Emerging Pharmacology

Sleep Promoting Agents – Dennis Auckley
Alertness Promoting Agents – Lynn Trotti
Delirium and Sleep After Surgery – Balachunder Subramaniam
Gabapentin: ERAS Darling to the Dark Side – Michael Pilla

Sleep Promoting Pharmacologics: New Agents and Challenges

Dennis Auckley, MD
Director, Center for Sleep Medicine
MetroHealth Medical Center
Professor of Medicine
Case Western Reserve University

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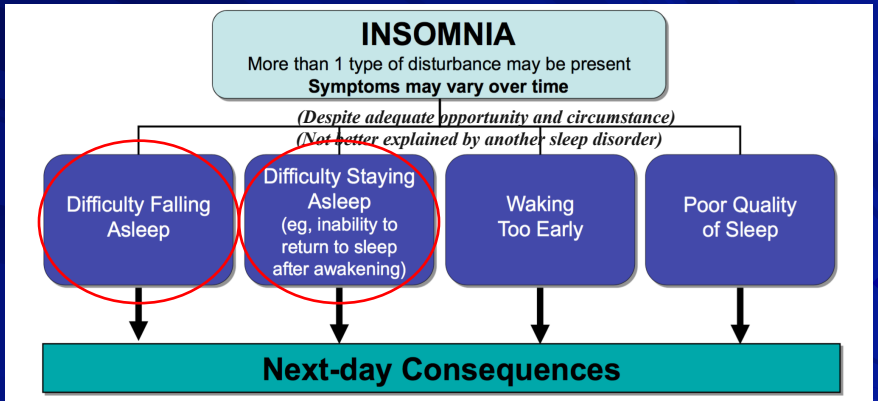
- UpToDate – written 2 sections
- ABIM Sleep Medicine Exam Committee
  - No exam questions will be disclosed during this presentation

Objectives

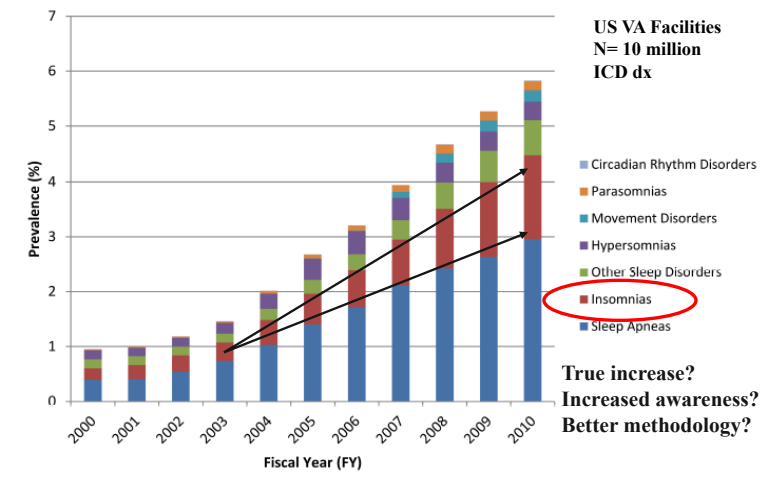
- Define insomnia and prevalence
- Briefly review the anatomy and pathophysiology of insomnia
- Discuss pharmacologic therapies for insomnia
  - Emphasis on newer agents
  - Perioperative considerations
- Consider challenges in the development of new pharmacotherapies

What is Insomnia?



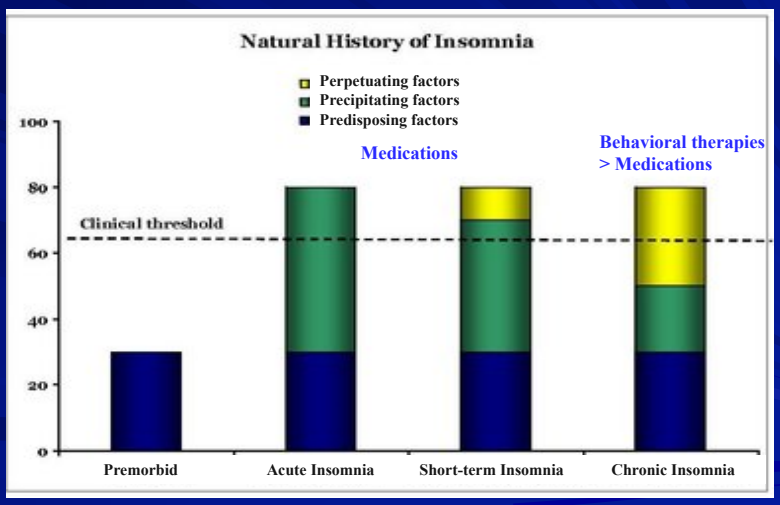
Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association Press; 1994; *The International Classification of Sleep Disorders: Diagnostic & Coding Manual, ICSD-2.* 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005.

Insomnia Prevalence



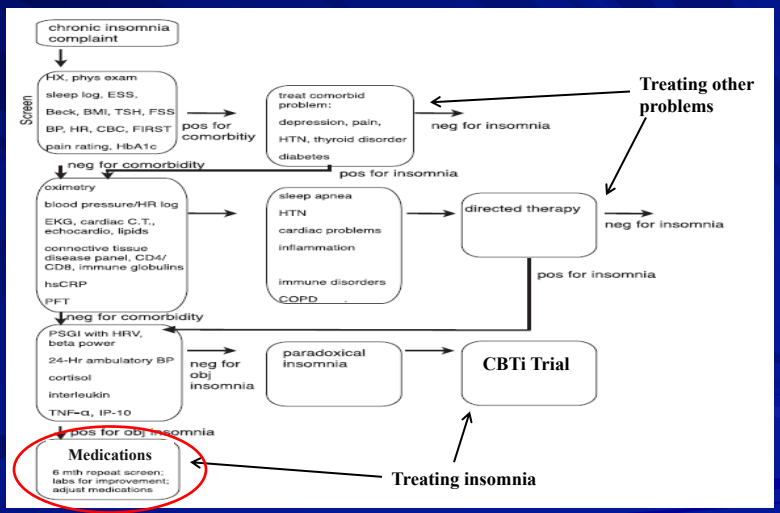
Alexander et al, Sleep 2016

Insomnia Pathophysiology: The 3 P's of Insomnia



Spielman et al, Case Studies in Insomnia 1991

Insomnia Therapy



Bonnet et al, Sleep Med Rev 2014

Insomnia Pathophysiology

- Hyperaroused state
  - Increased heart rate and altered heart rate variability
  - Increased whole-body metabolic rate (cortisol, ACTH) (particularly near sleep onset)
  - Increased body temperature
  - Increased high-frequency EEG activity (NREM sleep)
  - Increased catecholamine levels
  - Increased daytime alertness and reactivity to stress
- *No discrete structural brain pathology can be identified in most individuals with insomnia*

Mechanisms of Sleep: Neurotransmitters

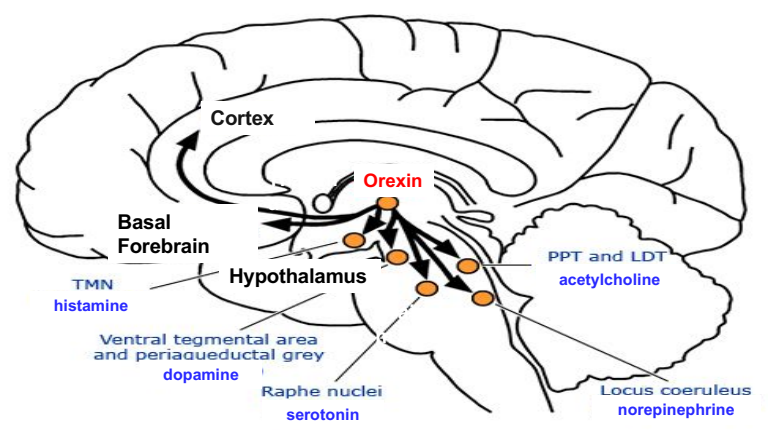
Wake-promoting neurotransmitters	NREM	REM
Glutamate	GABA	Acetylcholine
Acetylcholine ✕	Galanin	Glutamate
Dopamine ✕	Adenosine	GABA
Norepinephrine ✕	Melatonin	Glycine (muscle atonia)
Serotonin ✕	Glutamate	
Histamine ✕ ✕		
Orexin/hypocretin ✕		

= traditional therapies

= newer therapies

Owens et al, J Atten Dis 2012

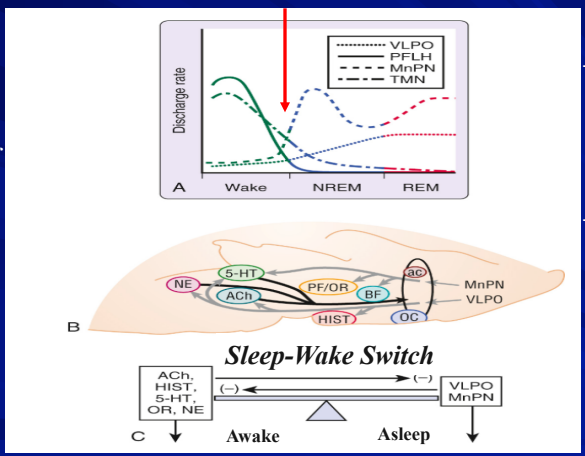
Wake Control Centers



Principles and Practice of Sleep Medicine, 6th Ed

Sleep Promotion

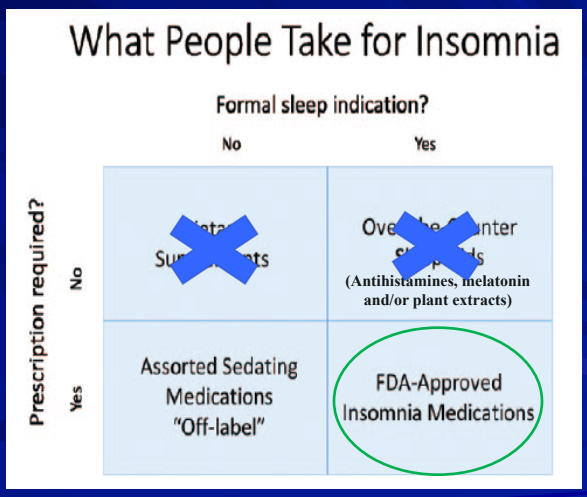
Sleep is the suppression of wakefulness



- VLPO and MnPN neurons are both in the anterior hypothalamus
- Activation leads to GABA release, that inhibits wake promoting areas

Principles and Practice of Sleep Medicine, 6th Ed

Insomnia Therapy



Neubauer et al, J CNS dz 2018

Insomnia Therapy: "Traditional" FDA-Approved Medications

GENERIC NAME	BRAND NAME	AVAILABLE DOSES (MG)	ELIMINATION HALF-LIFE (HR)
BENZODIAZEPINE RECEPTOR AGONISTS **(GABA agonists)**			
Benzodiazepine Immediate Release			
Estazolam	ProSom	1, 2	10 - 24
Flurazepam	Dalmane	15, 30	2.3/48 – 160 active metabolite
Quazepam	Doral	7.5, 15	39/73 active metabolite
Temazepam	Restoril	7.5, 15, 22.5, 30	3.5 – 18.4
Triazolam	Halcion	0.125, 0.25	1.5 – 5.5
Nonbenzodiazepine Immediate Release			
Eszopiclone	Lunesta	1, 2, 3	6/ 9 in elderly
Zaleplon	Sonata	5, 10	1
Zolpidem	Ambien	5, 10	2.8 in males
Nonbenzodiazepine Extended Release			
Zolpidem ER	Ambien CR	6.25, 12.5	1.6 – 4.5

Neubauer et al, J CNS dz 2018

Insomnia Therapy: "Newer" FDA-Approved Medications

GENERIC NAME	BRAND NAME	AVAILABLE DOSES (MG)	ELIMINATION HALF-LIFE (HR)
SELECTIVE MELATONIN RECEPTOR AGONIST	**(Melatonin receptor agonist)**		
Ramelteon	Rozerem	8	1–2.6
SELECTIVE HISTAMINE RECEPTOR ANTAGONIST	**(Histamine-1 receptor antagonist)**		
Doxepin (low dose)	Silenor	3, 6	15.3
DUAL OREXIN RECEPTOR ANTAGONIST	**(Orexin A and B receptor antagonist)**		
Suvorexant	Belsomra	5, 10, 15, 20	12

Neubauer et al, J CNS dz 2018

Insomnia Therapy

MEDICATION	DEA CLASS	PC	MOST COMMON SIDE EFFECTS
Estazolam	IV	X	Somnolence, hypokinesia, dizziness, abnormal coordination
Flurazepam	IV	X	Dizziness, drowsiness, lightheadedness, loss of coordination, staggering, falling
Quazepam	IV	X	Drowsiness, headache
Temazepam	IV	X	Drowsiness, dizziness, lightheadedness, difficulty with coordination
Triazolam	IV	X	Drowsiness, headache, dizziness, "pins & needles," coordination difficulty, lightheadedness
Eszopiclone	IV	C	Unpleasant taste, headache, somnolence, rash, respiratory and viral infections, dizziness, dry mouth, anxiety, hallucinations
Zaleplon	IV	C	Drowsiness, lightheadedness, dizziness, "pins & needles," difficulty with coordination
Zolpidem	IV	C	Drowsiness, dizziness, diarrhea, drugged feeling
Zolpidem ER	IV	C	Headache, next-day somnolence, dizziness
Ramelteon	—	C	Somnolence, dizziness, fatigue, nausea, exacerbated insomnia
Low-dose doxepin	—	C	Somnolence/sedation, nausea, upper respiratory tract infection
Suvorexant	IV	C	Somnolence

Neubauer et al, J CNS dz 2018

Insomnia Therapy: "Traditional" FDA-Approved Medications

Benzodiazepines and NBRA

- Bind to several (B) / single (NBRA) GABA type A receptors
- Reduce sleep latency and awakenings, and increase TST
  - Approved for sleep-onset and sleep-maintenance insomnia *(agent depd)*
- All hepatically metabolized (CYP3A4)
- SE: daytime sleepiness, ***cognitive impairment, motor incoordination***, ***worsen OSA (B), respiratory depression (B), and*** complex sleep-related behaviors (NBRA)
  - ***Inpatient: increased fall risk and increased delirium***
  - ***Rebound insomnia*** can occur with withdrawal

*AASM 2017 Strength of Recommendation: all WEAK

Insomnia Therapy: "Newer" FDA-Approved Medications

Melatonin receptor agonist *(Ramelteon)*

- Targets melatonin receptors *(MT1 and MT2)*
- Reduces sleep latency and increases TST (though marginally)
  - Approved for ***sleep-onset insomnia***
- Hepatically metabolized (CYP1A2)
- SE: somnolence, dizziness, HA
  - No withdrawal or rebound insomnia

*AASM 2017 Strength of Recommendation: WEAK

Insomnia Therapy: "Newer" FDA-Approved Medications

Antidepressants *(Doxepin)*

- Antihistamine antidepressants have sedation as a SE
- Decrease wake time after sleep onset, increase TST
  - Approved for ***sleep-maintenance insomnia***
- Hepatically metabolized (CYP2D6)
- SE: somnolence, nausea, HA
  - May see withdrawal syndrome or ***rebound insomnia***

*AASM 2017 Strength of Recommendation: WEAK

Insomnia Therapy: "Newer" FDA-Approved Medications

Orexin receptor antagonist *(Suvorexant)*

- Orexin receptor antagonists are relatively new/novel therapies
- Reduce sleep latency and awakenings, and increase TST
  - Approved for ***sleep-onset and sleep-maintenance insomnia***
- Hepatically metabolized (CYP3A4)
- SE: somnolence, HA, narcolepsy-like sxs
  - ***May worsen OSA***
  - ***Rebound insomnia*** can occur with withdrawal

*AASM 2017 Strength of Recommendation: WEAK

Insomnia Therapy: NonFDA-Approved Medications

- Trazodone: antidepressant serotonin modulator, has sedation as a SE
  - Can reduce sleep latency, awakenings, and increase TST
  - Hepatically metabolized (CYP3A4)
  - SE: somnolence, ***confusion***, dizzy, nausea, dry mouth, HA
    - ***Orthostatic hypotension, arrhythmias***
    - May see ***severe withdrawal syndrome***

*AASM 2017: NO

- Mirtazapine (Remeron): antidepressant serotonin agonist / alpha2 antagonist, has sedation as a SE
  - Can reduce sleep latency and increase TST
  - Hepatically metabolized (CYP3A4 + others)
  - SE: somnolence, appetite/weight gain, dry mouth

Insomnia Therapy: NonFDA-Approved Medications

Over-the-counter medications

- OTC preparations: antihistamine, melatonin or herbal
- Little evidence for their clinical effectiveness
- Common drugs
  - Diphenhydramine ("PM") / Doxylamine (Unisom)
  - Melatonin
  - Valerian (Sleep Aid)
- Hepatically metabolized
- SE: mostly antihistamines – somnolence, ***cognitive impairment, delirium, anticholinergic effects***

*AASM 2017: NO
*Recent systematic review: NO

Insomnia Therapy:
NonFDA-Approved Medications

- Propofol?
  - Controlled trial of patients with refractory chronic primary insomnia (n=103)
  - 2 hours of IV propofol per night x 5 nights (vs placebo)
  - Results: improved subjective and objective sleep at the end of the 5 days that held to 6 months f/u

Xu et al, Cell Biochem Biophys 2011

Insomnia Therapy:
ClinicalTrials.gov

- Orexin receptor antagonists – "me too" agents
- Esmirtazipine
- Quetiapine (Seroquel): antipsychotic with serotonin, dopaminergic, histamine and adrenergic effects
- Gamma Hydroxybutyrate (GHB/Xyrem): GABA B receptor agonist / GHB receptor agonist
- Lavender oil: aroma therapy
- *No studies on THC or cannabinoids*

Insomnia and Perioperative / Inpatient Considerations

- The perioperative / inpatient provider should be aware of insomnia therapies *(prescribed or self-medicated)*
  - Side effects relevant to the perioperative / inpatient environment can occur *(CNS, cardiac and pulmonary effects)*
    - Some may be enhanced in the inpatient environment
    - Liver failure can be a major problem
  - Drug-drug interactions exist
    - Watch for overlapping effects with opioids
  - However, abruptly stopping therapies may be deleterious
  - *Beware of ETOH used as a sleep aid*

Insomnia Therapy: Challenges for New Agents

- Desire a rapid onset of action
  - And "appropriate" duration of action
  - And OK for intermittent administration
- Consider gender-related and age-related factors
- Minimize side effect profile
- Limited to no abuse potential
- Impact on / by co-morbidities
- *Need a better understanding of sleep neurophysiology*

Sleep Promoting Pharmacologics:
New Agents and Challenges

- New, more physiologically-appropriate, medical therapies are available for Insomnia
  - All have limitations in terms of efficacy and side effects
- Current work is mostly comparative, population specific or involves combinations of therapy
- Common therapies for insomnia have the potential to impact perioperative / inpatient care
- Further work based on a better understanding of sleep neurophysiology is needed

See you DC!
SASM2020

Thank You

dauckley@metrohealth.org