

# Sleep Dysfunction in Parkinson's disease

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# Sleep

- state of decreased awareness of environmental stimuli that is distinguished from states such as coma or hibernation by its relatively rapid reversibility
- universal behavior, demonstrated in all animals
- SLEEP IS NOT A LUXURY IT IS A NECESSITY!
- necessary for survival
  - prolonged sleep deprivation leads to severe physical and cognitive impairment, and finally death

# Sleep Functions: Learning, Memory, and Mood

- form new learning and memory pathways in the brain
- people can learn a task better if they are well rested
- one study suggests that sleep is needed for creative problem- solving
- Proper folding of certain proteins in the brain and clearance of worn off proteins/toxins
- **lack of sleep**
  - thinking processes slow down
  - harder to focus and pay attention and more easily confused
  - Poor decision making and more risk taking
  - Slows down your reaction time (important to driving)
  - Irritability and in time depression
  - Misfolding of protein leads to formation of “clumps” that then choke the brain cells (i.e. Alzheimer, Parkinson)

# Sleep Functions -Hormones

- release of growth hormone and boosts muscle mass and the repair of cells and tissues
- release of sex hormones contributes to puberty and fertility
- Maintain an adequate function of immune system
- regulator of appetite, energy use, and weight control

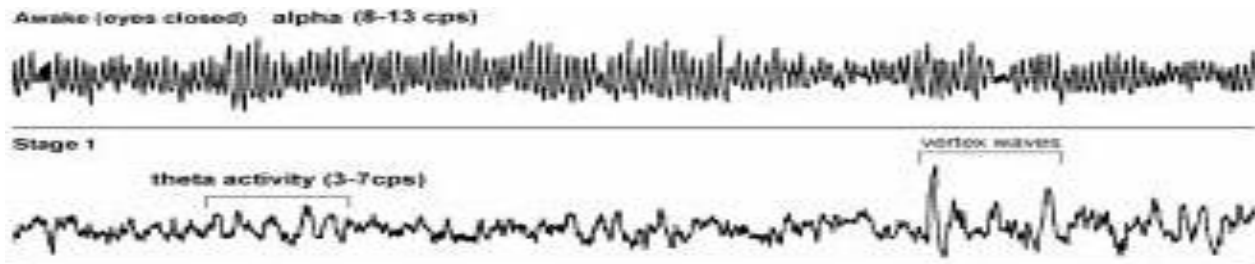
# Stages of Sleep

- Human body goes through different stages when laying down to rest
  - Short-term interference with sleep stages can lead to irritability, poor concentration and tiredness
  - Long-term interference can lead to significant health problems: obesity, cardiac, poor immune response, depression, possible dementia, other
- **Rapid eyes movements (REM) sleep**
- **Non-REM Sleep**
  - Stage 1
  - Stage 2
  - Stage 3
  - Stage 4
- Each stage of sleep has its specific electrical pattern that can be recognized on an electroencephalogram (EEG)

# NREM sleep: Stage 1

- First minutes after you lay down in bed at night with eyes closed
- Eye movements become slow and rolling, and muscle tone relaxes.
- decreased awareness of stimuli and mental activity more dream-like
- Occasionally sudden muscle contractions, accompanied by a sense of falling and/or dreamlike imagery: **hypnic jerks**
  - More frequent in sleep deprived people

EEG

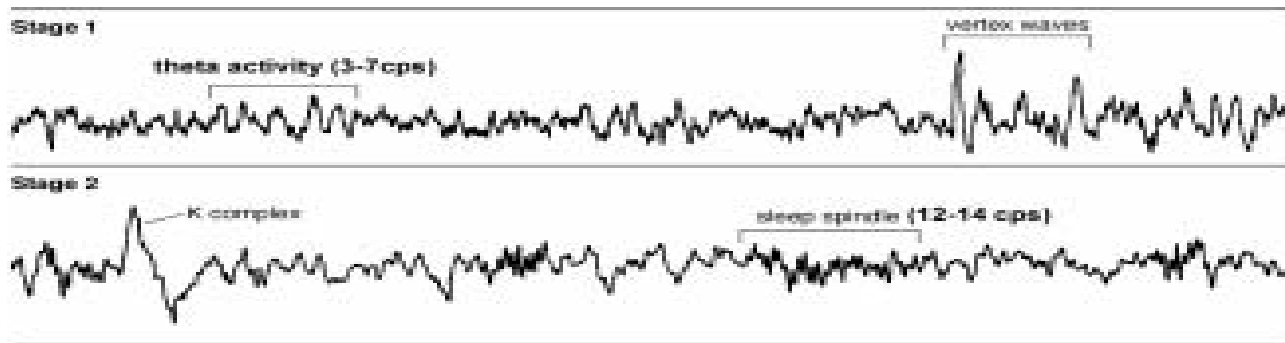


Awake

Stage 1

# NREM Sleep: Stage 2

- We are actually asleep
- Loss of awareness of surroundings
- Body temperature drops, regular heart rate and breathing, eye movements reduced



Stage 1

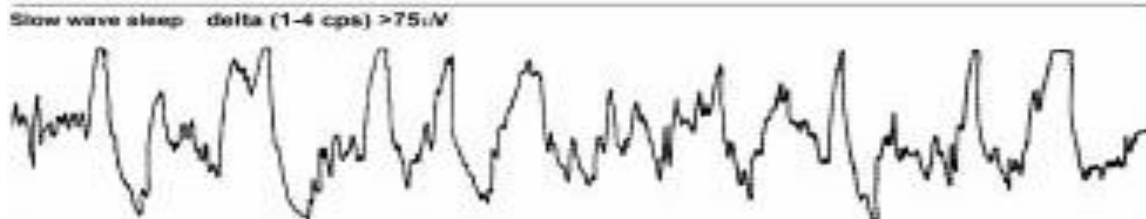
Stage 2

# NREM Sleep: Stages 3 & 4

- Deepest stages of sleep
- Breathing slows and muscles relax
- Difficult to be awoken from this phase
- Important brain tissue repair activity and secretion of hormones of growth and development are secreted in these stages



Stage 2



Stage 3-4

# REM Sleep

- This is the stage of sleep when we dream
- Rapid eyes movements with eyes closed
- Breathing is rapid, irregular and shallow, heart rate and blood pressure increase
- Arms and legs muscles are in a paralysis-like state
- Role of dreaming is not fully understood but likely place a significant role in consolidating learning and memory

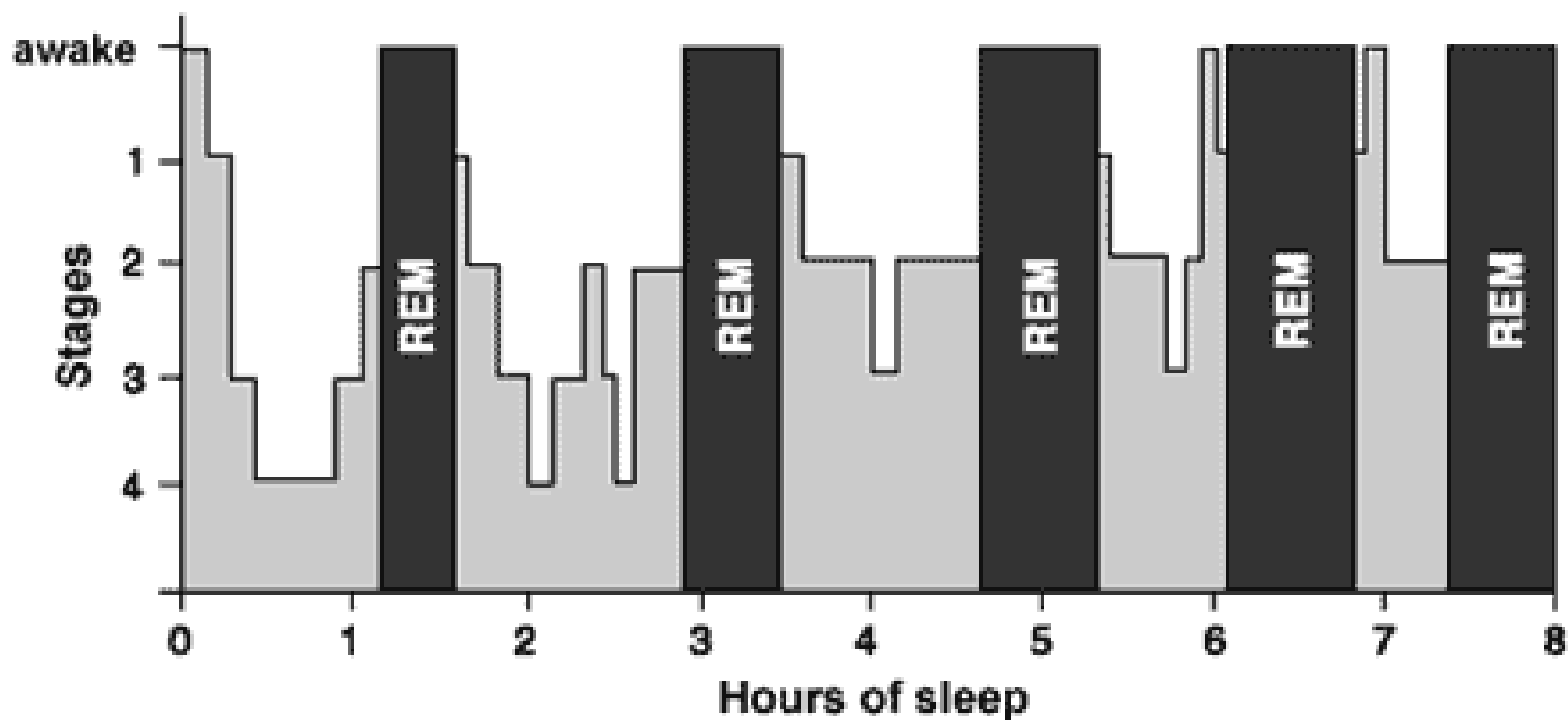


Stage 1

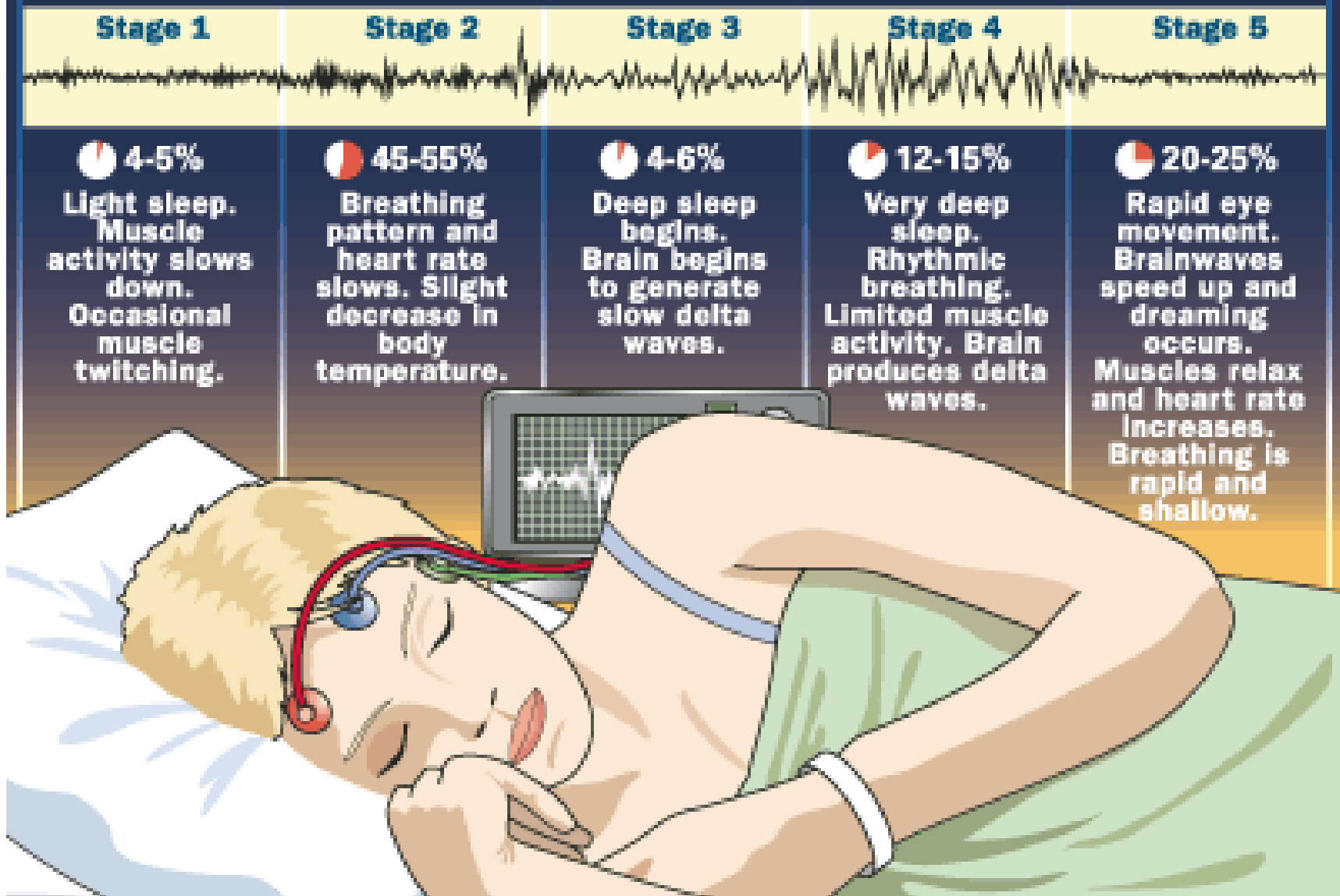


REM Sleep

# Normal Sleep Cycle



## 100% Sleep Cycle



# Sleep/wake 24-hours cycle (circadian)



# Sleep-Wake Hormones

## SEROTONIN



- Secreted by central nervous system
- Regulates mood, sleep, appetite
- Levels are influenced by good sleep

## MELATONIN



- Secreted by the pineal gland from serotonin in low light conditions
- Synchronizes the biological clock
- Powerful natural antioxidant
- Important in regulating the killer cells of the immune system

# Sleep Hygiene

- Stick to a sleep schedule and plan for 7-8 hours of sleep/night
- Exercise daily but avoid exercise 2-3 hours before bedtime
- Avoid caffeine after lunch
- Avoid alcohol and large meals before bed
- Avoid taking medicines that delay or disrupt sleep before bedtime
- Avoid naps after 3 PM
- Take a hot bath before bed, avoid electronics in the bedroom, keep bedroom dark, quiet and cool
- Don't lie in bed if awake
- Get proper light exposure during the daytime

# Polysomnography (sleep study)

- a test used to diagnose sleep disorders
- The following are recorded:
  - Brain wave through a limited EEG
  - Oxygen level in blood
  - Heart rate and breathing
  - Eye and leg movements
- Usually done in hospital/sleep center; overnight
- Additional sleep test: multiple sleep latency test- done the morning following a polysomnography

# Sleep Disorders

- **Sleep apnea or another sleep-related breathing disorder;** In this condition, breathing repeatedly stops and starts during sleep.
- **Periodic limb movement disorder.** In this sleep disorder, you involuntarily flex and extend your legs while sleeping. This condition is sometimes associated with restless legs syndrome.
- **Narcolepsy.** You experience overwhelming daytime drowsiness and sudden attacks of sleep in this condition
- **REM sleep behavior disorder.** This sleep disorder involves acting out dreams as you sleep.
- **Unusual behaviors during sleep.** Your doctor may perform this test if you do unusual activities during sleep, such as walking, moving around a lot or rhythmic movements.
- **Unexplained chronic insomnia.** If you consistently have trouble falling asleep or staying asleep, your doctor may recommend polysomnography.

# Sleep in Parkinson's Disease

***“...the sleep becomes much disturbed. The tremulous motion of the limbs occurs during sleep, and augment until they awaken the patient, and frequently with much agitation and alarm...”***

*“An Essay on the Shaking Palsy”*. James Parkinson, 1817

# Sleep and Wakefulness Dysfunction in Parkinson's Disease

- Initiation and sleep-maintenance insomnia
- Sleep apnea and parasomnias
- Excessive daytime sleepiness and sleep attacks
- Sleep-benefit in Parkinson's disease

# Insomnia in PD

- 60% to 76% of PD patients experience insomnia
- Sleep-onset insomnia
- Sleep-maintenance/fragmentation

# Causes of sleep-onset insomnia

- Motor symptoms of PD: tremor, stiffness, difficulties rolling in bed
- Restless legs
- Musculoskeletal pain
- PD Medications with awakening effect
  - Amantadine, selegiline
- Excessive daytime sleepiness with frequent naps
- Depression

# Sleep-fragmentation Insomnia

- Causes
  - Wearing-off phenomenon/dyskinesia
  - Early morning dystonia
  - Nocturia-multiple episodes of urination at night
  - Hallucinations,
  - Early awakening
  - Parasomnias: REM sleep behavior disorder, sleep apnea

# Adverse Effects of PD Medications on Sleep

- Selegiline
  - Insomnia through amphetamine metabolite
- Levodopa
  - Increases REM latency/reduces REM sleep duration
- COMT inh
  - Enhance levodopa effect
- Dopamine agonists
  - Low dose: insomnia
  - High dose: daytime sleepiness
- Anticholinergics
  - Daytime sleepiness
  - Alerting effect at night
- Amantadine
  - Alerting effect
- Antidepressants (some)
  - Stimulating
- Benzodiazepines:
  - Sedating
  - Withdrawal: rebound insomnia

# Management of insomnia

- Apply principles of sleep hygiene
- Adjust timing/dose of PD medications to avoid OFF time or ON time with dyskinesia at bedtime
- Avoid taking alerting medications too late
- Manage restless legs symptoms: dopamine agonist, gabapentin, pregabalin
- manage sleep disorders: discussed later
- Manage depression
- Sleep-inducing medications: no proven medications
  - zolpidem may worsen REM sleep disorder
  - Antidepressants: trazodone, mirtazapine, amitriptyline
  - Antipsychotics: quetiapine, clozapine

# Sleep-disordered breathing in PD

- Sleep apnea: serious sleep disorder that occurs when a person's breathing is interrupted during sleep
  - Obstructive sleep apnea: more common form that occurs when throat muscles relax too much
  - Central sleep apnea: occurs when brain doesn't send proper signals to the muscles that control breathing
  - Complex sleep apnea syndrome: mix of both central and obstructive sleep apnea

# Sleep Apnea Symptoms

- Loud snoring, which is usually more prominent in obstructive sleep apnea
- Episodes of breathing cessation during sleep witnessed by another person
- Abrupt awakenings accompanied by shortness of breath (more in central sleep apnea)
- Awakening with a dry mouth or sore throat
- Morning headache
- Difficulty staying asleep
- Excessive daytime sleepiness
- Attention problems
- Irritability

# How frequent is sleep apnea in PD

- High frequency of excessive daytime sleepiness and snoring in PD patients has led to the suggestion that sleep disordered breathing (SDB) is more common in these individuals than in normal subjects
- However, there is no strong evidence to support this assumption based on the available clinical studies that used polysomnography

- A PubMed search was performed to identify controlled studies, published from January 1990 through October 2012, which addressed the prevalence of sleep apnea diagnosed by polysomnography in idiopathic PD
- 7 studies included;
  - 5 reported similar or lower prevalence of sleep apnea in patients when compared to healthy age-matched controls
  - Two studies reported less drops in O<sub>2</sub> desaturation during sleep among patients

# Parasomnias in PD

- category of sleep disorders that involve abnormal movements, behaviors, emotions, perceptions, and dreams that occur while falling asleep, sleeping, between sleep stages, or during arousal from sleep
- Periodic leg movements in sleep
- REM sleep behavior disorder

# REM Sleep Behavior Disorder

- loss of normal skeletal muscle atonia during rapid eye movement (REM) sleep with prominent motor activity and dreaming
- Manifestations:
  - Vocalizations, swearing, screaming
  - Motor activity varies from simple limb jerks to complex motor behavior, with injuries to patient or bed-partner
  - Dreams often involve attacks by animals or humans
  - Exhibited behaviors mirror dream content
  - Behaviors tend to occur in latter half of the sleep period



# REM Sleep Behavior Disorder in PD

- PD patients with RBD are more likely to
  - be older and male
  - orthostatic hypotension
  - Freezing of gait
  - Non-tremor subtype of PD
  - Depressed
  - Herald future development of dementia
- Treatment:
  - Clonazepam
  - Melatonin: 3 mg-12 mg at bedtime

# REM Sleep Behavior Disorder (RBD) in PD

- prevalence 15% to 45% based on interviews, but 46% to 58% when a PSG is performed in PD patients
- 28% and 45% of patients with idiopathic RBD develop neurodegenerative disorder (PD, MSA, DLB) at 5 yrs follow up and 40-65% at 10 yrs
- Median latency between RBD symptom onset and defined disease ranged from 12 to 14 years
- Diagnosis: polysomnography

# RBD as a prodromal feature of PD

- PROs
  - RBD is the strongest clinical predictor of  $\alpha$ -synucleinopathy (PD the most common)
    - 40-65 % risk of neurodegenerative disease at 10 years
    - Low sensitivity (<50 % patients have RBD)
  - Long latency to clinical disease (~13 years)
    - Long window to intervene with neuroprotective therapy
- Cons
  - Most RBD patients do not present to doctor
  - Dx is not simple (a sensitive/specific screening questionnaire not available )
  - “Milder” RBD cases may have a lower risk of developing PD
  - Relatively low specificity (DLB, MSA, other)
  - 30-50 % of patients with PD develop RBD;

# Excessive daytime sleepiness in PD

- occurs in 15%-50% of PD patients
- Risk factors: male gender, longer disease duration, and high disease severity and dopaminergic medication
- poor sleep quality and duration
- taking dopamine agonists or levodopa, is associated with increased daytime sleepiness
- Untreated PD patients do not seem to have EDS compared with controls

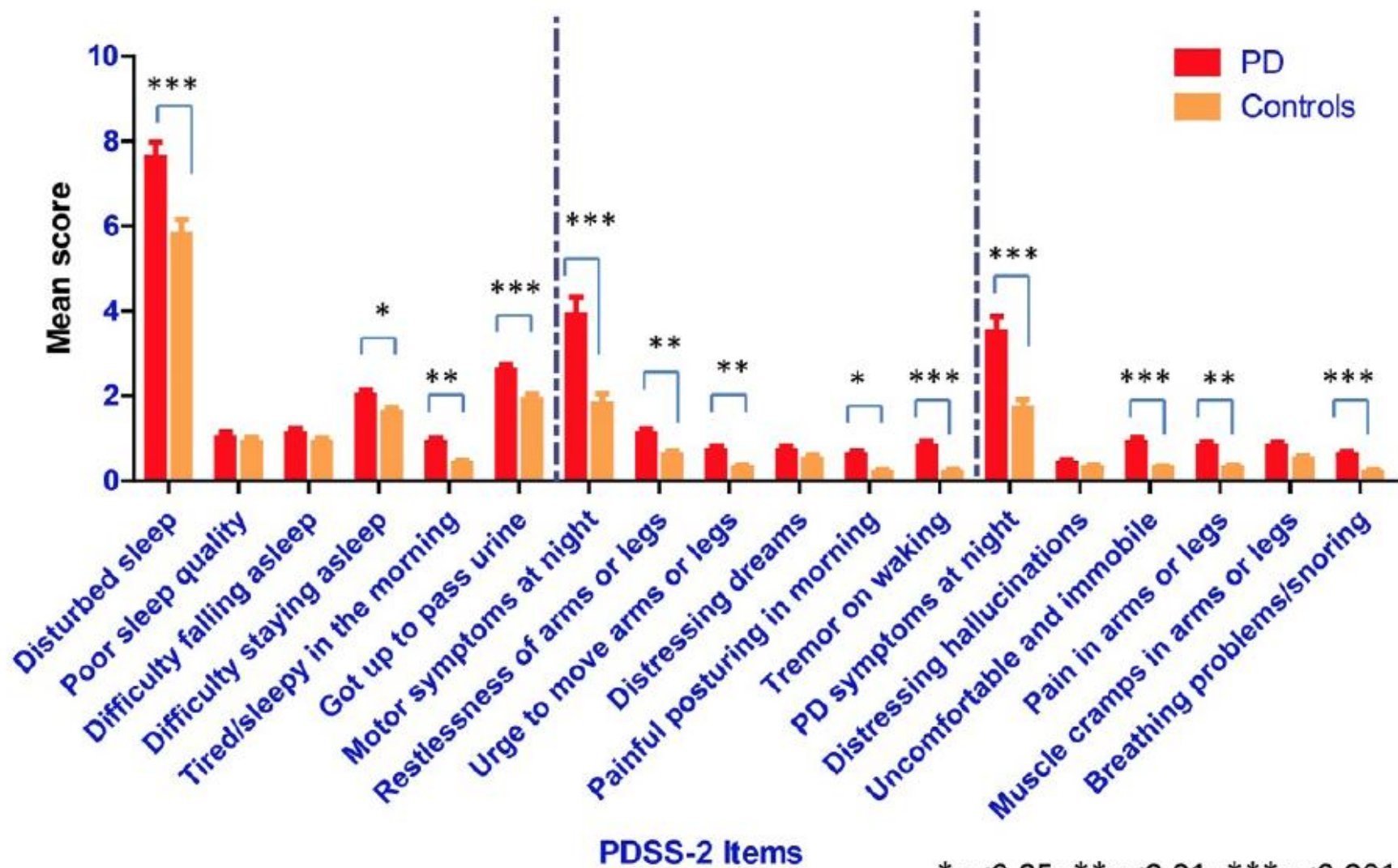
# Sleep Attacks

- sudden, unexpected, and irresistible sleep episodes while engaged in some activity
- Sudden-onset sleep episodes while driving have been reported in 3.8%-22.8% of PD patients
- Overall daytime sleepiness does not appear to correlate with a higher risk for sleep attacks
- Treatment with dopamine agonists or dopamine agonists/levodopa combination appears to be important risk factor

# PD Sleep Scale

Please rate the severity of the following based on your experiences during the past week (7 days). Please make a cross in the answer box

	Very often (This means 6 to 7 days a week)	Often (This means 4 to 5 days a week)	Sometimes (This means 2 to 3 days a week)	Occasionally (This means 1 day a week)	Never
1) Overall, did you sleep well during the last week?	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
2) Did you have difficulty falling asleep each night?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
3) Did you have difficulty staying asleep?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
4) Did you have restlessness of legs or arms at nights causing disruption of sleep?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
5) Was your sleep disturbed due to an urge to move your legs or arms?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
6) Did you suffer from distressing dreams at night?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
7) Did you suffer from distressing hallucinations at night (seeing or hearing things that you are told do not exist)?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
8) Did you get up at night to pass urine?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
9) Did you feel uncomfortable at night because you were unable to turn around in bed or move due to immobility?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
10) Did you feel pain in your arms or legs which woke you up from sleep at night?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
11) Did you have muscle cramps in your arms or legs which woke you up whilst sleeping at night?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
12) Did you wake early in the morning with painful posturing of arms and legs?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
13) On waking, did you experience tremor?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
14) Did you feel tired and sleepy after waking in the morning?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
15) Did you wake up at night due to snoring or difficulties with breathing?	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0



\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$

# Conclusions

- Sleep is significantly impaired in Parkinson's disease
- Treatments are available for most sleep disorders encountered by PD patients
- Improvement of the nocturnal Parkinsonism and reducing bathroom awakenings on themselves can reduce the sleep difficulties in PD
- Use judiciously daytime medications in PD and recognize the drugs that may contribute more to daytime sleepiness
- Strict adherence to the principles of sleep hygiene is a must!

Thank You!