REM Sleep Behavior Disorder

Clinical Spectrum and Management of REM Sleep Behavior Disorder

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Conflict of Interest Disclosures
ALON Y. AVIDAN, MD, MPH

2. I wish to disclose the following potential conflicts of interest:

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<tr>
<th>Type of Potential Conflict</th>
<th>Details of Potential Conflict</th>
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<tr>
<td>Grant/Research Support</td>
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<td>UCB, Xenoprot</td>
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3. The material presented in this lecture has no relationship with any of these potential conflicts.
REM Sleep Behavior Disorder
The parasomnia most commonly associated with neurodegenerative disease

Dream-enactment behavior associated with loss of muscle atonia in REM sleep
Clinical Features (N=93 patients):

- Gender = 87% males, 13% females
- Mean age of onset = 61
- Mean age of diagnosis = 64
- Injuries to self/bed partner = 32%/16%

Olson EJ, Boeve BF, Silber MH. Brain 2000;123:331-9
**REM Sleep Behavior Disorder**

Characterized by complex vigorous motor activities and injurious behaviors representing attempts of vivid, action filled violent dreams

Occur at least 90 minutes after sleep onset and predominantly in the second half of the night

Risk for injury-self and bed-partner
PATHOPHYSIOLOGY

Pathophysiology of REM Sleep Behavior Disorder

- Pedunculopontine Nuclei
- Peri-Locus Ceruleus
- Lateral Tegmentoreticular Tract
- Medullary Reticular Formation
- Magnocellularis neurons
- Spinal Cord
- Ventrolateral Reticulospinal Tract

Stimulation
Inhibition

RBD
Lack of pontine-mediated medullar inhibition of spinal motor neurons

Lack of medullary-mediated spinal motor neuron inhibition

Lack of REM Atonia

REM-associated Atonia
DIAGNOSIS

RBD Diagnostic Requirement
Suspected clinically, confirmed by PSG

Diagnostic Criteria:

- **PGS abnormality**: Elevated EMG tone during REM sleep in either submental or limb leads.
- Either a **history** of dream enactment behavior or **observation** of abnormal REM sleep behavior during the PSG.
- Absence of EEG epileptiform activity during REM sleep.
- The disturbance in not explained by another sleep/medical/neurological/mental disorder, and is not related to medication/substance use.

ICSD-II

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**REM Sleep Behavior Disorder**

Lack of muscle atonia in chin & limb EMG

**REM Sleep Without Atonia (RSWA):**
- Electrographic finding of EMG augmentation during REM Sleep

**Dream Enactment Behavior:**
- Behavior exhibited during sleep that is interpreted by the observer as acting out dreams

**REM Sleep Behavior Disorder:**
- RSWA +/- complex behaviors during REM sleep in patients with recurrent dream enactment.

![Note: Lack of muscle atonia in chin & limb EMG](image)

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**Proper RBD Etiquettes**

- **REM Sleep Without Atonia (RSWA):**
  - Electrographic finding of EMG augmentation during REM Sleep

- **Dream Enactment Behavior:**
  - Behavior exhibited during sleep that is interpreted by the observer as acting out dreams

- **REM Sleep Behavior Disorder:**
  - RSWA +/- complex behaviors during REM sleep in patients with recurrent dream enactment.

![Image of RBD](image)


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RISK FACTORS

You are seeing a 41 y/o woman with Multiple Sclerosis who presents with new onset RBD. What should you do?

1. Reassure the patient.
2. Tell her that she may likely develop Parkinson’s disease
3. Careful neurologic exam and imaging
4. Careful neurologic exam, safety evaluation & imaging
Demyelinating lesion in the patient's dorsal pons (A-sagital & B-coronal views) consistent with her demyelination lesion.

Muscle atonia during REM sleep results from pontine-mediated perilocus ceruleus inhibition of motor activity. In RBD, the brainstem mechanisms generating muscle become disrupted.

Excessive limb muscle tone during REM sleep as reflected by abnormal electromyography (EMG) augmentation. Normal REM sleep is reflected by EMG atonia which is not seen here.

Acute RBD

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Neurologic Disorders</th>
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<tr>
<td>Alcohol intoxication, psychoactive drugs, withdrawal states: pathological, intense REM-rebound states.</td>
<td>Relapsing Multiple Sclerosis</td>
</tr>
<tr>
<td>Medication intoxication (e.g. anticholinergics)</td>
<td>Vascular</td>
</tr>
<tr>
<td>Therapeutic pharmacotherapy: SSRIs, TCAs, MAOIs, venlafaxine, etc.</td>
<td>Toxic/metabolic</td>
</tr>
<tr>
<td></td>
<td>Tumor</td>
</tr>
<tr>
<td></td>
<td>Infectious, post-infectious</td>
</tr>
<tr>
<td></td>
<td>Degenerative</td>
</tr>
<tr>
<td></td>
<td>Traumatic</td>
</tr>
</tbody>
</table>
Which of the following/s have been associated with inducing RBD?

1. Selegiline
2. Venlafaxine
3. Caffeine
4. Cholinergic agents
5. Mitrazepine
6. All of the above

Louden, 1995
Vorona, 2002
Nash, 2003
Onofrj, 2003
Winkelman, 2004
A 6 year old boy is presenting with dream enactment. In fact, a polysomnogram demonstrates REM sleep without atonia.

- He is not taking any medication and his neurological examination is completely normal.
RBD In Children

- What is the implication of RBD in children?

1. Increased risk for alpha-synuclein disorders
2. Possible underlying diencephalic tumors
3. First sign of narcolepsy
4. Cannot be diagnosed until after age 18 years.

REM Sleep Behavior Disorder Comorbidities:

- RBD can be one of the first symptoms of childhood Narcolepsy

- 36% of patients with narcolepsy report symptoms suggestive of RBD.

Nevismalova et al. Sleep Medicine, 2007
Nightingale, Sleep Med. 2005

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IMPLICATIONS

REM Sleep Behavior Disorder

The majority of patients will have an underlying neurodegenerative disorders: \( \alpha \)-synucleinopathies

- Parkinson’s disease
- Dementia with Lewy Bodies
- Multiple System Atrophy
- OPCA
**REM Sleep Behavior Disorder**

**Limbic Encephalitis & RBD**

- Anti-Ma2 paraneoplastic encephalitis (usually associated with testicular cancer).

- Voltage-gated potassium channel associated encephalitis

Iranzo, Sleep 2007; Ann. Neurol 2006

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**RBD in Parkinson’s Disease (PD)**

- RBD may be the heralding manifestation of PD by many years

- RBD Occurs in 15-50% of patients with PD
MANAGEMENT

Why is Tx so critical?

Why Rx is Critical

Reference: Potentially Lethal Behaviors Associated With Rapid Eye Movement Sleep Behavior Disorder: Review of the Literature and Forensic Implications

Carlos H. Schenck M.D. 1, Samuel Adams Lee B.A. 3, Michel A. Cramer Bornemann M.D. 4, Mark W. Mahowald M.D.

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**ELABORATION: WHEN IS TX USEFUL**

- Minimize precipitating factors
- Maximize Safety

**Pre-event**

**Event**

**Post-event**

- Formal Neurological Exam
- Safety
- Avoid aggravating Rx: SSRIs,
- Clonazepam QHS (~90% effective)
- Melatonin
- Levodopa, dopamine agonists
- Anticonvulsants

RBD: Treatment

• No randomized controlled clinical trials to date to evaluate efficacy of treatment for RBD.

• Most studies are cases or small series of case reports

Suggested level of evidence is available for:

1. Clonazepam
2. Imipramine
3. Pramipexole
4. Melatonin
5. Behavioral Modification & environmental safety
## Pharmacologic treatment of RBD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Level of Recommendation</th>
<th>Special considerations</th>
</tr>
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<tbody>
<tr>
<td>Clonazepam</td>
<td>0.25-4.0 mg before bedtime (usual recommended dose is 0.5-2.0 mg)</td>
<td>Suggested (*)</td>
<td>Use with caution in patients with dementia, gait disorders, or concomitant OSA. Side effects include sedation, impotence, motor incoordination, confusion and memory dysfunction.</td>
</tr>
<tr>
<td>Melatonin</td>
<td>3 mg to 12 mg before bedtime</td>
<td>Suggested†</td>
<td>Effective in patients with alpha-synucleinopathies, memory problems, and sleep-disordered breathing. Side effects include headaches, sleepiness and delusions/hallucinations.</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>3.5-7.5 mg before bedtime</td>
<td>May be considered ††</td>
<td>Side effects include rash and nausea</td>
</tr>
<tr>
<td>Yi-Gan San</td>
<td>2.5 gm tid.</td>
<td>May be considered ††</td>
<td>Studied mainly on patients that could not take clonazepam. No side effects were reported when used for the treatment of RBD.</td>
</tr>
<tr>
<td>Sodium oxybate</td>
<td>unknown</td>
<td>May be considered ††</td>
<td></td>
</tr>
<tr>
<td>Donepezil</td>
<td>10-15 mg</td>
<td>May be considered ††</td>
<td></td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>3.5-6 mg bqd.</td>
<td>May be considered ††</td>
<td>Studied mainly on patients with dementia of Lewy body.</td>
</tr>
<tr>
<td>Temazepam</td>
<td>10 mg</td>
<td>May be considered ††</td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>1-3 mg</td>
<td>May be considered ††</td>
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<tr>
<td>Desipramine</td>
<td>50 mg qhs.</td>
<td>May be considered ††</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>500 to 1500 mg qd.</td>
<td>May be considered ††</td>
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(*) Not FDA approved for the treatment of RBD.  
†† Supported by sparse high grade evidence data, or a substantial amount of low-grade data and/or clinical consensus.  
†† Supported by low grade data.
RBD - Treatment

- Pharmacologic intervention may not be needed if symptoms are intermittent/mild.

- Clonazepam has most data.

- Safety is the first step before any pharmacologic intervention.


RBD –Safety: Level A Evidence

- Modifying sleep environment: safety:
  - Bedroom Safe
  - Remove hard/sharp objects
  - Sleep in padded mattress
  - Place mattress on floor
  - Cover windows with heavy curtain
  - Use pillow barricades

- Until managed:
  - sleep alone, or
  - in a sleeping bag

• sleep-related injury caused by RBD.
• Doses: 0.25-2mg QHS
• No evidence of tolerance
• Mechanism of action: suppression of phasic motor activity
• ~ 80-90% success rate

RBD – Clonazepam Tx: Level B

• The Downsides:
  – AM sedation
  – Memory dysfunction
  – Aggravation of pre-existing SDB
  – Ineffective in ~ 10% of patients
  – ↑ risk of falls & confusion in older adults

Aurora et al J Clin Sleep Med 2010; 6 (1): 85-95

RBD-Melatonin Tx: Level B

• **Advantages:** Few Side effects, partial restoration of REM sleep atonia.

• 3mg partially restored atonia in 85% of those with I-REM (6/7). ¹

• 3-9mg improved symptoms in 13/15 I-RBD patients. ²

• **3-12mg** improved symptoms in 12/14 of patients with RBD-associated with neurodegenerative disease. ³


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RBD-Melatonin Tx: How does it work?

1. SCN- mediated rostral pontine restoration of REM sleep atonia
2. Up regulation of glycine-mediated alpha motor neuron inhibitions
3. REM sleep suppression
4. Currently unknown mechanism

Mechanism of Action of Melatonin in RBD

- Not entirely understood
- May restore RBD-related circadian rhythm desynchronization\(^1,2\)
- Possible direct restoration of the mechanism producing REM sleep muscle atonia. \(^2,3\)

\(^1\) Kuntz, 1997,
\(^2\) Kuntz 1999
\(^3\) Takeuchi, 2001
Level C Medications for RBD

- **Donezepil**
- **Dopaminergic agents**
- **L-tryptophan**
- **Antipsychotics**
- **CMZ**
- **Gabapentin**
- **Clonidine**

↓ REM Atonia

Limited Evidence; Levodopa

↓ REM Sleep %

Contradictory Results: Pramipexol

- **Antipsychotics**
- **Dopaminergic agents**

Other Possible Rx for RBD

- **Anticholinesterase Inhibitors**. Rational: RBD Pathophysiology may be explained by dysfunction of cholinergic transmission

- **Yi-gan san**: herbal preparation affecting 5-HT₂ & GABA receptors.

- **Clonidine**: A potent suppressor of REM sleep

- **Desipramine/imipramine** (TCAs that can also trigger or aggravate RBD).

- **Paroxetine** (MAOI)

- **Immunosuppressive Rx in autoimmune limbic encephalitis**
Novel treatments for RBD

- May be useful for patients with RBD who experience refractory episodes despite Rx
- A customized bed alarm may be an effective method to prevent Sleep Related Injury (SRI) in RBD patients.


http://www.posey.com/Products/Posey-Sitter-Selectandtrade--8361.aspx

Disclosure of RBD & Supportive Counseling

Subject: Re: Classification of Condition
Date: May 29, 2013 02:37:47 AM PST
To: "Avidan, Alon M.D., M.P.H"

Dr. Avidan,

I wanted to write to you because I was concerned about what my condition may indicate for future health concerns. Specifically, it seems as though there is a much higher risk for Parkinson's and other neurodegenerative disorders.

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RBD: Discussion at Follow Up Visits

- Risk for future development of Parkinsonism
- Arrange regular follow-up with a sleep neurologist
- Obtain baseline & regular neurologic exam, especially when movement cognitive disturbances arise
- Conduct serial Mini Mental State (MMSE) exams

Final Case: Disclosure of RBD

A 49 year old man presents with dream enactment and is confirmed to have RBD on PSG.
Final Case: Disclosure of RBD

• Because RBD is associated with an increased risk of developing a neurodegenerative disease, the neurologist felt that the risk should be disclosed to the patient and his wife.

• You decide to:
  1. Agree to disclose
  2. Disagree to disclose as being aware of the risk would only cause worry for them.
  3. Disclose only when neurologic findings are present

Con1nuum Lifelong Learning Neurol
2013;19(1):00–00

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Final Case: Disclosure of RBD

• This case raises the following ethical questions:

  “Should the physician disclose the risk of neurodegenerative disease in patients with RBD? If so, how? If not, why?”

Con1nuum Lifelong Learning Neurol
2013;19(1):00–00

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Disclosure of RBD

- Disclosing a diagnosis versus disclosing the risk of a diagnosis.

- The diagnosis of RBD is not absolutely predictive of the development of a neurodegenerative disease, but rather suggests an increased susceptibility probability.

- The ethical principles of autonomy, informed consent, and respect for persons support disclosure of information to patients.

- In RBD patient’s individual risk of developing a neurodegenerative disorder is uncertain, and physicians are unable to provide definitive information.

Anatomy of PD as it relates to sleep Problems: Using the Braak System

Stage 1 of PD
- dorsal motor, olfactory

Then, marches UP brainstem

Stage 2
- coeruleus, sub-ceruleus complex (function in sleep, mood)

Stage 3
- motor symptoms

Stages 4-6 - cortical involvement
- dementia, etc.

Disturbances in sleep should be seen before motor symptoms
RBD Predicts Neurodegeneration

Idiopathic RBD patients progression
- Life table (Kaplan-Meier Curve)

Postuma, et al
Neurology 2009

~20% at 5 years
~40% at 10 years
~50% at 12 years

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Disclosure of RBD: Recommendation

- Promoting transparency about the potential future risk of neurodegenerative disease with RBD
- Disclosing the uncertainty of the risk enhances patient autonomy, is helpful, and will facilitate the patient’s trust in the physician.
- Communicating the diagnosis of RBD and offering to discuss the potential long-term implications would be appropriate.

Vertrees, S. Greenough, GP, Continuum Lifelong Learning Neurol 2013;19(1):00–00

RBD-Summary

**How to evaluate?**
Multiple nights/expanded EEG & multiple limb EMG channels, Video-monitoring. Home video

**How to Treat?**
Safety (A must)
Clonazepam 0.25-0.5mg, Melatonin 9-12mg (if OSA, older, refractory)

**Future Implications:**
Place RBD patients on neuroprotective agents to delay or stop the progression to future parkinsonism.