

## Sleep Medications in Primary Care

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## Disclosure

- No real or potential conflict of interest to disclose.
- No off-label, experimental or investigational use of drugs or devices will be presented.

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## Objectives

- Upon completion of the learning activity the participant will be able to:
  - Describe the process of naturally-occurring sleep.
  - Identify the pharmacokinetics and pharmacodynamics of medications and herbal products to enhance sleep.

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## Objectives (continued)

- Upon completion of the learning activity the participant will be able to: (cont.)
  - Recognize the anticipated sleep outcomes with select medications commonly prescribed or used to enhance sleep as well as the risks associated with these products.

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## Sleep Defined (Or Best Defined in its Absence?)

- Difficult to define and characterized by observable changes in behavior and responsiveness
  - Decreased activity
  - Recognizable posture
  - Brain is less attentive to external stimuli
  - Altered consciousness yet easily aroused
- Source:  
<http://healthysleep.med.harvard.edu/healthy/science/what/characteristics>

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## Insomnia: The Cost of the Problem

- Costs the average American worker
  - 11.3 days per year, \$2,280 in lost productivity each year
    - Presenteeism vs. absenteeism
- Entire USA
  - \$63.2 billion in lost productivity
  - Source: <http://healthland.time.com/2011/09/01/the-high-cost-of-bad-sleep-63-billion-per-year/>

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### Insomnia: The Cost of the Problem (continued)

- In primary care
  - Up to 1/3 of all patients have a complaint of disordered sleep
  - One in 6 patients describing problem as “serious or severe”
  - One in 12 patients describing problem as “chronic”



– Source: <http://www.medscape.org/viewarticle/478849>

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The focus of this program is medications used to induce/maintain sleep.

- Not addressed in program
  - Sleep apnea, central or obstructive
  - Restless leg syndrome
  - Parasomnias, sleepwalking, sleep terrors
  - Narcolepsy
  - Others



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### Insomnia Disorders

Source:

[http://www.dsm5.org/File%20Library/Psychiatrists/Practice/DSM/APA\\_DSM-5-Sleep-Wake-Disorders.pdf](http://www.dsm5.org/File%20Library/Psychiatrists/Practice/DSM/APA_DSM-5-Sleep-Wake-Disorders.pdf)

### Insomnia Disorders (continued)

- Defined
  - Complaint of difficulty in falling asleep, maintaining sleep (awakening frequently during the night), or an inability to easily fall back asleep
  - Dissatisfaction with sleep
  - Significant negative impact on daytime functioning

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### Insomnia Disorders (continued)

- Dissatisfaction with sleep defined
  - Difficulty initiating and/or maintaining sleep
  - Non-restorative sleep
  - $\geq 3$  nights per week for  $\geq 3$  months, despite adequate opportunity to sleep

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### Insomnia Disorders (continued)

- Significant negative impact on daytime functioning defined
  - Significant fatigue
  - Sleepiness
  - Poor concentration
  - Low mood
  - Impaired ability to perform social, occupational or caregiving responsibilities
- Not explained by other health issues

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### Cognitive Behavioral Therapy (CBT) for Insomnia

Consider medications as an aid to gap while working with patient on CTB.

Resources:

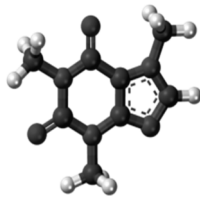
[http://www.mentalhealth.va.gov/coe/cih-visn2/Documents/Provider\\_Education\\_Handouts/CTB\\_for\\_Insomnia\\_Information\\_Sheet\\_for\\_BHPs\\_Version\\_3.pdf](http://www.mentalhealth.va.gov/coe/cih-visn2/Documents/Provider_Education_Handouts/CTB_for_Insomnia_Information_Sheet_for_BHPs_Version_3.pdf)

<http://www.sleepeducation.org/treatment-therapy/cognitive-behavioral-therapy>

The focus of this program is medications used to induce/maintain sleep.

Assumed that the NP has appropriately assessed the patient and that a sleep medication is a prudent clinical action with risks and benefits shared with patient

### One Culprit of Modern-day Life Caffeine



Source image: <https://en.wikipedia.org/wiki/Caffeine>

### Caffeine's Pharmacokinetics Clinical Significance?

- MW=194.19
- Lipophilic
- $T_{1/2}$  range=1.5–9 h
- $C_{max}$ =~15–100 mins
- Minimum first-pass effect
- CYP 450 substrate 1A2

– Source: <http://books.nap.edu/openbook.php?isbn=0309082587>

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### True or false?

- When compared with a healthy 40-year-old adult, CYP 450 isoenzyme levels can drop by up to 30% in elders after age 70 years.
- CYP 450 1A2's activity is influenced by the presence or absence of estrogen in women.

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### Caffeine PK

- Common 1A2 inhibitors?
  - Remember the "Cs"
    - Ciprofloxacin
    - Cimetidine
- Common 1A2 inducer?
  - Nicotine
  - And remember to advise when cutting down...

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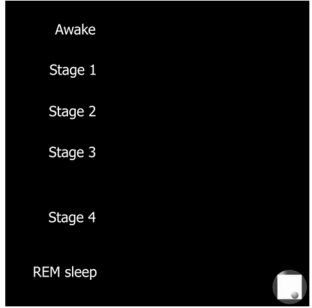
### Sleep Architecture Naturally-occurring Sleep's 2 Stages

1. Non-rapid eye movement (NREM)
  - Stage 1 – Transitional
  - Stage 2 – Light sleep
  - Stage 3 – Deep sleep
  - Stage 4 – Deepest sleep
2. Rapid eye movement (REM)

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### Non-REM: Stages 1 and 2

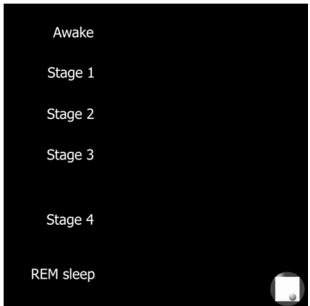
- Stage 1
  - Easily awakened
  - "muscle jump" (hypnic myoclonia)
- Stage 2
  - Heart rate slows, body temperature drops
  - 50% of total sleep time



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### Non-REM: Stage 3

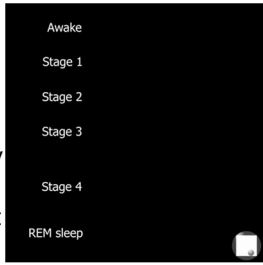
- Stage 3
  - Delta waves (slow waves)
  - Moving to deeper sleep



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### Stage 4: "Deep Sleep"

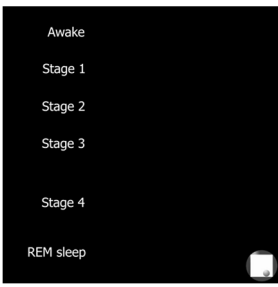
- Stage 4
  - Delta waves exclusively, difficult to arouse, no eye movement or muscle activities
  - When interrupted, "groggy and disoriented"
  - Stage of bedwetting, night terrors or sleepwalking occur during deep sleep



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### REM Sleep 20% of Adult Sleep

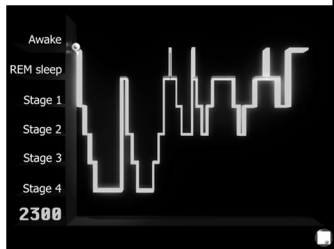
- Rapid, irregular and shallow breathing
- Rapid eye jerks in various directions
- Temporary paralysis of limb muscles
- Increased HR, BP
- Penile erections
- Most vivid dreams



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### Sleep Stages Movement Through 5 Stages

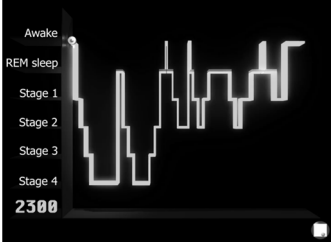
- Adults actively move through the sleep process from NREM stages 1-4 to REM
  - Complete cycle typically 90-100 minutes
  - Complete 4-5 cycles per night



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### Sleep Stages Movement Through 5 Stages (continued)

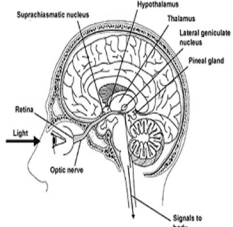
- Length of REM sleep becomes progressively longer and time in deep sleep decreases throughout the night



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### Circadian Rhythm

- Biologic "internal clock"
  - Housed in suprachiasmatic nucleus in anterior hypothalamus
  - Fully developed by age 25 years
  - Source: [http://www.howsleepworks.com/how\\_circadian.html](http://www.howsleepworks.com/how_circadian.html)



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### Potential Influence of Sleep Aids on Sleep Architecture:

Potential Increase in Stage 1, Stage 2 Sleep  
Potential Reduction in Stage 3, Stage 4,  
REM Sleep

Consider as short-term therapy!

Source: [http://www.medscape.com/viewarticle/723907\\_2](http://www.medscape.com/viewarticle/723907_2)

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### Sleep-Wake Homeostasis

- The pressure to sleep
  - Also known as sleep drive
- Unable to overcome
  - With use of stimulants, can only mask need to sleep
  - With medications, can mildly promote or enhance sleep drive

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### Pharmacology of Insomnia Treatment Therapeutic Approaches

- Stimulate/activate sleep-promoting system
  - GABA
    - Inhibitory neurotransmitter (NT)
    - Main hypothalamic NT, projects to several sleep-regulating centers of the brain
      - Increase in GABA inhibits ("blocks") the wake-promoting chemicals
  - Melatonin

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### Pharmacology of Insomnia Treatment Therapeutic Approaches (continued)

- Suppress the wake-promoting systems
  - Histamine
  - Cholinergic
  - Serotonin
  - Orexin

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In particular, for sleep medications that induce sedation, what is the medication's half-life ( $T_{1/2}$ )?

How much of the medication will be on board upon AM awakening?

Onset of action?

Peak of action?

Reference:

*PL Detail-Document, Comparison of Insomnia Treatments. Pharmacist's Letter/Prescriber's Letter. May 2012.*

$T_{1/2}$

- Time required for the amount of drug in the body to be reduced or eliminated by  $1/2$ 
  - Also known as elimination or biological  $T_{1/2}$
  - 3–5  $T_{1/2}$  needed to reach steady state
  - 3–5 drug-free  $T_{1/2}$  needed to eliminate drug from body

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What % is left of original drug dose?

- 1  $T_{1/2}$ 
  - 50% left
- 2  $T_{1/2}$ 
  - 50% of 50%=25% left
- 3  $T_{1/2}$ 
  - 50% of 50% of 50%=12.5% left
- 4  $T_{1/2}$ 
  - 50% of 50% of 50% of 50%=6.25% left
- 5  $T_{1/2}$ 
  - 50% of 50% of 50% of 50% of 50%=3.125% left

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True or false?

- The  $T_{1/2}$  of a medication is a predictable number regardless of the patient's age, gender, and overall state of health.
- If a sleep med is taken at 10 PM and has a  $T_{1/2}$  of about 2 h, then approximately 6.5% of the original dose will be on board with 6 AM awakening.

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True or false?

- In order to exploit optimal PK, all sleep medications should be taken on an empty or near-empty stomach.
- When taken with a meal, the onset of sleep latency with many sleep meds will be delayed by 1.5–3.5 h.

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With Many if Not Most Sleep Meds

- When coadministered with alcohol
  - Additive psychomotor impairment
- Habituation/misuse
  - Reported in most clinical trials
  - Controlled substance
    - Most are Schedule 4 with exception of psychotropics used for conditions other than sleep, OTCs, herbal products

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What would you want to prescribe, if appropriate, for the patient who states,

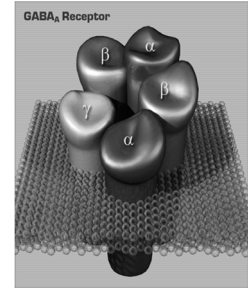
- "I have an 8-h overnight flight where I need to walk off the plane and go right to an important meeting. Can I have something to help me get some shut-eye on the plane?"
- "My patient is in a subacute care hospital for a few days and cannot fall asleep. Once asleep, he stays asleep fairly well."

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## Sleep Medications with GABA-generic Effect=Enhances Sleep Promotion

- Non-benzodiazepines
  - GABA role= Blocks action of excitatory brain chemicals
  - Zolpidem (Ambien®, Intermezzo®)
  - Zaleplon (Sonata®)
  - Eszopiclone (Lunesta®)

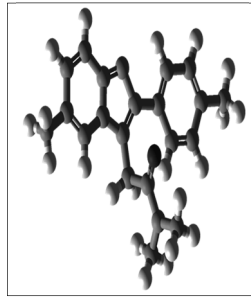


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Short  $T_{1/2}$   
Onset of Action= $\sim$ 30 mins  
Peak= $\sim$ 1h

- Zaleplon
  - Ultra-short,  $T_{1/2}$ =1h
- Zolpidem
  - Short,  $T_{1/2}$ =2–2.5 h



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## FDA Advisory about Zolpidem Dose

FDA Drug Safety Communication: Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem, available at <http://www.fda.gov/drugs/drugsafety/ucm334033.htm>

## From FDA Advisory

- Dosing
  - Recommended zolpidem immediate-release dose: 5 mg for women and either 5 mg or 10 mg for men
  - Recommended zolpidem extended-release dose: 6.25 mg for women and either 6.25 or 12.5 mg for men
    - CR formulation=Special warning about next-day performance issues
  - Higher doses should be used with caution.

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## Zolpidem Tartrate

Specifically Labeled for Middle-of-the-night Awakening with  $\geq$ 4 h Sleep Duration Available

- Dose
  - Men=3.5 mg
  - Women=1.75 mg
    - Only one dose per night, only if needed
- Source: Intermezzo® Prescribing Information, available at <http://app.purduepharma.com/xmlpublishing/pi.aspx?id=i>

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What would you want to prescribe, if appropriate, for the patient who states, "I fall asleep with that sleep med you gave me, but I do not stay asleep. I am back up at 4 AM."

NB: Consider possible contribution of depression.

Longer  $T_{1/2}$   
Onset of Action= $\sim$ 30 mins  
Peak= $\sim$ 1h

- Eszopiclone
  - $T_{1/2}$ =6 h in adults, 9 h in elders
  - Taken at 10 PM=50% of dose on board at 4 AM
  - Dose=Start with 1 mg, can increase to 2–3 mg if needed

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Common to all Sedative-hypnotics:  
FDA Advisory

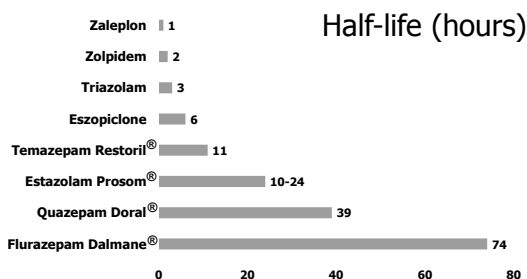
### FDA Warning in Patient Drug Information

- "...sedative-hypnotic drug products, a class of drugs used to induce and/or maintain sleep, strengthen their product labeling to include stronger language concerning potential risks. These risks include severe allergic reactions and complex sleep-related behaviors, which may include sleep-driving. Sleep-driving is defined as driving while not fully awake after ingestion of a sedative-hypnotic product, with no memory of the event."

– Source: <http://www.fda.gov/drugs/drugsafety/ucm352085.htm>

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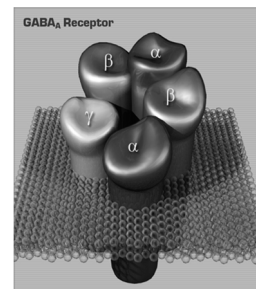
All brand names are the property of their respective owners.  
Source: Dikeos DG, Soldatos. *Primary Care Companion. J Clin Psychiatry.* 2002;4(suppl 1):27-32.

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### Sleep Medications with GABA-generic Effect=Enhances Sleep Promotion

- Benzodiazepines
  - -pam suffix
  - Temazepam
  - Triazolam
  - Estazolam
  - Flurazepam
  - Quazepam



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### BZD Pharmacokinetics Appropriate Sleep Aids?

	Dose equivalent	Half-life in hours
Alprazolam (Xanax®)	0.5	6–20
Chlordiazepoxide (Librium®)	10	30–100
Clonazepam (Klonopin®)	0.25	18–50
Clorazepate (Tranxene®)	7.5	30–100
Diazepam (Valium®)	5	30–100
Lorazepam (Ativan®)	1	10–20
Oxazepam (Serax®)	15	8–12

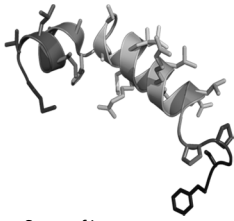
Source: <http://www.vhpharmsci.com/vhformulary/tools/benzodiazepines-comparison.htm>

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- ### Pharmacology of Insomnia Treatment Therapeutic Approaches
- Suppress the wake-promoting systems
    - Histamine
    - Cholinergic
    - Serotonin
    - Orexin
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### Suvorexant (Belsomra®) Mechanism of Action

- What is it?
  - Orexin-receptor antagonist
    - Any drug that occupies a receptor site and prohibits its activation is an antagonist.




Source of image:  
[https://en.wikipedia.org/wiki/Orexin#/media/File:1CQ0\\_crystallography.png](https://en.wikipedia.org/wiki/Orexin#/media/File:1CQ0_crystallography.png)

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### Suvorexant Mechanism of Action (continued)


- Blocking the binding of neuropeptides orexin A and orexin B to receptors OX1R and OX2R=Thought to suppress the wake drive



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### Suvorexant C-IV

- Indication
  - For treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance in adults age ≥18 years
- What would you expect for PK?



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### Suvorexant PK Information

- Peak plasma time
  - 2 h post dose
  - With high-fat meal= 1.5-h delay
- $T_{1/2}$ =12 h
  - As a result, when taking at 10 PM, 50% of the dose still on board at 10 AM
- Zolpidem
  - $T_{1/2}$ =2.6 h
    - $2.6 \text{ h} \times 3=7.8 \text{ h}$ , take at 10 PM, approx. 12.5% of dose on board at 6 AM
  - Time to  $C_{max}$ =1.6 h

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### Suvorexant Recommended Dose

- How supplied
  - 5 mg, 10 mg, 15 mg, and 20 mg tablets
- Recommended daily dose
  - 10 mg, taken  $\geq 30$  mins prior to bedtime, only if  $\geq 7$  h of sleep time available, only 1 dose per night
    - If 10 mg dose is well-tolerated but not effective, dose can be increased up to a maximum dose of 20 mg daily.

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### Suvorexant Precaution

Do we have this information on older meds?

- Per FDA-required study
  - Exposure to suvorexant increased in obese compared to non-obese patients
    - AUC and  $C_{max}$  increased by 46% and 25% respectively compared to nonobese females
  - Women compared to men
    - Consistent with warnings about other sleep aids including zolpidem

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### Suvorexant Adverse Effects and Precaution (continued)

- Patient advised about these in handout provided with medication
  - CNS depressant effects and daytime impairment
  - Abnormal thinking and behavioral changes
  - Worsening of depression/suicidal ideation
  - Sleep paralysis, hallucinations, cataplexy-like symptoms

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### Antidepressants as Sleep Medications

Potential Advantages: Not scheduled, possibly less abuse potential, low cost

Potential Disadvantages: Adverse effects

### Two Patients Possible TCA or Trazodone Candidates

- A 60-year-old woman with DM neuropathy with partial improvement with pregabalin, difficulty initiating and maintaining sleep in part due to leg burning
- A 56-year-old man with 30-year hx alcohol abuse, now sober  $\times 5$  years, difficulty initiating and maintaining sleep

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### Commonly-prescribed Psychotropic Medications

- Tricyclic antidepressants (TCA)
  - Block reuptake of NE, 5-HT
    - Amitriptyline, nortriptyline
- Issues with use
  - Significant AE in overdose
  - Sedating, possibly helpful with chronic pain
  - Inexpensive

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### TCA as Sleep Aids

- Nortriptyline, amitriptyline
  - Onset of action=1–3 h
  - Time to peak=7–8 h
  - $T_{1/2}$ =24–31 h
- Perhaps helpful
  - Chronic painful conditions such as DM neuropathy, recurrent headache, others
- Perhaps problematic
  - Daytime drowsiness

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### Action of Psychotropic Medications (Katzung, 2014)

Drug	Sedation or activation	Anti-cholinergic	Serotonin	NE	Dopamine
Amitriptyline	Sedation +++ Activation 0	++++	+++	++	0
Nortriptyline	Sedation ++ Activation 0	++	+++	++	0
Trazodone	Sedation +++ Activation 0	0	0/+	0	0
Mirtazapine	Sedation ++++ Activation 0	+	0	0	0

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### Adverse Effects Meds with Anticholinergic Effect

- Dry as a bone (dry mouth)
- Red as a beet (flushing)
- Mad as a hatter (confusion)
- Hot as a hare (hyperthermia)
- Can't see (vision changes)
- Can't pee (urinary retention)
- Can't spit (dry mouth)
- Can't (something that rhymes with spit) (constipation)

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### American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

Available at:  
<http://onlinelibrary.wiley.com/doi/10.1111/jgs.13702/abstract>

### Doxepin (Silenor®)

- Tricyclic antidepressant
  - FDA-approved as sleep aid
  - Significant systemic anticholinergic effect
- PK parameters
  - $T_{max}$ =3.5 h post dose when taken on an empty stomach
    - Doubled when taken with a high-fat meal, labeled warning
  - $T_{1/2}$ =15.3 h

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### Doxepin (Silenor®) (continued)


- Recommended dose
  - 3 mg (elder) or 6 mg (adult)
    - Per Beers Criteria, do not Rx  $\geq 6$  mg in the older adult
  - Take within 30 mins of going to bed
  - Do not take within 3 h of a meal
    - Alters PK

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### Doxepin (continued)

- Pharmacogenomics warning
  - Poor CYP2C9, 2C19 metabolizers will likely have greater doxepin exposure.



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### Tetracyclic Antidepressant

- Trazodone
  - FDA-approved for treatment of depression
    - Effect on cholinergic and serotonin neurotransmitters
      - Seldom used to treat depression due to sedation
  - Pharmacokinetics
    - Peak=1–3 h
    - $T_{1/2}$ =7–8 h

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### Q and A

- When using trazodone or a TCA to aid sleep, the drug should be optimally taken \_\_\_\_\_ prior to sleep.
  - A. Immediately
  - B. 15–45 minutes
  - C. 1–2 hour
  - D. 2–3 hours

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### Mirtazapine (Remeron®)

- Mechanism of action
  - Blocks presynaptic  $\alpha_2$ -adrenergic autoreceptor; blocks 5-HT<sub>2</sub>, 5-HT<sub>3</sub>
    - Net effect, enhance serotonin and NE activity
- Dose
  - 7.5–15 mg at bedtime for sleep helpful
    - More sedating at lower dose
  - Depression dose=45–60 mg/d
- PK
  - Peak=2 h
  - $T_{1/2}$ =20–40 h

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### Mirtazapine (continued)

- Not FDA-approved for insomnia
  - Some evidence on reducing insomnia in depression, especially early in treatment
  - Increases the risk of restless leg syndrome and periodic limb movements in sleep

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### Action of Psychotropic Medications

(Katzung and Trevor, Basic and Clinical Pharmacology, 13<sup>th</sup> ed. 2014)

Drug	Sedation or activation	Anti-cholinergic	Serotonin	NE	Dopamine
Amitriptyline	Sedation +++ Activation 0	++++	+++	++	0
Nortriptyline	Sedation ++ Activation 0	++	+++	++	0
Trazodone	Sedation +++ Activation 0	0	0/+	0	0
Mirtazapine	Sedation ++++ Activation 0	+	0	0	0

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### Second-generation Antipsychotics (SGA, AKA Atypicals) as Sleep Aids

Sleep-inducing due to largely  
antihistamine and serotonin effect.  
Potential drugs of abuse ("Baby Heroin," etc.)  
Is there a therapeutic indication  
for use of these meds beyond sleep?

### SGAs as Sleep Aids

- The evidence
  - Particularly more sedating members of the class demonstrated to be helpful in the presence of schizophrenia
  - Not extensively studied in unipolar depression as a sleep aid

– Source: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC487011/>

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### SGA: Most Sedating= Greater H1 Antagonism

- H1 antagonism=possible weight gain
  - Clozapine (Clozaril®)
    - Seldom used for sleep due to need for WBC monitoring due to neutropenia risk
  - Olanzapine (Zyprexa®)
  - Quetiapine (Seroquel®)
  - Risperidone (Risperdal®)

– Source: Comparison of atypical antipsychotics. *Pharmacist's Letter/Prescriber's Letter*. July 2015;310701.

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### Less Sedating SGA=Less Antihistaminic Effect=Less Weight Gain

- But how helpful for sleep?
  - Ziprasidone (Geodon®)
  - Aripiprazole (Abilify®)
  - Asenapine (Saphris®)
  - Lurasidone (Latuda®)
  - Paliperidone (Invega®)

– Source: Comparison of atypical antipsychotics. *Pharmacist's Letter/Prescriber's Letter*. July 2015;310701.

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### SGA PKs: When should the med be taken if used to enhance sleep?

- Olanzapine PK
  - Plasma peak=6 h post dose
  - $T_{1/2}$ =21–54 h
- Quetiapine
  - Plasma peak with IR formulation=1.5 h
  - $T_{1/2}$ =6 h

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### SGA PKs: When should the med be taken if used to enhance sleep? (continued)

- Risperidone
  - PK related to CYP 2D6 activity
    - Plasma peak in extensive metabolizers=3 h
    - Plasma peak in poor metabolizers=17 h
    - $T_{1/2}$  in extensive metabolizers= 3 h
    - $T_{1/2}$  in poor metabolizers=20 h

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Source: *Ann Pharmacother.* 2012;46:718-22.

- “There are potential safety concerns when using low-dose quetiapine for treatment of insomnia. These concerns should be evaluated in further prospective studies. Based on limited data and potential safety concerns, use of low-dose quetiapine for insomnia is not recommended.”

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## Antihistamines Sold OTC, Significant Anticholinergic Effect

Avoid in elders.  
Dangerous in overdose  
Best candidate is younger adult  
with temporary issue with sleep.

## Antihistamines as Sleep Aids

- Potential tolerance
  - Most often noted with  $\geq 10$  nights/use
  - Consider an “off” night after three days of use to reduce tolerance.
  - Avoid using more than ten days without consulting a healthcare professional.

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## Antihistamines as Sleep Aids (continued)

- Hydroxyzine (Vistaril<sup>®</sup>, Atarax<sup>®</sup>)
  - Rx only
  - Dose 10–50 mg at bedtime
  - Onset of action=15–30 mins
  - Peak=2 h
  - $T_{1/2}$ =3–7 h

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## Antihistamines as Sleep Aids (continued)

- Diphenhydramine (Benadryl<sup>®</sup>)
  - In the majority of OTC sleep aids
  - Dose=12.5–50 mg
  - Onset of action=15–30 mins
  - Peak=2 h
  - $T_{1/2}$ =2–8 h
    - Up to 13 h in elderly

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## Antihistamines as Sleep Aids (continued)

- Doxylamine
  - Dose 12.5–25 mg at bedtime
- In OTC sleep aids that do not have diphenhydramine as a primary ingredient
  - $T_{1/2}$ =10 h
  - $T_{max}$ =2 h

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### Role of Melatonin in Sleep

- Produced endogenously by pineal gland
  - Released in rhythm that is largely in synch with the body's circadian rhythm
  - Signals darkness, brain and body should get ready for sleep
- Sleep-enhancing
  - Consider this as a sleep facilitator rather than sedating medication.

– Source: <http://www.ncbi.nlm.nih.gov/pubmed/12622846>

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### Melatonin as Sleep Aid

- Available OTC
  - Be aware of quality of nutraceutical
  - Choose USP-verified with distinctive label
- Dose
  - 0.3 to 3 mg, usually taken around the time a reasonable person would expect to be getting sleepy
    - For example, around 9 PM for a person who will go to bed at 10 PM and get up at 6 AM

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### Melatonin as Sleep Aid (continued)

- Best suited for person with
  - Jet lag, AKA desynchronosis
  - Chronic circadian disorder
- Adverse effects
  - Vivid dreams reported



Source: [https://en.wikiz.org/wiki/Pok%C3%A9mon\\_Jet#/media/File:Pokemon\\_Jets.jpg](https://en.wikiz.org/wiki/Pok%C3%A9mon_Jet#/media/File:Pokemon_Jets.jpg)

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### Ramelteon (Rozerem™)

- What is it?
  - FDA-approved for treatment of insomnia characterized by sleep-onset difficulty
  - Dose
    - 8 mg dose taken within 30 mins of bedtime
  - Avoid use with high-fat meal
- Studied in long-term use
  - Not a controlled substance
  - Initially promoted as without abuse potential
    - Source: Hirai et al., 2005

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### Ramelteon PD

- Highly selective, nonspecific MT<sub>1</sub>/MT<sub>2</sub> agonist
  - 6- and 3-fold higher affinities for MT<sub>1</sub> and MT<sub>2</sub> than melatonin, respectively
- No measurable affinity for a large number of tested ligand binding sites (i.e., including GABA<sub>A</sub> receptors, dopamine receptors, opiate receptors, ion channels and transporters)

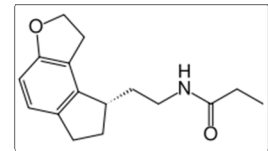
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(Kato, 2005)

### Ramelteon PK

- Rapidly absorbed within 0.5–1.5 h
  - T<sub>max</sub>=0.75 h
- T<sub>1/2</sub>
  - 1.36 h (1–2.6 h)
- Metabolized
  - CYP1A2 isozyme



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### Easily-found Online "Ramelteon (Rozerem™) Poppers"

- "The usual dosing is in 8 mg tablets, but people seeking "ramelteon (Rozerem™) highs" might take as much as a total of 24–32 mg at a time, mix it with booze or other anti-anxiety benzos or sleep aids (such as zolpidem)... a wonderful weed-like high that lasts about 1 h."

– Source: <http://www.urbandictionary.com/define.php?term=rozerem>

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### Tasimelteon (Hetlioz®)

- Indication
  - Treatment of Non-24-Hour Sleep-Wake Disorder (Non-24)
    - Most commonly noted in people who are blind who do not get light/dark signals
- Mechanism of action
  - Agonist at melatonin MT1 and MT2 receptors
    - Receptors believed to be involved in circadian rhythm control

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### Tasimelteon (continued)

- Dosage
  - 20 mg per day taken before bedtime, at the same time every night
  - Effect typically not seen until weeks or months of regular use

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### Plant-based Products as Sleep Aids

### Kava Kava as Sleep Aid

- Mechanism of action
  - Kavalactones act on limbic system
  - Mixed evidence of impact on GABA, dopamine or opioid receptors
- Dose as sleep aid
  - 180–210 mg at bedtime



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### Kava Kava as Sleep Aid (continued)

- Efficacy
  - Mixed as sleep aid or treatment of anxiety
- Caution
  - Hepatotoxicity
    - Increased when taken with acetaminophen
    - Noted in absence of underlying liver disease



– Source: [https://naturalmedicines.therapeuticresearch.com/databases/food\\_herbs/supplements/professional.aspx?productid=972#background](https://naturalmedicines.therapeuticresearch.com/databases/food_herbs/supplements/professional.aspx?productid=972#background)

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## Valerian Root

- Mechanism of action
  - Not clearly understood, likely via multiple mechanisms
- Dose
  - 400–900 mg aqueous extract up to 2 h prior to bedtime
  - Source:  
<https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=870#background>



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## Anesthesia and Herbal Products Avoid Concomitant Use

- Valerian, kava
- Kava kava
  - Potential for prolongation of anesthesia
    - Source: Nutritional Supplements and Perioperative Evaluation, available at <https://www.aao.org/complimentary-therapy-assessment/nutritional-supplements-perioperative-implications>

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## End of Presentation

Thank you for your time and attention.

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