD tends to precede the onset of other dopaminergic deficient disorders such as Parkinson

Table 2
Dosing, treatment length and efficacy of pramipexole for 10 consecutive patients presenting with RBD

| Patient characteristic | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Initial total dose of prampiexole (in mg) | 0.5 | 0.25 | 0.25 | 0.25 | 0.5 | 0.25 | 0.25 | 0.75 | 0.25 | 0.25 |
| Final total dose of prampiexole (in mg) | 1.0 | 0.5 | 1.0 | 1.5 | 1.0 | 1.0 | 0.75 | Stopped | 0.75 | 0.5 |
| Single (1) or split (2) dose | 2 | 1 | 2 | 1 | 2 | 2 | 2 | 1 | 1 | 1 |
| Treatment length | 9 | 23 | 18.5 | 25 | 22 | 4 | 10 | 1 | 13 | 5 |
| Effect of prampiexole on RBD frequency[a] | +++ | +++ | ++ | ++ | +++ | 0 | +++ | NA | ++ | ++ |
| Effect of prampiexole on RBD intensity[a] | +++ | +++ | ++ | + | +++ | 0 | +++ | NA | ++ | + |

Abbreviations: mg, milligrams; RBD, rapid eye movement behavior disorder.
[a] Effect scored as: 0, no change; +, slight reduction; ++, moderate reduction; +++, resolved.

syndromes or synuclienopathies, including MSA and DLB [1]. The severity of RBD correlates with the loss of monoaminergic innervation of the striatum [8,9]. Moreover, decreased presynaptic dopaminergic transporters in the striatum have been demonstrated in RBD patients by positron emission tomography (PET) and single photon emission computerized tomography (SPECT) scans [10]. Finally, other dopamine-responsive disorders are also associated with RBD [1], including RLS and PLMS, as was also seen in our patient population.

Although 7 of the 10 patients in our case series presented with an additional dopamine-responsive disorder such as parkinsonism ($n=3$), RLS ($n=5$), or both ($n=1$), we could find no evidence to suggest that the presence of a dopamine-responsive disorder increased the likelihood of a response to pramipexole in this small sample. Indeed, the only patient who reported no change in RBD frequency or severity while on pramipexole had clinically significant RLS, whereas two patients without an additional dopamine-responsive disorder reported at least a moderate reduction in RBD frequency during treatment on pramipexole. Future research is required to determine if RBD patients with a pre-existing dopamine-responsive disorder are more likely to respond to a dopaminergic agonist for the treatment of RBD.

The current standard treatment for RBD is clonazepam, but there are several potential adverse side effects or drawdacks associated with this medication in the RBD patient population. First, the sedating effects of clonazepam can be problematic in RBD patients who, as a population, are elderly, appear to have a predisposition to neurodegenerative syndromes and cognitive decline, have increased risk for falls, or may have underlying narcolepsy. The long half-life of clonazepam may result in a 'hang-over' effect and compromise daytime alertness and overall cognitive performance. Second, 8 of the 10 patients in our case series had at least mild sleep-disordered breathing, and benzodiezapines such as clonazepam may exacerbate OSA. Treatment alternatives for RBD would be beneficial for this patient population.

Our results from this case series represent the second clinical trial to demonstrate at least moderate success in improving RBD frequency and severity with pramipexole. There are several important differences between our study and that of Fantini et al. [11], who also have shown an improvement in idiopathic RBD patients with pramipexole. First, our study included the first 10 consecutive patients presenting to our clinic with RBD. Although the majority of our patients had idiopathic RBD, two had a recent cognitive decline and two had PD. Second, subjects in our study appear to report better success in controlling both RBD frequency and intensity with respect to the Fantini et al. study. Indeed, this earlier study found only a few patients with complete resolution of RBD symptoms on pramipexole. The higher rate of symptom resolution in our study may be in part due to the divided dose regimen, on which more than one-half of our study patients were placed. Pramipexole has a delayed gastric absorption of 1–3 h, and perhaps even longer in the elderly. We found that a single dose before bedtime was less effective in resolving RBD symptoms in our patient population, particularly for the RBD symptoms reported during the first half of the night. For this reason, we moved to a divided dose regimen with the first dose given in the early evening. Patients using this divided dose regimen reported better control of their RBD symptoms during the first half of the night. We hypothesize that a divided dose regimen may overcome a delayed absorption effect and provide the therapeutic levels needed to suppress RBD when REM sleep is entered.

There are a number of concerns and unresolved questions regarding the use of pramipexole in RBD. Future studies are required to determine if RBD patients previously on clonazepam will respond as well to dopaminergic agonists as our benzodiazepine-naive subjects. We had only one patient who was previously on clonazepam. This patient reported limited success with clonazepam but had a moderate improvement in RBD frequency and intensity with pramipexole. Moreover, future studies will be required to determine which patient populations represent the best candidates for dopaminergic agonist therapy. For example, it remains to be determined if patients with more severe cognitive decline will respond to pramipexole. Indeed, the only patient in the study who did not tolerate the medication withdrew secondary to hallucinations and later developed a severe cognitive impairment with underlying dementia; this patient died approximately 1 year after withdrawal from pramipexole.

There are several weaknesses regarding this case series that will also need to be addressed in future studies. Outcome measures for this study relied on subjective assessments from patients, spouses, and/or close family members without objective post-treatment PSGs. The Fantini et al. [10] study included objective post-treatment measures and found a decrease in behavioral activation on the follow-up PSG when on pramipexole. Second, the sample sizes of current trials using pramipexole have been small, and larger trials will be needed to better evaluate the efficacy with dopaminergic agonists. Furthermore, no control group was included in either study using pramipexole.

Although future research is needed to further address the use of dopaminergic agonists in the treatment of RBD, our results suggest that pramipexole may be a treatment alternative to clonazepam. We suggest that a divided dose regimen with the first dose given in the early evening may be most efficacious in this regard. Given the potential adverse events associated with clonazepam such as sedation and exacerbation of underlying OSA, as well as the effectiveness of pramipexole in improving other associated dopamine-responsive disorders in RBD such as PD and RLS, the use of dopaminergic agonists as a first-line therapy for RBD warrants further investigation.

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