Unravelling the Sleep-Stroke Connection

Understanding, managing, and preventing

L Charlesworth MD FRCPC Zzzz
Sept 27, 2024

Disclosures

- No relevant financial disclosures or conflict of interest.
- Consultant: Transport Canada Aviation Medical Review Board.

Contents

Sleep ⟶ Stroke

Sleep ⟵ Stroke

1) Sleep Terminology & Physiology
2) Sleep disordered breathing (OSA)
3) Other sleep disorders
    I. Insomnia
    II. Hypersomnia
    III. Periodic limb movements & RLS

01

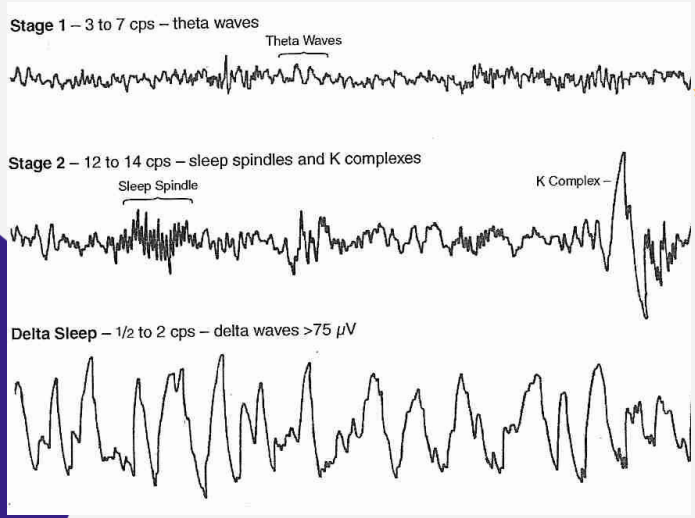
Sleep Basics

Terminology & Physiology
Circadian rhythm
Sleep restriction

~80% of the night
Homeostatic driven; frontloaded in night.

- N1 – Light sleep.
- N2 – Deeper.
  - K-complexes, sleep spindles.
  - Roles in motor learning.
- N3 – Deepest.

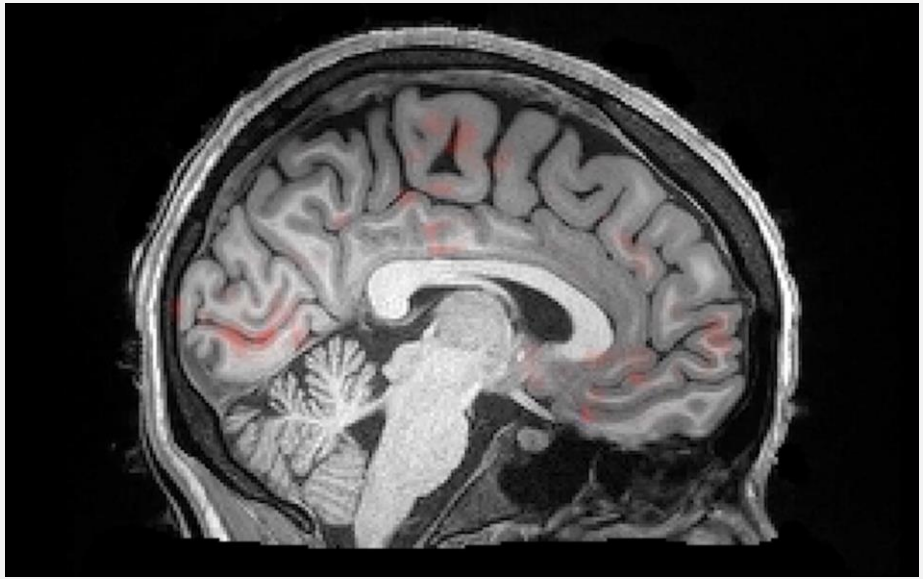
nREM



N3 sleep is responsible for:

- Memory consolidation, selective destruction of synapses.
- Facilitates waste clearance (glymphatic system).
- ?immune function.

nREM

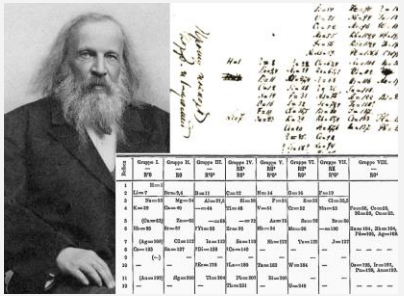


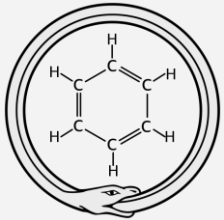
Fultz et al. Science. 2019: 366(6465):628–31.

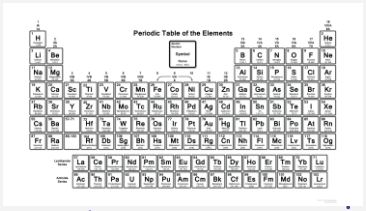
Associated with dreaming and atonia.

Responsible for:

1. processing knowledge & memories
2. regulating emotion & introspection
3. forming cognitive “bridges”







REM

~20% of the night, backloaded

Circadian Rhythm

All ~24h cycles within the body.

Nutrition, social cues, hormone cycles, temperature, blood pressure, insulin/glucose...

Governed by the suprachiasmatic nucleus in the hypothalamus via melatonin pathways.

Circadian factors and stroke

- Ischemic stroke incidence by time of day:

  0600-1200: 37%*
  1200-1800: 26%
  1800-0000: 19%
  0000-0600: 18%

  **Partially but not fully driven by wake-up strokes.*

- Hemorrhagic strokes not as clearly circadian.

Lo et al. *Stroke* 2021.

Sleep Timing & Duration

- Circadian aberrancies:
  - Higher risk **cardiovascular disease** with circadian misalignment (ie. shift work).
  - Higher risk **metabolic syndrome** / insulin over-secretion with dim light at night.

- Average sleep requirements 7-9h per night.
- Higher cardiovascular & cerebrovascular risk with sleeping too much *or* too little.

Sleep & Stroke Recovery

Sleep is neuroprotective and promotes neuroplasticity. Guides formation of new connections.

Axonal sprouting associated with synchronous low-frequency oscillations in peri- and contralesional cortical areas. Comparable frequency to N3 sleep.

Duss et al. *Neurobiology of sleep and circadian rhythms (2016).*

1. Sleep serves a vital function; not to be overlooked.
2. Important to sleep the right amount at the right time.

02

Sleep Disordered Breathing

Obstructive Sleep Apnea (OSA)
Snoring / Upper Airway Resistance Syndrome (UARS)
Central Sleep Apnea (CSA) and Cheyne-Stokes Respirations (CSR)
Hypoventilation

02
Sleep Disordered Breathing

Obstructive Sleep Apnea (OSA)
Snoring / Upper Airway Resistance Syndrome (UARS)
Central Sleep Apnea (CSA) and Cheyne-Stokes Respirations (CSR)
Hypoventilation

Obstructive Sleep Apnea (OSA)

- Condition of repetitive airway collapse in sleep.
- Associated with arousals and desaturations.

- Scored according to apnea-hypopnea index (AHI):
  5-15 mild 15-30 moderate >30 severe

- *Higher risk cardiovascular outcomes for AHI ≥20/hr.*
- *AHI is likely not the best measure of true "severity".*

Beyond the AHI

Highest risk OSA:

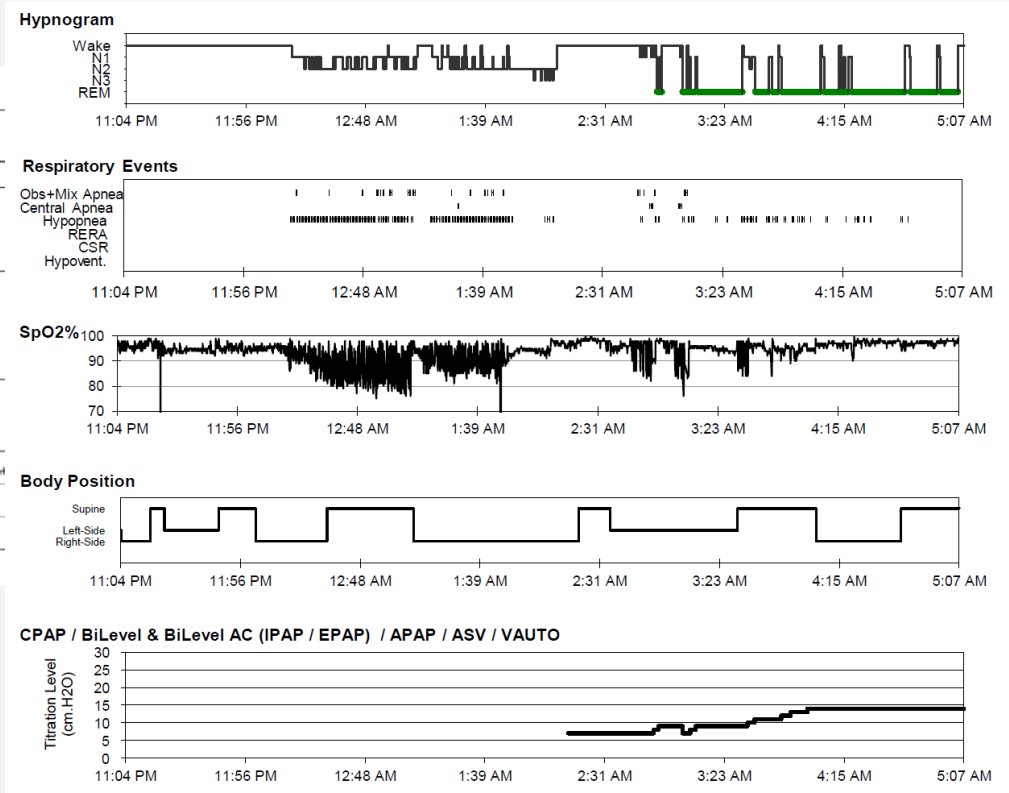
spO_2 <90% for ≥10% total sleep time.

Low arousal threshold, fragmented sleep.

Autonomic instability (heartrate variability, BP spikes).

Generally, symptomatic patients are higher risk.


Hypnogram
Wake
N1
N2
N3
REM
9:44 PM
10:51 PM
11:58 PM
1:04 AM
2:11 AM
3:17 AM
4:24 AM
Respiratory Events
Obs+Mix Apnea
Central Apnea
Hypopnea
RERA
CSR
Hypovent.
SpO2%
100
90
80
70


Hypnogram
Wake
N1
N2
N3
REM
11:04 PM
11:56 PM
12:48 AM
1:39 AM
2:31 AM
3:23 AM
4:15 AM
5:07 AM
Respiratory Events
Obs+Mix Apnea
Central Apnea
Hypopnea
RERA
CSR
Hypovent.
SpO2%
100
90
80
70
Body Position
Supine
Left-Side
Right-Side
CPAP / BiLevel & BiLevel AC (IPAP / EPAP) / APAP / ASV / VAUTO
Titration Level (cm.H2O)
30
25
20
15
10
5
0

Sleep Disordered Breathing & Stroke - Mechanisms

Oxidative stress

Endothelial dysfunction, atherosclerotic plaque formation.

↑ inflammation (inflammatory markers & cytokines).

Cardiac disease

R heart strain, provokes atrial fibrillation.

Hypertensive heart disease.

Metabolic syndrome

Poor glycemic control, higher blood glucose variability.

Dyslipidemia.

Sympathetic activation

Frequent nocturnal arousals associated with elevated BP. Reduced nocturnal BP "dipping".

Arrhythmias.

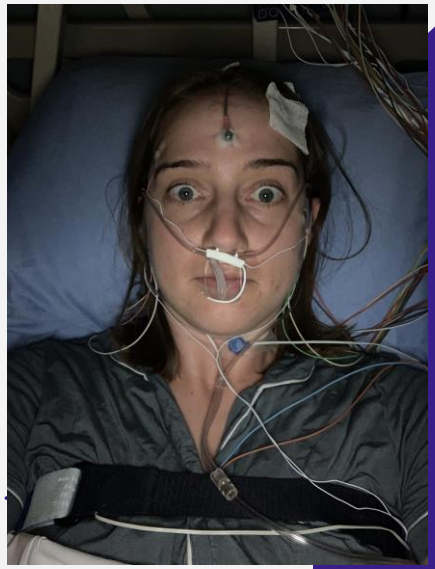
OSA Risk Factors

- Demographics: older, male.
- Elevated body mass index
- Genetics:
  - Family history.
  - Arousal threshold & respiratory drive.
- Upper airway:
  - Nasal airway: deviated septum, allergic rhinitis (polyps, congestion), adenoids.
  - Oral airway: arched palate, small jaw, large tongue base, tonsils.
- Resp comorbidities: COPD, smoking

OSA Symptoms

Common	“Sneaky”
Snoring Witnessed apneas Fragmented sleep Daytime somnolence	Insomnia (maintenance or terminal) Nocturia Vivid dreams Awakening with dry mouth Restless sleep Concentration troubles Parasomnias
Morning headache	Atypical headaches (TACs, stabbing headache)

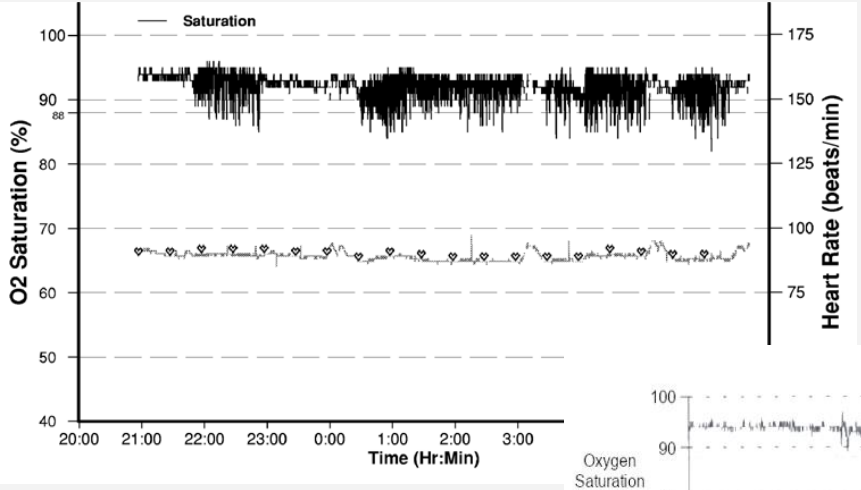
OSA Diagnosis

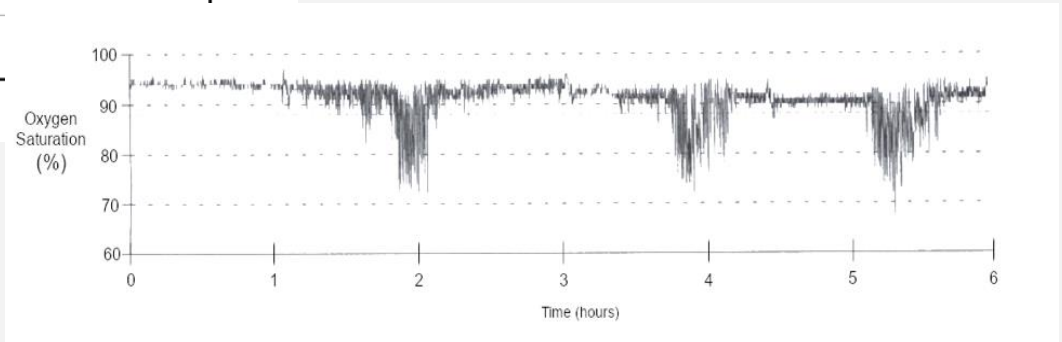


- In Ontario, diagnosis requires a level 1 (in-lab) polysomnogram to qualify for CPAP funding.
  Limitations:
  - Logistically challenging post stroke.
  - 1x lifetime sleep study covered by OHIP.
  - Long sleep medicinewait lists.

- Other methods:
  - At home sleep test (HSAT).
  - Cardiopulmonary coupling (CPC).
  - Overnight oximetry (OvOx).

Overnight Oximetry – screening





Sleep Disordered Breathing & Stroke

- Independent risk factor for ischemic and hemorrhagic stroke, regardless of comorbidities.
  - Adjusted hazard ratio 2.86 (moderate to severe OSA).
  - Increased risk of ICH, OR 1.7.
- OSA more common among stroke patients:
  - 70-80% of patients post-stroke have OSA.
    The more you look, the more you find.
  - 30% have severe OSA.
- Stroke/TIA patients with untreated OSA are more likely to experience recurrent stroke.

1. Gottesman, R. F. American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; and Council on Hypertension (2024). Impact of Sleep Disorders and Disturbed Sleep on Brain Health: A Scientific Statement From the American Heart Association. Stroke.
2. Geer et al. Stroke, 2021.

OSA and Stroke *Recovery*

- Stroke patients with OSA have:
  - Worse **functional** outcomes.
  - Worse post-stroke **cognitive** deficits.
  - Higher risk of **recurrent stroke**.

- Stroke patients with OSA who use CPAP demonstrate improved neurological outcome, improved independence with ADLs, and lower subjective symptoms.

OSA treatment & Stroke

Clear association between OSA & stroke incidence, recurrence, and recovery…

- YET – very limited / unclear data that treatment improves outcome.
- Issues:
  - Heterogenous trials, often per protocol.
  - Limited by CPAP adherence.
  - Limited by exclusion of symptomatic patients.

- Better outcomes in patients who are adherent to CPAP.
- Better outcomes in patients who are symptomatic.

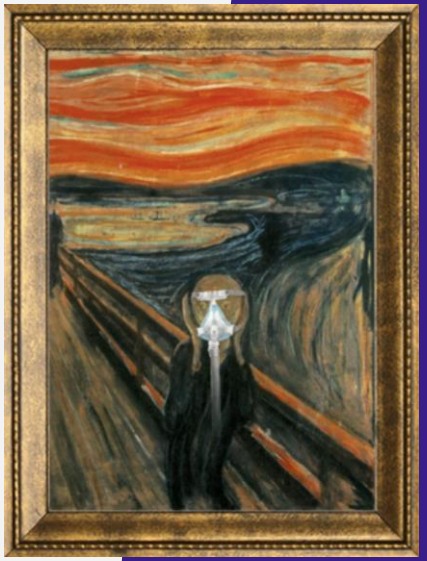
Continuous Positive Airway Pressure (CPAP)

- **Pneumatic splint for the upper airway.**
- Main viable treatment option for moderate to severe OSA, and in post-stroke patients.

- Non-adherence common:
  - **Comfort** is the most common reason for non-adherence.
  - In stroke patients, also facial palsy & cognitive deficits.
  - Troubleshooting is possible!

CPAP troubleshooting

- **Step 1**: Direct patient to their CPAP vendor.
  Encourage them to trial different masks.
- **Step 2**: Assess the airway for modifiable contributors:
  Screen for allergies, nasal congestion. Try nasal rinse ± nasal steroids.
- **Step 3**: Screen for other sleep disorders (RLS, insomnia).
- **Step 4**: Encourage *practice* not *perfection*.
  Start with goal 4h, 70% of nights.



OSA treatment & Stroke

Treatment options – Not just CPAP.

(Note: none of these are specifically indicated in post-stroke population).

- Weight loss
- Dental device
- Positional therapy
- Myofunctional therapy
- Surgery – MMA, UPPP, tonsillectomy
- *Medications?*
- *Hypoglossal nerve stimulation*

Other sleep disordered breathing

Central Sleep Apnea:

- Less common post stroke (~8%).
- Not clearly associated with outcome.
- Approach:
  - Assess for alternate cause (cardiac, resp, medications).
  - CPAP (esp if coincident OSA), or ASV.
  - If asymptomatic, may not require treatment.

Snoring / upper airway resistance (UARS):

- Minimal data post-stroke. Possible association with cardiovascular disease.
- Associated with fatigue; consider treating symptomatically.

Sleep disordered breathing: bottom line

High risk OSA features include nocturnal desaturations and disrupted sleep. Generally higher risk in symptomatic patients.

For all patients with known moderate to severe OSA, encourage treatment to lower stroke risk (primary and secondary prevention).

All patients with stroke should be screened for OSA, with low threshold to send for a sleep study for any sleep-related symptoms.

There may be benefit to treating CSA or snoring, but effects are not well established.

03

Other Sleep Disorders

Insomnia
Hypersomnia
PLMs and RLS

Insomnia

2-8x

Increased risk of stroke in patients with insomnia.

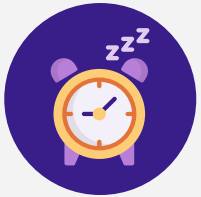
50%

Of post-stroke patients have insomnia.

Insomnia: diagnosis

Nocturnal Symptoms

Initiation
Maintenance
Terminal



Diurnal Symptoms

Fatigue, concentration troubles, social or occupational effects, sleepiness...

Frequency & Duration

At least 3 nights per week.
At least 3 months (chronic).

Post-stroke insomnia

Up to 50% of patients post-stroke.

Rule out:

- Screen for accompanying **mood disorder**.
- Review **new medications** (next slide).
- Screen for accompanying **sleep disorder**.
  - Onset: RLS, DSWPD, anxiety.
  - Maintenance: PLMs, OSA.
  - Terminal: OSA, ASWPD, depression.

Management:

- 1st line: Cognitive behavioural therapy for insomnia (CBT-i)
  Evidence for typical CBTi and virtual CBTi post stroke.
- Could consider: Short term pharmacologic management.*

NOTE: Sleep hygiene is important, but alone is insufficient to treat insomnia!

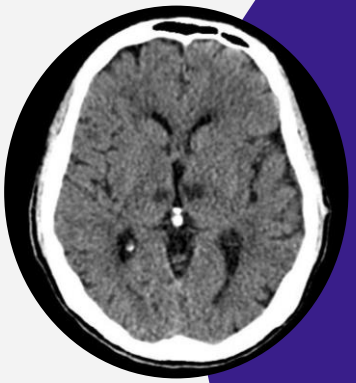
Sneaky (and not so sneaky) Alerting medications

CNS stimulants: methylphenidate, modafinil, amphetamine	**Anti-seizure medications**: • Lamotrigine (esp in peds) • Topiramate • Levetiracetam?	**Diuretics**: 2ry to urination, not inherent drug effect.
Anti-depressants: • MAOIs (common) - & MAOBs (selegiline) • SSRIs: fluoxetine, paroxetine, sertraline. • SNRIs: duloxetine, venlafaxine • Bupropion • TCAs: protriptyline, imipramine, clomipramine	**Anti-psychotics**: • Loxapine, haloperidol, aripiprazole	**Glucocorticoids**
		NSAIDs
	Bronchodilators • Also resp stimulants: theophylline	**OTC**: weight loss medications / appetite suppressants, nasal decongestants, cold medications
	Beta antagonists!! • WASO and vivid dreams. • Worst: labetalol, metoprolol, propranolol • Moderate: sotalol, carvedilol, timolol	**Statins**: • Lipophilic statins • Esp lovastatin, atorvastatin, simvastatin.
		Caffeine, Alcohol, Nicotine

Hypersomnia

Hypersomnia & Stroke

- Condition of **excessive daytime sleepiness** (EDS). Independent of fatigue, though often linked.
- Stroke-free patients with hypersomnia have higher burden of subcortical white matter disease.
- Associated with higher disability, poor recovery post-stroke.
- Common localizations:
  - Brainstem (esp pons, midbrain – RAS).
  - R hemispheric.
  - Subcortical (caudate, putamen).
  - Paramedian thalamus, hypothalamus.



Ramos et al. (2014). J Sleep Res.
Harris et al. (2014). Transl Stroke Res, 5:292-300.

Hypersomnia & Stroke

Assessment & Management

- Screen for accompanying **mood disorder**, **sleep disorder**, and **medications**.
- Assess for accompanying features:
  - KLS: Agoraphobia, hyperphagia, derealization.
  - Narcolepsy: parasomnias, REM intrusions, cataplexy.

- Minimal data to guide management.
- **Consider symptomatic medications**:
  - Modafinil 100-200 mg OD or BID.
  - Alerting antidepressant (bupropion, venlafaxine).
  - Methylphenidate CR 10-40 mg.

Periodic Limb Movements & Restless Legs

RLS & Stroke

- More common after stroke (ischemic or hemorrhagic) – up to 10% of patients.
- No direct association with worse outcomes.
  Can be very symptomatically troubling.
- Aggravators post-stroke:
  - Sleep restriction (insomnia, hospital).
  - Medications (SSRIs, antipsychotics, antiemetics).
  - Sedentary behaviour, dependent edema.

Restless Legs Syndrome

Clinical syndrome. “URGED” mnemonic.

U – urge to move the legs
R – rest makes it worse
G – gets better with movement
E – evening worsening
D – diagnosis of exclusion

Caution!

If patients cannot adequately describe symptoms, be suspicious of circadian behavioural changes.

Periodic Limb Movements

PSG finding.
Increases with age.

Not necessarily pathologic, though can be associated with poor sleep quality / fragmentation.

RLS – Management

- Address non-pharmacologic measures first!*
  - Stop offending substances (caffeine, alcohol).
  - Compression stockings during the day.
  - Sequential compression devices.
  - Regular bedtime with appropriate sleep hygiene.
- Stop/minimize offending medications.
- Supplement ferritin for target ≥75-100 mcg/L
- Pharmacologic: pregabalin/ gabapentin 1st line.
- PLMs – often do not require treatment.
  Treat as per RLS.

*Non-exhaustive list.

04

Operator error

Circadian bias
Physician performance and fatigue

Circadian Bias: Research in Stroke Care

- Most stroke trials recruit predominantly diurnally.
- Mouse models often diurnal (mouse's biochemical "night").

- Heart responds to cardiac ischemia variably in circadian cycle.
- Likely circadian contribution to ischemic stroke as well.

Thosar, Butler, & Shea. *J Clin Invest*. 2018.

Stroke management & outcomes

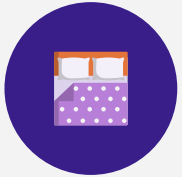
- Ischemic stroke outcomes:
  - Door-to-needle time better during day.
  - Possible improved functional outcome for daytime presentation.
  - Often attributed to **healthcare worker fatigue** and resources.

- ICH:
  - *Possible* ↑ hematoma expansion at night.
  - Higher mortality for ICH and SDH presenting overnight.

Lo et al. *Stroke*, 2021.

Summary

Adequate quality and quantity sleep is important in stroke prevention and recovery.



REVIEW

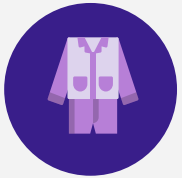
Ask your patients about their sleep. Flag short *and* long sleepers.

SCREEN

Consider a PSG for fragmented sleep, especially if features of SDB.

TREAT

Treat sleep comorbidities as part of routine stroke care.



OPTIMIZE

Address sleep habits and sleep hygiene for both 1º and 2º prevention.

Questions?