Pharmacotherapy for Wake After Sleep Onset Insomnia

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Objectives

1. Review the physiology and neuropharmacology of sleep.
2. Define insomnia and, in particular, wake after sleep onset insomnia (WASO).
3. Review precipitating, predisposing and perpetuating factors for insomnia.
4. Review treatment goals for insomnia.
5. Review nonpharmacologic and pharmacologic therapies for WASO and recommendations for treatment.

Sleep

Two phases: 4-6 cycles

NREM: 3 stages

- Stage 1: Between wakefulness and sleep
- Stage 3: Delta sleep

REM: brain becomes electrically and metabolically active

- Dreaming
- Tend to lengthen in later stages of sleep cycle
- Acetylcholine (on), noradrenergic (off)

Each cycle lasts 70-120 minutes

Healthy sleep: 4 stages NREM before first REM

Circadian rhythm

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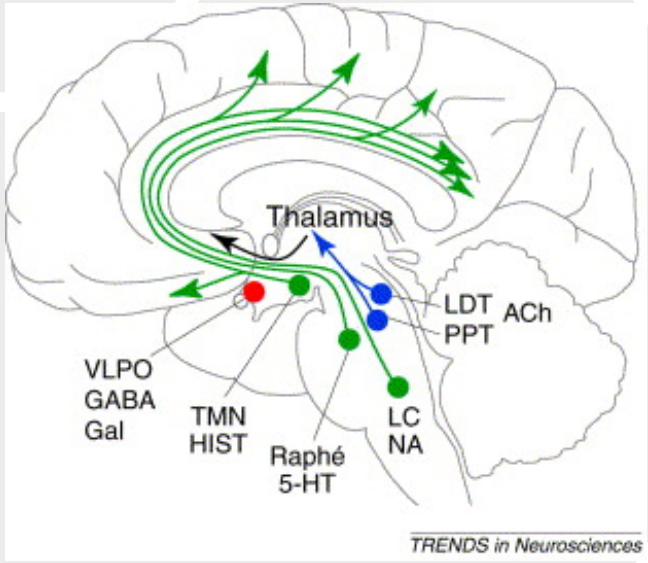
Neurotransmitters

Wakefulness

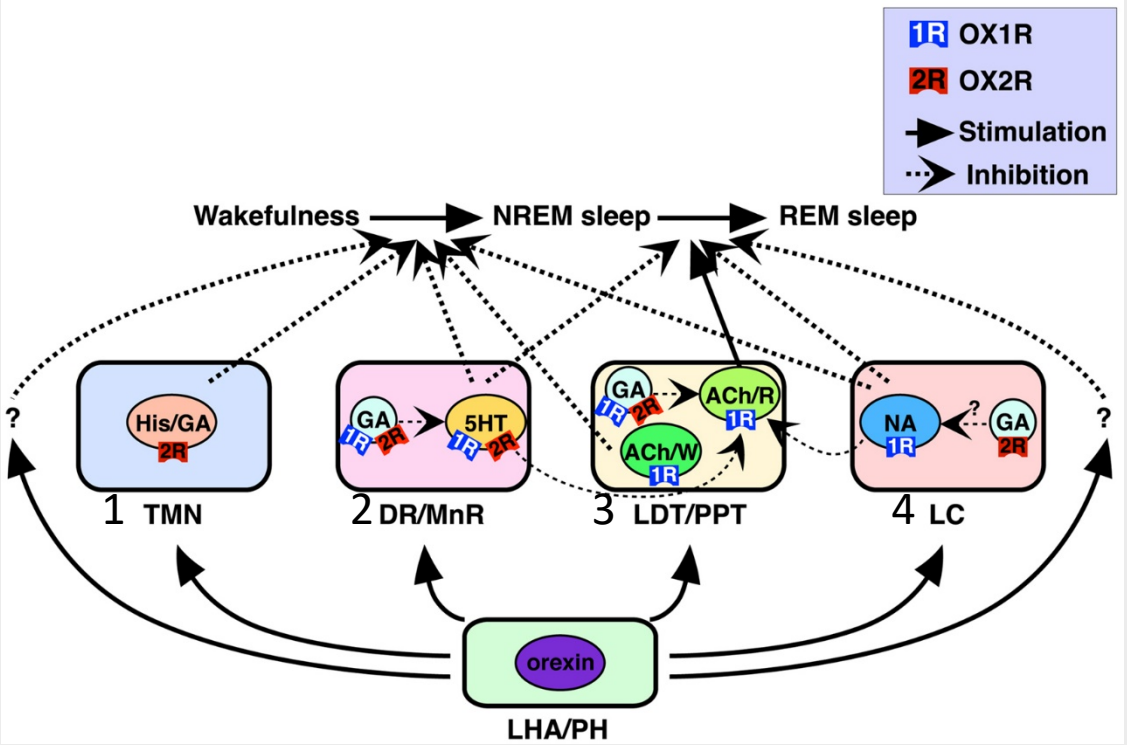
- Monoamines
  - Dopamine
  - Norepinephrine
  - Serotonin
- Acetylcholine
- Histamine (H_1)
- Orexin

Sleep

- Adenosine
- Gamma-amino butyric acid (GABA)
- Melatonin
- Galanin



His = Histamine H1
GA = GABA
5HT = Serotonin
ACh = Acetylcholine
NA = Noradrenergic



1. tuberomammillary nucleus (TMN)
2. dorsal raphe (DR) and median raphe (MnR)
3. laterodorsal tegmental nucleus (LDT)
4. pedunculopontine tegmental nucleus (PPT)
5. locus ceruleus (LC)

LHA, lateral hypothalamic area; PH, posterior hypothalamus

Front. Endocrinol., 16 May 2013. https://doi.org/10.3389/fendo.2013.00057

Insomnia Disorder

- Defined in the International Classification of Sleep Disorders, 3rd Edition:
  1. Trouble initiating or maintaining sleep
  2. Daytime consequences
  3. Not attributable to environmental circumstances
  4. Not inadequate opportunity to sleep.
  5. ≥ 3 times per week
- One of the most common complaints in adults
  - Short term 30-50% of pop.: < 3 months
  - Chronic 5-10% of pop.: at least 3 months
- A strong and highly regulated biologic drive
- But also fragile

Common Complaints

- Sleep onset latency (SOL) > 30 minutes
- Wake after sleep onset (WASO) > 30 minutes
  - Periods of wakefulness occurring after defined sleep onset
- Sleep efficiency < 85%
  - $SE = \left[\frac{Total\ Sleep\ Time}{Time\ in\ Bed}\right] \times 100$
- Total sleep time (TST) < 6.5 hours

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Precipitating and Predisposing Factors

- Precipitating
  - E.g. pain, nocturia, or shortness of breath
  - Situational
    - Work or financial stress, major life events, interpersonal conflicts
    - Jet lag or shift work
  - Unlikely to improve without maximal treatment of the precipitating factor
- Sleep disorders other than insomnia
  - E.g. obstructive sleep apnea, restless legs syndrome
  - Unlikely to improve without treatment directed at the specific sleep disorder
- Psychiatric disorders and insomnia have a bidirectional relationship:
  - E.G. depression causes insomnia and insomnia causes depression
  - Concomitant treatment for both disorders is often necessary; increase the likelihood of sustained response
- Childhood trauma or chaotic home environment at night may increase vulnerability as an adult
  - Even in the absence of PTSD
  - Awareness of this history is valuable as it may shed light on etiology and help identify targets of cognitive therapy

Medication Side Effects

- Stimulants
  - Amphetamines and amphetamine-like
    - Methylphenidate, modafinil
    - Pseudoephedrine
  - $T_{½}$ greater than 10 hours
  - Lower the dose, shorter-acting agent, and administer earlier in the day
- Antidepressants
  - SSRIs, SNRIs: treatment-induced insomnia in approximately 20% of patients.
  - Often transient, temporary use of sedative-hypnotic
  - Morning dosing – long $T_{½}$
  - Lowering the dose
- Glucocorticoids
  - Oral or inhaled
  - Lower dose, administer earlier in day
  - Sedative-hypnotic if does not improve
- Opioids
  - Sleep fragmentation with chronic use
  - Disordered breathing, polysomnography
  - Lowering or eliminating the opioid dose
  - CPAP

Perpetuating Factors

- Maladaptive responses to sleeplessness
  - Poor sleep habits
  - Unrealistic expectations of sleep
  - Inappropriate attributions about daytime smx and nocturnal sleep
- Assess perceived consequences of sleeplessness and attributions of daytime function and health to sleep

- Sleep diary
  - Is the patient actually sleepy at bedtime
  - Napping and dozing during the day or evening
  - Level of anxiety regarding sleeplessness
  - Clock-watching
  - Nocturnal environmental disturbances (e.g. children, pets, bed partner, electronics)
  - Expectations:
    - Sleep onset time
    - Number of awakenings
    - Total sleep time, age appropriate

Treatment Goals

- Primary Goals:
  1. Improvement in sleep quality and/or time.
  2. Improvement of daytime impairment
- Secondary Goals:
  - Improvement in an insomnia symptoms:
    - **WASO <30 minutes and/or**
    - SOL <30 minutes and/or
    - Decreased frequency of awakenings or other sleep complaints
    - TST > 6 hours and/or sleep efficiency > 80% to 85%.
  - Positive association between bed and sleeping
  - Improvement in sleep-related psychological distress

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Sleep Hygiene

Sleep Hygiene

Cognitive-Behavioral Therapy for Insomnia (CBT-I)

CBT:

- Changing thoughts, changes emotions, which changes actions
- Recognize and change beliefs
- Control or eliminate negative thoughts and worries

CBT-I techniques:

- Stimulus control therapy
- Sleep restriction
- Sleep hygiene
- Sleep environment improvement
- Relaxation training
- Remaining passively awake
- Biofeedback

American Academy of Sleep Medicine (AASM):

- Certification in Behavioral Sleep Medicine
- Not widely available
- Often group therapy settings

Outcomes by Intervention.

	TST	SL	WASO	QOS
Diphenhydramine	✓	✓	✓	✓
Doxepine	✓	✓	✓	✓
Eszopiclone	✓	✓	✓	✓
Melatonin		✓		✓
Ramelteon		✓		✓
Suvorexant	✓	✓	✓	✓
Temazepam	✓	✓	✓	✓
Tiagabine	✓		✓	✓
Trazodone	✓	✓	✓	✓
Triazolam		✓		✓
Tryptophan		✓	✓	✓
Valerian-hops		✓		✓
Zaleplon	✓	✓		✓
Zolpidem	✓	✓	✓	✓

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Melatonin		✓		✓
Ramelteon		✓		✓
Suvorexant	✓	✓	✓	✓
Temazepam	✓	✓	✓	✓
Tiagabine	✓		✓	✓
Trazodone	✓	✓	✓	✓
Triazolam		✓		✓
Tryptophan		✓	✓	✓
Valerian-hops		✓		✓
Zaleplon	✓	✓		✓
Zolpidem	✓	✓	✓	✓

Suvoxerant (Belsoma®)

- Class: Orexin receptor antagonist
  - Orexin plays a role in wakefulness
- FDA indication: Sleep onset, WASO
- WASO: Mean reduction was 16–28 min greater, compared to placebo
- Contraindication: narcolepsy
- Dosage: 10 mg start, 20 mg max, 30 min prior to HS
- ADE: daytime somnolence
- Drug Interactions: CYP3A4 inhibitors or inducers; digoxin
- AASM recommendation: Tx for WASO (versus no treatment) in adults
  - Benefits outweigh risks

Doxepin (Silenor®, Sinequan®)

- Class: Tricyclic antidepressant
  - Histamine H_1 receptor antagonist
- FDA indication: Sleep onset, WASO
- WASO: Mean reduction was 22–23 min greater, compared to placebo
- Contraindication: Hypersensitivity, MAO inhibitors, narrow-angle glaucoma, urinary retention
- Dosage:
  - Initial: Elderly 3 mg HS, adults 6 mg HS, 30 min prior
  - Off-label: 10-25 mg HS
- ADE: “Sleep-driving”, hallucinations, worsening depression/suicidality, CNS depressant effects, worsening of sleep apnea
- Drug Interactions: MAO inhibitors, alcohol, CNS depressants
- AASM recommendation: treatment for WASO (versus no treatment) in adults
  - Benefits outweigh harms

Eszopiclone (Lunesta®)

- Class: Nonbenzodiazepine hypnotic
  - Probably works at benzodiazepine receptors
- FDA indication: Sleep onset, WASO
- WASO: Mean reduction was 10–14 min greater, compared to placebo
- Contraindication: hypersensitivity
- Dosage:
  - Initial: 1 mg HS; increased to 2-3 mg if needed (max dose: 3 mg daily)
  - Debilitated patients: Initial: 1 mg HS (max dose: 2 mg)
  - Concurrent use with strong CYP3A4 inhibitor: Initial: 1 mg HS (max dose: 2 mg)
  - Avoid in geriatric
- ADE: unpleasant taste, headache, somnolence
  - Abnormal behavior, depression/suicidality, withdrawal
- Drug Interactions: CNS depressants, rifampin (decrease effects), ketoconazole (increase blood levels)
- AASM recommendation: Tx for sleep onset and WASO
  - Benefits outweigh harms

Zolpidem (Ambien®, Ambien CR®, Edluar®, Intermezzo®, Zolpimist®)

- Class: Benzodiazepine (BZ_1) receptor agonist
  - Enhances GABA selectively at
- FDA indication: Sleep onset, WASO
- WASO: Mean reduction was 25 min greater, compared to placebo
- Contraindication: hypersensitivity, complex sleep behaviors while on zolpidem
- Dosage: start with lower doses in females
  - ER tablet: Initial: 6.25-12.5 mg HS ≥7 to 8 hours of planned sleep before waking. Use lowest effective dose, not to exceed 12.5 mg.
  - IR tablet, spray, sublingual tablet (off-label use): Initial: 5 mg (females) or 5 to 10 mg (males) HS immediately before bedtime with ≥ 7 to 8 hours of planned sleep before waking. Use lowest effective dose, not to exceed 10 mg.
  - IR sublingual tablet: 1.75-3.5 mg once per night upon awakening in the middle of the night with ≥ 4 hours of planned sleep remaining.
- ADE: Sleep driving, sleep eating, headache, CNS
- Drug Interactions: many
- AASM recommendation: sleep onset and sleep maintenance insomnia (versus no treatment) in adults
  - Benefits outweigh harms

Trazodone

- Class: Antidepressant, Serotonin Reuptake Inhibitor/Antagonist
  - Probably acts at histamine H_1 receptors
- FDA indication: Major depressive disorder (unipolar)
  - Off-label: insomnia
- WASO: Mean reduction was 8 min greater, compared to placebo
- Contraindication: hypersensitivity, MAO inhibitors, linezolid or IV methylene blue
- Dosage: 50-100 mg HS
- ADE: Drowsiness, dizziness, headache, nervousness, fatigue, xerostomia, nausea and vomiting, blurred vision
- Drug Interactions: a lot
- AASM recommendation: not use for sleep onset or maintenance
  - Harms outweigh benefits

Diphenhydramine

- Class: H_1 receptor antagonists
- FDA indication: Allergies, sleep onset, sleep maintenance, anxiety
- Off-label: many
- WASO: (diphenhydramine) Mean improvement was 12 min longer, compared to placebo
- Contraindication:
  - Hypersensitivity to diphenhydramine, other structurally related antihistamines, or any component of the formulation; neonates or premature infants; breast-feeding
  - OTC labeling: When used for self-medication, do not use in children < 6 years, **to make a child sleep**, or with any other diphenhydramine-containing products (including topical products)
- Dosage: 25-50 mg HS
- ADE: anticholinergic
- Drug Interactions: many
- AASM recommendation: Not use
  - Harms outweigh benefits

Tiagabine (Gabitril®)

- Class: Anticonvulsant
  - Probably enhances activity of GABA
- FDA indication: Adjunct for partial seizures
  - Off-label for insomnia
- WASO: Mean reduction was 1–9 min greater, compared to placebo
- Contraindication: hypersensitivity (long list of warnings)
- Dosage:
- ADE: Dizziness, drowsiness, nervousness, lack of concentration, nausea, weakness, tremor
  - Miscellaneous: Accidental injury
- Drug Interactions: CNS depressants, CYP3A4 inducers and inhibitors (long list)
- AASM recommendation: not use tiagabine as a treatment for sleep onset or sleep maintenance insomnia (versus no treatment) in adults
  - Harms outweigh benefits

Benzodiazepines

- Temazepam
  - WASO: indicated for sleep maintenance, but no data showing improvement
- Triazolam
  - WASO: no data
- AASM: Not recommended for WASO
  - Harms approx. equal to benefits

Questions

- andersond@Cedarville.edu
- https://calendly.com/andersond/cpfi-waso-discussion

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Guidelines and References

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