# Sleep Disorders

John Dopp
Associate Professor (CHS)
University of Wisconsin – Madison
School of Pharmacy
4125 Rennebohm Hall

# Educational Outcomes

- At the conclusion, the student should...
  - Recognize the importance of sleep disorders and the impact they have on health and other medical conditions
  - Identify types of insomnia and potential causes
  - Differentiate among available prescription and non-prescription sleep aids
  - Describe appropriate use of benzodiazepines and sedative hypnotics

# Educational Outcomes

Continued….

- Recognize the KEY presenting symptoms of and develop a therapeutic plan (including monitoring) for:
  - insomnia
  - restless legs syndrome
  - narcolepsy
  - sleep apnea



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# SLEEP - Definition

## *SLEEP*

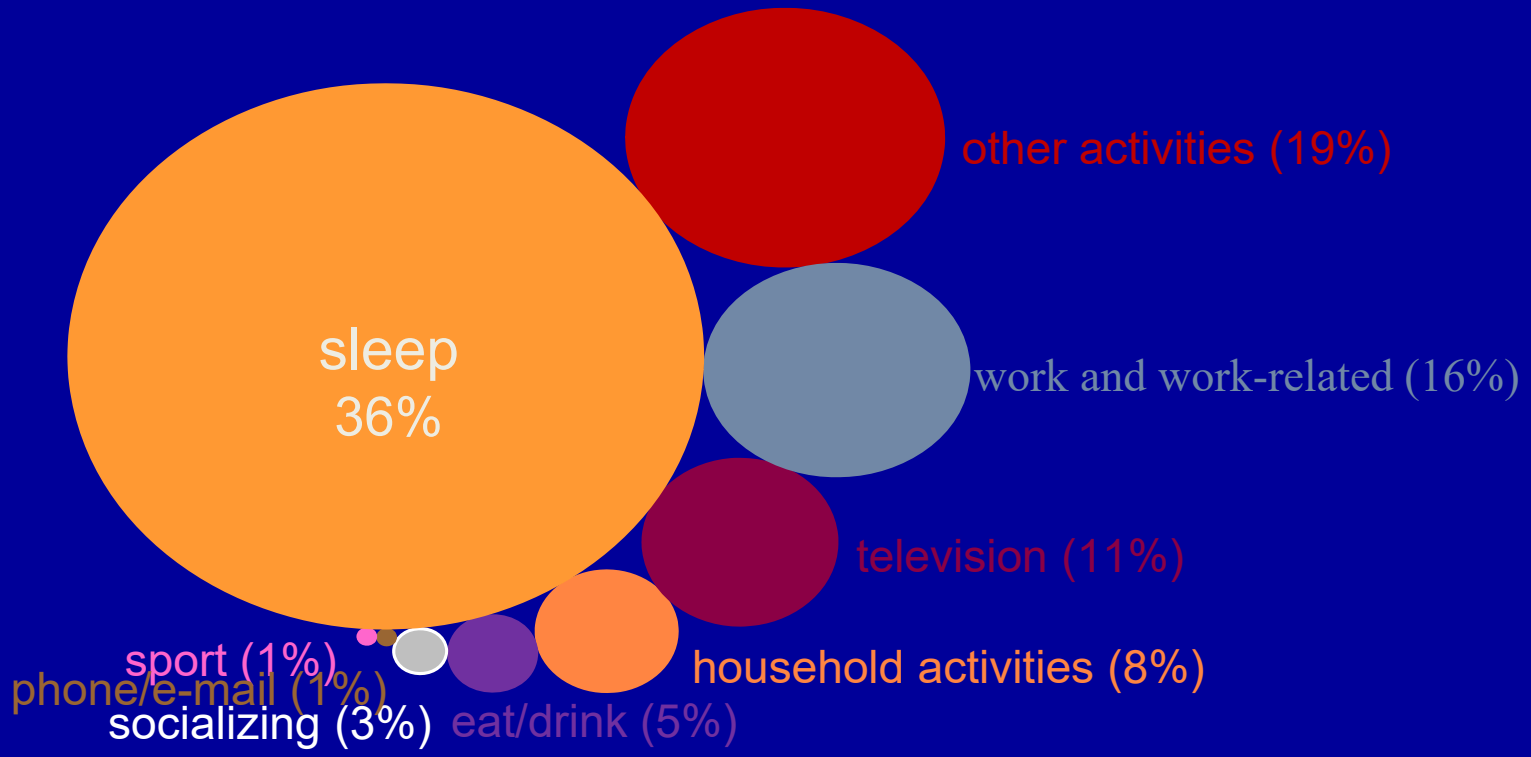
*"A reversible behavioral state of perceptual disengagement from and unresponsiveness to the environment"*

Carskadon MA, Dement WC. Normal Human Sleep: An overview. In: Kryger MH, Roth T, Dement WC, eds. Principles and Practice of Sleep Medicine. 4th ed. Philadelphia, PA: Elsevier Saunders, 2005:13-23.

# Normal Sleep

- 6-9 hours of sleep (on average) is optimal
  - Zeitgibers (cues) orient us to 24 hour clock
- Adequacy of sleep is function of:
  - Duration
  - Timing
  - Quality

# The hours of our life




*American Time Use Survey, Bureau of Labor Statistics, 2007 annual averages. Calculations based on U.S. life expectancy of 77.8 years (which includes ~ 243,362 hours of sleep)*

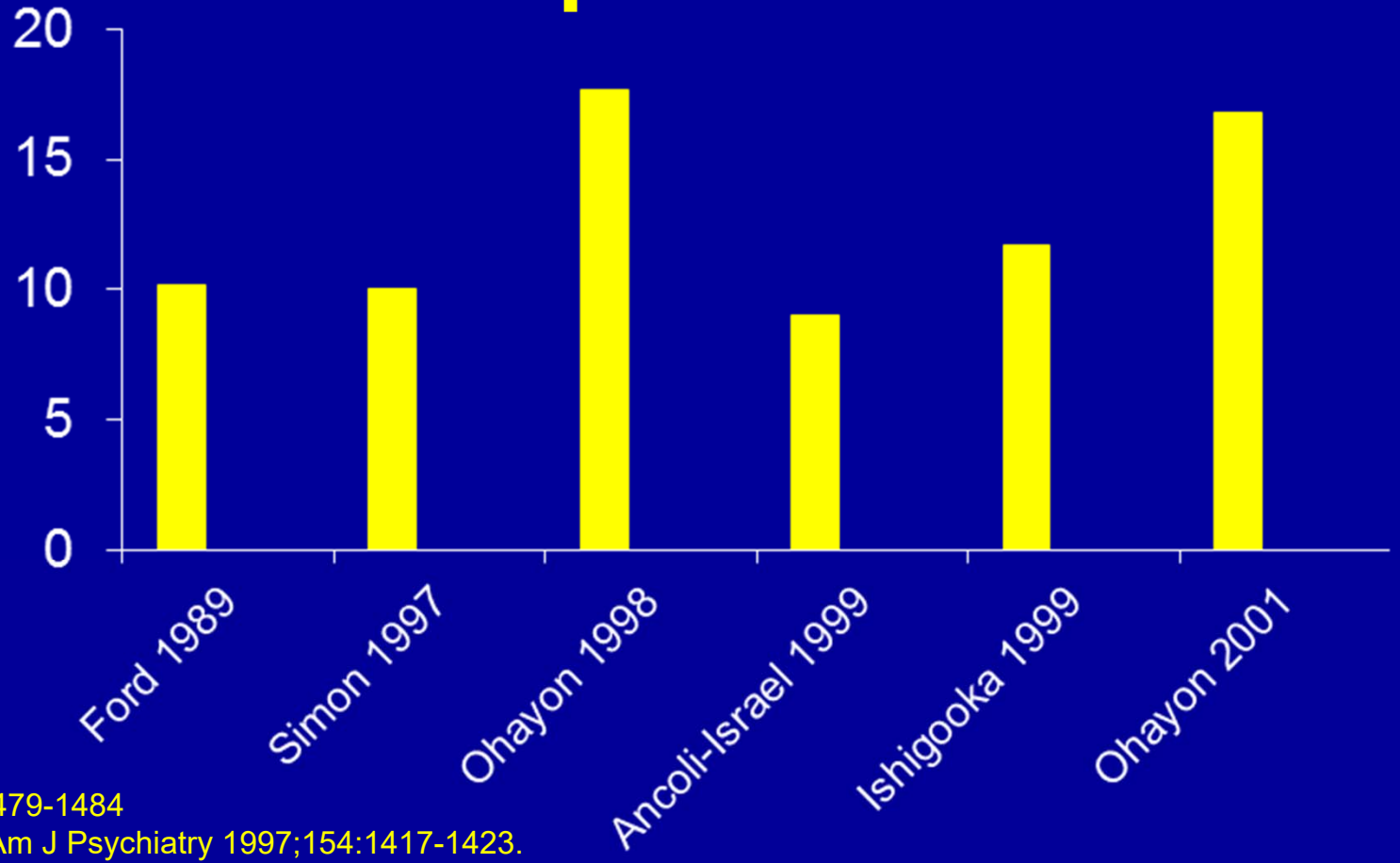
# Prevalence of Sleep Disorders

- Insomnia — 30 to 35%

- PLMS / RLS — 6 to 12%
- Sleep Apnea — 10-24% (age 30-60)
- Narcolepsy — 0.05% in U.S.
- Primary Snoring — 45%

# Epidemiology – Prevalence in General Adult Population

Percent Reporting Disturbance Nightly for > 2 weeks




Ford DE. JAMA 1989;262:1479-1484
Simon GE and VonKorff M. Am J Psychiatry 1997;154:1417-1423.
Ohayon MM, et al. Compr Psychiatry 1998;39:185-197.
Ancoli-Israel S and Roth T. Sleep 1999;22(suppl2):S347-S353
Ishigooka J, et al. Psychiatry Clin Neurosci 1999;53:515-522.
Ohayon MM and Roth T. J Psychosom Res 2001;51:745-755

# Neurochemistry of Sleep

- Wakefulness
  - NE, histamine, acetylcholine, glutamate, hypocretin
- Sleep
  - 5HT, GABA, adenosine, opioids, interleukins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# Sleep Stages

- Non-REM sleep – 75% of sleep
  - Stage 1 - “relaxed wakefulness”
  - Stage 2 - rapid wave sleep
  - Stage 3 - slow wave / deep sleep
  - Stage 4 - slow wave / deep sleep
- REM sleep – 25% of sleep


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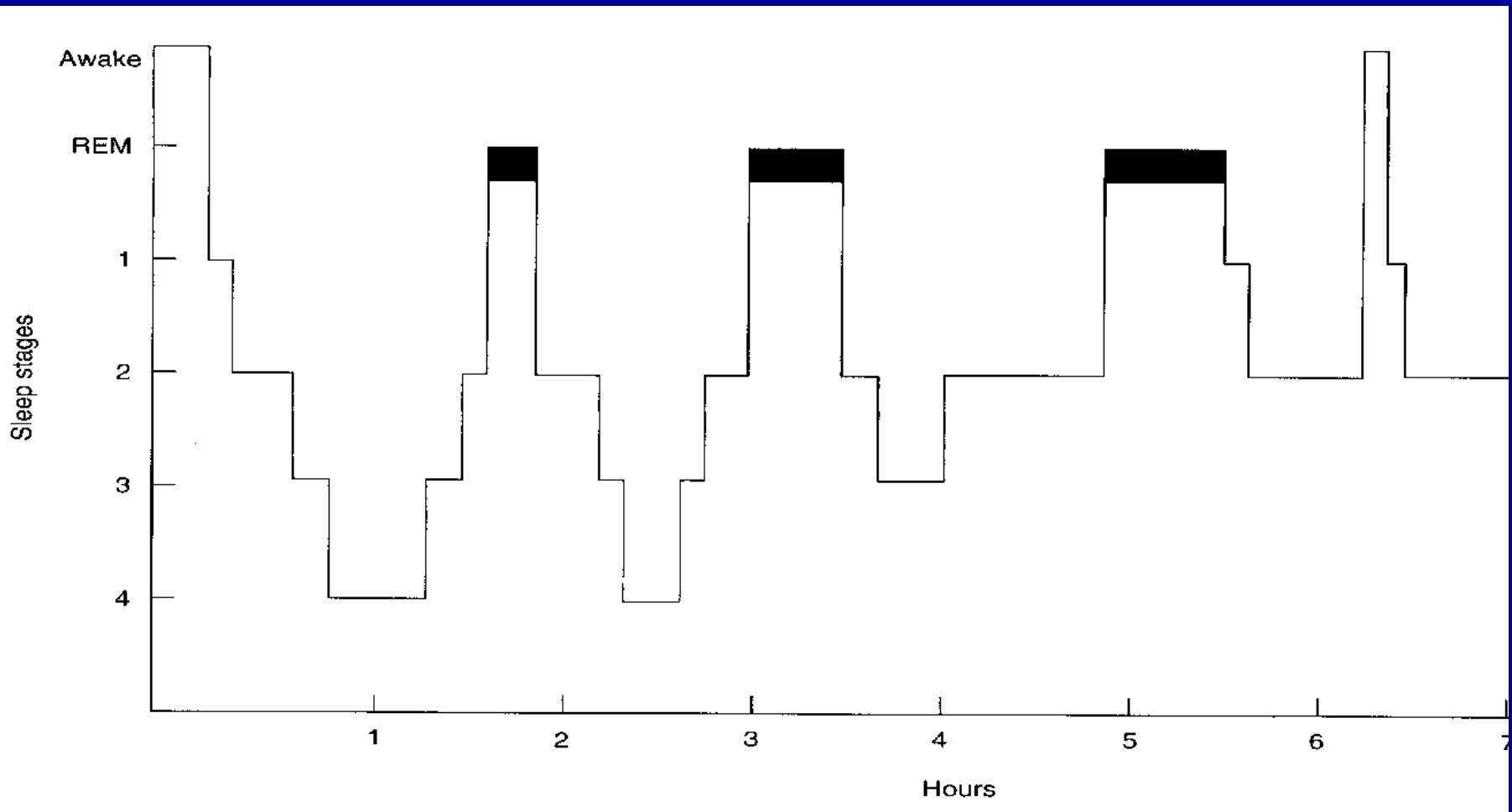
# Sleep Histogram



# Sleep in the Elderly

- Decreased
  - deep sleep with age (stage 3 and 4)
  - total sleep time (at night)
- increased nocturnal awakenings
- frequent daytime naps

# DSM-5 Sleep Disorders

1. Insomnia disorder
2. Hypersomnolence disorder
3. Narcolepsy
4. Breathing-related sleep disorders
5. Circadian rhythm sleep disorders
6. Non-REM sleep arousal disorders
7. Nightmare disorders
8. REM-sleep behavior disorder
9. Restless legs syndrome
10. Medication-induced sleep disorder

# Insomnia – Key Features

- Difficulty initiating sleep (> 30 minute sleep latency)
- Difficulty maintaining sleep
- Waking up too early
- Sleep difficulty despite adequate sleep opportunity
- Daytime consequences
- **Absence of other underlying sleep disorder or problem!!**

# Terminology of Insomnia

- Difficulty initiating asleep
- Difficulty maintaining sleep

# Causes of Sleep Impairment

- Medical
- Psychiatric
  - 40% of patients with insomnia will have psychiatric disorder
- Drug induced / related
- Environmental
- Social

# Approach to Sleep Disorders
## - Assessment –

- History
  - Sleep diary
  - Medication use
  - Bed partner interview
- Physical exam
- Psychiatric history
- Sleep studies

# Non-Pharmacological Therapy

- Sleep Hygiene
  - Keep regular sleep / wake schedule
  - Exercise frequently
    - Not immediately before bedtime ?
  - Avoid alcohol and stimulants in the late afternoon or evening
  - Avoid blue light prior to bedtime
  - Maintain comfortable sleep environment
    - Dark, quiet, free of intrusions (television)

# Non-pharmacologic Therapy

- Stimulus control
  - Go to bed only when sleepy
  - Avoid daytime naps
  - Always wake up at the same time each day

- Cognitive Behavioral interventions
  - Very effective, need to work with psychologist/counselor

# Hypnotics – 21st Century
## -Currently Approved Agents-

Traditional BZDs

- Estazolam
- Flurazepam
- Quazepam
- Temazepam
- Triazolam

Antidepressants

- Doxepin (Silenor)

GABA-A agonists

- Zolpidem (Ambien)
- Zaleplon (Sonata)
- Eszopiclone (Lunesta)

Melatonin Agonists

- Ramelteon (Rozerem)

Orexin Antagonists

- Suvorexant (Belsomra)
- Lemborexant (DayVigo)

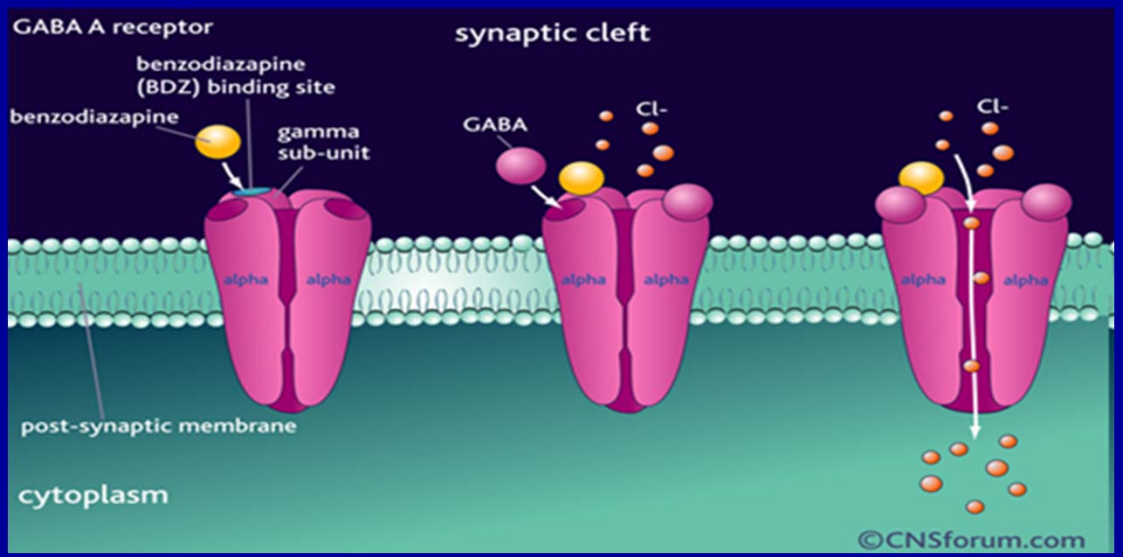
# Considerations When Selecting a Sleep Medicine

1. Symptom pattern (difficulty initiating or maintaining sleep)
2. Treatment goals
3. Past treatment responses
4. Contraindications
5. Comorbid conditions
6. Medication interactions
7. Patient Preference
8. Side effects
9. Availability of other treatments
10. Cost

J Clin Sleep Med 2008;4:487-504

# Benzodiazepine Receptor Agonists (BZDRAs)

- Two subtypes typically referred to:
  - Traditional benzodiazepines (BZDs)
  - Non-benzodiazepine agonists




http://www.cnsforum.com/imagebank/item/drug_benzo/default.aspx

# BZDRAs – Differences

Table 89-3 DiPiro

- Onset – lipophilicity, absorption
- Duration - lipophilicity, $t_{1/2}$
- Daytime effects - ($t_{1/2}$)
- Active metabolites
- Adverse effects

# Precautions with BZDRAs

- Tolerance with continued use
- Rebound insomnia upon discontinuation
- Withdrawal upon discontinuation
- Anterograde amnesia
- Risk of falls
- Carryover sedation

- FDA labeling:
  - Risk of anaphylaxis and facial angioedema, and complex sleep behaviors (for all BZD receptor agonists)

# BZDRAs Principles for Appropriate Use

- Use lowest dose for shortest possible duration
- Screen for contraindications/cautions
- Patient education about adverse effects
- Match duration of action to sleep complaint

# Discontinuation and Tapers

- Taper
  - Minimize withdrawal or rebound symptoms:
    - Anxiety, irritability, insomnia, tachycardia, tremor, etc.
  - Slowly over period of weeks to months (depends on duration of use).
  - If experience symptoms resume last tolerated dose and decrease rate of taper.
  - Switch from short-acting to long-acting agent for taper

# Sample Taper - short

- Patient taking triazolam 0.5 mg at bedtime for four years.
- Switch to clonazepam 0.5 mg or estazolam 1-2 mg
- Taper 25% every 1-2 weeks or 50% every 2-4 weeks based on tablet size.

# Withdrawal symptoms

Low-dose withdrawal

- Nausea, vomiting
- Irritability, tremor
- Incoordination, sweating
- Blurred vision, anorexia
- Anxiety, insomnia
- Depersonalization, sensitivity to light/sound

Higher-dose withdrawal

- Seizures
- Disorientation
- Psychosis
- Depression
- Low-dose withdrawal symptoms

J Subst Abus Treat 1991;8:9-17

| Name | Tmax (hrs) | Parent $t_{1/2}$ (hours) | Daily dose range (mg) | Signif. Metabolites |
|---|---|---|---|---|
| Estazolam | 2 | 12-15 | 1-2 | -- |
| Flurazepam | 1 | 8 | 15-30 | **two |
| Quazepam | 2 | 39 | 7.5-15 | # two |
| Temazepam | 1.5 | 10-15 | 7.5-30 | -- |
| Triazolam | 1 | 2 | 0.125-0.25 | -- |
| Zolpidem | 1.6 | 2.5 | 5-10 | -- |
| Zaleplon | 1 | 1 | 5-10 | -- |
| Eszopiclone | 1-1.5 | 5-6 | 1-3 | (S)-N-desmethylzopiclone |

** Flurazepam metabolites: Hydroxyethlflurazepam, N—desalkylflurazepam (t1/2 47-100 hours)

# Quazepam metabolites: 2-oxo-quazepam, N-DAF

# Non-benzodiazepine Agonists

Zolpidem

Eszopiclone

Zaleplon

In general, non benzodiazepines are associated with less withdrawal, tolerance, and rebound insomnia than traditional benzodiazepines

# Zolpidem (Ambien)

- Effective medication for difficulty initiating sleep, and for some – difficulty  maintaining sleep
- Little effect on sleep stages
- Food delays absorption
  - take on empty stomach for best effect

- Controlled release formulation available for longer duration of action
- Sublingual tablet and oral spray
- Reduced dose for female and elderly patients

- Has the most reports of complex sleep behaviors

# Zaleplon (Sonata)

Zaleplon

- Ultra-short half-life (1 hr) and duration of action (3-4 hours)

- Approved for difficulty with sleep onset only
- However, may be used for middle-of-night rescue dosing
- Generic zaleplon available
- High fat meals prolong absorption

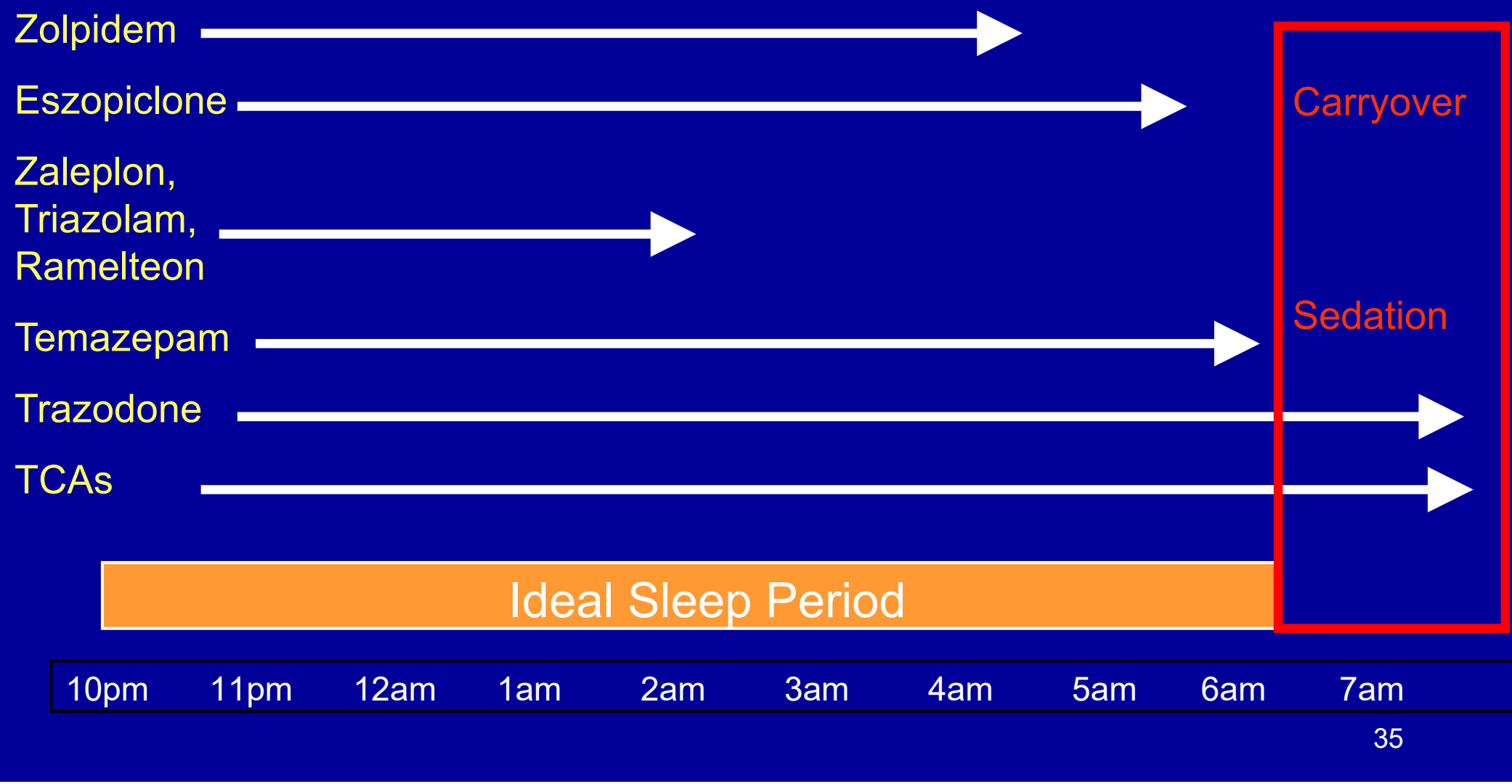
# Eszopiclone (Lunesta®)

- 6-8 hour duration of action – good choice for difficulty maintaining sleep
- Metabolized by CYP 3A4 and 3E1
- Efficacious up to 6 months taken nightly
- Dose: 2-3 mg po at bedtime
  - 1 mg po in elderly or patients with hepatic dysfunction
  - Avoid taking with high fat meal (reduces absorption)

# Eszopiclone (Lunesta®)

- Side Effects:
  - Rash, carry-over sedation, dyspepsia, dizziness
  - Dysgeusia (awful taste in mouth)
    - More common in morning than evening after taking
    - More common in female patients
    - May last days after drug is discontinued
    - Management:
      - Do not crush or chew tablet
      - Masking – gum, chocolate milk, mints

# Duration of Action of Hypnotics



# Insomnia Treatment Guidelines

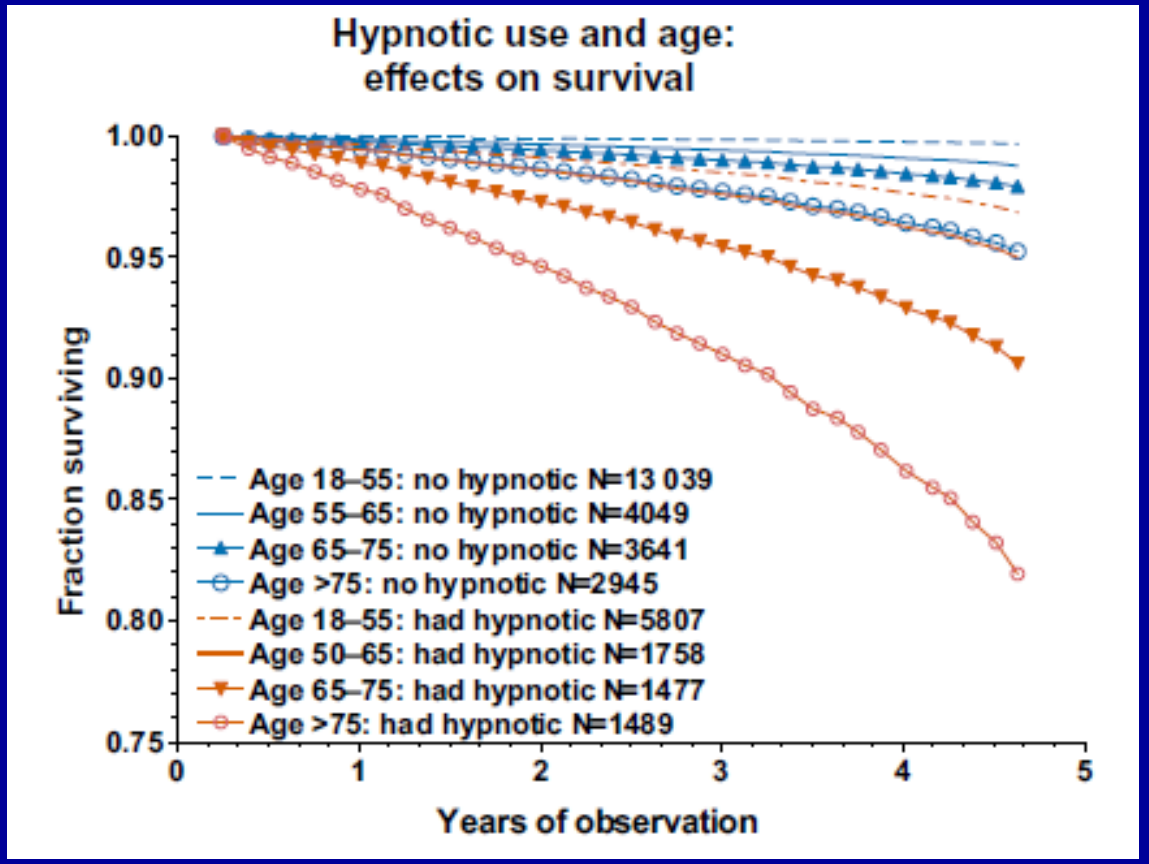
## J Clin Sleep Med 2017;13:307-349

| Recommend for Difficulty With Sleep Onset |
| --- |
| Zolpidem |
| Zaleplon |
| Triazolam |
| Temazepam |
| Eszopiclone |
| Ramelteon |

| Recommend for Difficulty With Sleep Maintenance |
| --- |
| Zolpidem |
| Doxepin |
| Suvorexant |
| Temazepam |
| Eszopiclone |

# Hypnotics and Increased Mortality

- Hypnotic use increased mortality over 5 yrs in PA health system
- Confounding variables
  - psychiatric disorders, substance abuse




BMJ Open. 2012 Feb 27;2(1):e000850.

# Melatonin Receptor Agonists

# Ramelteon (Rozerem®)

- Dose:  8 mg at bedtime
- Non-controlled substance
- FDA indicated ONLY for difficulty with sleep onset
- Useful for treating patients with history of substance abuse
- Does not affect middle of the night balance in the elderly
- Safely treats insomnia in COPD and sleep apnea
- Do not use in combination with fluvoxamine or other CYP1A2 drugs

# Orexin antagonists

Suvorexant (Belsomra)

Lemborexant (DayVigo)

MOA: blocks orexin (Ox1R and Ox2R) receptors which suppresses wake promotion pathways

# Orexin Antagonists

| | Suvorexant | Lemborexant |
|---|---|---|
| **Dose** | 10-20 mg QHS | 5-10 mg QHS |
| **Controlled Substance?** | C-IV | C-IV |
| **Food considerations** | ↑ conc when used with grapefruit juice | High fat meal may delay absorption |
| **Notes:** | Safe in COPD and OSA | Safe in mild OSA |
| **Half-life (hrs)** | 12 | 17-19 |

# Orexin antagonists

- Precautions
  - CNS depression and carry-over sedation
  - Sleep paralysis, cataplexy
  - Use not recommended in severe hepatic impairment
  - Do not use with alcohol or other CNS depressants
  - Do not use with strong CYP3A inhibitors or inducers
  - Dose-dependent worsening of suicidal ideation
  - Do not use in patients with narcolepsy

- Adverse Effects
  - Mild increases in cholesterol
  - Headache, cataplexy, sleep paralysis
  - Sleepiness

# Orexin antagonist drug interactions

- Increased suvorexant or lemborexant exposure:
  - diltiazem, HIV medications, clarithromycin, Azole antifungals, nefazodone, verapamil, telithromycin, grapefruit juice, ciprofloxacin
  - Use lower doses of orexin antagonist
- Decreased suvorexant or lemborexant exposure:
  - carbamazepine, phenytoin, rifampin, st. john's wort
  - Use higher doses of orexin antagonist
- Others:
  - Digoxin – increased digoxin concentrations

# Antidepressants
# - mostly used as adjunct therapy -

- Sleep / wake problems in depression
- Treat the underlying problem
- Alternative treatment for patients who shouldn't receive BZD's (history of substance abuse)

- Problems:
  - the doses used for sleep (e.g. amitriptyline 10 mg at bedtime) are not effective antidepressant doses
  - Side Effects

# Antidepressants

| Drug | Doses used (mg) | Sleep Effects | (Dis) Advantages |
|---|---|---|---|
| Amitriptyline | 10-75 mg at bedtime | ↑ sleep time, ↓REM | Anticholinergic, CV risk |
| Trazodone | 25-200 mg at bedtime | ↑ sleep time, ↓SL, ↓ REM | No tolerance develops?; orthostasis |
| Mirtazapine (Remeron) | 7.5-30 mg at bedtime | ↑ sleep time, ↓SL, ↓ REM | Daytime sedation, weight gain |
| Doxepin (Silenor) | 3-6 mg at bedtime (25-225 mg in older studies) | ↓ wake during sleep, ↑ sleep time | Approved for long-term use of difficulty maintaining sleep |

# Antihistamines

- Diphenhydramine (citrate 38mg = HCl 25mg)
  - FDA labeled as “safe and effective” but not as effective as BZDs
  - antihistaminic and anticholinergic effects
  - Study compared vs. temazepam in elderly and found diphenhydramine to be less effective

    J Clin Psychopharmacol 2008;28:182-188.

- Doxylamine - little supporting evidence for use in insomnia

# Diphenhydramine

- Adverse effects
  - Sedation (hangover)
  - anticholinergic - BPH, CV, glaucoma
- Avoid in
  - Late pregnancy (may increase uterine activity)
  - Lactation – may reduce milk production
  - Elderly patients at risk for falls

# Valerian Root

- Increases GABA release
- Dosing formulation:  tea, tincture, extract (all oral)
  - Systematic review found 6 studies using doses ranging from 225mg – 1215mg per day
  - Study concluded valerian may modestly improve sleep quality but methodologic problems limit conclusions and recommendations
- Drug interactions:
  - BARBITURATES, BENZODIAZEPINES , ETHANOL, OPIOID ANALGESICS

# Cannabidiol

- No controlled studies on use for insomnia
- Does not affect sleep architecture in healthy volunteers
  - Front Pharmacol 2018;9:315
- No documented benefit in insomnia
  - A few case reports document benefit
  - Animal studies suggest it has sedative effects
  - Role of endocannabinoid system in sleep and wake

- Case reports suggest possible benefits in restless legs syndrome and REM behavior disorder

# Alcohol

- Decreases sleep latency
- Disrupts sleep cycle
  - Glutamine rebound
- NEVER use as sleep aid

# General Considerations for Sleeping Medications

1. Not recommended during pregnancy or nursing
2. Caution and lower doses used in elderly
3. Caution in patients at risk of falls
4. Avoid combination with alcohol and other CNS depressants
5. Caution in patients with depression, compromised respiratory function (asthma, COPD, sleep apnea)
6. Avoid controlled substances in patients with history of substance abuse

# Key Presenting Symptoms - OSA

| Presenting Symptom | Likelihood of patient having OSA |
|---|---|
| Habitual Snoring | ++ |
| Loud Snoring | +++ |
| Witnessed Apneas | +++ |
| Daytime Sleepiness | +++ |
| Morning Headaches | + |
| Hypertension | ++ |
| Nocturnal reflux | ++ |

+ = slight

++ = moderate

+++ = high

# What to look for if you suspect sleep apnea….

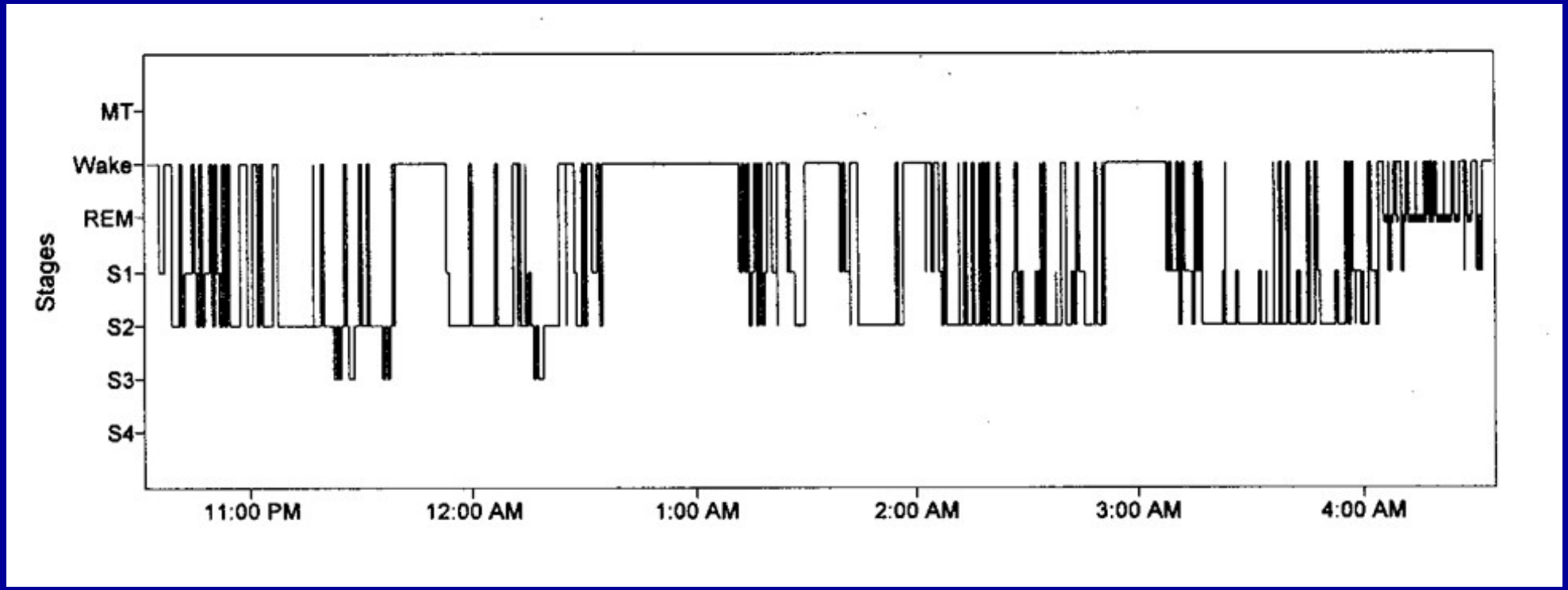
# Obstructive Sleep Apnea

## *- pharyngeal airway collapse -*

# Sleep Disordered Breathing

- Repeated apneas and hypopneas result in:
  - Disrupted sleep architecture
    - Excessive daytime somnolence
    - Impaired cognitive function
  - Cyclical (intermittent) hypoxemia
    - Potential source of oxidative stress
    - Sympathetic activation
    - Many physiological consequences

# Fragmented Sleep in OSA patients



# OSA and CVD

- Obstructive sleep apnea associated with cardiovascular disease.
  - Hypertension (*N Engl J Med* 2000;342:1378-84)
  - Stroke (*Stroke* 1996;27:401-407)
  - Ischemic Heart Disease (*Eur Resp J* 1999;14:179-184)
  - Present in 50% of patients with heart failure
  - Arrhythmias (*Am J Resp Crit Care Med* 1995;151:215-218)
- Also associated with:
  - Resistant Depression
  - Hypothyroidism

# OSA - therapy

- Weight loss
- CPAP *(therapy of choice)*
- Surgery (uvulopalatopharyngoplasty)
- Positional Avoidance (supine avoidance)
- AVOID alcohol and CNS depressants
- Mandibular advancement devices
- Medications not used
- Tracheostomy (emergency only)

# Drug Therapy of Sleep Apnea

***Sleep* 2006;29:1031-1035**

Recommendations:

- Modafinil (Provigil®) is recommended for the treatment of residual excessive daytime sleepiness in OSA patients who:
  - Have sleepiness despite effective CPAP treatment
  - Who are lacking other identifiable cause for sleepiness
- Topical nasal corticosteroids in patients with OSA and concurrent rhinitis

# OSA – Therapy - CPAP

# Narcolepsy

Syndrome characterized by abnormal sleep tendencies.

- Excessive daytime sleepiness (EDS)
- Disturbed nocturnal sleep
- Pathological manifestations of REM sleep

Criteria – Tetrad of symptoms

1. EDS
2. Cataplexy
3. Sleep Paralysis
4. Hypno-gogic Hallucinations

# Narcoleptic Cataplexy

- Sudden loss of partial or whole body striated muscle tone during wakefulness
- Often evoked by strong emotion
- Consciousness is preserved
- Episodes last for a few seconds to a few minutes

# *Narcolepsy – Video of cataplexy*

# What Causes Narcolepsy?

Cell, Vol. 98, 365–376, August, 1999, Copyright © 1999 by Cell Press

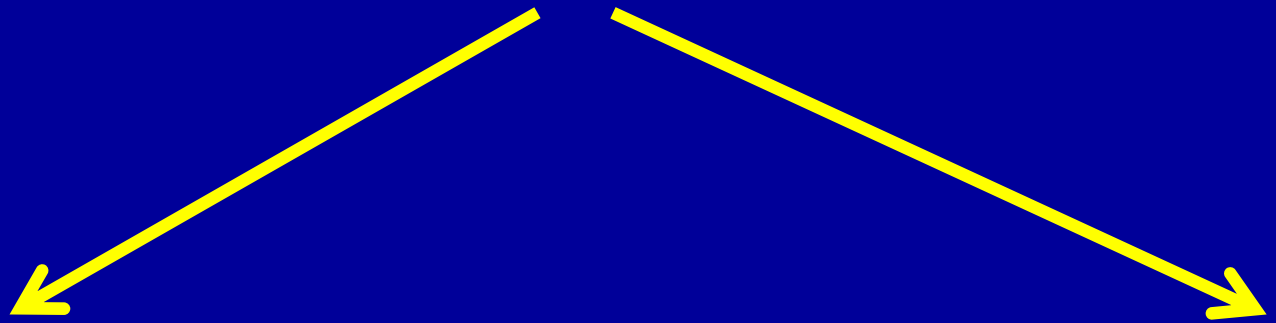
## The Sleep Disorder Canine Narcolepsy Is Caused by a Mutation in the *Hypocretin* (*Orexin*) *Receptor 2* Gene

**Ling Lin §[1], Juliette Faraco §[1], Robin Li §[1], Hiroshi Kadotani §[1], William Rogers[1], Xiaoyan Lin[1], Xiaohong Qiu[1], Pieter J. de Jong[2], Seiji Nishino[1], and Emmanuel Mignot ‡[1]**

[1] Center for Narcolepsy, Department of Psychiatry, Stanford University School of Medicine, Stanford, California 94305-5485

[2] Department of Cancer Genetics, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, New York 14263

# Goals of Narcolepsy Therapy



Reduce excessive Daytime sleepiness

Reduce Abnormal REM sleep manifestations

# Narcolepsy – Therapy – 2 goals

## 1. Treat EDS

- Strategic naps (two per day)
- Regular sleep/wake schedule, good sleep hygiene
- CNS Stimulants

# CNS Stimulants

| Name | Daily dose range (mg) | Pearls |
|---|---|---|
| Methylphenidate<br>Methylphenidate SR | 5-60 | Several controlled release products available (Concerta, Metadate CD, etc.) |
| Amphetamine Dextroamphetamine | 5-60 | Do not take within 2 hours of citrus or acidic foods – it may decrease absorption |
| Lisdexamfetamine (Vyvanse) | 10-70 | May open capsule and dissolve in water (~8 oz) and consume immediately if cannot swallow capsule |

# Stimulant Formulations

- Methylphenidate
  - Concerta – 22% IR, 78% SR osmotic core
  - Metadate CD – 30% IR, 70% SR beads
  - Metadate ER – wax-like matrix formulation
  - Ritalin LA – 50% IR beads, 50% SR beads

# Stimulant Formulations

- Amphetamines
  - Dexedrine Spansule – SR beads in capsule
  - Adderall XR – four amphetamine salts (d,r) in capsule. 50% of beads IR, 50% beads dissolve in 4-6 hours.
  - Lisdexamfetamine – prodrug of dextroamphetamine only active when taken orally

# Modafinil (Provigil) and Armodafinil (Nuvigil)

- CNS stimulant (Schedule-IV)
  - unique lack of peripheral effects
- Dose:  200 - 400 mg / day in 1-2 doses (Provigil);
  - 150-250 mg/day in 1-2 doses (Nuvigil)
- CYP2C19 inhibitor
- CYP3A4 inducer (chronic)
  - – oral contraceptives potentially less effective

# Solriamfetol

- Dopamine and NE reuptake inhibitor
  - Approved for treatment of sleepiness in narcolepsy and sleep apnea
  - Increases blood pressure (3-7 mmHg SBP) and heart rate (3-5 bpm)
  - Adverse effects similar to methylphenidate
  - C-IV controlled substance

# Solriamfetol

| Estimated GFR ($mL/min/1.73m^2$) | Dosing Range (mg/day) |
|---|---|
| ≥ 60 | 37.5 - 150 |
| 30-59 | 37.5 – 75 |
| 15-29 | 37.5 |
| < 15 | Use not recommended |

# Pitolisant

- Selective histamine 3 receptor antagonist/inverse agonist
- Approved for EDS in narcolepsy
  - May have benefits for cataplexy also
  - Role may be in add-on to other stimulants (different mechanism of action may produce additive effects on promoting wakefulness)
  - Comparative study found may be less effective than modafinil
  - Contraindicated in patients with severe liver impairment

# Pitolisant

- Dose is 8.9-35.6 mg daily (may increase by 8.9mg/wk)
  - Available in 4.45 and 17.8 mg tablets
- CYP2D6 and CYP3A4 substrate (and slight 3A4 inducer)
  - Adjust doses for patients taking strong 3A4 inducers and 2D6 inhibitors
- Adverse effects:
  - Headache, insomnia, anxiety, depression, nausea, weight gain, and gastric hyperacidity, QT prolongation

# Narcolepsy – Therapy – 2 goals

## 2. Treat REM Sleep Abnormalities

- Cataplexy – increase aminergic signaling
  - SSRIs (fluoxetine, venlafaxine)
  - TCAs (protriptyline, imipramine, clomipramine)
  - Atomoxetine
  - MAO-Is (selegiline)
    - Doses less than 10 mg/day to maintain MAO-B selectivity

# Cataplexy - Therapy

- **Xyrem® (sodium oxybate) Xywav ® (low sodium version)**
  - C-III controlled substance - liquid
  - Available only from manufacturer (Xyrem® Success Program)
  - Start dose: 2.25 grams twice a night
    - (bedtime and 2.5 to 4 hours later)
    - 820 mg sodium per 4.5 grams
    - Xywav 92% less sodium than sodium oxybate
  - Drug interactions:
    - alcohol, other CNS depressants, sedative hypnotics
    - Divalproex sodium (increases exposure to sodium oxybate)

# Key Presenting Features – Restless Legs Syndrome

- A disorder characterized by an almost irresistible urge to move, usually associated with disagreeable leg sensations , worse during inactivity, and often interfering with sleep.

Symptoms:

- Creepy, crawly, tingly
- Like worms or bugs crawling under the skin
- Painful, burning, or achy
- Like water running over the skin

# Primary and Secondary RLS

## PRIMARY

- No identifiable predisposing factor
- Tends to occur in families – genetic component
- Iron handling abnormalities in dopamine producing cells in substantia nigra of brain

## SECONDARY

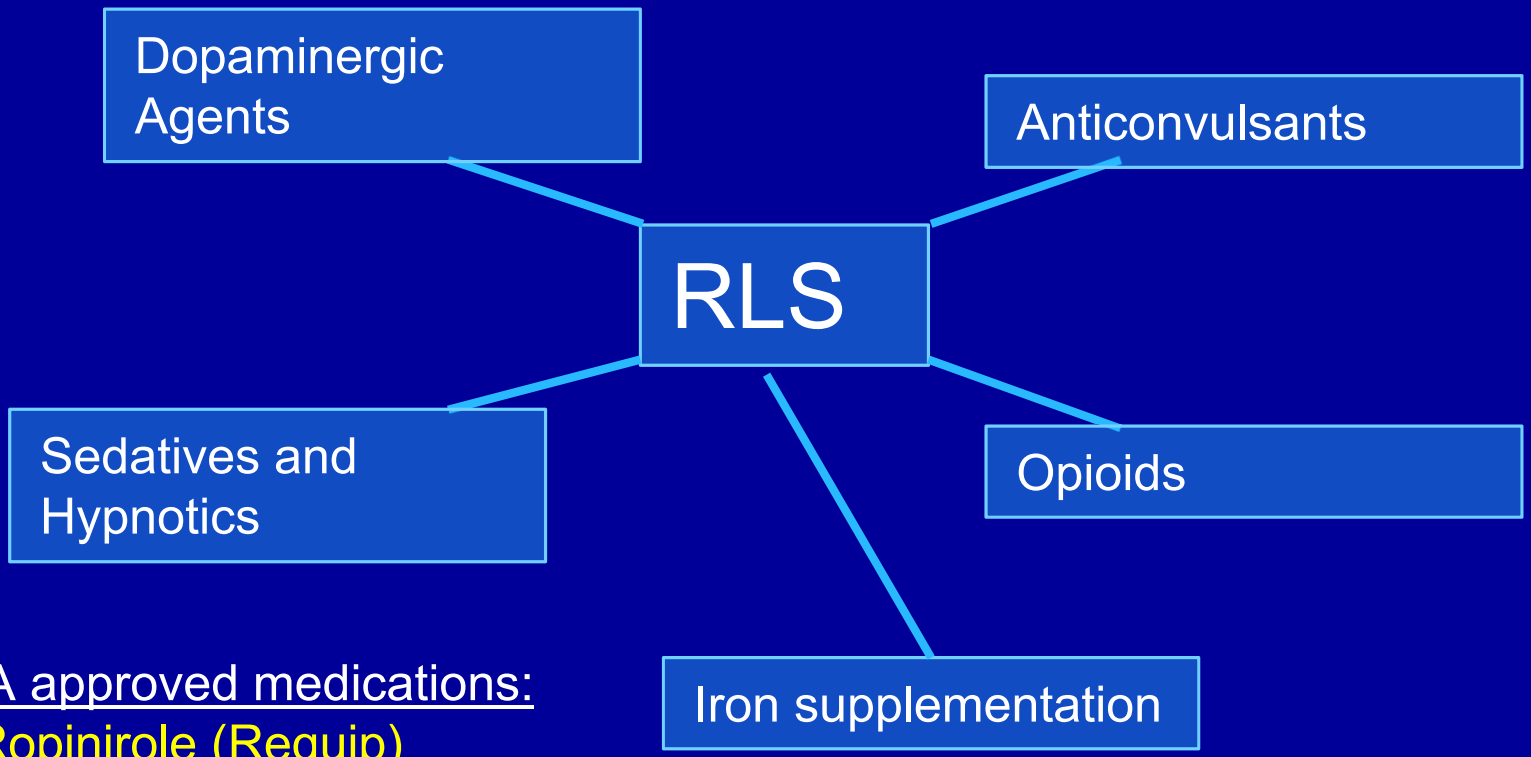
- Iron-deficiency anemia
- Uremia (20-40% of dialysis patients)
- Pregnancy (up to 27%)
- Drug-induced
  - tricyclics, SSRI's, lithium, dopamine blockers (e.g., neuroleptics), xanthines

# Restless Legs Syndrome

## Diagnostic Criteria

1. Desire to move limbs associated with paresthesias
2. Motor restlessness
3. Symptoms worse in evening or night
4. Symptoms worse or only present at rest with temporary relief by movement

# Restless Legs Syndrome
# - Therapy -




FDA approved medications:

- Ropinirole (Requip)
- Pramipexole (Mirapex)
- Gabapentin Enacarbil (Horizant)
- Rotigotine (Neupro)

# RLS Treatment Guidelines

1. Begin treatment with gabapentin or pregabalin
2. Give iron if ferritin < 50-75 ng/mL
3. If need to start dopaminergic therapy – keep dose low and do not exceed recommended doses
4. If augmentation occurs, switch dopaminergic agent to gabapentin or longer-acting dopamerigic agent (rotigotine).

Sleep Med 2016;21:1-11.

# Dopaminergic Agents

- Pramipexole
  - 8 hour half-life (longer duration than levodopa)
  - Comes in ER formulation
  - High affinity for D3, D2 receptors
  - Renally eliminated - Need to slow down drug up-titration with reduced renal function
  - Dosing range 0.125 – 0.5 mg 2-3 hours prior to bedtime

# Ropinirole

- 6-hour half life
- Selective D2 receptor agonist
- Hepatically metabolized
- Dosing:  0.25-4 mg 1-3 hours before bedtime

# Rotigotine

- D3/D2/D1 receptor agonist
- Also agonist at alpha-1 and 5-HT receptors
- Hepatically metabolized
- Dose 1-3 mg transdermally every 24 hours

- Medications with long duration of action show largest effects on RLS severity and health-related QOL

## Complications of RLS Therapy

- Symptom augmentation
- Impulse control disorders
- Sleep attacks
- Aggravating medications and factors

# Impulse Control Disorders

- Compulsive Behaviors:
  - Gambling (D3), eating (D3), shopping (D3), hypersexuality (D3), punding (D1 and D2)

  - 22-33% incidence
  - Appears to be dose-related
  - ICD Risk:

  Pramipexole > Ropinirole > Rotigotine

# Anticonvulsants

| Medication | Dose | Advantages or Disadvantages |
|---|---|---|
| Gabapentin | 300-900 mg at bedtime | Useful in painful RLS or with neuropathy |
| Gabapentin Enacarbil (Horizant) | 600 mg at 5pm | Better absorption than gabapentin, may also reduce PLMS |
| Pregabalin (Lyrica) | 75mg to 300 mg at bedtime | Weight gain, sedation |

# Sedative Hypnotics

Hypnotics (clonazepam, temazepam, zolpidem, eszopiclone)

- more experience with clonazepam, all dosed at bedtime
- may see hangover effect with clonazepam (long half life)
- keep the patient asleep and less aware of RLS symptoms, good for patients with awakenings from symptoms

Disadvantages: tolerance, somnolence, confusion, worsened snoring/SDB

# Opioids and Iron

5. Opioids (propoxyphene, hydrocodone, oxycodone, fentanyl etc.)
   - Dosed at bedtime or when symptoms occur
   - Advantages: Useful for painful RLS symptoms or comorbid pain. Fentanyl patch can provide consistent relief for 3 days.
   - Disadvantages: Tolerance may develop, constipation, opioid use viewed as problematic for RLS

6. Iron supplementation in patients with serum ferritin < 50-75 ng/mL

# Medications that Exacerbate RLS/PLMS

- Antipsychotics (dopaminergic blockade)
- Antidepressants (SSRIs, TCAs, SNRIs)
- Prochlorperazine
- Metoclopramide
- Antihistamines
- Xanthines (caffeine, theophylline)
- Alcohol

# Circadian Rhythm Disorders

- Jet lag, shift work, sleep phase advancement or delay
- Prevention
  - Slowly shift “home” sleep / wake schedule prior to travel
- Therapy
  - Jet lag – medication taken prior to bedtime (2-3 hours) at travel destination for first few nights (melatonin)
  - Shift work – sedative hypnotics to initiate/maintain sleep

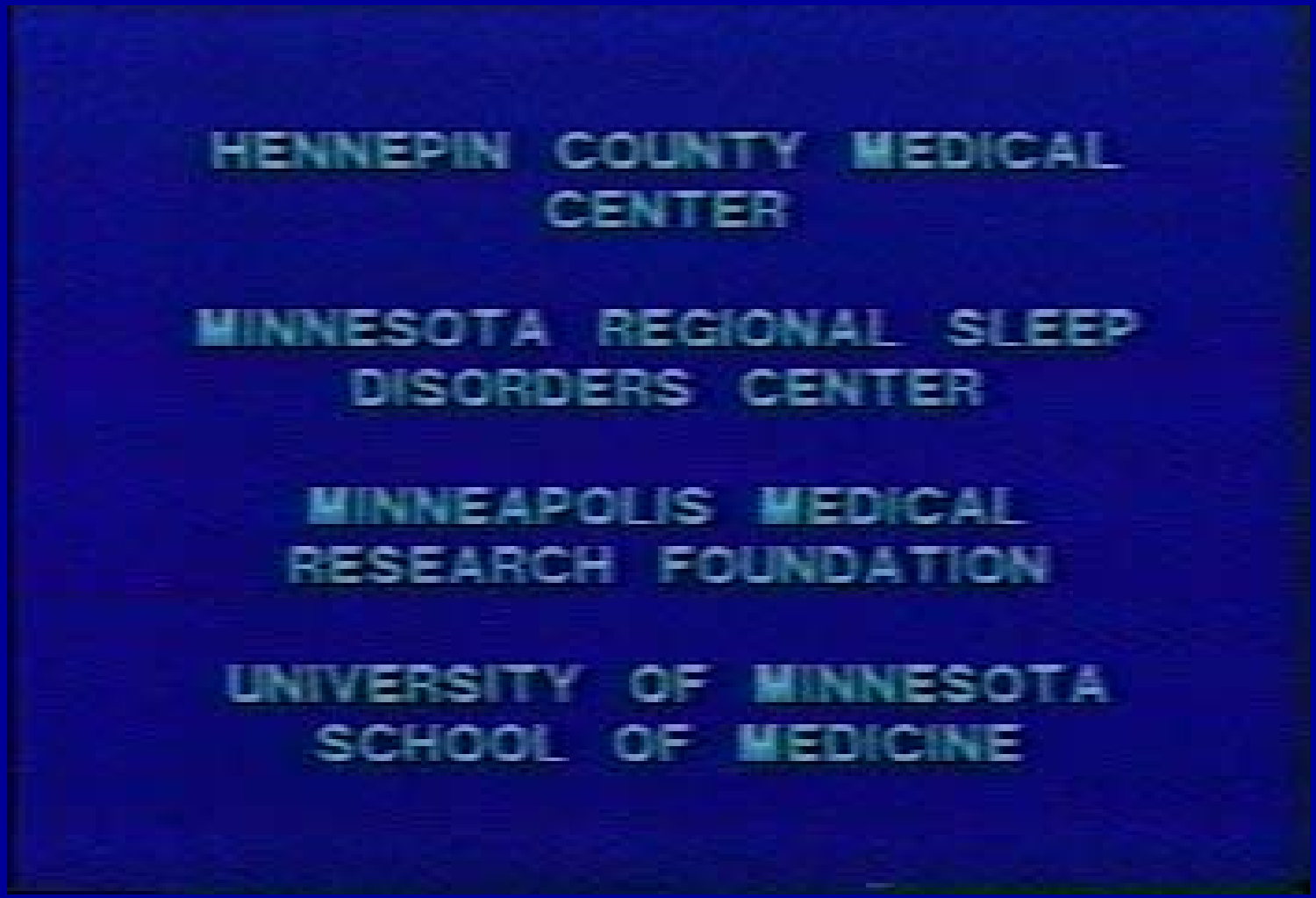
# Melatonin

- Endogenous hormone released with onset of sleep
- USEFUL for Jet Lag - Doses of melatonin between 0.5 and 5mg.
  - Patients fall asleep faster and sleep better after 5mg than 0.5mg.
  - Avoid 2mg slow-release melatonin
  - Greater benefit for more zones are crossed, and less for westward flights.
  - Caution in patients with epilepsy and patients on warfarin

# REM Behavior Disorder (RBD)
# - aka “nightflying” -

- Intermittent loss of muscle atonia during REM sleep, results in excessive and often violent motor activity
- In other words, people act out their dreams
- Associated with a significant potential for injuries to oneself or the bed partner
  - Make environmental changes to prevent injury
  - Clonazepam 0.5-2 mg po each night at bedtime is therapy of choice
  - Pramipexole, melatonin also used for RBD

# REM Behavior Disorder



# Bruxism (teeth-grinding)

- Consequences:
  - Wear and damage to teeth
  - TMJ and jaw problems
  - Sleep disruption and daytime sleepiness
  - Headaches, pain
- Medications may cause teeth clenching/grinding
  - SSRIs – 25% of patients!
  - Dopaminergic blockers
  - Methylphenidate
  - Alcohol, nicotine
  - Lithium
  - Flecainide
- Treatment: behavioral approaches, mouth guards, clonidine