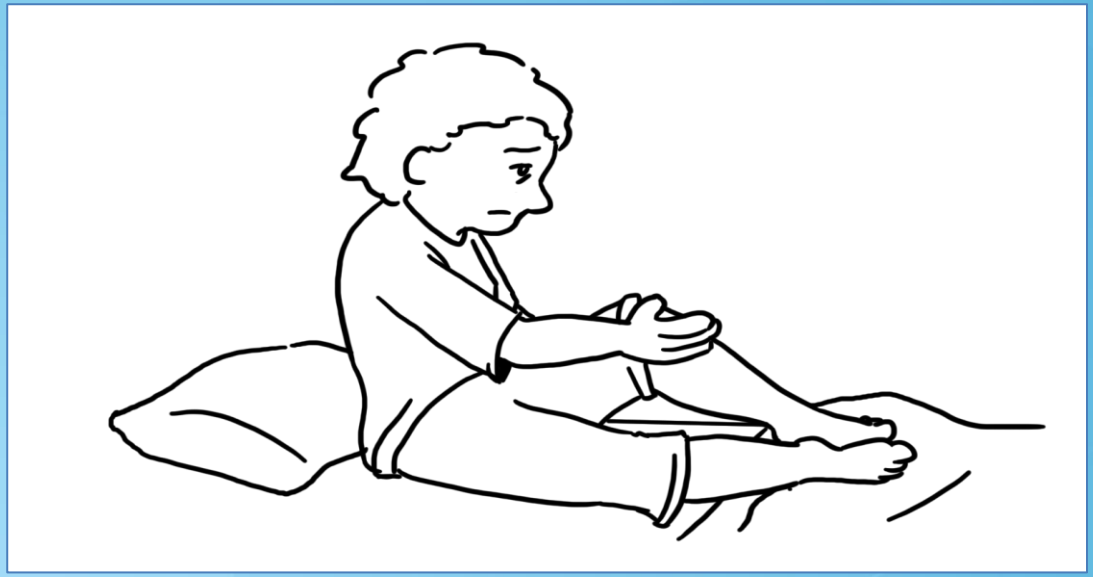
Restless Legs Syndrome (RLS)

(Willis Ekbom Disease)



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May 14, 2016 American Psychiatric Association Meeting, Atlanta, GA

Picture courtesy FOAMed

Financial Disclosures

- No financial disclosures to declare

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- Review the definition and clinical features of Restless Legs Syndrome (RLS) and periodic limb movements (PLMS)
- Evaluate epidemiology, etiology and psychiatric comorbidities
- Understand pharmacological and non pharmacological treatment options

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Restless Legs Syndrome – DSM-5

- "URGE" Unpleasant sensation

  U – rge to move legs

  R – est – symptoms worsened at rest

  G – ets better with movement

  E – vening – symptoms worse in evening
- ≥ 3x/week, ≥ 3months
- Significant distress
- Not due to medical condition, substance

MR. D., A 45 YEAR OLD MALE WITH A COMPLAINT OF INSOMNIA AND LEG DISCOMFORT

These are not RLS

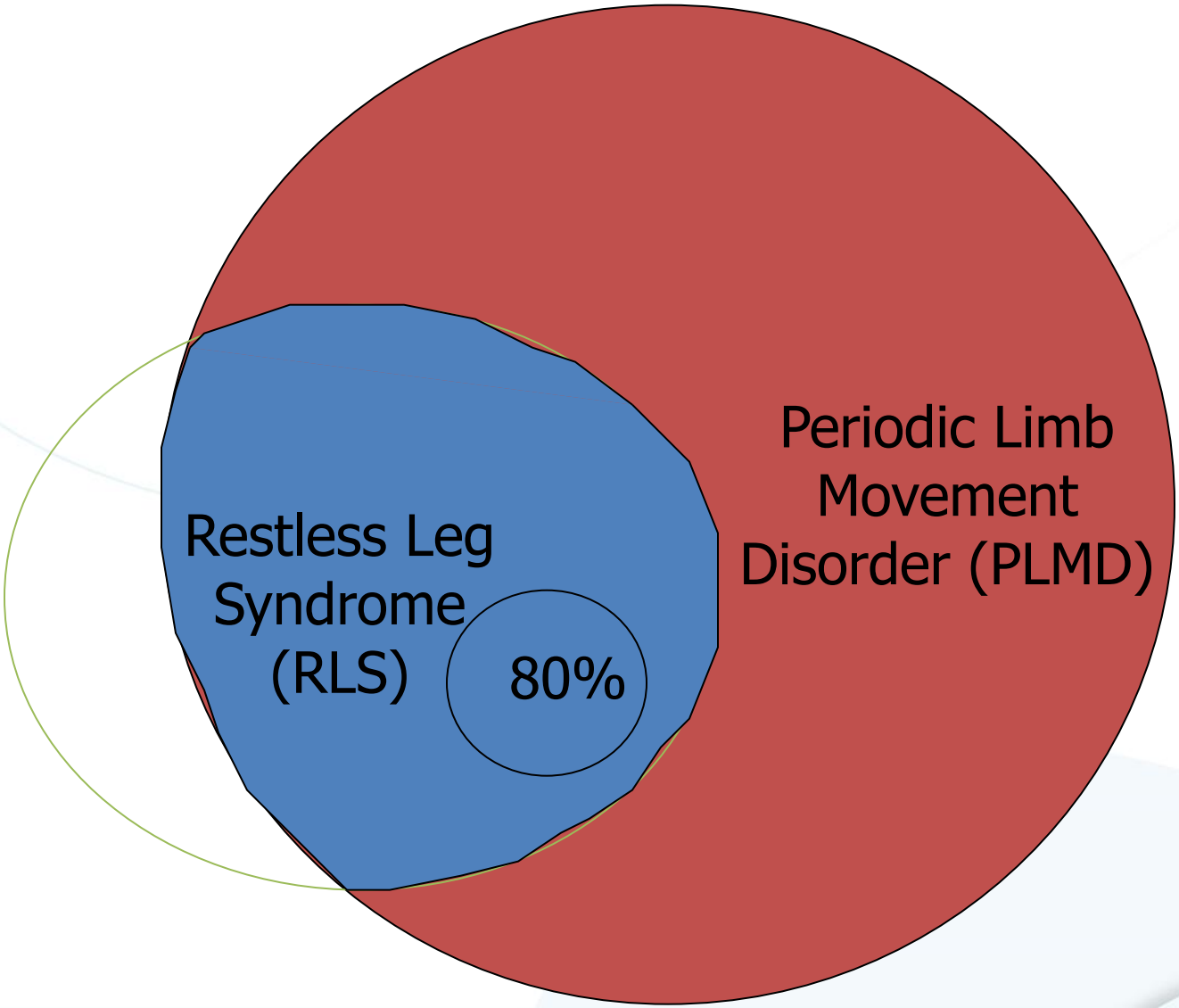
Slide courtesy of Dr. Winkelman

	How many criteria met?	Differentiate from RLS	Co-exist With RLS
Leg cramps	4 of 4	Muscle spasm easily identified	+
Neuropathy	1 of 4	Numbness, burning, and tingling without an urge to move	+++
Arthritis	2-3 of 4	Discomfort in joints, at rest, improves with movement	++
Vascular	2-3 of 4	Varicosities and PVD. +/- relief with movement; rub helps more. Walking is worse.	++
Positional discomfort	1-2 of 4	Foot or leg “asleep” from compression. Shift and its gone.	--
Akathisia	3-4 of 4	Urge to move, all over, caused by dopamine antagonists	+

Benes H, von Eye A, Kohnen R. Empirical evaluation of the accuracy of diagnostic criteria for Restless Legs Syndrome. Sleep Med. 2009 May;10(5):524-30.

Periodic Limb Movements (PLMs)

- Repetitive leg (limb) movements DURING SLEEP
- Typically 20-40 seconds apart
- Cause awakenings and fragmentation
- Patient often unaware. Bedpartner reports “kicking”
- c/o frequent awakenings, light sleep
- aka Nocturnal Myoclonus


Periodic Limb Movement Disorder (PLMD)
Restless Leg Syndrome (RLS)
80%

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Epidemiology/Etiology - RLS

- 5-10% of the population affected (♀/♂=2/1)
- The leading hypothesis is brain dopamine dysfunction
- Involves a circadian fluctuations in dopamine
- Deficiencies in other substances, especially iron, likely play a role. Others? – Mg, opioids, Vit B12
- Key diagnostic question:
  Do your legs ever bother you at night?

Allen RP et al. Sleep Medicine (4). 2003: 101-19

RLS and Psychiatric Comorbidity

Winkelman and Colleagues-
238 pts with RLS – evaluated for psychiatric disorders vs controls (12 m prevalence):

	OR
• Panic Disorder	4.65
• Generalized Anxiety Disorder	3.52
• Major Depressive Disorder	2.55

Winkelman et al. J. Neurol (2005) 252 : 67–71

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Address Exacerbating Factors

- Caffeine
- Tobacco
- Alcohol
- Medications
  - dopamine blockers
    (antipsychotics, GI motility agents)
  - antidepressants (SSRI's)
  - mirtazapine*

Exacerbating Influence of Psychotropics on RLS/PLMS

- Neuroleptics[1,2]
- Lithium[3,4]
- Antidepressants (PLMS)[5,6]
  - Consider bupropion[7,8]

1. Horiguchi J, et al. *Int Clin Psychopharmacol.* 1999;14:33. 2. Kraus T, et al. *J Clin Psychopharmacol.* 1999;19:478.
3. Heiman EM, Christie M. *Am J Psychiatry*. 1986;143:1191. 4. Terao T, et al. *Biol Psychiatry*. 1991;30:1167.
5. Brown LK, et al. *Sleep Med.* 2005;6:443-450. 6. Yang C, et al. *Biol Psychiatry*. 2005;58:510.
7. Kim S, et al. *Clin Neuropharmacol*. 2005; 28:298. 8. Nofzinger EA, et al. *J Clin Psychiatry*. 2000;61:858.

Slide courtesy Dr. Robert Auger

Check Iron (Ferritin)!

- Intake – food?
- Absorption - GI difficulties
- Blood loss?
  - Anemia – Cough? Poop?
  - Menstrual Periods/Pregnancy
  - Blood donations
- Target ferritin > 75 µg/L
- May replace e.g. $FeSO_4$ with vitamin C tid 2 hours before or after meals

Dopaminergic Agents

- Intermittent (<3x/week)
  Levodopa (Sinemet)
  (Sinemet CR 25/100,
  1 tab po qhs prn)
  take as abortive therapy when symptoms arise

- Daily or almost daily (>3x/week)
  - Pramipexole (Mirapex)
  - Ropinirole (Requip)

  eg Pramipexole 0.25-0.5 mg po q2h before bed
  take 2 hours before symptoms are worst

Silber MH et al. Mayo Clin Proc (2004) 79(7): 916-22
Silber MH et al. Mayo Clin Proc (2013) 88(9): 977-86

Side Effects – Pramipexole

- Nausea
- Nasal stuffiness
- Constipation
- Leg swelling
- Insomnia
- *Sleepiness (caution driving)
- *Pathological gambling and impulsive behaviors

Side Effects – with longer use

- Augmentation

  Symptoms begin earlier in the day
  (may add earlier or change med)

- Rebound

  Symptoms return in the middle of the night
  (change med)

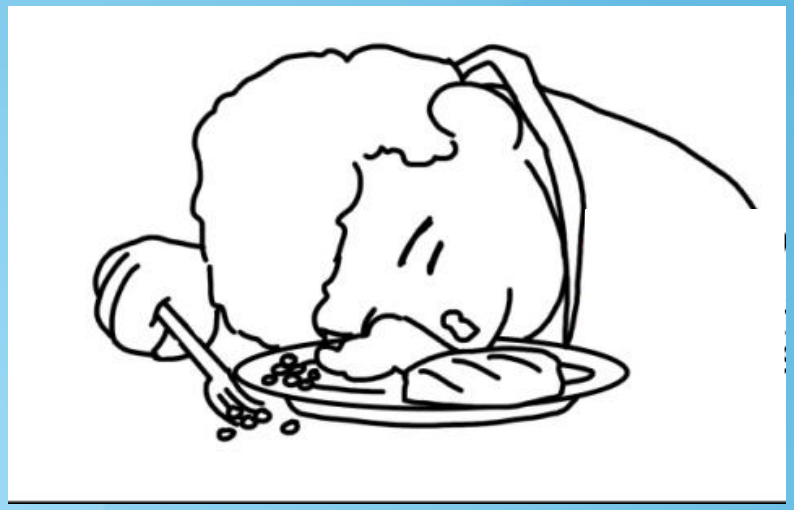
Second and Third Line Agents

- Gabapentin (Neurontin)
  Pregabalin (Lyrica)
- Benzodiazepines (sedative hypnotics)
  - Clonazepam (rivotril / klonopin)
  - Lorazepam (ativan)
- Opioids
  - Codeine
  - Hydrocodone
  - Methadone*
- (Quinine obsolete)

Summary

- RLS is very common (~10%)
- Symptoms are difficult to describe
- Use URGE criteria to diagnose
- Dopaminergic drugs are the first line of treatment and are very effective
- RLS is very treatable, but often unrecognized, and significantly impacts quality of life as a result

Primary Disorders of Hypersomnolence



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- Understand differential diagnosis of excessive daytime sleepiness and primary disorders of hypersomnolence
- Recognize narcolepsy with cataplexy:
  - definition and clinical features
  - epidemiology and etiology, diagnosis
  - therapeutic options
    - non pharmacological
    - pharmacological

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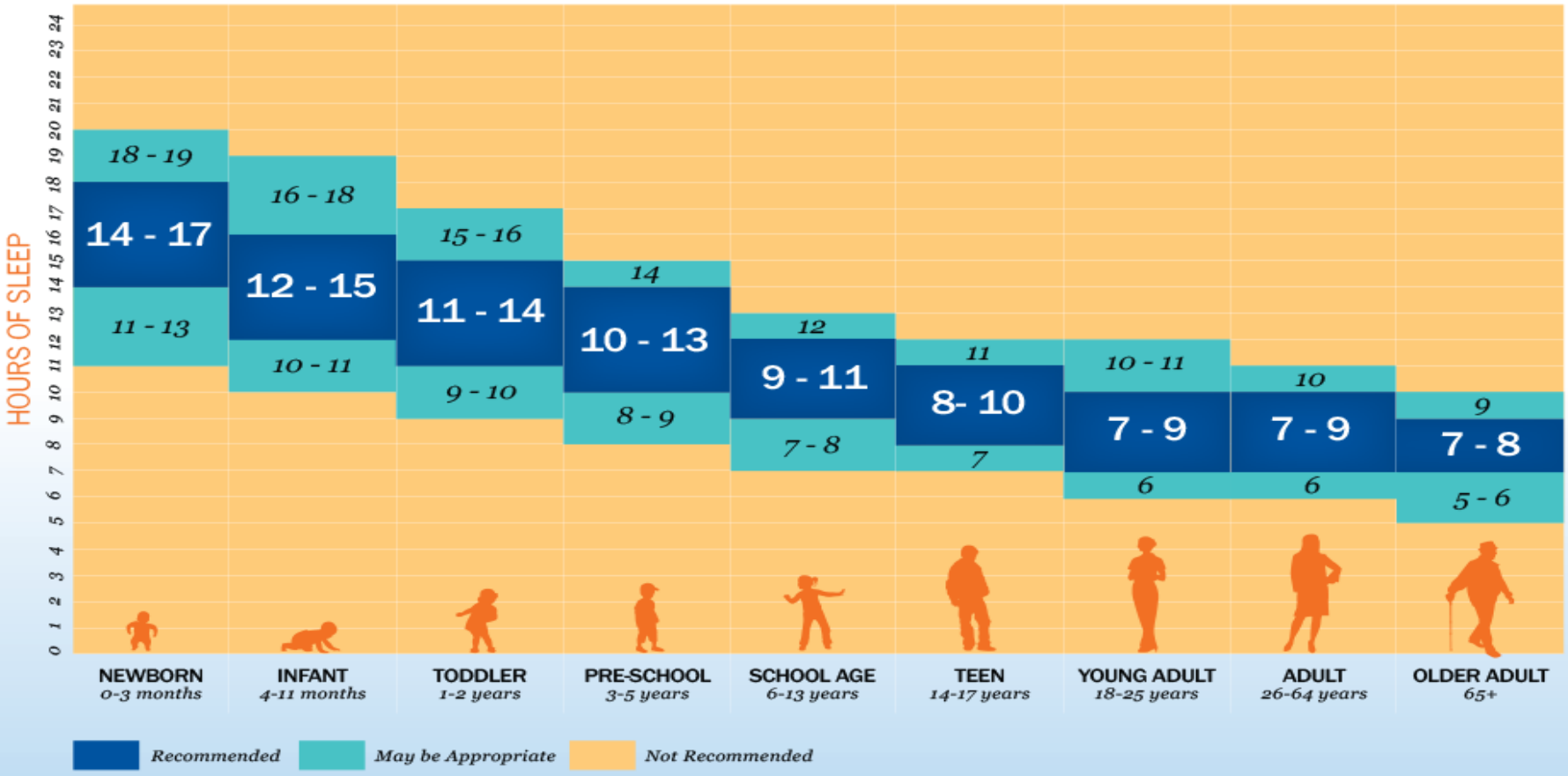
NATIONAL SLEEP FOUNDATION

SLEEP DURATION RECOMMENDATIONS



SLEEPFOUNDATION.ORG | SLEEP.ORG

Hirshkowitz M, The National Sleep Foundation's sleep time duration recommendations: methodology and results summary, Sleep Health (2015), http://dx.doi.org/10.1016/j.sleh.2014.12.010

Excessive Daytime Sleepiness

- Lack of sleep (Inadequate quantity of sleep)
  - Insufficient time in bed
- Inadequate quality of sleep
  - Sleep Apnea, PLMD, environment
- Intrinsic sleepiness
  - Hypersomnolence disorders (Narcolepsy; Idiopathic Hypersomnia)
- Medical/psychiatric disorder
  - Mood disorder
  - Medications, medical – thyroid, anemia etc.
- Circadian Rhythm Disturbance
  - Shift work, delayed sleep phase, etc.

Hypersomnolence Disorders

- Hypersomolence disorder
  - Idiopathic hypersomnia
  - Kleine Levin Syndrome
  - Kluver Bucy Syndrome
- Narcolepsy
  - with cataplexy*
  - without cataplexy

  (+/- hypocretin)

Hypersomnolence disorder

- Self reported sleepiness despite a main sleep period lasting 7 hours, with ≥1 of
  - recurrent lapses to sleep in the day
  - a prolonged episode >9 hrs unrefreshing sleep
  - difficulty being awake after abrupt awakening
- >3x/wk, >3months
- Significant distress
- Not due to substance, medical condition

Narcolepsy - DSM-5

- Recurrent periods of irrepressible need to sleep, ≥ 3x/wk, ≥3 months
- Cataplexy*
- Hypocretin deficiency (CSF Hcrt-1<110pg/mL)
- PSG – REM latency ≤ 15 min, or MSLT with
  - SL ≤ 8 min and ≥ 2 SOREMPs

REBECCA, A 19 YEAR OLD FEMALE WITH A COMPLAINT OF EXCESSIVE DAYTIME SLEEPINESS

Narcolepsy “Pentad”

- **Excessive Daytime Sleepiness**
  - May fall asleep without warning, unusual situations
- **Cataplexy (75%)**
  - Flaccid muscle paralysis; eyes and diaphragm OK; pt. remains awake but paralyzed.
- **Hypnagogic / pompic hallucinations (50-60%)**
  - “Multimodal”. Often highly emotional, sexual, frightening
- **Sleep Paralysis (50-66%)**
  - Awakes unable to move anything but eyes. Can’t breathe voluntarily or talk. HH often occur.
- **Disturbed nocturnal sleep**

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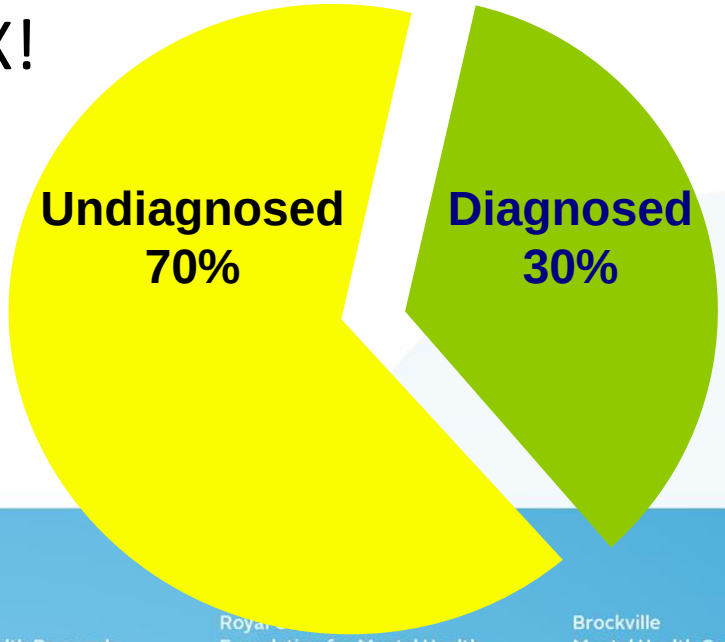
Narcolepsy: Prevalence

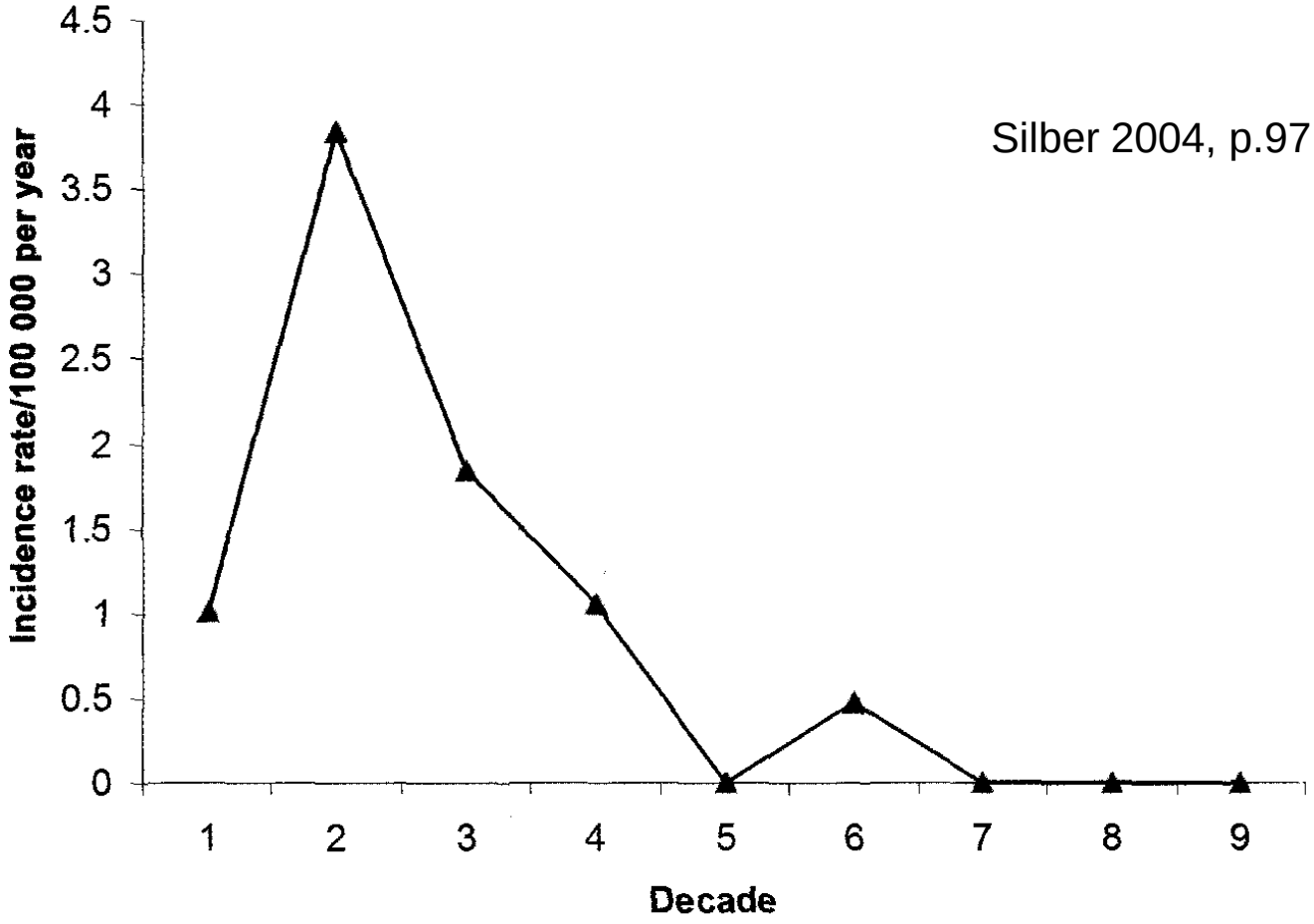
- Approximately 1/2000 US patients suffer from narcolepsy
- Estimated 15-30% are currently diagnosed
- Under –DX!



Silber MH et al. Sleep, 2002; 25(2): 197-205

Chakroverty SS and Rye DB. Drugs Aging. 2003;20(5 361-76.

Narcolepsy: Age of onset



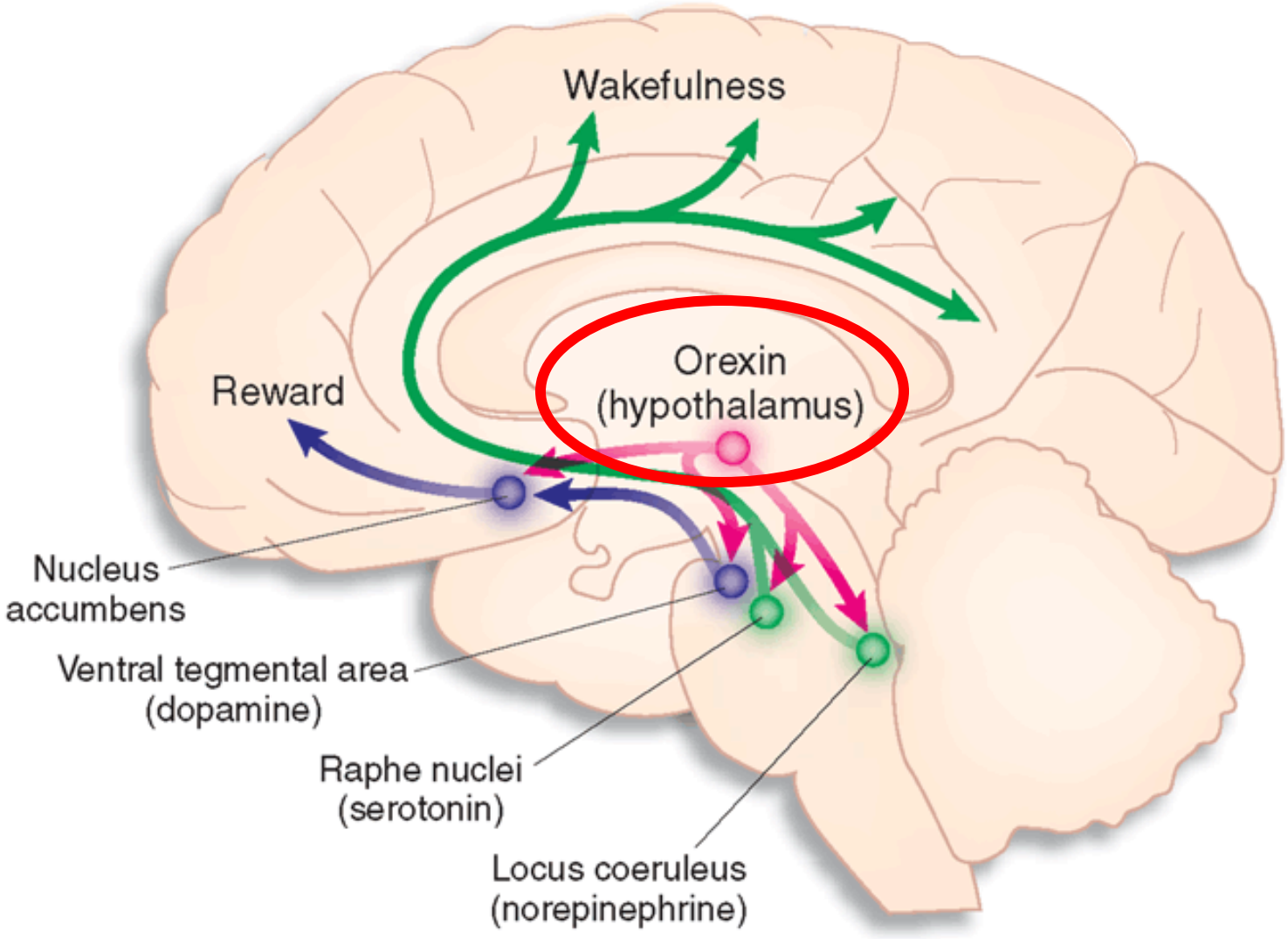
Silber 2004, p.97.

Figure 7.4 Age of onset of narcolepsy. This graph demonstrates that narcolepsy most commonly commences in the second decade followed by the third and then the first and fourth decades

Markers of Narcolepsy

- Hypocretin/Orexin
  90-95% of narcolepsy with cataplexy – are CSF hypocretin deficient
- HLA DQB1*0602 – strongly associated with hypocretin deficiency (95%)
- Recent association - H1N1, + Pandemrix flu vaccine
- HLA DQA1*0102
- HLA DRB1*1503

Hypocretin/Orexin Projections



Excessive Daytime Sleepiness (EDS)

- Multiple Sleep Latency Test (MSLT)
  - Following an NPSG
  - 4 or 5 X 20 minutes naps at 2 hour intervals
  - Example: 9am, 11am, 1pm, 3pm
  - Check for: 1) Avg. SOL & 2) REM sleep x2
  - Pathological Sleepiness =
    fall asleep < 8 mins + 2 or more SOREMPS

Narcolepsy: A Missed Diagnosis?

- Epilepsy
- Schizophrenia
- Depression, Bipolar
- Personality Disorder
- “Neurotic” Disorder
- Adjustment Reaction
- Substance abuse

Correct Diagnosis? Study of Physician Narcolepsy recognition

- Neurologists %?
- Family Med %?
- Internists %?
- Pediatricians %?
- Psychiatrists %?

Kryger MH et al, Sleep. 2002; 25(2): 36-41

Douglass AB, CNS Spectr; 2003; 8(2): 120-6

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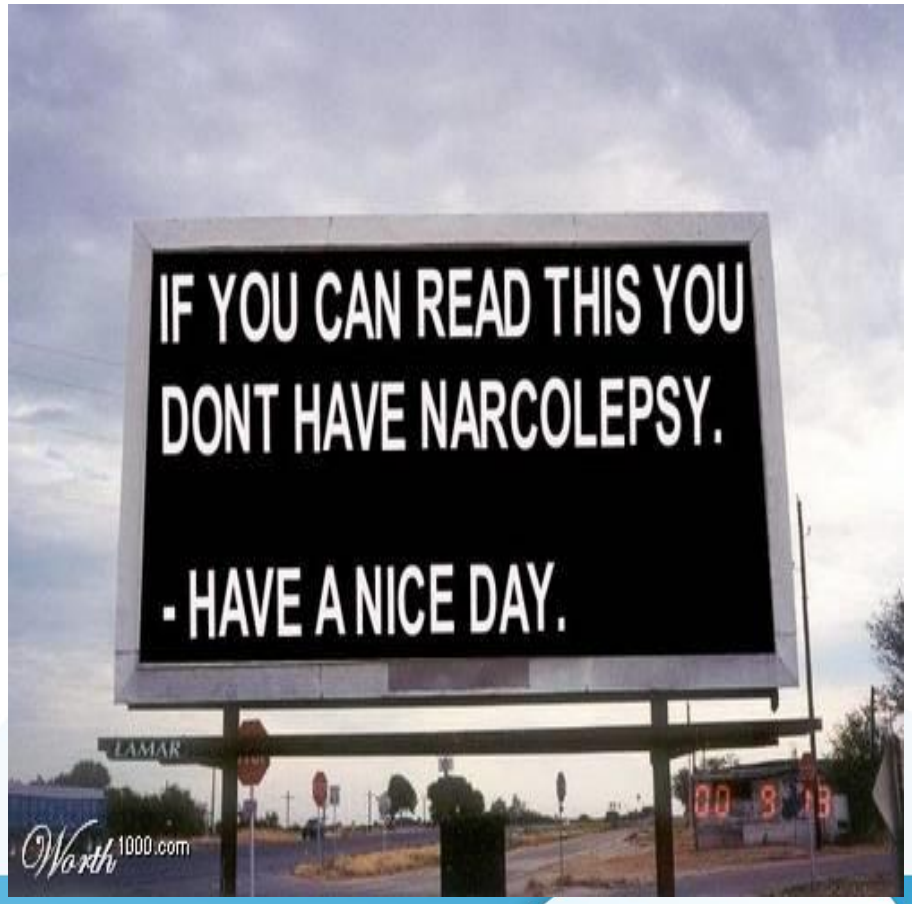
Narcolepsy Treatment

- Education
  - Not their fault
  - Not “lazy”
- Prophylactic naps
- Avoid activities/jobs where sleeping is an issue (e.g. shift work)



Narcolepsy Treatment

- Rx: Stimulant medication
  - Modafinil (Alertec)
  - Methylphenidate (Ritalin)
  - Dexedrine
- REM suppressant medications for cataplexy
  - SSRI – e.g. Fluoxetine, Venlafaxine
  - TCA – e.g. Clomipramine
- Strongest anticataplectic = Sodium oxybate (Xyrem, GHB) – powerful amnestic

Sodium Oxybate (Xyrem)

- Used for sleepiness and cataplexy
- Given hs and again 2.5-4 hours later
- Start – 3-4.5 g/day, increase by 1.5 g/day every 2 weeks until max of 9 g/day
- Side-effects: dizziness, nausea, sleepwalking, confusion, resp depression
- Do not use with CNS depressants (including BZD, alcohol), untreated OSA, COPD, obesity-hypoventilation syndrome

Summary

- Narcolepsy is a disorder of excessive daytime sleepiness, with specific sx (REM intrusion)
- Hypocretin/Orexin plays a significant role
- Significantly under-diagnosed
- Current diagnosis is with the MSLT; other options may be available in the future
- Education is important in treatment
- Stimulants, antidepressants, sodium oxybate are the most effective treatments currently

Questions ?

La Fondation de santé mentale
RoyalOttawa
Foundation for Mental Health