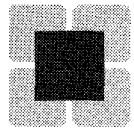

Polysomnographic, neurologic, psychiatric, and clinical outcome report on 70 consecutive cases with REM sleep behavior disorder (RBD): sustained clonazepam efficacy in 89.5% of 57 treated patients

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THE REM sleep behavior disorder (RBD) is a syndrome of injurious or disruptive behaviors emerging during rapid eye movement (REM) sleep, which ordinarily exhibits a generalized skeletal muscle atonia. The syndrome was originally described in 1965 in cats with experimental pontine tegmental lesions.[1] This animal model served to predict the occurrence of RBD and permitted its identification in humans. In 1985, our center published a series of 5 patients with RBD.[2] We have subsequently reported on a total of 55 cases, with the vast majority having no identified brainstem disorder.[3–12] Recent reports of 17 patients from five other centers have corroborated our polysomnographic (PSG) findings.[13–17] RBD syndrome has been incorporated within the revised, official sleep/wake disorders nosology.[18]

The series of RBD cases reported herein was gathered in a clinical setting with an extensive referral base. These patients came to our regional sleep disorders center for evaluation of frequently injurious and potentially life-threatening conditions requiring specialized diagnostic tests as well as a search for safe and effective treatment. The first patient described his RBD as "moving violent nightmares" which he wanted eliminated so he could enjoy retirement without the fear of sustaining nocturnal injury.

The focus of this paper is our experience to date in evaluating 70 patients with RBD and in treating 57 of them. The data to be presented further define a syndrome of bold and unusual features, the understanding of which interlinks diverse fields of both clinical and basic neurosciences.

METHODS

Our protocol was devised to detect a broad range of disorders, since the first 5 RBD patients had been misdiagnosed and inappropriately treated elsewhere for nocturnal seizures, psychopathology, or sleep apnea.[3] The extensive neurologic evaluation we have conducted has been based on the pontine RBD cat model.

During routine clinical practice over a 6.5-year period, 70 patients were diagnosed as having RBD according to recognized polysomnographic (PSG) and clinical criteria.[7,18] 32.8% (23/70) of these individuals came to us following media features about our work with RBD.

The evaluation protocol was as follows:

1. *Clinical sleep/wake interview* of patient and spouse/family; review of a standard questionnaire covering

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both lifetime sleep/wake, medical, neurologic, and psychiatric history, and a current review of systems, including 31 questions on medication/substance use and 9 questions from the Michigan Alcoholism Screening Test. Past medical reports were inspected and appropriate laboratory testing ordered.

2. *PSG monitoring* included an electro-oculogram; 9-channel electroencephalogram (EEG) including the standard C3/A2 and C4/A1 channels used for scoring sleep stages; electromyogram (EMG) of chin, bilateral anterior tibialis, and extensor digitorum muscles; electrocardiogram (EKG); and nasal-oral thermocouple airflow. Full respiratory monitoring was utilized whenever indicated. The EEG paper speed on the first night was 15 mm/sec, increasing to 30 mm/sec for at least 5 minutes every hour. Patients were continuously videotaped and closely monitored by a certified technician who also made ongoing notations of observed behaviors and attempted to elicit dream recall immediately after every sequence of complex behaviors. Our protocol included standardized methods for PSG recording and scoring,[19] with an allowance for persistence of EMG tone during an otherwise well-characterized REM sleep (eg, presence of typical REMs, and saw-tooth waves on an activated EEG).

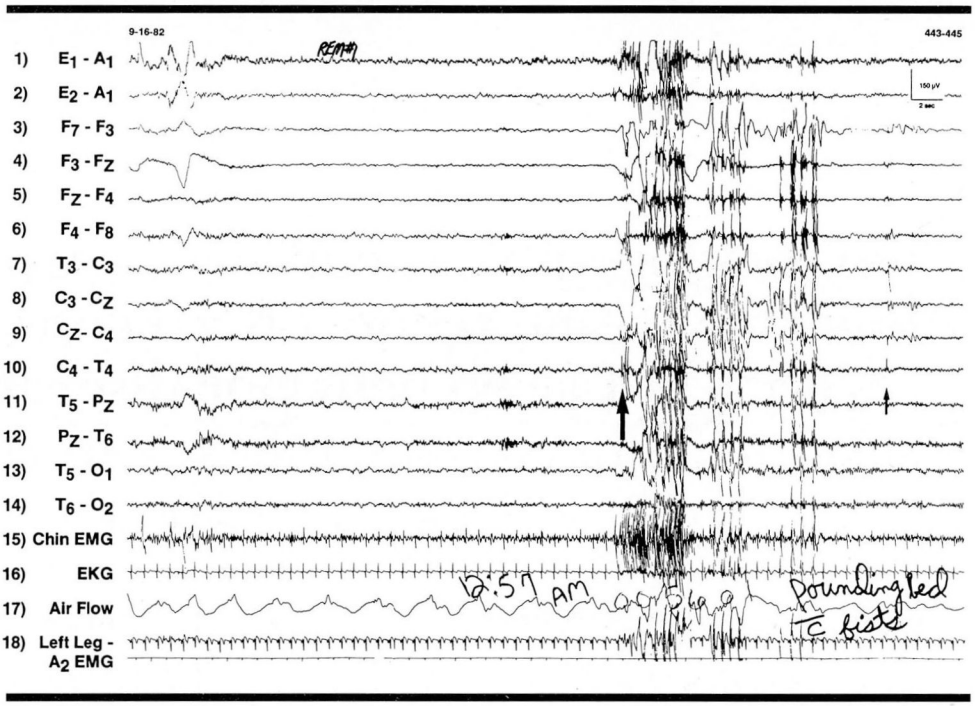


FIGURE 1. Polysomnographic (PSG) Correlates of the REM Sleep Behavior Disorder (RBD): A. Onset of the first REM sleep epoch during the initial PSG study of the first patient in our series of 70 cases. REMs lasting 4 secs (channels 1–2, far left) mark the onset, in conjunction with low voltage, fast frequency EEG (3–14). Chin electromyographic (EMG) tone, however, is moderately elevated. 31.5 secs elapse before bursts of chin (15) and right leg (18) EMG twitching emerge abruptly with violent behaviors, as the right arm punches the bed repeatedly. For 14 secs, 3 sets of punches are thrown, separated by pauses whose EEG tracings maintain the characteristic REM sleep appearance. The 5 punches of the first set are the most vigorous and associated with the greatest muscle artifact (large arrow). After the next sets of less intense punches, there is a 4-sec pause followed by 2 secs of minor right arm movements (whose onset is indicated by the small arrow). Remarks: (12:57 AM; pounding bed with fist.)

3. *The Multiple Sleep Latency Test (MSLT)*[20] was administered to the occasional patient suspected to have daytime somnolence/fatigue and to as many other patients as could be scheduled.

4. Psychotropic medications were discontinued at least 10 days prior to the PSG studies, with few exceptions.[12] Routine urine toxicology screens were generally ordered.

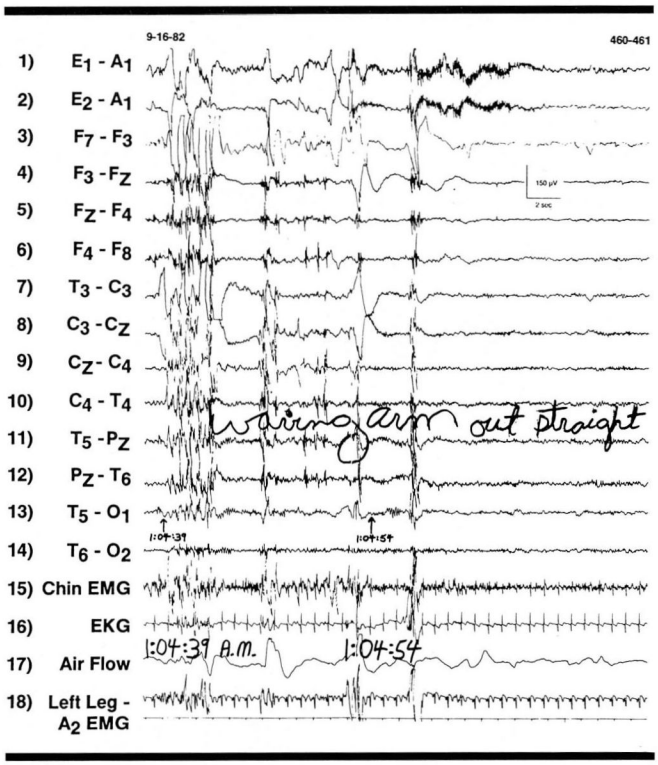
5. *Neurologic evaluation* consisted of:

i. Neurological consultation, in most cases conducted by experienced neurologists at our sleep center (Scott R. Bundlie, MD, ACP; or M. W. M.).

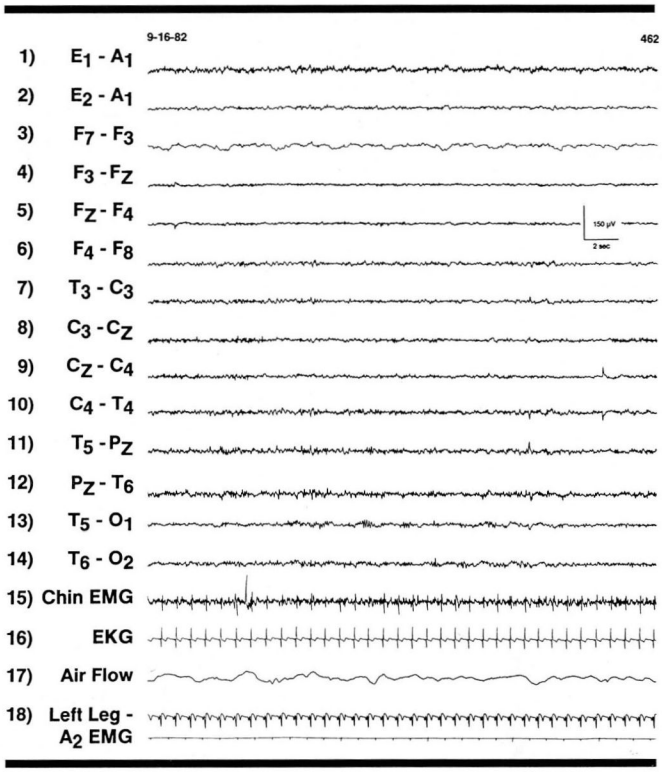
ii. Magnetic resonance imaging (MRI) brain scans, utilizing methods previously described,[3] with T1 and T2 weighting and including a detailed brainstem search. Computerized tomographic (CT) brain scans were conducted on patients unable to complete the MRI scans.

iii. Brainstem auditory evoked potential studies (BAEPs) and somatosensory evoked potential studies (SSEPs), utilizing methods previously described.[3]

iv. Formal neuropsychological testing, administered by the experienced staff of our hospital neurology department. The test battery assessed cognitive abilities, including attention, verbal/nonverbal memory, executive and motor functions. We considered this



B. Continuation of *Figure 1A*, 6 min later during REM epoch #1. The patient is noted to wave his arm for 15 secs, during which time there is considerable REM activity (channels 1–2) and phasic chin/leg (15, 18) EMG bursts, along with an activated EEG (3–14) having intermittent muscle artifact. Remarks: (waving arm out straight: 1:04:39 AM; 1:04:54.)



C. Continuation of *Figure 1B*. A lengthy interval of tonic REM sleep—with absence of phasic activity—immediately follows the intense phasic activity depicted in *Figure 1B*; it lasts >45 secs.

battery to be sensitive to subcortical and cortical dysfunction; it included the Wechsler Adult Intelligence Scale-Revised (WAIS-R), Wechsler Memory Scale (WMS), Buschke Selective Reminding Verbal Learning Test, Porteus Maze Test, and Controlled Word Association.

6. *Psychiatric evaluation* consisted of:

i. Psychiatric interview conducted, with few exceptions, by one of the authors (C.H.S.), utilizing a checklist of *Diagnostic and Statistical Manual of Mental Disorders*, third edition (DMS-III), Axis 1 diagnostic criteria. These interviews generally occurred before the PSG studies.

ii. Psychometric testing, which included the Minnesota Multiphasic Personality Inventory (MMPI), Hopkins Symptom Checklist-90 (SCL-90), Beck Depression Inventory (BDI), and Zung Self-Rating Anxiety Scale (SAS). The MMPI profiles were interpreted by an experienced staff psychologist at our hospital, who was blind to all information regarding the patients except for age, sex and referral source. The SCL-90, BDI and SAS were added to the protocol beginning with our 14th patient.

The established minimum diagnostic criteria for RBD[7,18] are all the following:

A) Intermittent or persistent EMG augmentation during REM sleep (ie, loss of customary atonia).

B) A history of problematic sleep behavior (injury and/or sleep disruption) or sleep laboratory documentation of complex behaviors during REM sleep.

C) Absence of EEG epileptiform activity during REM sleep.

RESULTS

PSG data

Polysomnographic studies were completed for 2 or more consecutive nights in 77.1% (54/70) of the patients (with a range, for individual patients, of up to 14 cumulative PSG studies over a 5-year period). Both the sleep architecture (ie, quantitative distribution of

sleep stages) and the customary cycling among the sleep stages were generally well-preserved, as shown in previous reports.[3,10] However, the REM sleep percentage was elevated (ie, >25% of total sleep time) in 43.1% (28/65) of the patients (5 were excluded from analysis because of continuous positive airway pressure [CPAP] treatment and/or sleep stage cycling abnormalities). The mean REM sleep % for the 28 elevated cases was 30.0 (± SD 4.7), with comparable scores for the 5 narcoleptic and the 23 non-narcoleptic patients included in this subgroup; their range extended to 39.8% of total sleep time.

The REM sleep latency (REM-L) was reduced (ie, <75 minutes) in 66.1% (43/65) of the patients (5 were excluded for the reasons stated above). The mean REM-L for the 43 patients with reduced REM-L was 51.0 (±16.2) minutes: 32.1 (±24.1) minutes for 7 narcoleptics, and 54.8 (±11.2) for 36 non-narcoleptics. The shortest REM-Ls were 29 and 32 minutes, respectively. Finally, the REM activity (RA) and REM density (RD) of the RBD patients have usually been elevated.[5,7]

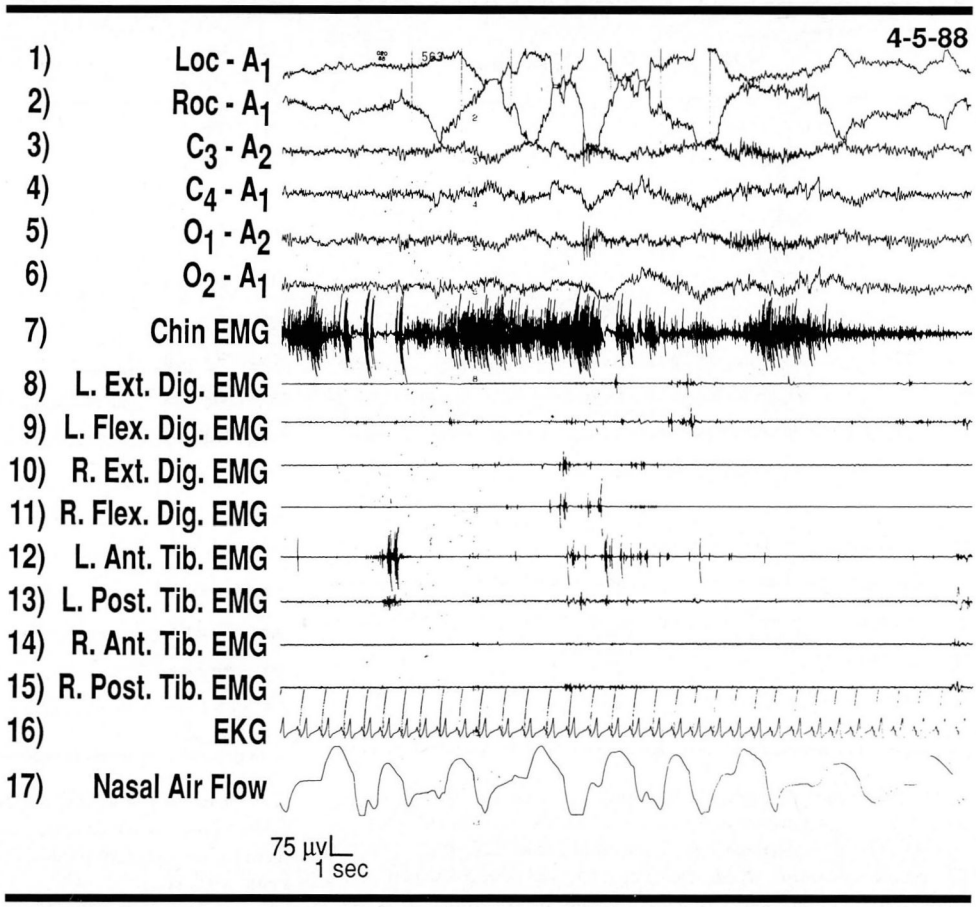
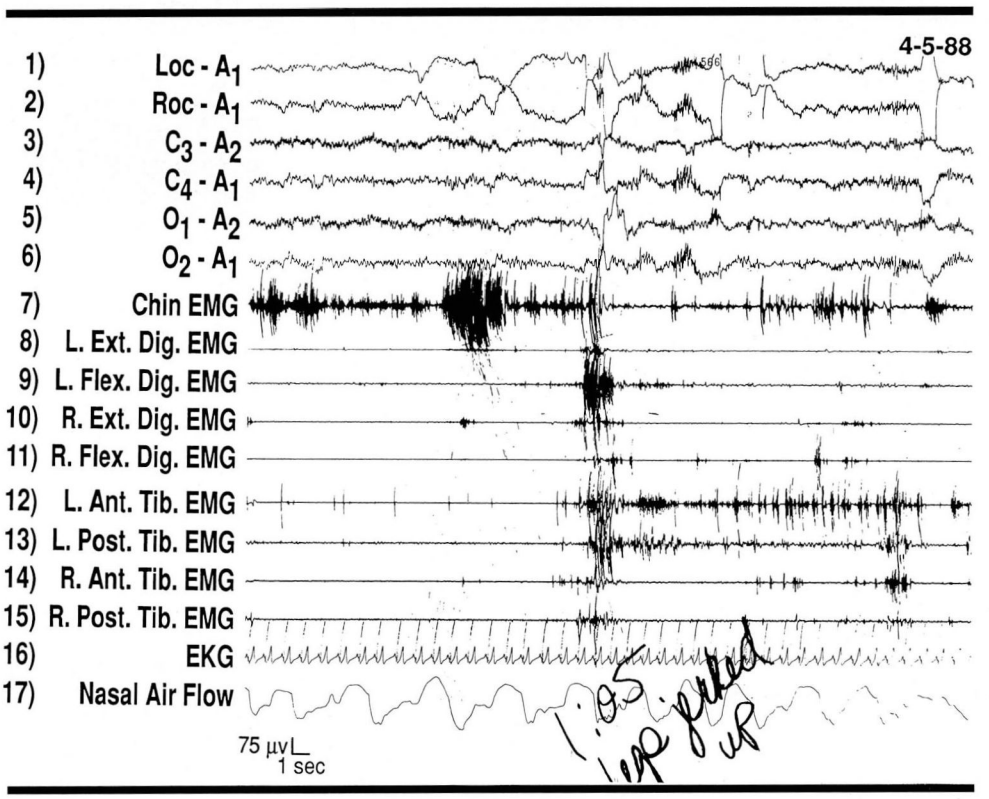


FIGURE 2. PSG Correlates of RBD: A. Example of predominantly elevated, though highly variable, chin EMG tone with superimposed high frequency/amplitude phasic bursting appearing either alone or together with REMs. The prominent chin EMG activity (channel 7) is in contrast to the minimal phasic EMG extremity activity (8–15). Of note is the simultaneous coactivation of brief chin atonia (7) and the most intense EMG activity present in this tracing (12). The abrupt onset and offset of the chin atonia are bordered by high amplitude phasic chin EMG activity (7).

Figures 1 to *3* illustrate the range of PSG findings in RBD, which encompass fluctuating levels of skeletal motor—but rarely autonomic—dyscontrol during REM sleep. However, for any given patient, certain EMG findings could be relatively constant throughout one night's REM epochs as well as throughout REM epochs in longitudinal PSG studies, for example, preferential upper/lower extremity and/or lateralized EMG behavioral activations and dissociation of limb EMG bursts from REMs.[21] *Figure 4* documents typical PSG findings in night terrors/frenzied somnambulism—a non-REM sleep phenomenon/and serves as a distinct contrast to the PSG findings in RBD. There is a striking contrast between the precipitous autonomic activation seen with night terrors and the absent autonomic reactivity found in RBD (lack of tachycardia despite vigorous limb movements). In fact, REM sleep is characterized by marked suppression of sympathetic tone which "may be one of the most fundamental and functionally important aspects of this state."[22]

Clinical sleep/wake data

Table 1 describes the major findings in the 70 cases studied. As can be seen, the older male predominance in chronic RBD is overwhelming. Almost 25% of our patients had a prodrome—at times very lengthy—involving behavioral release with or without recall of



B. Continuation of *Figure 2A*, 90 secs later. The patient begins to kick 5 secs after a burst of intense chin EMG twitching (7). In contrast to consistent elevation of chin EMG tone for >30 secs prior to the leg movements, the chin EMG becomes atonic or considerably diminished for about 15 secs in conjunction with the abrupt onset of generalized phasic EMG extremity twitching (8–15). The EKG rate remains constant despite the observed behaviors. Remarks: (1:05 AM; legs jerked up.)

associated dreams. Only very few cases had histories of childhood or adolescent sleepwalking or night terrors.

Typically, RBD is progressive—either gradually or rapidly—irrespective of the presence of identified neuropathology. Both the frequency and severity can worsen over time, with a reported maximum of four episodes nightly for 10 consecutive nights. Most patients had at least one major episode every 2 to 3 weeks, while some had at least one nightly episode for 10 to 20 years. Complex RBD behaviors are generally aggressive or exploratory but never appetitive (feeding, sexual). A full range of vocalizations and verbalizations during REM sleep has been documented. No case of spontaneous remission has been identified.

Over 75% of our RBD patients sustained repeated injury, including not only ecchymoses but also lacerations requiring up to 40 sutures. Fractures involved the odontoid process of the C2 vertebra, sternum, ribs, and digits. Other injuries included dislocations, joint hyperflexions / hyperextensions, cartilage tears, ripped nails, abrasions ("rug burns"), pulled hair, epistaxis, and traumatic headaches. Spouses were also injured.

Self-protection measures chosen by these patients included restraint devices (sleeping bags; and belts, ropes, dog leashes attaching patients to their beds), padded waterbeds, pillow barricades, plastic screens, and sleeping on a floor mattress in an empty room. Frequently, the spouse would sleep vigilantly and respond quickly to the husband's initial movements, so as to prevent any progression to violence. These spouses often commented on their own resultant sleep disruption and daytime fatigue, noting ironically that their dream-enacting husbands generally did feel rested. Most RBD behaviors were documented to occur not during arousals from REM sleep, but rather *within* REM sleep, often without associated tachycardia. Despite an impressive behavioral repertoire during sleep for the entire group, only a small percentage of patients complained of sleep disruption and daytime fatigue.

There was an almost inextricable link between altered dreams and dream-enacting behaviors; patients did not enact their customary dreams but, rather, their stereotypically altered dreams. Almost all the patients reported that they were never the primary aggressor in their dreams; instead, they would fight to defend either themselves or their loved ones from an attacker—usually, an unfamiliar human or animal. A common situation involved a husband dreaming that he was defending his wife from an attacker—while in reality he was usually beating on her in bed.

The abnormal behaviors of RBD generally emerged more than 60 to 90 minutes after sleep onset, coinciding with the expected latency for the first REM sleep period. The elevated percentage of slow-wave sleep for

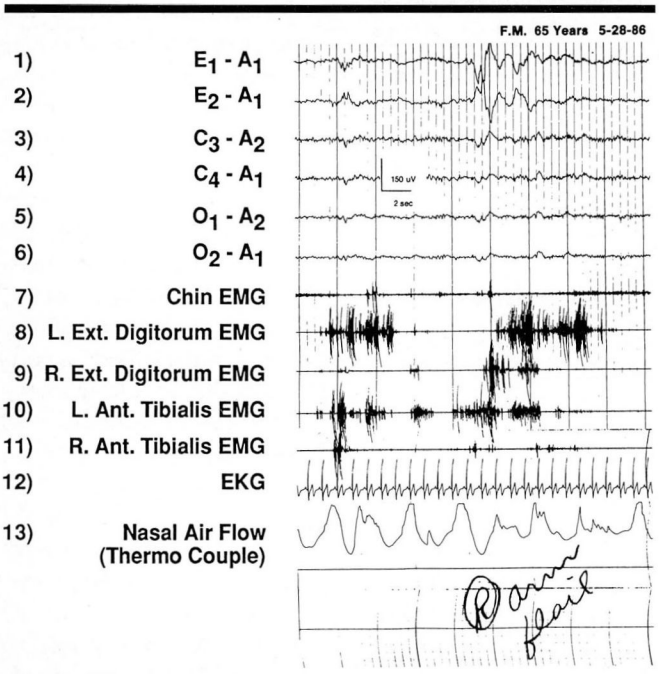
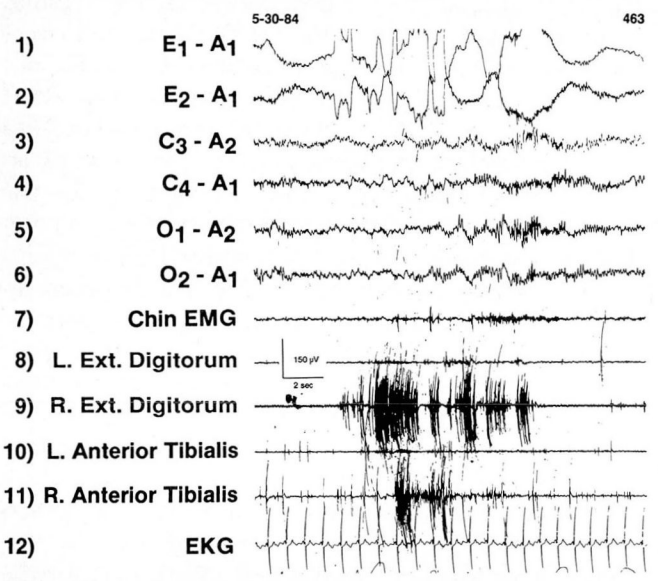


FIGURE 3. PSG Correlates of RBD: A. Example of pathological REM sleep behaviors and phasic extremity EMG twitching emerging with normal background chin EMG atonia. EKG remains constant. Remark: (R arm flail.)



B. Another example of generally preserved chin EMG atonia (channel 7)—except for brief and modest elevation of tone—despite intense phasic extremity EMG twitching which, in this tracing, is lateralized for both upper and lower extremities (9–11). REM activity is intense (1–2).

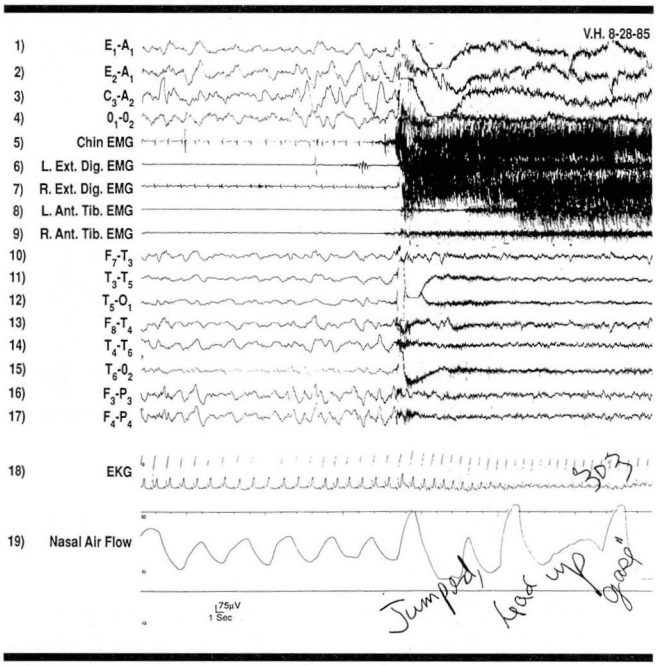


FIGURE 4. PSG Correlates of Somnambulism: For the initial half of the above tracing, there is well-established slow-wave (delta) sleep; then a precipitous arousal occurs, characterized by agitated behavior accompanied by sustained tachycardia (channel 18). Remarks: (3:03 AM; jumped, head up; "gasp").

age in RBD is quite prominent and highly prevalent (*Table 1*), contrasting with the very low percentages ordinarily found in a comparable age group.[23]

The frequent appearance of periodic and aperiodic movements of non-REM sleep in RBD suggests a generalized disorder of motor regulation throughout all sleep stages, but with problematic behaviors usually being restricted to REM sleep. Arousals only infrequently accompanied the bursts of EMG twitching and simple movements during non-REM sleep, even in patients with periodic movement indices as high as 111/hour. Of our 7 narcoleptic patients with RBD, 57.1% (4/7) complained of sleep disruption compared to only 19.0% (12/63) of the non-narcoleptic cases. Their complaint of sleep disruption was similar to that generally reported by narcoleptics without RBD.

An MSLT was completed in 67.1% (47/70) of the patients. The group mean sleep latency was 11.2 (±6.1) minutes over 4 to 5 naps per patient, establishing the lack of hypersomnolence (the standard cut off is 5 minutes[20]). For the 40 RBD patients without narcolepsy, the MSLT mean sleep latency was 12.4 (±5.7) minutes; 10.0% (4/40) had a mean sleep latency of <5 minutes; 95.0% (38/40) had no REM sleep during the

TABLE 1
MAJOR FINDINGS IN 70 CONSECUTIVE PATIENTS WITH THE CHRONIC REM SLEEP BEHAVIOR DISORDER (RBD) DOCUMENTED BY POLYSOMNOGRAPHY

Categories	% (number) of patients	Comments
1. Sex		
Male	90.0 (63/70)	Mean age at onset (N=70):
Female	10.0 (7/70)	52.6 (± SD 16.1) yrs; range: 9–73 yrs. Mean age at presentation: 59.3 (± 15.4) yrs; range: 10–77 yrs
2. Prodrome	24.3 (17/70)	Sleeptalking, yelling, limb twitching and jerking began a mean 22.3 (± 16.8) yrs before RBD onset; range: 2–48 yrs
3. Chief complaint		
Sleep injury	77.1 (54/70)	Ecchymoses (N=54); lacerations (N=24); fractures (N=5)
Sleep disruption	22.9 (16/70)	
4. Altered dream process and content	91.4 (64/70)	More vivid, unpleasant, action filled, violent (reported as severe nightmares)
5. Dream-enacting behaviors	91.4 (64/70)	Talking, laughing, yelling, swearing, gesturing, reaching, grabbing, arm flailing, punching, kicking, sitting, jumping out of bed, crawling, running
6. Elevated % of slow-wave (Stage 3/4) sleep for age (≥ 58 yrs)*	84.0 (42/50)	Not associated with prior sleep deprivation; often pronounced—mean % for the 42 elevated cases was 25.0 (± 5.8); range—15–41%
7. Periodic movements of non-REM sleep	62.9 (44/70)	Infrequently associated with arousals; involve legs/arms and occurring throughout entire sleep cycle
8. Aperiodic movements of non-REM sleep	40.0 (28/70)	Infrequently associated with arousals; involve legs/arms and occurring throughout entire sleep cycle
9. Central nervous system (CNS) disorders**	37.5 (24/64)	Degenerative disorders: N=11 dementia (5) parkinsonism (4) olivopontocerebellar degeneration (1) Shy-Drager syndrome (1) Narcolepsy: N=7 Vascular disorders: N=3 ischemic cerebrovascular disease (2) subarachnoid hemorrhage (1) Brainstem astrocytoma: N=1 Multiple sclerosis (MS): N=1 Guillain-Barré syndrome: N=1
10. Psychiatric disorders***	8.9 (6/67)	Chronic abstinence states: N=3 from ethanol abuse (2) from ethanol/amphetamine abuse (1) Adjustment disorders: N=2 (major stressors were divorce and an automobile accident without injury) Combined disorder: N=1 RBD induced by rapid imipramine withdrawal in a patient with chronic major depression
11. Endocrinologic disorder	1.4 (1/70)	64-yr-old woman abruptly developed RBD after total parathyroidectomy 10 yrs previously
12. Clonazepam efficacy		
Complete	77.2 (44/57)	Rapid control of problematic sleep behaviors and altered dreams, sustained for up to 7 yrs
Partial	12.3 (7/57)	
Total	89.5 (51/57)	

* Stage 3/4% elevation was defined as ≥15% of total sleep time. Twenty patients <58 years old were excluded from analysis.

** The timing of onset and clinical course indicated a causal association with RBD. Six patients whose dementia, ischemic cerebrovascular disease, or extrapyramidal disorder had an indeterminate association with RBD were excluded from analysis.

*** The timing of onset and clinical course indicated a causal association with RBD. Three patients were excluded from analysis because their mood disorders and treatment (N=1) or mood disorders, treatment and ethanol/cocaine abuse disorders (N=2) had an indeterminate association with RBD.

MSLTs, and 5.0% (2/40) had only one REM sleep epoch during their test. For the 7 RBD patients with narcolepsy, the MSLT mean sleep latency was 5.2 (±4.1) minutes, with REM sleep occurring during a mean 3.4 (±1.7) of the 4 or 5 MSLT naps.

Neurological data

A substantial minority of RBD cases was causally associated with identified neurological disorders; there was, however, great diversity in the type and location of the neuropathology. Patients with neurodegenerative disorders were observed by family members to become highly energized during sleep and to display behaviors that were not volitionally possible while awake and impaired ("amazing feats of strength"), such as turning over in bed ("flipping over"), running in bed, jumping out of bed, etc.

A *neurological consultation* has been completed in 82.9% (58/70) of the patients, with a screening neurological examination conducted on all other cases. Apart from the 7 narcoleptic patients, in only 2 cases was a previously unrecognized disorder identified by our own examination—both cases were found to have parkinsonism. A total of 42.9% (30/70) of patients were identified as having central nervous system (CNS) disorders, of which 24 cases were considered to be causally associated with RBD and 6 cases considered

TABLE 2
COMPARATIVE DATA FOR FEMALES AND MALES WITH CHRONIC RBD (N=70)

Categories	Female	Male
1. % of total patients	10.0 (7/70)	90.0 (63/70)
2. Age at onset, yrs (mean ± SD)	37.9 (±23.8)*	54.3 (±16.1)
3. Age at presentation, yrs (mean ± SD)	42.3 (±22.4)	61.4 (±8.3)
4. % of patients with disorders identified to be causally associated with RBD**	85.7 (6/7)	47.2 (25/53)
i. CNS disorder***	57.1 (4/7)	36.4 (20/55)
ii. Psychiatric disorders+	14.3 (1/7)	8.2 (5/61)
iii. Endocrinologic disorder	14.3 (1/7)++	0
5. % of patients treated with clonazepam	57.1 (4/7)	84.1 (53/63)
6. Clonazepam efficacy (N=57): full control of RBD	100.0 (4/4)	75.5 (40/53)
i. Treatment duration, yrs (mean ± SD)	3.0 (±1.8)	2.0 (±1.3)
ii. Dose, mg hs (mean ± SD)	1.4 (±0.4)	0.68 (±0.4)

* Age at onset, females: 9, 13, 20, 42, 54, 60, 67 yrs.
** The timing of onset and clinical course indicated a causal association with RBD. Ten male patients whose CNS or psychiatric disorders had an indeterminate association with RBD were excluded from analysis.
*** CNS disorders in females: narcolepsy (2), brainstem astrocytoma (1), Guillain-Barré syndrome (1). (Note: In one of the 2 cases of narcolepsy, a persistent intensification of RBD was induced by a dose increase of imipramine in the treatment of cataplexy.)
CNS disorders in males: narcolepsy (5), dementia (5), parkinsonism (4), OPCD (1), Shy-Drager syndrome (1), MS (1), ischemic cerebrovascular disease (2), subarachnoid hemorrhage (1).
\+ Psychiatric disorder in a female: A 67-year-old woman with longstanding major depression had a persistent RBD emerge 1 week after rapid withdrawal from imipramine.
Psychiatric disorders in males: Adjustment disorders with depressed mood (2); chronic abstinence from ethanol abuse (2); chronic abstinence from ethanol/amphetamine abuse (1).
++ Endocrine disorder: parathyroidectomy-induced RBD in a 64-yr-old woman.

TABLE 3
CLONAZEPAM TREATMENT DATA FOR 57 PATIENTS WITH CHRONIC RBD

% (number) of patients	Group 1 full RBD control 77.2 (44/57)	Group 2 partial RBD control 12.3 (7/57)	Group 3 Rapid drug discontinuation 10.5 (6/57)
Duration of treatment (yrs)			
Mean (± SD)	2.1 (±1.3)	2.8 (±1.0)	<1 month
Range	0.5–7.0	1.0–4.0	—
Dose (mg hs)			
Mean (± SD)	0.7 (±0.4)	1.2 (±0.9)	0.75 (±0.6)
Range	0.25–2.0	0.25–3.0	0.5 (N=5) 2.0 (N=1)
% of patients requring dose increase	29.5 (13/44)	100.0 (7/7)	—
% of patients with drug-related side effects	2.3 (1/44)	100.0 (7/7)	83.3 (5/6)
No. of patients with side effects (N=13)			
Morning sedation	1	4	3
Impotence	—	2	1
Alopecia	—	—	2
Headaches	—	1	—

Comments:
The small number of patients in *Group 1* who did require increased dosage generally needed only one or two such increments; there was no relentless dosage escalation in any patient.
Two patients in *Group 2* discontinued clonazepam treatment after 2 to 3 years because of limited efficacy and also side effects.
For *Group 3*, there was immediate clonazepam efficacy in 5 of 6 patients who then discontinued treatment because of side effects. The sixth patient discontinued treatment due to complete lack of efficacy.

to be indeterminately associated with RBD.

An *MRI brain scan* has been completed, to date, in 60.0% (42/70) of the patients and a CT brain scan in 27.1% (19/70). MRI results were as follows: completely unremarkable, 41.5% (17/41); definite abnormalities of likely clinical importance, 14.6% (6/41—brainstem astrocytoma, white and gray matter infarcts, extensive cerebral atrophy); borderline abnormalities of uncertain clinical significance, 46.3% (19/41—high intensity foci in deep white matter, of unknown but unlikely clinical importance for age, particularly in view of the general absence of clinical correlates). For the 8 patients who had a CT but no MRI brain scan, 6 scans were considered to be unremarkable and 2 were abnormal (cerebellar atrophy in a patient with olivopontocerebellar degeneration [OPCD]; extensive cerebral atrophy in a patient with dementia).

Evoked potential studies have been completed, to date, in 61.4% (43/70) of the patients. There was normal central conduction in 82.0% (32/39) of the BAEPs (4 cases, whose results were indeterminate or not technically valid, were excluded from analysis). Abnormal findings in 7 cases included: prolonged I to III interpeak latency, indicating pontine dysfunction, in the patient with OPCD; prolonged conduction in the pontomesencephalic region, in a patient

TABLE 4
POLYSOMNOGRAPHIC (PSG) DATA ON ACUTE (FIRST NIGHT) EFFECTS OF CLONAZEPAM IN 8 PATIENTS WITH TYPICAL CHRONIC RBD*

Sleep measures (mean ± SD)	The night before clonazepam treatment	The night of clonazepam treatment
1. Total sleep time, mins	378.9 (±39.1)	404.9 (±76.4)
2. Sleep efficiency, %	75.0 (±6.7)	79.4 (±11.7)
3. Sleep latency,** mins	40.7 (±41.6)	28.7 (±21.8)
4. REM latency, mins	79.0 (±19.0)	60.5 (±25.8)
5. Stage 1 %	10.9 (±10.4)	11.2 (±9.1)
6. Stage 2 %	49.7 (±12.5)	52.2 (±10.3)
7. Stage 3/4 %	19.8 (±9.0)	19.3 (±9.2)
8. REM %	19.6 (±4.8)	17.3 (±6.1)

* Eight male patients with a mean age of 67.1 (± SD 10.5) yrs, 87.5% (7/8) of whom had never previously taken clonazepam. The other patient increased his longstanding dose of 0.5 mg hs up to 1.0 mg hs on the third of 3 consecutive PSG studies.
75.0% (6/8) of patients received clonazepam (0.5 mg hs in 5 cases and 1.0 mg hs in 1 case) on the third of 3 consecutive PSG studies, and 25% (2/8) received 0.5 mg hs on the second of 2 consecutive PSG studies.
** Defined as the latency to the onset of 5 continuous mins of sleep.
A paired t test was not significant for any of the 8 listed sleep measures when comparing the night before treatment with the night of clonazepam treatment.

with multiple sclerosis (MS); dysfunction above the pontomedullary junction in a patient with dementia; delay between the distal N. VIII nucleus and low pons in 2 patients with dementia and in a patient with ischemic cerebrovascular disease; and dysfunction between the low pons and the midbrain in a patient without an identified neurological disorder.

There was normal central conduction in 91.9% (34/37) of the SSEPs (6 cases, whose results were indeterminate or not technically valid, were excluded from analysis). Bilateral central conduction delays were detected in one patient each with MS and parkinsonism, and in another patient without identified neurological disorder.

Neuropsychological testing has been completed, to date, in 68.6% (48/70) of the patients; a preliminary analysis of the first 34 cases has been reported.[24] Despite average intelligence on the WAIS-R, both the WMS and the Buschke Verbal Learning Test revealed short- and long-term verbal and visual memory impairment; the WMS visual memory was impaired in approximately half the cases. Furthermore, patients who were impaired in more than 3 of the 4 memory tests (WMS stories, word pairs, designs, and Buschke) comprised 38.2% (13/34) of the group. The memory deficits were circumscribed and not due to global dementia. About 25% of the patients were impaired on more than one frontal lobe (executive function) measure and all patients in this subgroup were also impaired in more than 3 of the 4 memory tests.

Psychiatric data

A psychiatric evaluation has been completed, to date, in 85.7% (60/70) of patients. Only 21.7% (13/60) had an active Axis 1 disorder at the time of interview and PSG studies; an additional 13.3% (8/60) had a past history of Axis 1 disorder. Thus, 65.0% (39/60) of our RBD patients had neither current nor past Axis 1 disorder. Among the 21 cases with Axis 1 disorders, 14 had affective disorders (predominantly recurrent major depressions) and 9 had alcohol/substance abuse disorders (7 of the latter were in remission at the time of clinical and PSG evaluations).

A total of 18.3% (11/60) of our RBD patients had an active affective disorder, at the time of evaluation, an incidence that may not be dissimilar to estimates of affective disorder being present in up to 11.9% among the noninstitutionalized elderly.[25]

Psychiatric disorders causally associated with RBD comprised a very small subgroup [8.9% (6/67)]; 4 of the 6 cases listed in *Table 1* were previously reported.[6,10] Our data indicate that chronic, progressive RBD can emerge in conjunction with time-limited adjustment disorders (ie, altered psychophysiologic states) as well as with abstinence from longstanding abuse of REM-suppressing agents (ethanol, amphetamine); these findings thus suggest that a subgroup of RBD may constitute a distinct form of pathological REM-rebound disorder.[6] No patient interviewed had current or prior history of psychosis nor any definite psychotic profile on the MMPI or SCL-90, despite a typically longstanding history of wild, dream-enacting behaviors that often had been misconstrued as some form of psychotic behavior disorder.

An MMPI has been completed by 75.% (40/53) of cases; 17 patients who could not complete the test because of neurological impairment, illiteracy or being too young, were excluded. MMPI profiles were normal for 55.0% (22/40) of the patients. Among the 45.0% (18/40) abnormal profiles—which tended to be of mild-to-moderate deviance—somatization/mixed neurosis was detected in 14 profiles and depression in 13 profiles. The mean T scores were all below the 70-point cut off level, with a mean T score of 68.6 (±13.3) for the depression scale. The mean raw score for the ego strength subscale was an intact 43.4 (±7.1) and for the MacAndrew alcoholism subscale a nonelevated 22.8 (±3.9).

There is as yet insufficient follow-up data available on repeat MMPI and other psychometric testing after

successful treatment of RBD. Such data could help assess the extent to which abnormal profiles and elevated psychopathological scores are related to chronic, progressive RBD rather than to underlying psychopathology.

Completion rates for the *BDI, SAS and* SCL-90 have been 80.0% (32/40), 72.5% (29/40) and 75.0% (30/40), respectively (30 from the total series of 70 cases were excluded: 17 patients as stated above for the MMPI, and the initial 13 RBD patients who had not been offered these tests). The mean scores for each test were not elevated: BDI (N = 32)—8.0 (±6.1); SAS index (N = 29)—41.0 (±10.2); SCL-90 global severity index (N = 30)—0.54 (±0.55); and SCL-90 subscale for somatization—0.69 (±0.66), depression—0.64 (±0.7), anxiety—0.60 (±0.8), and anger-hostility—0.29 (±0.36).

Patients and spouses were interviewed conjointly in 77.2% (54/70) of the cases. Of the 67 adults, 91.0% (N = 61) were married for a mean length of 36.5 (±12.1) years and all but 4 had been married only once. The wives typically attested to the longstanding gentle nature of their husbands during wakefulness. They did not view their spouse's RBD as an indicator of interpersonal difficulties or as a threat to their marriage, but rather as a disorder of sleep which was out of character from their customary waking personality. Most wives continued to sleep in the same bed with their husbands, despite the risk of repeated and severe injury, in order to protect their husbands from self-injury.

Comparative data: females vs males

Table 2 provides comparative data for females and males with chronic RBD. Sleep injury was the presenting complaint in 57.1% (4/7) of the females and in 79.4% (50/63) of the males. The one female without identified cause for RBD was 20 years old, with a >8-year history of parasomnia documented by PSG studies to be mixed RBD/night terrors/sleepwalking. Our data indicate that RBD in females may have an earlier age of onset and be more frequently associated with neurologic, psychiatric or medical disorders compared to males. The earlier age of onset for females may reflect the increased percentage of symptomatic cases of RBD, in contrast to the primarily idiopathic RBD seen in older males. Females also require higher doses of clonazepam (Klonopin) for controlling their RBD (see below).

An important fact deserving emphasis is that all PSG findings and behavioral features of RBD are indistinguishable across subgroups, irrespective of gender, age, or the presence/ absence of causal neurological, psychiatric or medical disorders. This suggests that a "final common pathway" for RBD may exist and can be accessed by a variety of mechanisms.

Clonazepam treatment data

Table 3 lists outcome data for clonazepam treatment in 57 patients with chronic RBD. Salient features include the very high efficacy rate of this agent, at low doses, for extended time periods and with minimal side effects. Clonazepam was equally effective in controlling both the dream and the sleep behavioral disorders of RBD. Failure to take clonazepam carried a high probability of immediate RBD relapse, with rapid control again being induced by resumption of treatment. Clonazepam generally was very well tolerated and appreciated by our patients (and their spouses). Dosage escalation was rare. There was no known instance of drug abuse or addiction. The therapeutic/toxic ratio for clonazepam in RBD is thus very high.

Clonazepam was found to be effective in RBD on an empirical basis—ie, after other treatments, such as tricyclic antidepressants (prescribed to suppress REM sleep percentage), had failed. We chose clonazepam because of the RBD-associated findings of periodic movements of non-REM sleep, a condition known to respond to this medication.[3,5,7]

The PSG data on 8 patients with typical RBD, treated acutely with clonazepam in our sleep laboratory, are presented in *Table 4*. Six of them spent 3 consecutive nights in the laboratory, and two spent 2 consecutive nights in the laboratory where treatment with clonazepam was initiated in seven cases. In the eighth case, the dose of clonazepam was increased in the laboratory. All 8 patients became full and sustained clonazepam responders. Nonetheless, as can be seen from the data in *Table 4*, no clues were found as to the therapeutic mechanism involved. Not only was there no suppression of REM sleep percentage but, in fact, the sleep architecture had remarkable constancy and was not perturbed in any measure at a dose which is usually therapeutic for RBD (ie, 0.5 to 1.0 mg hs). Stage 3/4 percentage was equally elevated, for age, in both the baseline and the clonazepam PSG studies.

Clonazepam demonstrated an additional benefit in 2 patients with RBD who each had a very unstable sleep stage cycling at baseline: the medication considerably normalized the unstable cycling in both patients—in conjunction with sleep behavioral control—during the first night of treatment.

A hierarchical responsiveness to clonazepam is

strongly suggested by these 8 PSG studies and by the case histories of the 57 treated patients, which can be listed in decreasing order of control: vigorous/violent behaviors and loud vocalizations > complex, non-vigorous behaviors > simple limb jerking and body movements > excessive EMG twitching in REM sleep. Restoration of PSG-monitored EMG atonia in REM sleep, however, is rarely achieved to any substantial extent.

DISCUSSION

The data here presented reinforce previous findings in RBD, further expanding our perspective on a complex and multifaceted syndrome that originally had been created in a cat model with experimental discrete pontine lesions.[1] We consider our data to accurately represent the range of findings for RBD in the general population, given the broad referral base and high volume of clinical activity at our sleep disorders center. However, as yet, there are no prevalence estimates for RBD.

Clinical and scientific aspects of RBD

The overwhelming male predominance in human RBD raises the question of hormonal mediation (testosterone?) in the genesis and perpetuation of RBD. Both animal and human data linking sex hormones to aggression and violence may also apply to the issue of male-dominated violent RBD.[26,27] The detection of RBD without identified cause in more than 50% of cases—despite an extensive search—suggests that subtle, age-related changes in the brain of older men may also play an important role in RBD. This possibility is supported by a recent report documenting gender differences in circadian temperature rhythms in older adults.[28] It is also possible that the behavior of older females during REM sleep may be frequently similar to that of older males, but in a less vigorous or disruptive manner and with lesser clinical consequence. The usual absence of childhood/adolescent history of sleepwalking or night terrors (ie, non-REM sleep parasomnias) in these patients indicates that RBD is not an extension or variation of a prior sleep disorder, but rather a *de novo* sleep motor disorder that carries a high risk for morbidity.

The close association between the dream disturbances and sleep behavioral disturbances of patients with RBD suggests a common pathophysiology, especially in light of their mutual responsiveness to clonazepam treatment. We have previously discussed this topic within the framework of the activation-synthesis hypothesis of dream formation.[3,7] The behavioral repertoire of humans with RBD—very few of whom were found to have brainstem disorders—conforms closely to that found in cats with pontine tegmental lesions. Four categories were identified in the latter animals, depending on the exact location and size of the experimental lesion: i) a minimal syndrome of limb/truncal twitching and jerking; ii) orienting and exploratory behaviors involving staring, head raising, reaching, grasping, searching; iii) episodes of attack behavior; and iv) locomotion.[29] In contrast to the cat model, however, our patients and spouses rarely reported nonfrenzied, nonviolent ambulation.

Basic science research has emphasized that loss of REM atonia alone is insufficient to generate RBD and that, presumably, there must also be disinhibition of motor pattern generators in the mesencephalic locomotor region to result in behavioral release during REM sleep.[30,31] Thus, separate control mechanisms for REM atonia and for REM behavioral release appear to exist, with each being located in the pons. *Figures 1* to *3* reveal a broad range of fluctuating and also stable tonic/phasic interactions in RBD. How the animal RBD pontine model relates to human RBD—with its various identified etiologies along the neuraxis (as seen in *Table 1*) as well as its unknown etiologies—remains speculative. However, the human RBD model clearly demonstrates that REM-atonia is vulnerable to disruption by a wide variety of pathological influences at multiple levels of the nervous system, which can result in major clinical consequences.

For REM sleep in cats (and presumably in humans), there is an *active mechanism* for inhibition of muscle tone: *REM–atonia*. This type of atonicity involves several relays, beginning with activation of dorsolateral pontine tegmental perilocus ceruleus nuclei (but not the locus ceruleus), which then activate medial medullary inhibitory nuclei, which in turn hyperpolarize spinal alpha motoneurons, resulting in skeletal muscle atonia.[32]

REM sleep is a highly energized state, with numerous physiological processes becoming activated either continuously (ie, tonically) or intermittently (phasically).[7] REM–atonia constitutes a tonic REM process in which a major share of REM energy is devoted to active inhibition of skeletal muscles, thus preventing the actual expression of behavioral intention present in dreams. Whether this core feature of REM sleep is a fortuitous epiphenomenon of yet more fundamental

REM processes and/or whether it was selected by evolutionary advantage in protecting against injurious dream enactment, remains an open question.

The elevated slow-wave sleep percentage in most of these patients may be an adaptive compensation for the presumably increased energy expenditure during REM sleep in RBD, insofar as metabolic rate is lowest and energy conservation greatest during slow-wave sleep.[33] This physiologic compensation may explain why most patients with RBD feel rested from their sleep in the morning, with sufficient vigor for a full day of activity. Another possible explanation, not mutually exclusive with the above, is that the postulated brainstem dysregulation mediating the "final common pathway" of REM behaviors and the loss of atonia in RBD may also be affecting non-REM sleep in the form of elevated slow-wave sleep percentage. Such an elevated percentage has not previously been identified with any disease state.[34]

Dysregulation of non-REM sleep may also be manifested by the frequent appearance of periodic and aperiodic movements of non-REM sleep in RBD. Aperiodic PSG twitching and simple movements of non-REM sleep have been documented in cats undergoing brainstem lesion experiments[35] as well as in humans with a variety of clinical sleep disorders.[36,37]

Only 48.3% (29/60) of the RBD cases in our series had an identified, causally associated condition, which chiefly was neurological (10 of the 70 cases listed in *Table 1* were excluded from analysis because of indeterminate findings). Thus, 51.7% (31/60) of the remaining RBD cases can be considered idiopathic. The high percentage of unidentified etiology remains one of the most intriguing aspects of chronic RBD, providing a compelling reason for performing careful postmortem brain examinations, preferably with histochemical analyses. To date, 8 of our RBD patients have expired but autopsies were not performed.

Aspects of the RBD syndrome in humans had been recognized prior to our own formal identification and extensive review,[7] particularly by Japanese (but also some American and European) investigators.[38–56] These early reports documented an acute form of RBD associated with alcohol withdrawal and from drug intoxication states, as well as chronic RBD associated with neurodegenerative brainstem disorders. However, the Japanese literature used confusing PSG terminology, did not mention any treatment considerations, and did not identify idiopathic RBD—which has been our largest subgroup—nor did it identify any of the other prominent features discussed in this report. Lastly, loss of REM-atonia without REM behaviors in humans has been recognized for over 20 years, as we have reviewed.[7]

The detection of 7 cases of narcolepsy in our series indicates that RBD can be another form of REM abnormality with the narcolepsy syndrome. Furthermore, the range of identified REM abnormalities in RBD extends beyond loss of REM-atonia and beyond the emergence of extensive EMG twitching and gross behaviors during REM sleep, to include increased REM sleep percentage, increased RA/RD, decreased REM-L, as well as narcolepsy. The preservation of normal REM/non-REM cycling in most of these cases demonstrates that there is a limit to REM abnormalities in RBD. In addition, a substantial number of patients had preserved chin EMG atonia throughout much of REM sleep despite increased limb EMG twitching and the emergence of gross behaviors.

The results of our neurological evaluations were surprising, insofar as most patients had unremarkable examinations, MRI or CT brain scans, and evoked potential studies. Equally surprising was the degree and type of findings on neuropsychological testing. Although the relationship between RBD and neuropsychological deficits is unknown, the pattern of memory and executive function deficits shares common features with the subcortical dementias. Serial testing will determine whether the circumscribed deficits will evolve into frank subcortical dementia or some other recognizable set of disorders.

In contrast to our largely negative MRI brain scan findings, one recent study of a series of 6 RBD cases, aged 64 to 74 years, reported clinically relevant MRI abnormalities in 5 patients.[16] However, only 3 of these 5 patients demonstrated pontine abnormalities. The other 2 patients had the nonspecific high-intensity findings which we, in our own series, classified as being of uncertain clinical significance (in view of the high prevalence of such findings in healthy elderly people[57]).

Clonazepam treatment

Treatment considerations for RBD usually are quite straightforward—provided that the diagnosis has been securely established by extensive PSG study, which would also exclude other disorders that can cause sleep injury or disruption. The chief differential diagnoses for RBD include night terrors/sleepwalking, nocturnal seizures, periodic movements of sleep (PMS), hypnogenic paroxysmal dystonia,[58,59] dissociative disorders, posttraumatic stress disorder (PTSD), nocturnal panic dis-

order, and obstructive sleep apnea. We have found that night terrors and sleepwalking can affect all age groups; they began after the age of 16 years in one-third of a large series reported by us.[10]

The successful use of clonazepam is the most gratifying aspect of treating RBD for the clinician. However, there are compelling reasons *not* to prescribe clonazepam for *presumptive* RBD, without PSG documentation. First and most seriously, undetected sleep apnea may become decompensated with benzodiazepine treatment. Second, dissociative disorders and post-traumatic stress disorder (PTSD) may become disinhibited with benzodiazepine treatment. Finally, several conditions which are part of the differential diagnosis of RBD may be partially responsive to clonazepam treatment; without PSG confirmation of the diagnosis, such response could lead to an initial false sense of security.

The success of clonazepam treatment in RBD is enhanced by a flexible approach in administration. Patients have been given a detailed information sheet, derived from our ongoing experience, encouraging them to participate actively in treatment by determining their optimal dose and timing—ranging from 2.5 to 0.5 hours before bedtime—so as to maximize benefit and minimize morning oversedation. Some patients split their dosing times on each night and a few have achieved ongoing RBD control with an every 2-to-3-night dosing interval. Since clonazepam is not available in 0.25 mg tablets, patients are encouraged to "fine-tune" the dose by cutting their tablets.

Clonazepam must be considered a life-long treatment, owing to the lack of spontaneous remissions of RBD. To date, no major complications have emerged during treatment intervals of up to 7 years. The long-term success of clonazepam in treating RBD at low doses, with minimal dosage tolerance, is remarkable when considering the generally much higher doses required and the frequent need for dosing escalations encountered in treating seizure disorders with this drug.

Both idiopathic and neurologically-related RBD has been reported in cats and dogs brought by their owners to a veterinary clinic because of sleep behavior disorders.[60,61] Based on our experience with human RBD, clonazepam was successfully prescribed for these animals, with beneficial results documented by follow-up sleep lab studies.[61] Thus, both the behavioral categories of RBD and its pharmacologic responsiveness may be phylogenically mediated.

Although clonazepam's mechanism of action in RBD is unknown, the data from *Table 4* suggest that REM sleep suppression is not involved. We believe that clonazepam preferentially controls phasic locomotor activity, at the brainstem level, without necessarily restoring atonia. Clonazepam may also modify the abnormal dreams in RBD, which, from the cortex, may then contribute to the control of enacted REM behaviors. An alternative hypothesis would be suggested by the activation-synthesis model,[62] in which the proposed brainstem generators of dream action patterns—to be then further elaborated and integrated in the forebrain—would be suppressed by clonazepam in tandem with inhibition of the brainstem locomotor pattern generators responsible for initiating actual movement.

The lack of clonazepam-induced Stage 3/4 sleep suppression, documented in *Table 4*, does not support the concept that benzodiazepines are reliable suppressors of slow-wave sleep—a belief based on a contradictory literature.[63–70] The fact that 6 of the 8 patients described in *Table 4* received clonazepam on the third consecutive PSG study minimizes the likelihood of any "adaptation night effect" in these results. Nevertheless, it is possible that the strong drive for elevated Stage 3/4 sleep percentage in RBD did overcome a mild slow-wave sleep-suppressing effect caused by clonazepam.

The list of ineffective treatments for RBD in our series of 70 patients includes tricyclic antidepressants, trazodone, diphenylhydantoin, carbamazepine, phenobarbital, and a variety of benzodiazepines (one possible exception is alprazolam which, in 2 cases, exerted partial benefit). We cannot yet disprove the hypothesis that high doses of other benzodiazepines can approximate the effectiveness of clonazepam; based on anecdotal information, however, we believe it is unlikely. Among the benzodiazepines, clonazepam appears to have unique properties, as exemplified by its particular efficacy in post-anoxic myoclonus.[71]

The most promising adjunctive/alternative treatments for patients only partially responsive to or not tolerant of clonazepam, in our experience, have been carbidopa/L-dopa (which is also an effective treatment for periodic movements of sleep (PMS),[72,73] clonidine, and L-tryptophan (which currently is not available).

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