Update on RBD and the Differential Diagnosis of Dream-Enacting Behaviors

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Tallahassee Memorial CME Sleep Symposium

February 24, 2018
Disclosure

Consultant, Axovant Sciences, Inc.
Paradox Lost
MIDNIGHT IN THE BATTLEGROUND OF SLEEP AND DREAMS

VIOLENT MOVING NIGHTMARES — REM SLEEP BEHAVIOR DISORDER

DR. CARLOS H. SCHENCK, M.D.
September 11, 1982
Donald Dorff, 67 years old
Golden Valley, Minnesota
Married 41 years
“Physical Moving Dreams”
“Violent Moving Nightmares”
American Football Dream
Sleep
9(2):293–308, Raven Press, New York
© 1986, Association of Professional Sleep Societies

Chronic Behavioral Disorders of Human REM Sleep: A New Category of Parasomnia

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One example of oneirism (dream-enacting behavior) in this patient is as follows:

“I was on a motorcycle going down the highway when another motorcyclist comes up alongside me and tries to ram me with his motorcycle. Well, I decided I’m going to kick his motorcycle away and at that point my wife woke me up and said, ‘What in heavens are you doing to me?’ because I was kicking the hell out of her.”
Mel Abel: RBD

“Hunting Deer Under the Blanket”

“The Man Who Mistook His Wife For a Deer”
Chronic RBD: Original Series of 5 Pts.

• 4 men, 67-72 years old, had 4-month to 6-year histories of injuring themselves or their spouses with aggressive & injurious behaviors during sleep—often during dream enactment.

• A 60 year old woman had disruptive but non-violent sleep and dream behaviors.
RBD behaviors (with abnormal dreaming) emerging with loss of REM-atonia:

1) **Minimal**: limb twitching and jerking

2) **Complex**: hand waving, hand grabbing, reaching and searching motions, gestures

3) **Vigorous** and violent: punching, kicking

4) **Vocalizations**: simple talking, yelling, swearing profanities, prolonged talking (with anger, laughter, or nonsensical)
Video-PSG findings: RBD

1) Loss of submental EMG atonia (“REM-atonia”): RWA (REM-without-atonia).

2) Increased REM phasic EMG twitching.

3) Frequent limb twitching and jerking in REM sleep.

4) Broad range of behaviors in REM sleep—usually dream-enactment.
Video-PSG findings in RBD

5) Frequent PLMs of Non-REM sleep

6) Non-periodic limb twitching in NREM

7) Lack of tachycardia with RBD behaviors
1986 (Sleep)

• RBD is a distinct parasomnia that occurs during unequivocal REM sleep—not a “peculiar stage.”

• Apart from loss of REM-atonia, and increased phasic muscle twitching, all other features of REM sleep remain intact in RBD:

  --REM sleep latency (except Narcolepsy-RBD)
  --REM sleep % of total sleep time
  --REM sleep/Non-REM sleep cycling
  --Number of REM sleep periods per night
L.H. 55 year old man

1) LOC-A₁
2) ROC-A₁
3) C₃-A₂
4) C₄-A₁
5) O₁-A₂
6) CHIN EMG
REM Sleep Behavior Disorder—Dream-Enacting Episode
Intermittent loss of REM-Atonia in Parkinsonism
RBD

1) Motor dyscontrol during REM and NREM sleep.

2) Behavior disorder and a dream disorder of REM sleep.

3) No associated psychiatric disorder.

4) A disorder predominantly affecting older males.
RBD—Altered Dreams

- Vivid, intense, full of action, unpleasant.  
  (dream process change)
- Dreamer is being threatened or attacked by unfamiliar people, animals, insects.  
  (dream content change)
- Dreamer is rarely the primary aggressor.
RBD dream-enacting behaviors

No Sexual Dream-Enacting Behaviors!

Sigmund Freud would be very surprised and disappointed.

RBD appears to be a prototypical “ID release state”—but no sexual release!
RBD—Altered Dreams

The Dream Changes in RBD
Rarely Have Psychodynamic Meaning

The Dream Changes in RBD are Not Relevant to the Person’s life—Past or Present
RBD and Dream-Enactment: Not a Universal Finding

• Comprehensive RBD literature review: 8-35% of patients with RBD (esp. those with neurodegenerative disorders) are not aware of dream-enacting behaviors.

RBD Without Dream-Enactment

• Clarke NA, et al. (Br J Psychiatry 2000;176:189-92) 74 y.o. man; violent sleep behaviors towards wife; “on awakening, no dream recall.”

  Idiopathic RBD, 9/9 males. Mean age, 68 years; Mean age of iRBD onset: 60 years. Mean duration of iRBD: 8 years. 4/9 patients did not have dream-enactment.
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RBD—Etiologic Diagnoses

N=1: Idiopathic RBD (Donald Dorff: 20 yrs)

N=4: Symptomatic RBD:
- n=1: Atypical dementia (Dementia with Lewy bodies)
- n=1: Subarachnoid hemorrhage
- n=1: Olivo-ponto-cerebellar degeneration
- n=1: Guillain-Barre syndrome
“Rapid Eye Movement Sleep Behavior Disorder: A Treatable Parasomnia Affecting Older Adults”


Schenck CH, Bundlie SR, Patterson AL, Mahowald MW.
Key Findings

- RBD was first named.
- N=10 patients (expanded initial series of N=5 patients reported in *Sleep*, 1986).
- Mean age, 62 years; 9/10 patients: males.
- N=5 patients: idiopathic RBD.
- N=5 patients: neurologic disorders etiologically associated with RBD.
Key Findings

• Atypical Dementia (DLB): N=2
• Olivo-ponto-cerebellar degeneration: N=1
• Subarachnoid hemorrhage: N=1
• Guillain-Barre syndrome: N=1
• Dream changes with RBD: 8/10 patients
• Clonazepam therapy, beneficial: N=7
• Abnormal RBD behaviors and dreams were controlled with clonazepam therapy.
Locus coeruleus et sommeil paradoxal.

par M. Jouvet et F. Delorme.

La coagulation extensive d’une zone de la formation réticulée (F.R.) pontique, située au niveau de la partie postérieure du noyau reticularis pontis oralis (R.P.O.) et antérieure du noyau reticularis pontis caudalis (R.P.C.) supprime l’abolition périodique du tonus musculaire au cours du sommeil comportemental : il n’apparaît plus alors de périodes de sommeil paradoxal caractérisé par une activité rapide, alors que l’éveil et le sommeil sont normaux (1*). Les structures responsables cependant sont encore à délimiter avec plus de précision au moyen de coagulation limitée du tegmentum pontique. Les résultats que nous résumons ici ont été obtenus chez 35 chats chroniques. Ils aboutissent à la conclusion que les noyaux locus coeruleus semblent être responsables de l’inhibition totale du tonus musculaire au cours du sommeil paradoxal. Les animaux porteurs d’électrodes chronique-
RBD—Animal Model
REM without atonia (1965)

Jouvet and Delorme (Lyons, France)

Created the experimental animal model of RBD in cats: “oneiric behaviors.”

Bilateral pontine lesions (peri-locus coeruleus): spectrum of behaviors released during unequivocal REM sleep.
RBD—Animal Model

4 Categories of Behaviors In REM Sleep

1. Unorganized head and limb movements ("minimal RBD syndrome")
2. Orienting, searching behaviors
3. Attack
4. Locomotion, including running ("complex RBD syndrome")

These positive findings closely match human RBD
RBD—Animal Model

Sexual behaviors, grooming, urinating, defecating--never found.

*These negative findings closely match human RBD*
REM-Atonia Generation:
Two Key Linked Brainstem Nuclei

1) Pontine Tegmentum:
   Sublateral Dorsal Nucleus

2) Ventromedial Medulla Inhibitory Neurons
Proposed Pathophysiology of REM Sleep Behavior Disorder in Humans

Lesions in sublaterodorsal nucleus + Sufficient locomotor drive = REM sleep behavior disorder

Fig 7
RBD Diagnostic Criteria

International Classification of Sleep Disorders, 3rd Edition, 2014 (ICSD-3)

American Academy of Sleep Medicine

N.B. RBD is the only parasomnia for which vPSG documentation is required.
RBD Diagnostic Criteria: ICSD-3 (2013)

A. Repeated episodes of sleep-related vocalization and/or complex motor behaviors.

B. These behaviors are documented by PSG to occur during REM sleep, or based on clinical history of dream enactment, are presumed to occur during REM sleep.
C. Polysomnographic recording demonstrates REM sleep without atonia (RWA).

D. The disturbance is not better explained by another sleep disorder, mental disorder, medication or substance use.
Comments (ICSD-3 Text)

1. The observed vocalizations or behaviors often correlate with simultaneously occurring dream mentation, leading to the frequent report of “acting out one’s dreams.”

2. The most current evidence-based data that are in accordance with AASM 30 sec epoch scoring guidelines should be utilized.
Any (tonic/phasic) chin EMG activity combined with bilateral phasic activity of the flexor digitorum superficialis muscles in >27% of REM sleep, scored in 30 sec epochs.*

RBD Prevalence Estimates

• 0.4%-0.8% (General Population)
  (Ohayon MM, Schenck CH. *Sleep Med* 2010; 11: 941-6)

• 7% (Geriatric Population)
“A single-question screen for Rapid Eye Movement Sleep Behavior Disorder: a multicentre validation study.”

*Mov Disord* 2012; 27: 913-916.

1. **RBD single-question screen:**

   “Have you ever been told, or suspected yourself, that you seem to ‘act out your dreams’ while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?”
“REM sleep behavior disorder in 703 sleep-disorder patients: the importance of eliciting a comprehensive sleep history”


Frauscher B, Gschliesser V, Brandauer E, Marti I, Furtner MT, Ulmer H, Poewe W, Högl B.
• 34 patients (4.8%): diagnosed with RBD.
• 27 men; 7 women; mean age, 58 years.
• 6/34 patients: referred for suspected RBD.
• 20/34: reported RBD symptoms only on specific questioning.
• 8/34: no history of RBD, but showed typical RBD behaviors during the video-PSG.
Conclusion

- The majority of RBD patients reported RBD symptoms on specific questioning only.
- This striking finding underlines the importance of eliciting a comprehensive sleep history for the diagnosis of RBD.
RBD—Sleep Related Injury
(first two large series)
“Classic RBD Clinical Profile”


J Sleep Res 1993 (N=96) [Minneapolis]

- Males: 87.5%
- Mean age of RBD onset: 52.0 years (9-81 yrs)
- Dream-Enacting Behaviors: 87%
- Sleep Related Injury (chief complaint): 79.0%

Brain 2000 (N=93) [Mayo Clinic]

- Males: 87.0%
- Mean age of RBD onset: 61.0 years (36-84 yrs)
- Dream-Enacting Behaviors: 93%
- Sleep Related injury (chief complaint): 97%
RBD—Sleep-Related Injuries

- Ecchymoses
- Subdural hematomas
- Lacerations (arteries, nerves, tendons)
- Fractures (including high cervical—C2)
- Dislocations
- Abrasions/rug burns
- Tooth chipping, hair pulling
Los Angeles Man with RBD
Los Angeles Man with RBD
Nonviolent Elaborate Behaviors May Also Occur in REM Sleep Behavior Disorder

*Neurology* 2009; 72: 551-557

Oudiette D, De Cock VC, Lavault S, Leu S, Vidailhet M, Arnulf I
RBD: Traditional Demographics vs. Changing Demographics.

- **Traditional Demographics**: Middle-aged and older males (with a neurological disorder, or who will eventually develop parkinsonism and/or dementia).

- **Changing Demographics**: Patients <50 yrs old.
RBD—Changing Demographics
(Patients <50 years old)

3 Retrospective Studies—
all published in *Sleep Medicine*
(2009-2011)
Conclusions: Early-Onset RBD Cases

1) Greater gender parity
2) Narcolepsy-cataplexy
3) Less severe behavioral expression of RBD
4) Psychiatric disorders
5) Antidepressant use
6) Autoimmune diseases?
7) Need for prospective studies
RBD in Children and Adolescents

- **Narcolepsy-Cataplexy**: #1 cause (RBD onset may precede NC onset by months).
- **Cataplexy therapy** (SSRI, venlafaxine, TCA)
- **Major Depression therapy** (SSRI, venlafaxine)
- **Parasomnia Overlap Disorder** (RBD + NREM Sleep Parasomnia)
- **Brainstem Tumors**
“The spectrum of REM sleep-related episodes in children with type 1 narcolepsy”

*Brain* 2017; 140: 1669-1679.


[Bologna group]
RBD--Treatment of Behavioral Disturbances

Initial (Environmental) Considerations

• Maximize the safety of the bedside environment:
  --Move bedside table and any hard objects that are close to the bed.
  --Bed away from any window (beyond arm’s length).
  --Mattress on the floor.
  --Bed partner goes to a separate bed/room?
Treatment of RBD

Two Co-First Line Medications: (>80%-90% published efficacy)

1) Clonazepam (suppresses phasic motor-behavioral activity in REM sleep)

1) Melatonin (partially restores REM-atonia)

2) Combined clonazepam-melatonin therapy
RBD—Treatment

“Best Practice Guide for the Treatment of REM Sleep Behavior Disorder (RBD)”


Standards of Practice Committee: Aurora RN, Zak, RS, Maganti RK, et al.
Treatment of RBD

Other Therapies

• Dopaminergics
• Sodium oxybate (Geert Mayer)
• Acetylcholinesterase inhibitors
• Clonidine
• TCAs, MAOIs
• Paroxetine
• Carbamazepine
• Gabapentin
RBD Mimics
(dream-enacting behaviors)

- Disorders of arousal (SW,ST):
- Nocturnal seizures: REM sleep seizures with dreaming and dream enactment.
- Obstructive sleep apnea: “pseudo-RBD.”
- PLMD “pseudo-RBD”
Nocturnal Seizures Presenting As Pseudo-RBD

“Paroxysmal ‘nightmares’: sequel of a stroke responsive to diphenylhydantoin”

(Boller et al. *Neurology* 1975;25:1026-8)

65 year-old man with violent dream-enacting behaviors.
Nocturnal Seizures Presenting As Pseudo-RBD (continued)

“Polyspikes in REM sleep mimicking REM sleep behavior disorder.”

(Sleep Res 1994;23:283)
Louden MB, Morehead MA, Schmidt HS

• 58 year-old man with 6 year history of vivid dreaming associated with ambulation and screaming.
• One time he awakened while striking the molding around his bedroom window.

• PSG revealed “frequent repetitive polyspike discharges…in REM sleep accompanied by generalized clonic activity lasting up to 20 sec.”

• “Frequent brief myoclonic jerks were also noted during REM sleep…After the longest episode he mumbled and made purposeful movements…”

• “Otherwise REM atonia was maintained.”
OSA Pseudo-RBD

“Severe Obstructive Sleep Apnea/Hypopnea Mimicking REM Sleep Behavior Disorder”

Sleep 2005; 28: 203-6

Iranzo A & Santamaria J.
• 16 patients (11 men), mean age 59.6 (± 7.7) yrs
• 16 patients with idiopathic RBD (of similar age & gender) with apnea/hypopnea index <10.
• 20 healthy controls.
• **Dual clinical complaints**: abnormal sleep behaviors *and* excessive daytime sleepiness.
• **Dream-enacting behaviors** with disturbed dreams—highly suggestive of RBD (along with older age and male predominance).
Time-synchronized video-PSG findings:

1) **Diagnostic of severe OSA/Hypopnea**, with a mean apnea-hypopnea index of $67.5 \pm 18.7$ (range, 41-105).

2) Parasomnia behaviors occurred **only** during apnea-induced arousals. Dream-enactment with gesturing, kicking, arm raising, talking.

3) **REM sleep EMG normal**: increased EMG tone & increased phasic twitching—ruled out.
• **Nasal CPAP therapy:** 13/16 patients (3 refused): Snoring, daytime somnolence, unpleasant dreams, and parasomnia behaviors—eliminated

• **Repeat PSG with nCPAP therapy:**
  1) Apnea-Hypopneas were eliminated.
  2) Normal oxygen hemoglobin saturation levels were documented: mean pressure level of 10 cm H$_2$O ±2.1 cm.
  3) **REM sleep EMG:** atonia preserved.
PLMD Pseudo-RBD

“Periodic limb movements during sleep mimicking REM sleep behavior disorder: a new form of periodic limb movement disorder”

Sleep 2017; March 1;40(3).

doi: 10.1093/sleep/zsw063

• 15 men, 2 women; median age, 66 yrs (48-77)
• Reported sleep behaviors: kicking (n=17), punching (n=16), gesticulating (n=8), falling out of bed (n=5), assaulting the bed partner (n=2), talking (n=15), and shouting (n=10).
• Injurious behaviors: self (n=1), bedpartners (n=3)
• 71% (12/17) of patients: not aware of their abnormal sleep behaviors that were only noticed by their bed partners.
Video-PSG:

- Frequent, vigorous PLMs of lower limbs, upper limbs, and trunk.

- Median PLM index: 61.2.

- NREM sleep: median PLM index, 61.9.

- REM sleep: median PLM index: 39.5 (n=8).

- Abnormal behaviors (e.g., punching, groaning) during some of the arousals that immediately followed PLMs in NREM sleep.
• **RBD/RWA/OSA**: excluded.

• **Dopaminergic therapy**: prescribed in 14/17 pts.

• **14/14 patients**: control of abnormal sleep behaviors and unpleasant dreams.

• **Follow-up video-PSG** in 7/14 patients:

  • Decreased median PLM index from baseline (109 vs. 19, $p = .002$) and absence of abnormal behaviors during the arousals.

• Therefore, **PLMD is a documented RBD mimic**.
Chronic RBD

A) Idiopathic (Cryptogenic)

B) Associated with Neurologic Disorders

C) Medication-induced

D) Miscellaneous
Medication-Induced RBD

- **Antidepressants**: SSRIs, venlafaxine, mirtazapine, TCAs, MAOIs—*but not* bupropion,(dopaminergic/noradrenergic)
- **Beta-blockers**: bisoprolol, atenolol
- Selegiline
- **Anticholinergics**
- **Rivastigmine** (acetylcholinesterase inhibitor)
Chronic RBD--Neurologic Disorders

Most Common Associations

- Neurodegenerative Disorders (esp. parkinsonian disorders)
- Narcolepsy-cataplexy ($\leq 60\%$ of cases)
- Cerebro-vascular Disorders
- But, virtually all types of neurologic disorders can cause RBD: Location of the lesion is critical.
What happens to the idiopathic RBD patients over time?
RBD and Parkinsonism:
Minnesota Regional Sleep Disorders Center
Experience: 1986-present

Newly diagnosed RBD patients:

1. 50% idiopathic

2. 50% symptomatic
   (neurologic disorder/medications triggered RBD)
“Delayed emergence of a parkinsonian disorder in 38% of 29 older males initially diagnosed with idiopathic REM sleep behavior disorder”

Neurology 1996; 46: 388-93

Schenck CH, Bundlie SR, Mahowald MW
Minnesota Group iRBD Outcome Data

- 80.8% (21/26): eventual conversion rate.
- 14.2 ± 6.2 years: mean interval, RBD onset to onset of parkinsonism/dementia.

“Delayed emergence of a parkinsonian disorder or dementia in 81% of older males initially diagnosed with idiopathic REM sleep behavior disorder (RBD): 16 year update on a previously reported series”

Sleep Med 2013; 14 (8): 744-748.
Schenck CH, Boeve BF, Mahowald MW
• N=13 Parkinson’s Disease
• N= 4 Dementia with Lewy Bodies
• N= 2 Multiple System Atrophy ("Parkinson’s plus” disorder”—PD-autonomic dysfunction)
• N= 2 Lewy body variant of AD (autopsy-confirmed)
Barcelona Group iRBD Outcome Data

82% (36/44) of patients with idiopathic RBD eventually developed neurodegeneration.

“Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study”


Iranzo A, Tolosa E, Gelpi E, et al.
• N=16 Parkinson’s Disease
• N=14 Dementia with Lewy Bodies
• N= 1 Multiple System Atrophy
• N= 5 Mild Cognitive Impairment
Onset of RBD to Onset of Parkinsonism/Dementia/MCI

Rate of Conversion From Idiopathic RBD
- 81%  Schenck et al. (2013)--Minnesota
- 82%  Iranzo et al.     (2013)—Barcelona

Mean Latency Period
- 14.2 yrs (range 5-29) Schenck et al. 2013
- 11.5 yrs (range 5-23) Iranzo et al. 2013
- 12.0 ±9.6 years Postuma et al. 2009
Important Clinical Question

- How to discuss the risk of future parkinsonism/dementia with a newly-diagnosed middle-aged or older patient (and the spouse) with RBD?
- This is an important and delicate matter that must be discussed.
RBD Prevalence in Parkinsonism

- \(<46\% \) in Parkinson’s Disease:
  - The presence of RBD in PD is associated with widespread increased PD morbidity.

- 90\% in Multiple System Atrophy
- 76\% in Dementia with Lewy Bodies
“Associated factors for REM sleep behavior disorder in Parkinson’s disease”

*Neurology* 2011; 77(11): 1048-1054.

Sixel-Döring F, Trautmann E, Mollenhauer B, Trenkwalder C.

- N=457 sleep-disturbed PD patients: video-PSG
- 46%: RBD
- Dopaminergic Rx did *not* protect against RBD!
RBD is a marker of widespread neurodegeneration and increased morbidity in PD

PD-RBD vs. PD (without RBD)
1) Increased level of PD motor impairment.
2) Increased level of cognitive impairment.
3) Increased visual hallucinations.
4) Increased autonomic dysfunction.
5) Greater impairment in quality of life status.
“Rapid Eye Movement Sleep Behavior Disorder: Current Knowledge And Future Directions”

Sleep Medicine 2013 (August); 14 (8)

Guest Editors:

Carlos H. Schenck, Claudia Trenkwalder

• 18 peer-reviewed papers
• Basic and clinical science
• Original research and review articles
RBD Special Issue
Sleep Medicine 2013;14
Preface (page 701)

• “RBD is situated at a strategic and busy crossroads of sleep medicine and the neurosciences.”

• “RBD offers great breadth and depth of research opportunities, including extensive inter-disciplinary and multinational research opportunities.”
International RBD Study Group

- Formed in 2007, legally incorporated in Marburg, Germany (2009).
- RBD clinical researchers and basic scientists.
- 9 peer-reviewed journal articles published to date by this group.
International RBD Study Group

• One focus of the research effort: identifying predictors of imminent conversion from idiopathic RBD to parkinsonism within 5 years, for inclusion of these patients in studies testing promising neuroprotective agents.