REM SLEEP BEHAVIOR DISORDER

Prodromal Synucleinopathy and Beyond

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Professor of Neurology and Medicine
# DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INDUSTRY

<table>
<thead>
<tr>
<th>Nature of relationship</th>
<th>Company</th>
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<tbody>
<tr>
<td>Research Grants</td>
<td>Sunovion, Inc.</td>
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<tr>
<td>Research Grant</td>
<td>Spark, Inc.</td>
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# REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

<table>
<thead>
<tr>
<th>Name</th>
<th>Therapeutic Use</th>
<th>Company</th>
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<tbody>
<tr>
<td>Melatonin, Clonazepam</td>
<td>Treatment of RBD</td>
<td>Several</td>
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</table>
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LEARNING OBJECTIVES

Upon conclusion of this activity, participants should be able to:

• Summarize the spectrum of clinical presentations and current diagnostic standards for isolated REM sleep behavior disorder (RBD).

• Recognize REM sleep without atonia (RSWA).

• Describe the strong association of iRBD with synucleinopathy neurodegeneration.

• Consider ethical dimensions of RBD prognostic counseling.

• Utilize symptomatic therapies for injury prevention for RBD.
SPECTRUM OF CLINICAL PRESENTATIONS AND CURRENT DIAGNOSTIC STANDARDS FOR ISOLATED REM SLEEP BEHAVIOR DISORDER (RBD)
ISOLATED (IDIOPATHIC) REM SLEEP BEHAVIOR DISORDER

• Dream enactment – complex vocal and motor behaviors during sleep – often violent, potentially injurious

• REM Sleep Atonia Loss
  • (aka REM Sleep without Atonia, RSWA) - PSG signature

• ICSD-3 standards require both elements, or recorded complex vocal/motor behavior during REM sleep during PSG

RBD: TYPICAL CLINICAL PRESENTATIONS AND CAUSES/ASSOCIATIONS

• Isolated (Idiopathic) RBD in Older Adults
  • *Prodromal synucleinopathy in most* - Strong association with synucleinopathy with concurrent onset or later development of a defined neurodegenerative disorder
  • HR for MCI/PD 2.2 (CI 1.9-3.9)

• RBD in Younger Adults
  • *Psychiatric disease and antidepressant*
  • Narcolepsy
  • Autoimmunity
  • Lesional RBD
CONVERSION RISK IN MAYO CLINIC IRBD COHORT (N=392): INFLUENCE OF AGE

What is young RBD? 50 yrs
97% sens
34% spec

Best age predicting conversion 67 yrs
80% sens
71% spec
(AUC 0.79)

Alexandres, McCarter, Boeve, Silber, St. Louis, 2023
70 year old male severe RBD
RBD: AN INJURIOUS PARASOMNIA

- 77 yo man *dreamt he was catching a punt*, dove from bed and struck head.
  - Large bilateral SDHs required evacuation.
  - 5 years later > DLB.
- Injury: in 55%; 11% serious
  - *iRBD diagnosis* (OR=6.8, *p*=0.016).
  - *Dream recall* (OR=7.5, *p*=0.03).
  - *Falls* (*p*=0.03).
- Treatment: melatonin 3-12 mg, clonazepam 0.25-2.0 mg

(Patient video)
HOW FREQUENT IS RBD IN THE GENERAL POPULATION?

1. 1-2%  
   - 25%
2. 2-5%  
   - 0%
3. 10-30%  
   - 50%
4. 30-90%  
   - 0%
5. It depends %  
   - 25%
How Frequent is RBD in the general population?

A. 1-2%
B. 2-5%
C. 10-30%
D. 30-90%
E. It depends %

Answer: E (or A, for general population). The general population RBD prevalence has been estimated as being closest to 1-2%. The prevalence of RBD is enriched in sleep clinic populations (5%), and in various synucleinopathy populations may vary from estimates of 30-90%.

REM-SLEEP BEHAVIOR DISORDER: EPIDEMIOLOGY

- Idiopathic/Isolated RBD
  - Initial Estimate (telephone survey): 0.5%
  - Swiss and Korean general populations: 1.06%, 2.01%
  - Enriched populations
    - Sleep clinics: 4.5%
      - 43% with RBD as a secondary/incidental complaint
    - Older adults/elderly
      - Probable RBD in older adults (>60 years): 4.6-7.7%
      - Elderly 70-99 years old: 6.8-13%

- Symptomatic RBD
  - In PD: 30-46%-considered specific marker for Prodromal PD
  - In DLB: 80-85% in PSG series
  - In MSA: 88% in a recent metaanalysis

RBD: MAYO SLEEP QUESTIONNAIRE

• Have you ever seen the patient appear to “act out his/her dreams” while sleeping? (punched or flailed arms in the air, shouted or screamed)

  • Sensitivity 97-100%
  • Specificity 69-95%

http://www.mayoclinic.org/sleep-disorders/research.html

ROCHESTER EPIDEMIOLOGY PROJECT
RBD PREVALENCE STUDY

Frequency of Self Endorsed DEB

1.00 -
0.75 -
0.50 -
0.25 -
0.00 -

DEB
No DEB

14.2%

486 Total responders

69 of 486 (14.2%) self-reported having been told they have DEB

Frequency of Bedpartner Only Endorsed DEB

1.00 -
0.75 -
0.50 -
0.25 -
0.00 -

DEB
No DEB

1.8%

7 out of 383 (1.8%) had bedpartners that disagreed with the subjects self-report of No DEB
(Subject said No for DEB, bedpartner said Yes for DEB)

Gossard, Feemster, McCarter, Timm, and St. Louis 2022
REM SLEEP WITHOUT ATONIA (RSWA):
THE NEUROPHYSIOLOGIC SIGNATURE OF REM SLEEP BEHAVIOR DISORDER
TOP: REM SLEEP WITHOUT ATONIA (RSWA; RED ARROWS)

BOTTOM: NORMAL REM ATONIA (ALSO SEE BLUE ARROW)
POLYSOMNOGRAPHY AND REM SLEEP WITHOUT ATONIA (RSWA)

• 3 Types:
  • **Phasic** – 2-4 x background, 0.1-4.9 sec
    • *Direct burst duration aids RBD diagnosis*
  • **Tonic** – 2 x background, >15s. (1/2) of 30 s. epoch
  • **Any** – 0.5-14.9 sec

• **Mini-epoch scoring** – +phasic burst in 3 s.

• **Muscle Activity % / Indices / Densities**
  • # +phasic-any / # tot REM miniepochs

RSWA PHASIC BURST SCORING:
0.1 - 4.9 SEC BURSTS EXCEEDING 2-4X BACKGROUND AMPLITUDE

Whole screen = 15 seconds (5 - 3 s. Mini-Epochs)

iRBD (4 Limbs) RSWA Thresholds

- *N*=40 adults, 66.5 ± 7.7 yrs

- Optimized RSWA percentages:
  - SM phasic, any 6.5, 6.5%
  - SM Tonic 0.50
  - Phasic *duration* ~ 0.72 sec.
  - RAI = 0.88

- SM/FDS any 15.1%

- AT phasic, any% both 7.7%

- Combined SM/AT phasic/any% 16.5, 21.0%

LeClair-Visonneau et al, 2022 (manuscript)
Normative RSWA

N=118 adults, 18-90 yrs

- **Older men** - greatest RSWA - mirrors RBD/LBD biology
- **Defined Isolated RSWA thresholds** - common!
  - 14% met RBD threshold
  - 25-32% exceeded cohort/age-sex 95%iles
- 95\textsuperscript{th} centile percentages:
  - SM phasic, any 8.6, 9.1%
  - SM tonic 0.99
  - AT phasic, any% both 17%
  - Combined SM/AT phasic, any% 22.3, 25.5%

Feemster et al, *SLEEP* 2019;42(10).
REM-SLEEP (WITHOUT) ATONIA SCORING

• No current well-accepted diagnostic standards

• Evolving RSWA Diagnostic Standards
  
  • **Visual/Manual scoring standards**
    • *Phasic/Any SM > 10% ‘phasic/any’ abnormal*
    • *Combined Limbs:*
      • SM+Bil FDS > 15%, OR
      • SM+AT ‘any’ > 15%, OR
      • SM+FDS+AT > 25%
  
  • **Automated standards** (RAI/Ferri, SINBAR, Meyer, STREAM, Frandsen, Kempfner)
    • RAI/RSA <0.85-0.9 (where 0=complete loss of, and 1=complete preserved atonia)

RSWA: ASSOCIATIONS WITH SYNUCLEINOPATHY SEVERITY AND OUTCOMES

• Associated with presumed SYN vs. TAU (n=138)

• RSWA severity (esp. SM tonic%) in IRBD predicts phenoconversion to PD (n=60)

• RSWA has greater association with PD than ET (n=73)

• RSWA independently associated with greater PD severity (H&Y stage $\geq$ 3.0) and symmetrical/akinetict-rigid vs. Tremor dominant phenotypes; also, poorer sleep quality, cognitive performance, and HRQoL

• Tonic RSWA associated with gait freezing PD phenotype, implicating common pathophysio. in dorsal pontine tegmentum

• In isolated RSWA; 7-14% develop iRBD, 71% have neurodegenerative markers

SYN VS. NSYN COGNITIVE AND MOTOR SYNDROME

n=138

SYN > TAU RSWA in SM muscle

MSA greater than all other subgroups

o/w no effect of parkinsonism/cognitive phenotype

even without RBD symptoms, RSWA was greater in SYN groups
CURRENT EVIDENCE FOR STRONG ASSOCIATION BETWEEN RBD AND SYNUCLEINOPATHY NEURODEGENERATION
MODEL OF RBD AND SYNUCLEINOPATHY

- **Isolated RBD develop:**
  - Cognitive Dysfunction (naMCI, DLB)
  - Motor (PD)
  - Autonomic (MSA)

- Progression variable

WHAT IS THE APPROXIMATE FREQUENCY OF PHENOCONVERSION TO PD OR DLB IN IDIOPATHIC/ISOLATED RBD FOLLOWING CONFIRMATORY POLYSOMNOGRAPHY?

1. 10-30% 16.67%
2. 30-50% 33.33%
3. 50-70% 16.67%
4. 70-75% 16.67%
5. 75-90% 16.67%
What is the approximate frequency of phenoconversion to PD or DLB in idiopathic/isolated RBD following confirmatory polysomnography?

A. 10-30%
B. 30-50%
C. 50-70%
D. 70-75%
E. 75-90%

Answer: D. The largest study to date has suggested an estimated rate of phenoconversion in iRBD patients to PD or DLB (or rarely, MSA) to be approximately 73.5%. Other prior studies have suggested the broad range may vary between 40% to 90%.

ISOLATED RBD (N=1,280): PHENOCONVERSION RISK

- Overall risk of conversion 6.25% per year
- 3 yrs: 17.9%
- 5 yrs: 31.3%
- 10 yrs: 60.2%
- 12 yrs: 73.5%

EVIDENCE THAT MOST ISOLATED RBD IS PRODROMAL LEWY BODY DISEASE

• Longitudinal cohort studies – 74-92% meet MDS criteria for prodromal PD
• Neurodegenerative markers in living patients
• Pathological specimens in living RBD patients – synuclein in peripheral tissues
• Autopsy studies – most RBD patients on post-mortem examination have a synucleinopathy

ISOLATED RBD: NEURODEGENERATIVE MARKERS HAVE PROGNOSTIC IMPORTANCE
PHENOCONVERSION RISK FACTORS FOR OVERT SYNUCLEINOPATHY (PD, DLB)

- Abnormal olfaction (HR 2.6, $P<0.001$)
- Abnormal quantitative motor testing (HR 3.5, $P<0.001$)
  - Motor symptoms (HR 2.6, $P<0.001$)
  - Subtle motor signs (HR 2.0, $P<0.001$)
- Constipation (HR 1.6, $P=0.003$)
- Increased RSWA (HR 1.6, $P=0.04$)
- Abnormal DAT scan (HR 3.2, $P<0.001$)

RBD AND DATSCAN

- DaTscan: Ioflupane (I-123) binds presynaptic DA receptors in striatum

**Normal:**

**Abnormal:** reduced tail,
RBD AND ALPHA-SYNUCLEIN PATHOLOGY

• Autopsy
  • 160/170 (94%) RBD at autopsy proven synucleinopathy (DLB most common)
  • 2 Idiopathic RBD cases: 15-20 year history lacking other obvious pathology
    • Lewy body pathology in subceruleus (sublateral dorsal), and pedunculopontine nuclei

• iRBD Patient Pathology: Synuclein found in submandibular, colonic mucosa, gonadal, skin nerve tissues

PROGNOSTIC COUNSELING IN RBD
RBD PROGNOSTIC COUNSELING:
WHAT SHOULD/DO WE TELL PATIENTS?

• Prognostic counseling practice is variable, only 50% of Mayo provider discussions documented, predominantly by neurologists.

• In a survey of 44 iRBDSG and NAPS providers: 93.2% of provider respondents provided prognostic counseling concerning phenoconversion.
  • Only 31.8% routinely asked patient preferences about receiving counseling.

• Vast majority of RBD patients desire complete information concerning prognostic counseling; 96% preferred even greater information.
RBD
SYMPTOMATIC
TREATMENT
RBD TREATMENT: MELATONIN VS. CLONAZEPAM

RBD TREATMENT:
MELATONIN VS. CLONAZEPAM

RBD TREATMENT: BEYOND MELATONIN AND CLONAZEPAM

- Other benzodiazepines (triazolam, lorazepam)

- Donepezil, rivastigmine

- Pramipexole

- Treatment of OSA comorbidity may help in some cases

- Better grade evidence sorely needed for symptomatic therapies
RBD LONGITUDINAL FOLLOW-UP

• **Interval history** for symptoms of prodromal parkinsonism
  - Hyposmia
  - Orthostatic hypotension
  - Constipation
  - Cognitive symptoms
  - Motor/balance symptoms: gait, hand-writing, falls/near-falls

• **Neurological examination**
  - Bedside cognitive assessment
  - Standing blood pressure – assure >90 mm Hg
  - Motor exam
    - Bradykinesia
    - Rigidity
    - Postural instability
    - Tremor
CONCLUSIONS

• Isolated RBD is common - 1-2% community adults, up to 5% of sleep clinic populations and 7-13% of older adults

• RBD is prodromal synucleinopathy in most older adults; 70-75% develop MCI, PD, DLB, or MSA, yet individualizing prognosis, especially counseling, remains challenging – longitudinal follow-up key.

• Treatment with melatonin 3-12 mg or clonazepam 0.25-2.0 mg.
NORTH AMERICAN PRODROMAL SYNUCLEINOPATHY CONSORTIUM
NAPS-RBD.ORG

Ju, Boeve, Postuma, Avidan, Bliwise, During, Howell, Huddleston, Lee-Ianotti, Lim, Schenck, Schprecher, St. Louis, Videnovic; NIH-NIA, 2018-2026

N=10 No. Am. Ctrs, 2023-2026
N=360
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