RBD AND NEURODEGENERATIVE DISEASE

By: Michael Ibarra, M.D.

Discloser

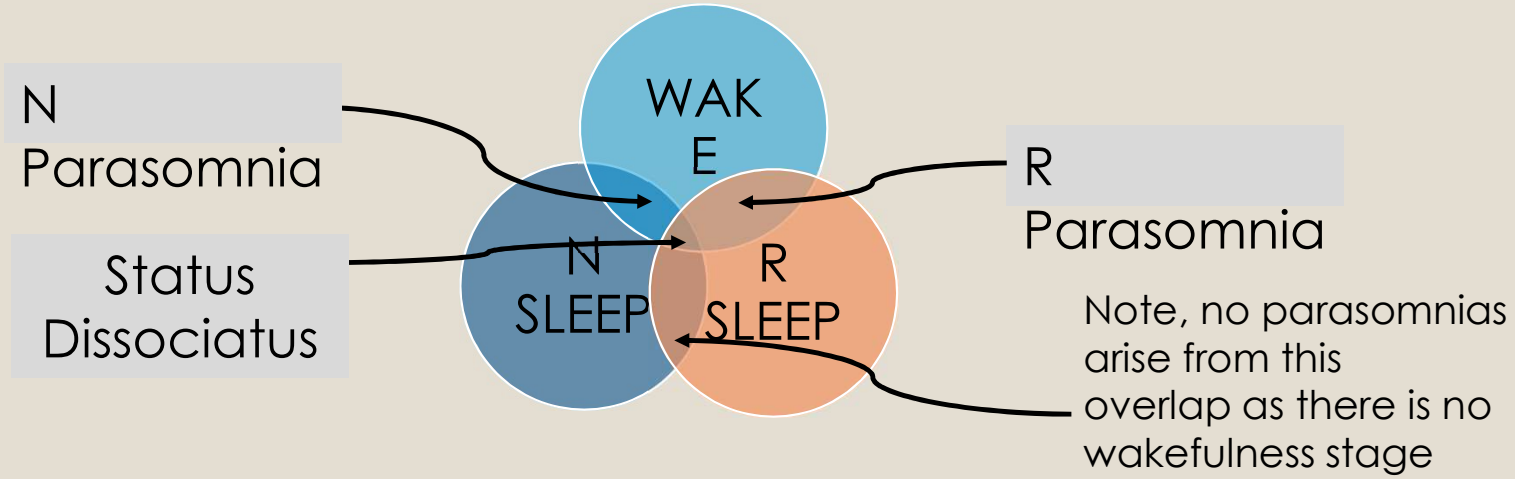
- None

Topics

- Introduction
- Normal sleep
- Definition
- Pathophysiology
- Symptoms and Testing
- Neurodegenerative disorders
- Variations of RBD and Prodromal RBD
- Treatment and Counseling

Introduction

- Parasomnias represent a collection of undesirable physical events or experiences that occur during *entry into sleep, within sleep, or during arousals from sleep*
- They can occur in both NREM and REM sleep, and may well represent an "overlap" between states of alertness *Mahowald et al, Sleep 1991*



Introduction

- NREM parasomnias are very common in children
  - In many cases it may be difficult to determine what is a normal variant versus a true disorder
  - NREM parasomnias in childhood often resolve over time / with aging

- REM parasomnias may occur more commonly in adults / elderly (REM Behavior Disorder) or across the age spectrum (Recurrent Isolated Sleep Paralysis, Nightmare Disorder)

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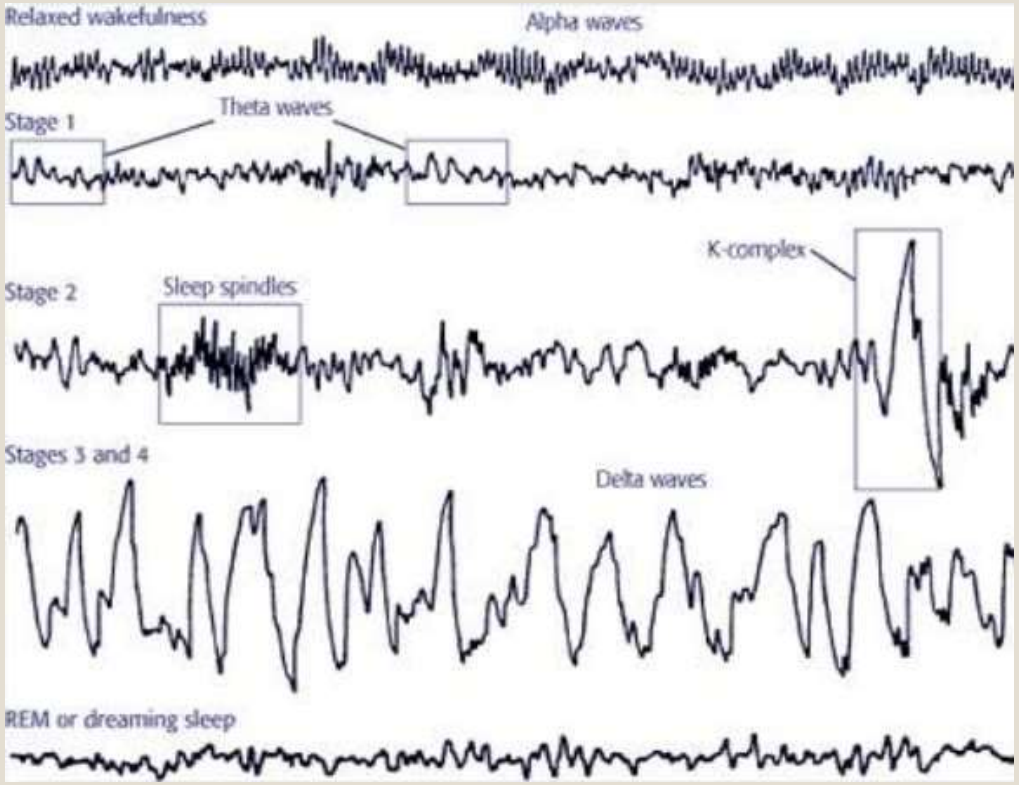
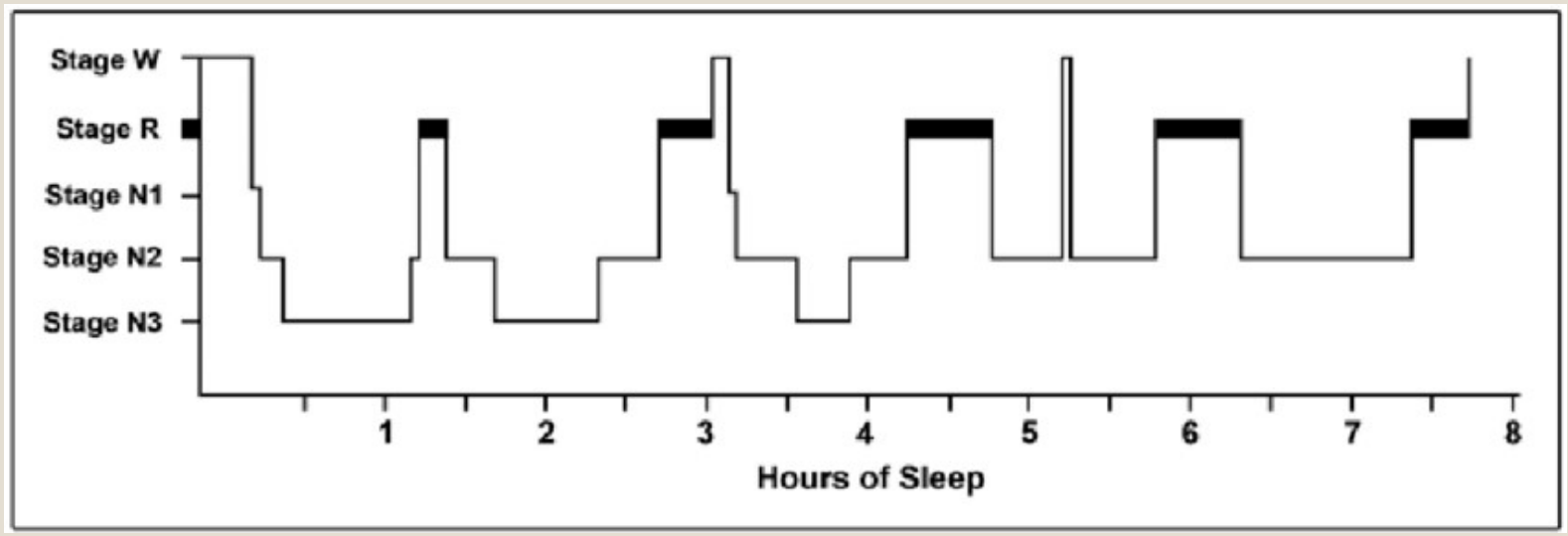
Sleep Stages

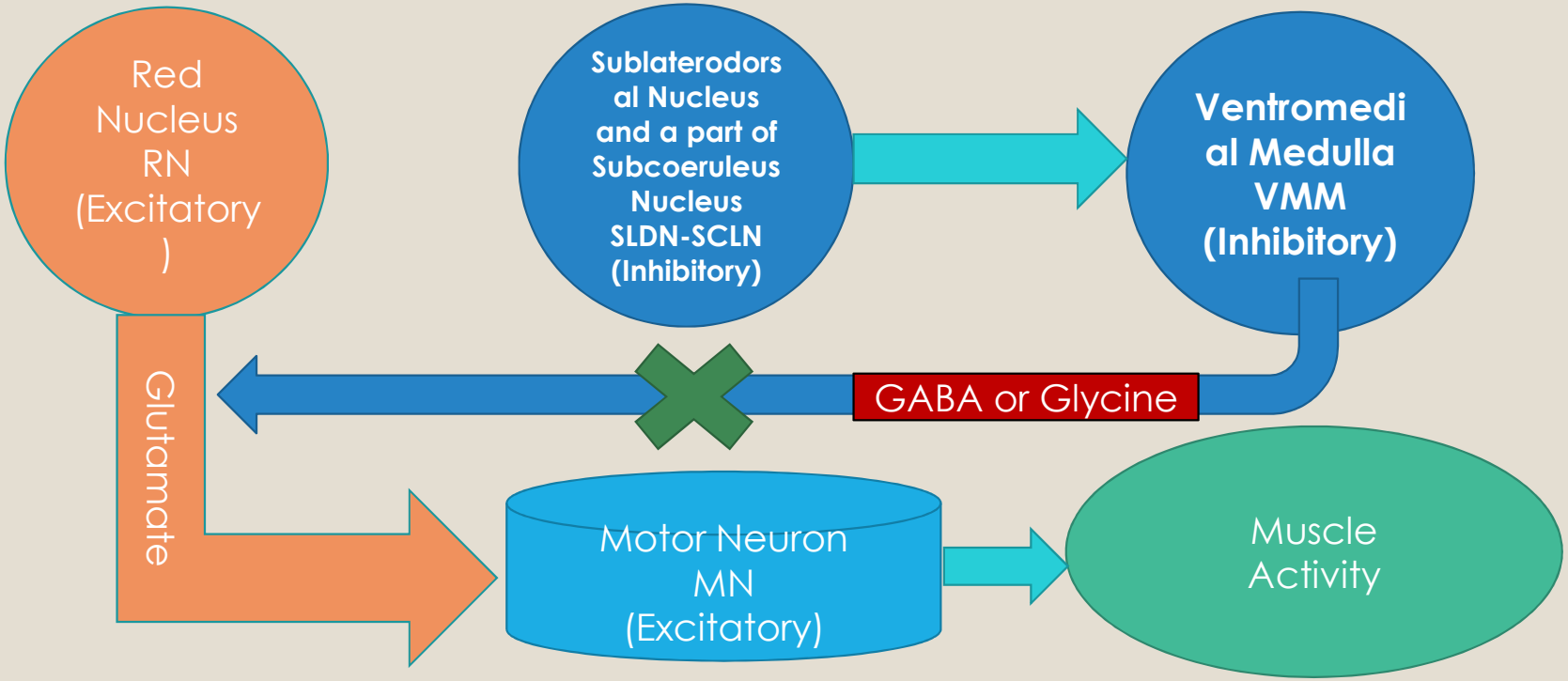


Blume C, del Giudice R, Wislowska M, Lechinger J, Schabus M. Across the consciousness

Sleep Stages



Normal REM Sleep



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What are REM-Related Parasomnias?

- REM-related parasomnias = undesired behaviors during REM sleep
- REM sleep is depicted by two distinctive features:
  - Dreaming
  - Loss of muscle tone

REM Behavior Disorder – ICSD-3 Definition

Diagnostic Criteria (Criteria A-D **MUST** be met)

A. Repeated episodes of sleep related vocalization and/or complex motor behaviors
B. These behaviors are documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep
C. Polysomnography demonstrates REM sleep without atonia (RWA)
D. The disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance abuse

Most Common REM Parasomnias

REM Parasomnias	Clinical Features
REM Sleep Behavior Disorder (RBD)	"Acting out violent dreams" as a result of loss of physiological inhibition of muscle activity during REM sleep
Recurrent Isolated Sleep Paralysis (RISP)	"Transient inability to move just before falling asleep or shortly upon wakening" as a result of state dissociation in which REM muscle atonia persists into conscious wakefulness.
Nightmare Disorder	"Repetitive disruptive dysphoric dreams" resulting in sleep disturbance or daytime dysfunction

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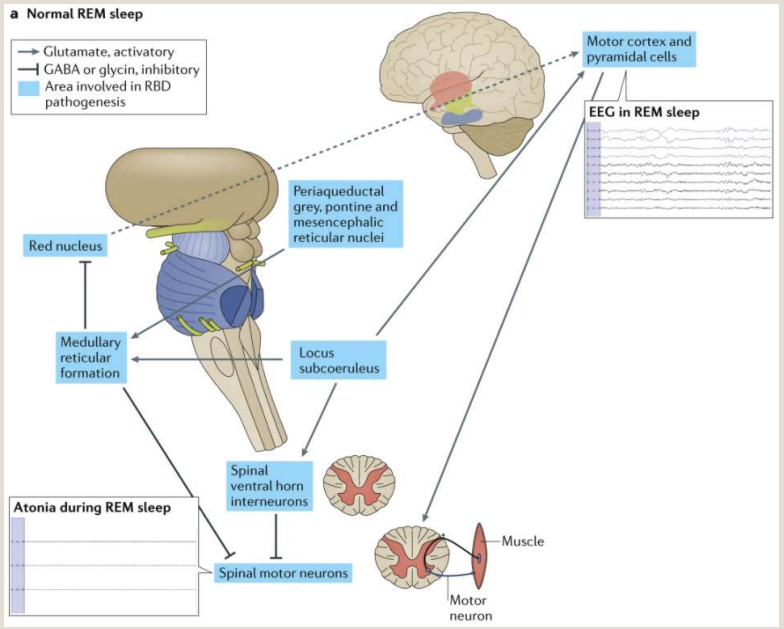
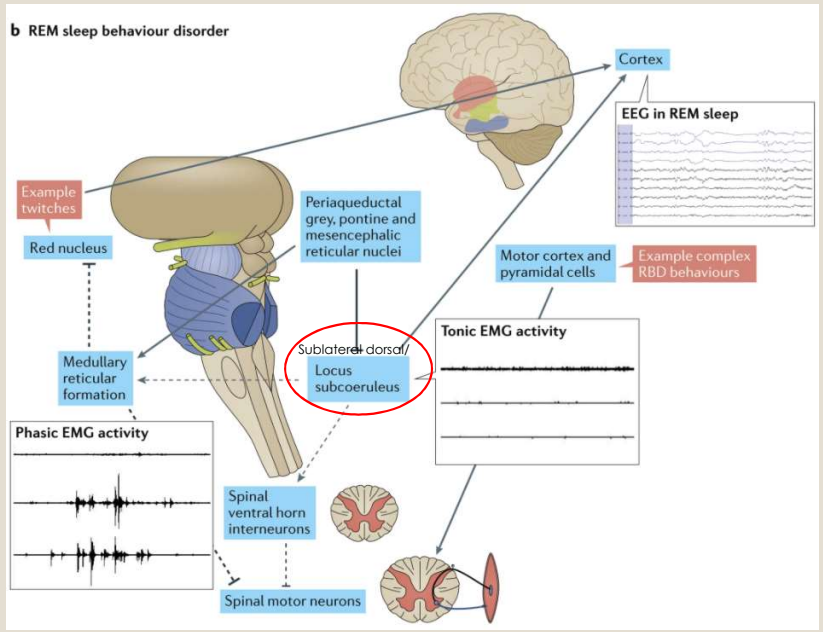
REM Behavior Disorder (RBD)

- Loss of physiological atonia during REM is the basis of RBD
  - Normally, protective inhibitory mechanism preclude "acting out" dreams that may pose a risk for injury to the patient and bed partner
- Behaviors seen in RBD are often violent and associated with vivid dreams
  - These may lead to injury to the patient or their bed partner
  - Sleepwalking is uncommon with this
- Content of dreams is usually easily recollected by the patient
- Patients with RBD do not exhibit these behaviors during the daytime

REM Sleep Behavior Disorder (RBD)





Högl B, Stefani A, Videnovic A. Idiopathic REM sleep behaviour disorder and

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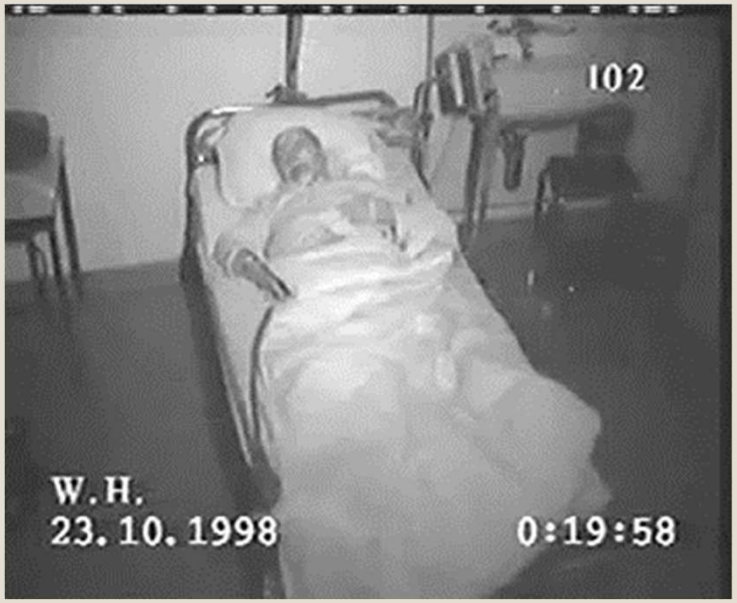
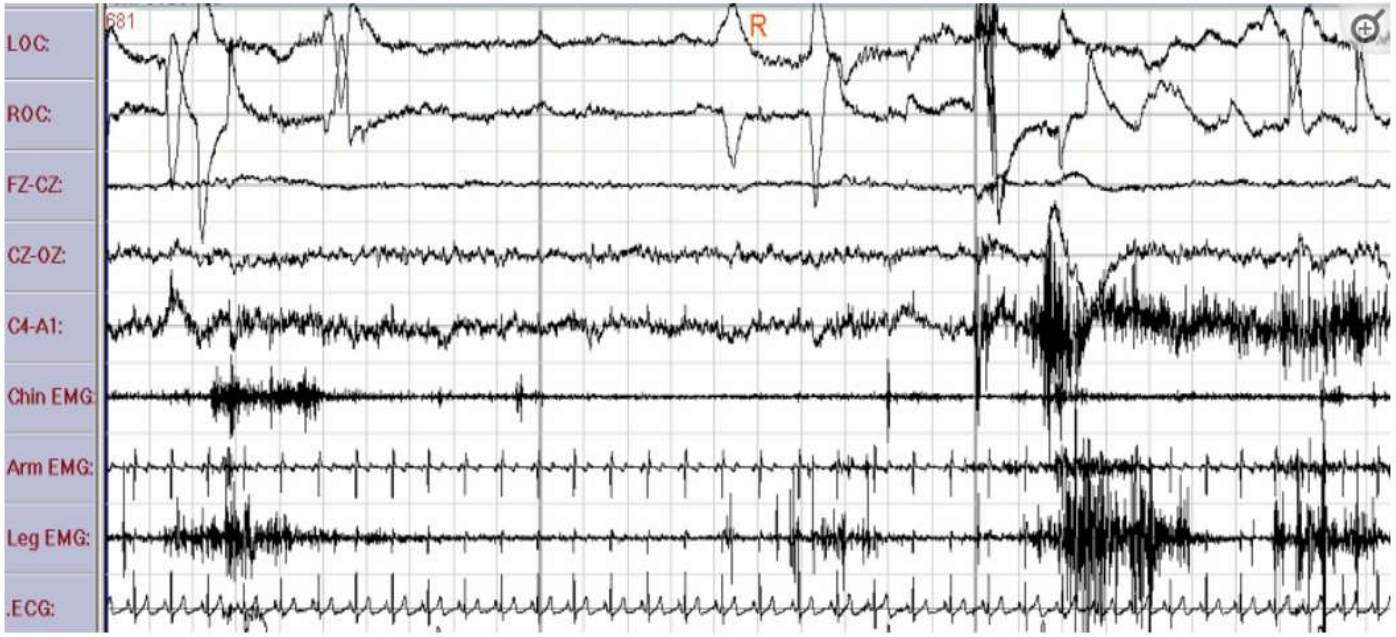
REM Sleep Behavior Disorder (RBD)

- Symptoms:
  - Act out dreams, vivid dreaming, vocalizations, cursing, violent activity, injuries
  - Can occur many years before other symptoms of neurodegenerative diseases
- Testing:
  - Sleep study with 4-limb EMG



Courtesy of Birgit Högl.MD, Sleep Disorders Unit, Dept of Neurology, University of Innsbruck



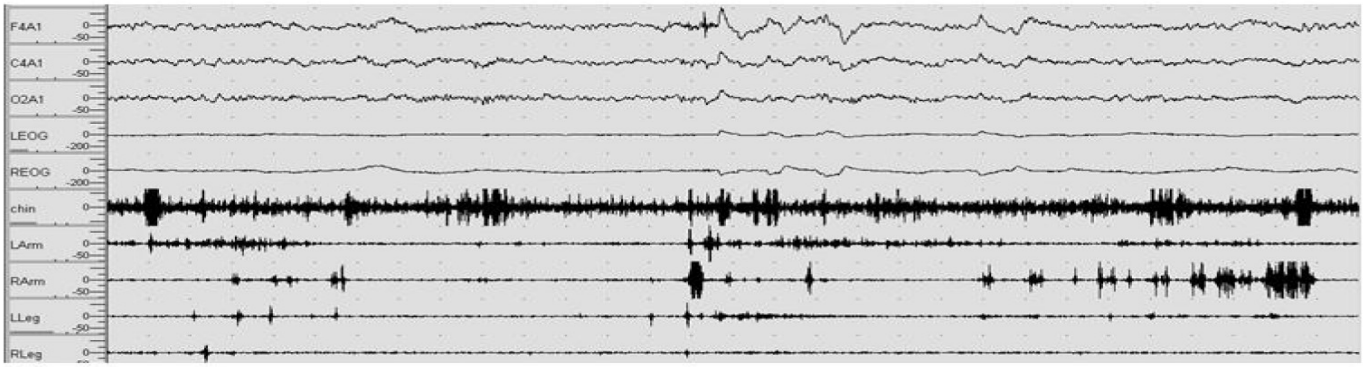
REM sleep without atonia in a 75 year-old man with parkinsonism and dream enactment behavior. Note the elevated muscle tone in channels 6, 7, and 8 corresponding to the chin, arm, and leg EMG leads, respectively.

St Louis EK. Sleep and Epilepsy: Strange Bedfellows No More. Minerva Pneumol. 2011 Sep;50(3):159-1

Polysomnographic Findings in RBD

- PSG in idiopathic RBD requires RWA: EITHER sustained (tonic) chin EMG activity OR excessive transient (phasic) chin or extremities EMG activity
- Dx of RBD: Requires both a partial or complete loss of muscle tone of chin and/or extremities EMG activity on the PSG AND a typical clinical presentation

PSG Epoch showing loss of muscle tone in chin and extremities



American Academy of Sleep Medicine. *An Introduction to Sleep Disorders.* Darien, IL: 2018

REM Behavior Disorder Severity Scale (RBDSS) Score

Motor events:

0 = no visible motor activity; chin RWA (REM without atonia) present

1 = small movements or jerks during REM (excluding PLMs and respiratory and/or arousal related movements)

2 = proximal movements including violent behaviors during REM

3 = axial movements including bed falls during REM

Vocalizations:

0 = no vocalization; snoring with some sound may be present

1 = all sleep associated sounds other than respiratory noises

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*ICSD, International Classification of Sleeo Disorders; RWA, REM sleep without atonia

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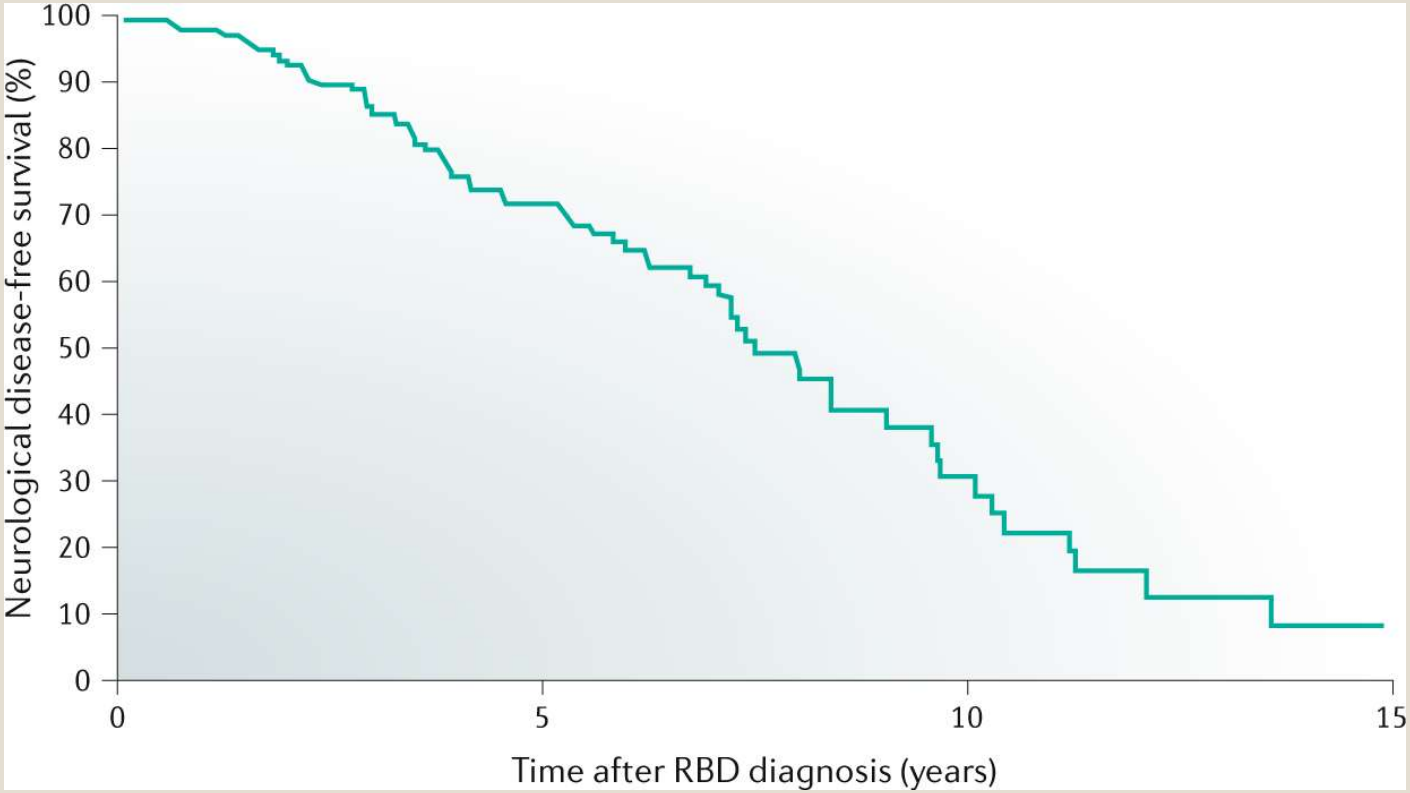
Prodromal Value of Idiopathic RBD

- Early targets – pontine and medullary nuclei that control REM sleep.
- Annual phenoconversion rate – 6%, 74% phenoconverting within 12 years of RBD diagnosis
- Patients with RBD, prior to neurodegenerative symptoms
  - DAT scan can be positive
  - Cholinergic denervation
  - Phosphorylated alpha-synuclein deposits in nerve fibers by skin biopsy

Prodromal Value of Idiopathic RBD

- Recent research advancements identify iRBD as potential prodrome of certain neurodegenerative diseases, preceding onset of PD symptoms by 10-15 years (sometimes even before onset of anosmia)
- As many as 70-91% of patients with idiopathic RBD go on to develop some form of alpha synucleinopathy:
  - Parkinson's Disease (PD)
  - Lewy Body Dementia (LBD) or
  - Multiple System Atrophy (MSA).
- Conversely, prevalence of RBD in patients with PD estimated at 30-40%, and >40% and >90% in those with LBD and MSA, respectively
- Pseudo-RBD has little or no value in risk stratification for future potential neurodegenerative diseases

a-synucleinopathy risk



Dauvilliers Y, Schenck CH, Postuma RB et al. REM sleep behaviour disorder. Nat Rev Dis Primers 2018;**4**(19).
Iranzo A, Fernández-Arcos A, Tolosa E, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. *PLoS One*. 2014;9(2):e89741.

Prodromal Value of Idiopathic RBD

Alpha Synucleinopathy	Prevalence of RBD	RBD preceding the onset of neurodegenerative disorder (% of patients)	Time interval between RBD onset and onset of neurodegenerative disorder
Multiple system atrophy	80-100%	16-54%	4-7 years
Parkinson's disease	30-41%	18-25%	3-4 years
Dementia with Lewy bodies	40-72%	71-100%	6-10 years

Fulda S. Idiopathic REM sleep behavior disorder as a long-term predictor of neurodegenerative disorders. EPMA Journal (2011) 2:451–458

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Variations of RBD

- Pseudo-RBD
  - Occurs when symptoms suggestive of RBD reported, but may represent a reversible secondary cause or mimicker, such as OSA
  - Usually characterized by less dramatic and less frequent occurrences of dream enactments in affected individuals.
  - Always consider central hypersomnia, underlying mood disorder, medications, etc.
- Latent RBD
  - May often be unmasked by medications (table on next slide) in those with preexisting RWA.
  - Medication-induced RBD can be classified as RBD, using clinical judgement, pending future longitudinal studies
- Idiopathic RBD (iRBD) - Ideally, diagnosis should be made only if symptoms persist after discontinuation and/or treatment of offending secondary causes (i.e. medications, OSA, etc.)

Medications Associated with RBD

Class	Medication examples
SSRIs	sertraline, fluoxetine, escitalopram, citalopram, paroxetine
SNRIs	venlafaxine
TCAs	amitriptyline, imipramine
Other antidepressants	mirtazapine
Beta blockers	bisoprolol, atenolol

RBD Prodrome

- Definition: unprovoked, new-onset, and aggressive sleep talking that occurs later in life.
- Can have a history of sleep talking but the key to this is new aggressive sleep talking.
- Can precede RBD and neurodegenerative diagnosis by years to decades.

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Treatment of RBD

Domains	Recommendations
Injury Prevention	Bedroom safety precautions: ▪ Sharp objects should be removed from the bedroom ▪ Padding may be applied to the bed and adjacent pieces of furniture ▪ Sleeping in a sleeping bag may help assure patient's safety
Medications	▪ Melatonin ▪ Clonazepam
Risk stratification	▪ Risk stratification for future risk for development of alpha synucleinopathies (PD, LBD and MSA) on case by case basis ▪ Early referral to a neurologist may be considered

Prognosis and Counseling

- RBD can potentially be used to monitor prodromal neurodegenerative disease and intervene with neuroprotective therapy.
- No single, accurate, cost-effective biomarker to determine risk of conversion from RBD to neurodegenerative disease.
- In isolated RBD, strongest risk factors to neurodegenerative conversion were – objective motor exam findings, olfactory dysfunction, ED, abnormal color vision, and constipation.
- DAT scan and tissue alpha-synuclein can predict increased risk for early conversion – but lack sensitivity/sensitivity and are not practical for isolated RBD.

Patient Disclosure

- Uncertainty must be balanced with possible significance of RBD.
- RBD does not necessarily equal PD – it suggests increased risk.
- Individualized approach but you need to rule out any mimickers.
- Share general information and gauge receptivity/distress while balancing confidence in diagnosis.

Questions?