NEUROLOGY AND PSYCHIATRY MEDICATIONS THAT HAVE EFFECTS ON SLEEP

NICOLE BARYLSKI DANNER DO, FACN

DISCLOSURE STATEMENT

- Nicole Barylski Danner DO, FACN
- No financial disclosures or conflicts.

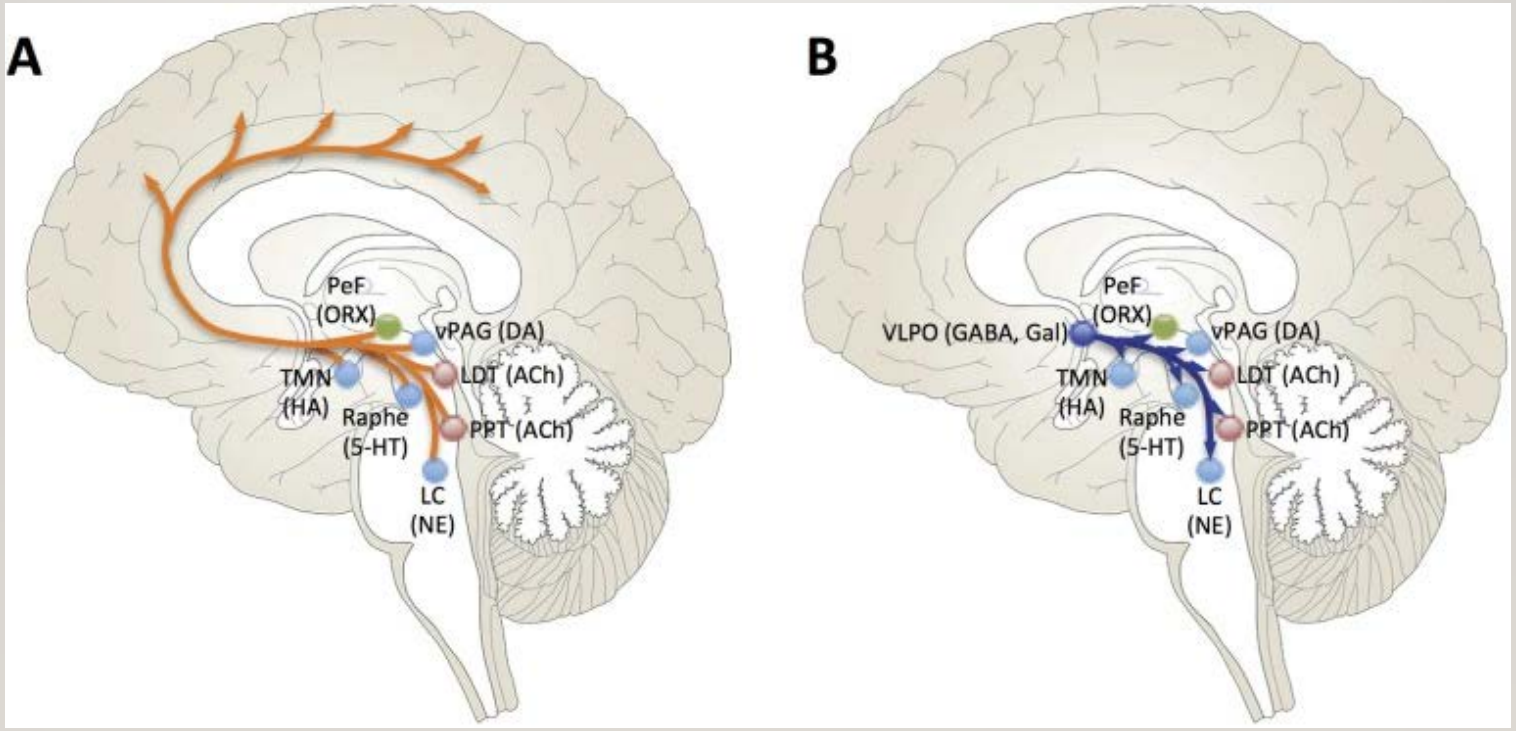
OBJECTIVES

- Be familiar with sleep wake pattern.
- Know different medications used for insomnia.
- Identify different classes of insomnia medications.
- Review the special warnings in elderly with insomnia medications.

SLEEP/WAKE CYCLE

- Sleep/wake cycle is a delicate balance affected by:
  - Multiple different hormones/neurotransmitter and pathways
  - Light and environment
  - Behaviors/schedules/sleep hygiene
  - Medications (CNS stimulants & depressants)
- Arousal:
  - "Ascending arousal system"
    - Excitatory ***norepinephrine*** arising from the locus ceruleus (LC)
    - ***Serotonin*** from the midline raphe nuclei
    - ***Histamine*** from the tuberomammillary nucleus
    - Dopamine from the ventral periacqueductal gray matter
    - Acetylcholine from the pedunculopontine tegmentum and the laterodorsal tegmentum of the pons
    - Orexin from the perifornical area

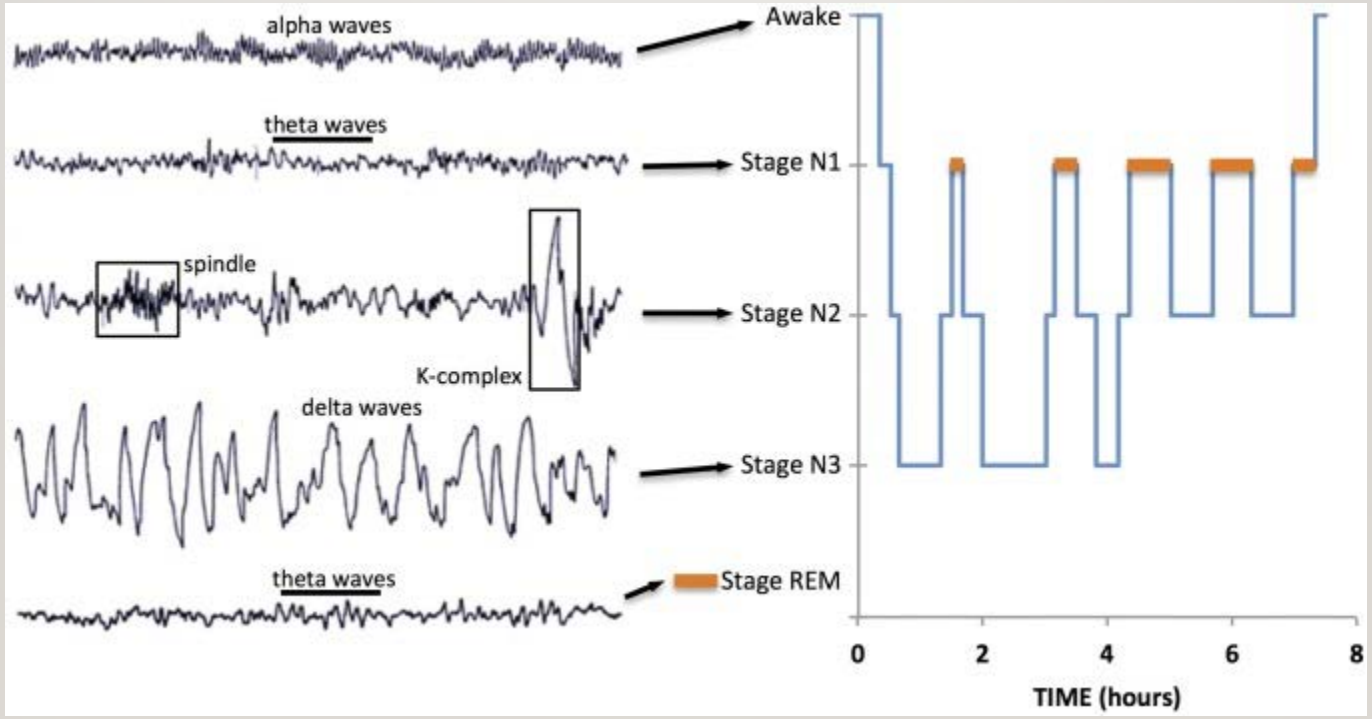
SLEEP PATHWAYS



SLEEP PATHWAYS

- Initiation and maintenance of sleep:
  - Suppression of activity in the ascending arousal systems due to inhibitory neurons of the ventrolateral pre-optic area: VLPO
    - Accumulation of adenosine may be responsible for activating the VLPO
    - The VLPO receives important circadian modulation from the suprachiasmatic nucleus resulting in the central circadian clock
  - Sleep stages
    - Non-REM: N1, N2, slow wave sleep
    - REM sleep

SLEEP STAGES



SLEEP PATHWAYS

- Process S is the homeostatic drive for generating sleep
  - The need for sleep accumulates across the day, peaks just before bedtime at night and dissipates throughout the night.
  - Sleep process S is regulated by neurons that shut down the arousal systems, thus allowing the brain to fall asleep.
    - Found in the preoptic area of the hypothalamus and turn off the arousal systems during sleep.
      - Loss of these nerve cells causes profound insomnia
      - There are inputs from the circadian system that allow the wake-sleep system to synchronize with the external day-night cycle, but also to override this cycle when it is necessitated by environmental needs.
    - Neurons in the pons intermittently switch from NREM to REM sleep over the course of the night and send outputs to the lower brainstem and spinal cord that cause muscle atonia, rapid eye movements, and chaotic autonomic activity that characterize REM sleep.

SLEEP PATHWAYS

- Process C is wake promoting and is partially regulated by the circadian system.
  - Builds across the day, serving to counteract process S and promote wakefulness and alertness.
  - Wake-promoting system begins to decline at bedtime, serving to enhance sleep consolidation

WAKE GENERATING

- Wakefulness is generated by an ascending arousal system from the brainstem that activates forebrain structures to maintain wakefulness with two major pathways that originate in the upper brainstem.
  - First pathway, which takes origin from cholinergic neurons in the upper pons, activates parts of the thalamus that are responsible for maintaining transmission of sensory information to the cerebral cortex.
  - Second pathway has groups of cells in the upper brainstem that contain the monoamine neurotransmitters (norepinephrine, serotonin, dopamine, and histamine) and enters the hypothalamus, rather than the thalamus, where it picks up inputs from nerve cells that contain peptides (orexin or hypocretin and melanin-concentrating hormone).
    - These inputs then traverse the basal forebrain, where they pick up additional inputs from cells containing acetylcholine and gamma-aminobutyric acid.
    - All of these inputs enter the cerebral cortex, where they diffusely activate the nerve cells and prepare them for the interpretation and analysis of incoming sensory information.

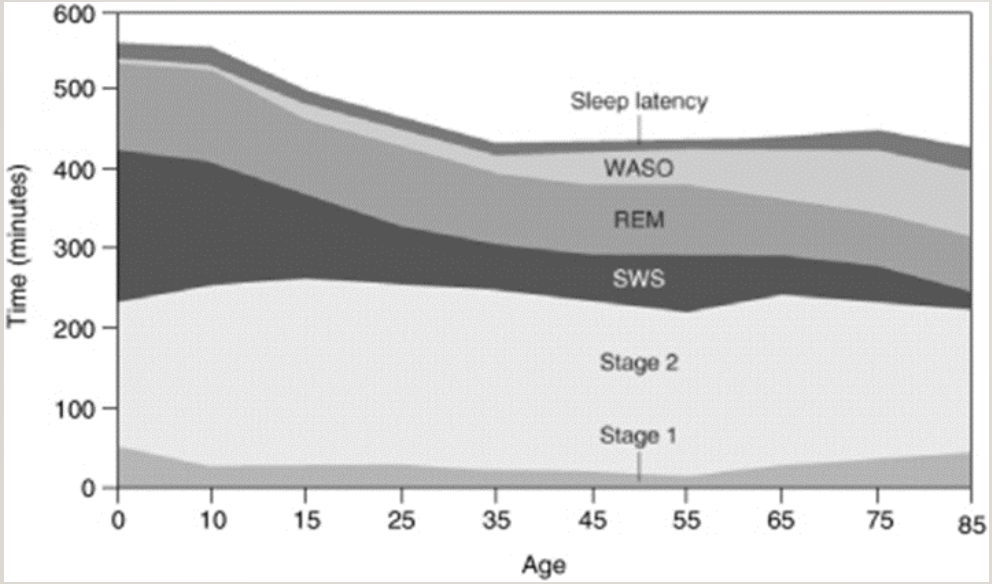
CIRCADIAN RHYTHM

- Circadian Rhythm is the daily rhythms in physiology and behavior.
  - Control the sleep-wake cycle, modulate physical activity and food consumption, and over the course of the day regulate body temperature, heart rate, muscle tone, and hormone secretion.
  - Rhythms are generated by neural structures in the hypothalamus that function as a biological clock
  - The circadian rhythm also contributes to many aspects of cellular function, including glucose and lipid metabolism (leptin and ghrelin secretion), signal transduction, secretion and oxidative metabolism

SCN

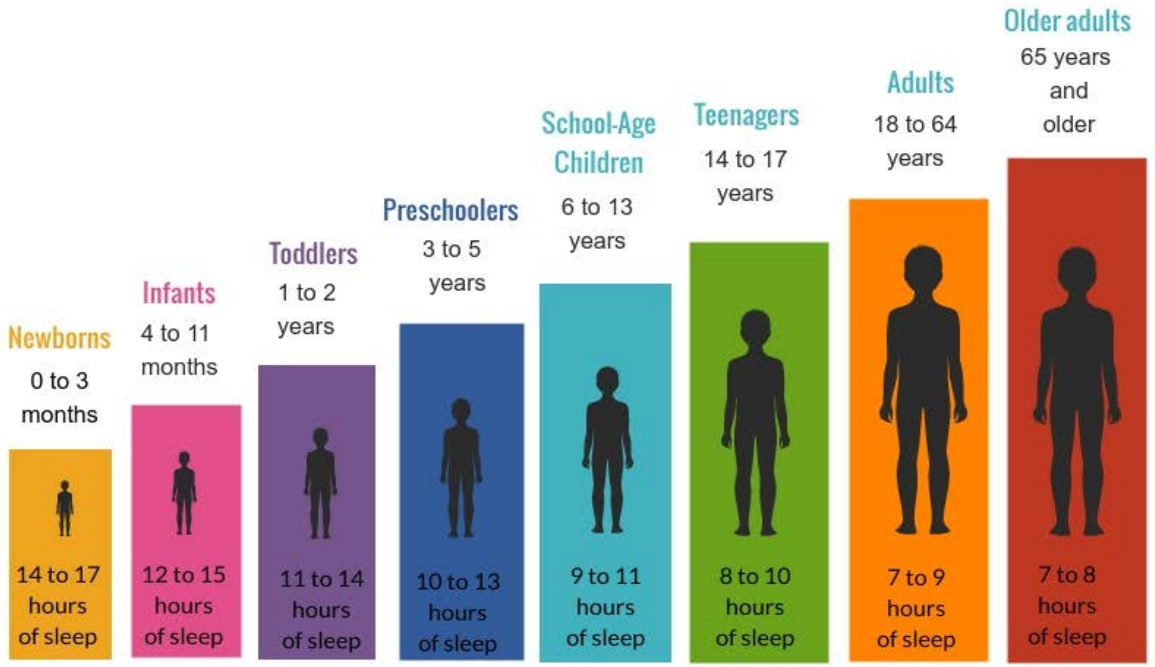
- The suprachiasmatic nucleus is responsible for regulating circadian rhythms in all organs.
  - Receives direct inputs from a class of nerve cells in the retina that act as brightness detectors
  - The main influence of the SCN on sleep is due to a series of relays through the dorsomedial nucleus of the hypothalamus, which signals to the wake-sleep systems to coordinate their activity with the day-night cycles.
  - SCN coordinates cycles of feeding, locomotor activity, and hormones, such as corticosteroids
  - SCN connected to a pathway that controls the secretion of melatonin in the pineal gland
    - Melatonin is mostly secreted at night and acts to further consolidate the circadian rhythms but has only limited effects directly on sleep.

SLEEP CHANGES WITH AGE



Time (in minutes) for sleep latency, amount of time spent awake after initially falling asleep (WASO), rapid eye movement (REM), non-rapid eye movement (NREM), stages 1, 2, and slow-wave sleep (SWS).

Recommended Amount of Sleep by Age



Source: National Sleep Foundation

SIMPLY GOOD SLEEP
https://simplygoodsleep.com


WHAT CAUSES INSOMNIA?
CROSSING TIME ZONES
BLUE LIGHT
STRESS
ALCOHOL, SMOKING OR CAFFEINE
HEAVY FOOD
MEDICINES
ENVIRONMENTAL FACTORS
UNCOMFORTABLE BED OR PILLOW
03:21

INSOMNIA

- Diagnostic criteria for insomnia include difficulty getting to sleep or staying asleep and results in daytime dysfunction in a patient who has an adequate opportunity to sleep.
  - Short-term if symptoms occur for less than 3 months
  - Chronic if symptoms occur 3 or more times per week for 3 months or longer
  - Often precipitated by a significant life stressor (eg, acute pain, traumatic event)
- Insomnia can occur as a primary sleep disorder, a symptom of another sleep disorder (eg, obstructive sleep apnea [OSA], restless legs syndrome [RLS]), periodic leg movements during sleep [PLMS]), or a comorbid sleep disorder.

INSOMNIA

- Insomnia is defined as dissatisfaction with sleep quantity or quality that results in clinically significant distress or impairment in social, occupational, or other important areas of functioning.
  - Associated with one or more of the following symptoms:
    - difficulty initiating sleep (sleep-onset insomnia or initial insomnia);
    - difficulty maintaining sleep (sleep-maintenance insomnia or middle insomnia);
    - and early-morning awakening with the inability to return to sleep (late insomnia).

INSOMNIA

- 50 million to 70 million adults in the U.S. have chronic sleep and wakefulness disorders
- Insomnia is more common in women (25%) than in men (18%)
  - Increases with age, affecting approximately 50% of the elderly population
  - 62% of adults in the U.S. slept seven to eight hours
  - 28% slept six or fewer hours in a 24-hour period
  - 4% of U.S. adults 20 years of age and older reported that they had taken prescription sleep aids during the previous 30 days

35%

of the adult population struggles with insomnia

40%

of the 35% of insomnia sufferers also have a mental health disorder (anxiety, depression, bipolar disorder, etc)

That means over 35 million people have comorbid insomnia and mental health disorders in the United States alone.

Insomnia can actually make mood and anxiety disorder symptoms worse. People with comorbid insomnia and depression have a higher risk for suicide.

Schwab, R. J. (2020, June). Insomnia: Difficulty Falling Asleep: Sleep Disorders: Manual Home Edition - Brain, Spinal Cord, and Nerve Disorders. Retrieved July 20, 2020. https://www.msdmanuals.com/home/brain,-spinal-cord,-and-nerve-disorders/sleep-disorders/insomnia-and-excessive-daytime-sleepiness-eds

Neckelmann, D., Mykletun, A., & Dahl, A. A. (2007). Chronic insomnia as a risk factor for developing anxiety and depression. Sleep, 30(7), 873–880. https://doi.org/10.1093/sleep/30.7.873

Ağargün, M. Y., Kara, H., & Solmaz, M. (1997). Sleep disturbances and suicidal behavior in patients with major depression. The Journal of clinical psychiatry, 58(6), 249–251. https://doi.org/10.4088/jcp.v58n0602

INSOMNIA

- Insomnia as a disorder of hyperarousal that manifests as hypervigilance during the day and difficulty initiating and maintaining sleep at night.
  - hyperarousal may result from chronic activation of the neuroendocrine system's stress response
    - Higher levels of urinary free cortisol in poor sleepers
    - Higher levels of both cortisol and adrenocorticotropic hormone (ACTH) in insomniacs suggest that the HPA axis is associated with the pathology of chronic insomnia
    - Dysregulation of corticotropin-releasing factor (CRF) has also been implicated in hyperarousal seen in primary insomnia
- Comorbid medical conditions can contribute to insomnia
  - obstructive sleep apnea, fibromyalgia, restless legs syndrome, cardiovascular diseases, diabetes, arthritis, migraine, asthma, chronic obstructive pulmonary disease, and chronic pain

INSOMNIA

- Basic types
  - Acute insomnia:
    - Results from a triggering causal factor that is easily identifiable in an individual who has not had insomnia before and does not last longer than four months
  - Primary chronic insomnia:
    - May be caused by several predisposing (genetic and constitutional) factors, including hyperactivity of stress response mechanisms or of the HPA axis; anxiety and depression; and abnormalities in the circadian rhythm (circadian sleep-wakefulness control).
      - Precipitating and perpetuating factors, such as psychosocial features (e.g., fatigue and irritability), behavioral changes, and cognitive characteristics
  - Associated insomnia
    - Primarily related to an underlying mental or mood disorder, such as depression, dysthymia, cyclothymia, bipolar disorder, anxiety, or schizophrenia.
    - May also be caused by inadequate sleep hygiene, such as psychologically stressful activities, caffeine/stimulants, nicotine, alcohol, or heavy meals; or vigorous physical activity near bedtime

INSOMNIA

- Other classifies insomnia
  - Episodic
    - lasting at least one month but less than three months
  - Persistent
    - lasting three months or longer
  - Recurrent
    - two or more episodes within one year

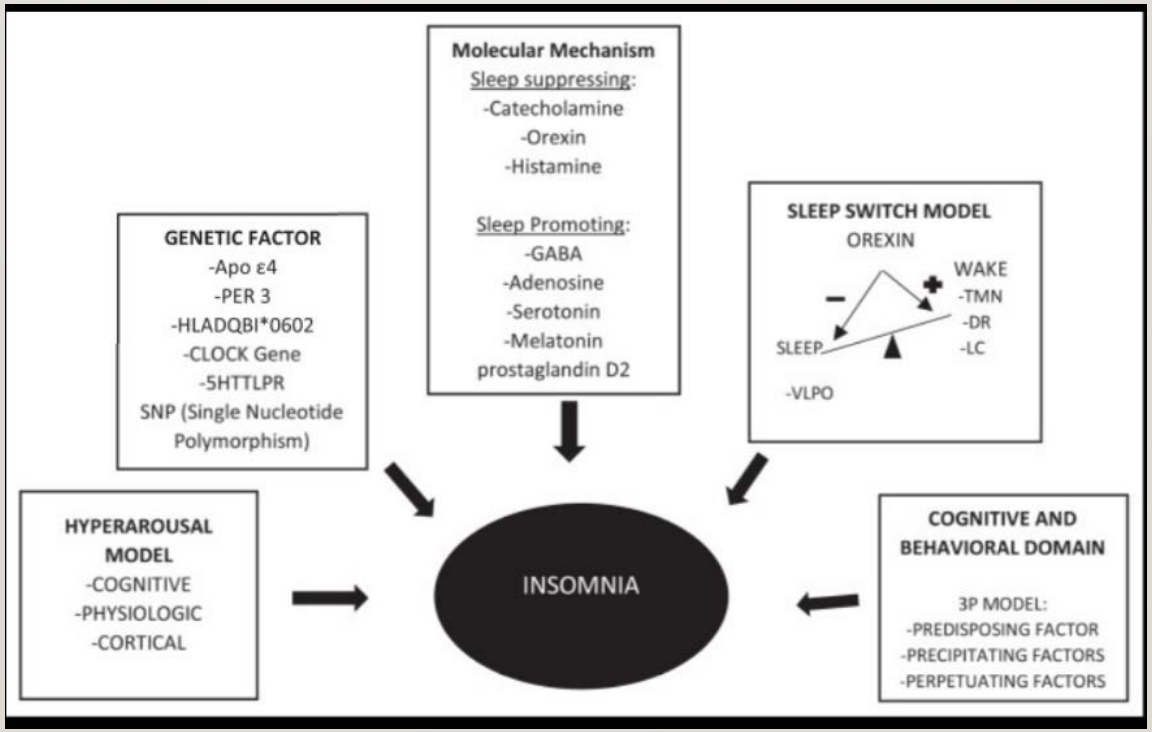
INSOMNIA

- Diagnosis :
  - At least one of the following complaints for at least three nights per week
    - Difficulty initiating and/or maintaining sleep
    - Sleep that is poor in quality
    - Trouble sleeping despite adequate opportunity and circumstances for sleep
    - Waking up too early

INSOMNIA

- Also results in different types of daytime impairment:
  - Attention
  - Concentration
  - Memory impairment
  - Concerns or worries about sleep
  - Daytime sleepiness
  - Errors or accidents at work or while driving
  - Fatigue or malaise; gastrointestinal symptoms
  - Lack of motivation
  - Mood disturbance or irritability
  - Social or vocational dysfunction or poor school performance
  - Tension headaches

INSOMNIA


Molecular Mechanism
Sleep suppressing:
-Catecholamine
-Orexin
-Histamine
Sleep Promoting:
-GABA
-Adenosine
-Serotonin
-Melatonin
prostaglandin D2
GENETIC FACTOR
-Apo ε4
-PER 3
-HLADQBI*0602
-CLOCK Gene
-5HTTLPR
SNP (Single Nucleotide Polymorphism)
SLEEP SWITCH MODEL
OREXIN
WAKE
-TMN
-DR
-LC
SLEEP
-VLPO
HYPERAROUSAL MODEL
-COGNITIVE
-PHYSIOLOGIC
-CORTICAL
INSOMNIA
COGNITIVE AND BEHAVIORAL DOMAIN
3P MODEL:
-PREDISPOSING FACTOR
-PRECIPITATING FACTORS
-PERPETUATING FACTORS

TREATMENT

- Treatment has two primary objectives:
  - Improving sleep quality and quantity
  - Improving daytime impairments
- Initial approaches to treatment
  - Behavioral intervention, such as stimulus control therapy or relaxation/meditation therapy. Biofeedback therapy is also used
  - Adequate sleep hygiene and sleep schedules
  - Control of other co-morbidities
  - Pharmacotherapy
  - Stop electronics before bed and none in bedroom

PHARMOCOTHERAPY

- Initiating medications:
  - Short- or intermediate-acting benzodiazepine receptor agonists (BzRAs) or the melatonin agonist.
  - Alternative short- or intermediate-acting BzRAs or melatonin agonist if the initial agent was ineffective.
  - Sedating antidepressants (e.g., trazodone, amitriptyline, doxepin, or mirtazapine).
  - The combination of a BzRA or melatonin agonist with a sedating antidepressant.
  - Other sedating agents, such as atypical antipsychotics.

  - Unfortunately some is based on what insurances will cover!!!!!

BENZODIAZAPINE RECEPTOR AGONISTS

- Includes both benzodiazepine (BZD) and non-BZD agents
  - These drugs bind to the gamma aminobutyric acid (GABAA) receptor complex, they differ in their affinity for binding sites
    - BZDs have similar selectivity for alpha subunits 1, 2, 3, and 5
    - Non-BZDs bind more selectively to the alpha 1 subunit
      - The various subunits of the GABAA receptors are responsible for the sedative–hypnotic, muscle-relaxant, anxiolytic, and anticonvulsant effects of the BzRAs
      - The selectivity of non-BZDs for the alpha 1 subunit is believed to result in fewer adverse effects on the central nervous system (CNS) and in a reduced potential for abuse compared with BZDs
  - BZDs are FDA-approved for the treatment of insomnia and all are Schedule IV controlled substances
    - Triazolam/Halcion = short acting
    - Estazolam/ProSom = intermediate acting
    - Temazepam/Restoril= intermediate acting
    - Quazepam/Doral = long acting
    - Flurazepam = long acting
    - Clonazapam/Klonipin = intermediate for PLMD, parasomnias, REM behavior do
  - Choice of drug is based on the desired onset and duration of action.
  - Can develop tolerance to the sedative effects of BZDs; therefore, long-term use of these drugs is not recommended

ELDERLY BEERS AND BLACK-BOX WARNING

- BZDs should be avoided in elderly patients because of the potential for cognitive impairment, delirium, falls, and fractures
  - Demented patient may have the reciprocal effect

NONBENZODIAZAPINES

- Non-BZDs aka "Z drugs"
  - Created to minimize the adverse effects and abuse potential associated with BZDs
    - Zolpidem (Ambien/Intermezzo/ZopiMist): IR, CR, SL, oral spray
      - Tx for sleep onset, maintenance and quick acting
      - Treatment-emergent adverse events, such as drowsiness, nausea, dizziness, nightmares, parasomnias, anterograde amnesia and agitation = DC drug.
      - CYP3A inhibitors may increase concentration of Zolpidem
      - New data had shown that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving and dose should be lowered
    - Eszopiclone (Sonata)
      - Sleep onset with rapid onset of action and significantly shorter duration of action or for middle of the night treatment
      - HA and dizziness most common SE
      - High fat or heavy meals may affect absorption

NONBENZODIAZAPINES

- Non-BZDs aka "Z drugs"
  - Eszopiclone (Lunesta)
    - Approved for the long-term treatment of insomnia
    - Longer acting so has affect on both sleep onset and sleep maintenance insomnia
      - should be used only in patients who can have at least seven to eight hours of sleep
    - Side Effects: unpleasant taste, headache, somnolence, and dizziness
    - Heavy meals may affect absorption
    - Warning that could impair driving the next day

MELATONIN AGONIST

- Remelteon (Remeron)
  - Sleep onset insomnia
    - Short half life so not for sleep maintenance insomnia
  - Targets MT1 and MT2 receptor agonist and does not have an affinity for GABA receptors therefore no potential for abuse
  - Side Effects: dizziness, nausea, and fatigue
    - Does not affect patients' balance, thereby reducing the risk of falls
    - Not associated with cognitive or psychomotor effects
  - Large meal will affect absorption

TRICYCLIC ANTIDEPRESSANTS

- Doxepin (Silenor)
  - High affinity for histamine (H1) receptors
  - Sleep maintenance
  - Side Effects are Headache and somnolence
  - Lower dose for sleep than depression so lesser side effects
  - High fat meal affects absorption
- Amitriptyline (Elavil), Nortriptyline (Pamelor)
  - Not FDA approved for sleep but can still have affect
  - Best when used for dual purpose: HA, Nerve pain
- TCA SE: anticholinergic effects, orthostatic hypotension, and slowed cardiac conduction (prolonged QT interval)
  - Caution with elderly or cardiac arrhythmia patients

ATYPICAL ANTIPSYCHOTICS

- Quetiapine (Seroquel), olanzapine (zyprexa), and risperidone (Risperdal):
  - Antagonistic effects on multiple neurotransmitter systems, particularly serotonin and histamine receptors
  - Best with co-morbid psychiatric conditions
  - Black-box warning (be sure to document)

BARBITUATES

- As a class are approved for treatment of insomnia but not highly recommended
  - High abuse rate
  - Potential for fatal overdose

OREXIN RECEPTOR ANTAGONIST

- Survorexant (Belsomra)
  - Schedule IV drug
  - Longer half life
  - Both sleep onset and sleep maintenance insomnia
  - Lower chance for abuse
  - Avoid with CYP3A inhibitors

OFF LABEL TREATMENTS

- Trazodone:
  - Modulating effect on serotonin receptor with a hypnotic effect
  - Low doses 50-100mg
- Mirtazipine (Remeron):
  - member of the piperazinoazepine group of compounds with sedation properties
    - potent antagonistic effects on histamine (H1) receptors
- Muscle Relaxers (Tizanadine/Zanaflex, Cyclobenzaprine/Flexeril)
  - Side effect of drowsiness

OTC MEDICATIONS

- Antihistamines:
  - Diphenhydramine (Benadryl) and doxylamine (Unisom)
  - PM preparations usually have Diphenhydramine as the sedating medication in them
  - Clinical use of these medications for insomnia has little supporting data
    - Easy to build tolerance
    - Only minimally effective in inducing sleep, may reduce sleep quality, and may cause residual drowsiness - the use of these drugs in insomnia patients is not recommended
    - Can cause confusion in the elderly/demented patient
    - Antihistamines are associated with potent anticholinergic effects, such as dry mouth, constipation, and confusion
    - Can be Seizure-genic in seizure patients

OTC MEDICATIONS

- Melatonin
  - Pineal gland hormone that typically treats jet-lag, shift work and delayed phase sleep syndrome
  - Has been associated with modest improvements in sleep and daytime parameters, including sleep latency, sleep quality, and morning alertness after 3 weeks of treatment for up to 6 month
  - No robust data on short term acute insomnia
  - High dose before bedtime as a sedative vs low-moderate dose 3-6 hours before bedtime to induce sleep

HERBAL MEDICATIONS

- Valarian root
  - Valeriana officinalis root
    - Interacts with GABA-ergic neurotransmission, thereby producing a sedative effect
    - No reliable data that is works
- Kava
  - Piper methysticum which is a shrub cultivated in the Pacific islands
    - Act on both GABA and BZD binding sites causing sedation along with acting as an anticonvulsant, antispasmodic, and central muscular-relaxant effects
    - Has also been used to treat anxiety, stress, and restlessness—major causes of chronic insomnia.
    - Has lack of clinical evidence
    - Have been cases of severe liver injury

NEW MEDICATION

- Daridorexant (Quviviq)
- Dual orexin receptor antagonists (DORAs)
  - Improves sleep and daytime functioning.
  - Binds to both orexin receptors, the orexin 1 (OX1R) and 2 receptor (OX2R)
    - Binds to and dissociates from orexin receptors rapidly, inhibits the actions of the wake-promoting orexin (also called hypocretin) neuropeptides.
    - avoids a more widespread inhibition of neuronal pathways and associated side effects that are intrinsic to positive GABA-A receptor modulators
  - Side Effects
    - Worsening depression and suicidal thoughts
    - Sleep paralysis
    - Parasomnias
    - Sedation
    - Headache
  - Schedule IV controlled substance

NEW MEDICATION

- Lemborexant (Dayvigo)
  - Also DORAs
    - Binds to the orexin 1 (OX1R) and 2 receptor (OX2R), with stronger inhibitory effects on OX2R
      - Improves sleep initiation and maintaining sleep
      - Lax of daytime sedation
    - Side Effects
      - Mental/mood changes: depression, hallucinations, suicidal ideation
      - Temporary weakness in the legs.
      - Sleep paralysis
      - Parasomnia

META-ANYLYSIS

- Meta-analysis of 154 placebo-controlled randomized trials of 30 different medications for insomnia in nearly 45,000 participants, of which only five trials were longer than four weeks, and nearly all comparisons relied on indirect evidence and a small subset of the total number of trials
  - Concluded that eszopiclone (Lunesta), a benzodiazepine receptor agonist (BZRA), and Lemborexant (Dayvigo), a dual orexin receptor antagonist (DORA), appeared to be the most favorable medications for overall efficacy and tolerability
    - There was no long term data
    - Some limitation due to known adverse effects of BZRAs

BEERS CRITERIA

- Objective is to improve care of older adults by reducing "potentially inappropriate medication"
- Quality of evidence
  - High
    - Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (≥ 2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects)
  - Moderate
    - Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (≥ 1 higher-quality trial with > 100 participants; ≥2 higher-quality trials with some inconsistency; ≥2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence
  - Low
    - Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes

BEERS

- Strength of recommendation
  - Strong:
    - Benefits clearly outweigh risks and burden OR risks and burden clearly outweigh benefits
  - Weak:
    - Benefits finely balanced with risks and burden
  - Insufficient:
    - Insufficient evidence to determine net benefits or risks

BEERS

- TCAs, alone or in combination:
  - Highly anticholinergic, sedating, and cause orthostatic hypotension; safety profile of low-dose doxepin (≥ 6 mg/d) is comparable with that of placebo
    - Avoid High Strong
- Antipsychotics, first (conventional) and second (atypical) generation
  - Increased risk of cerebrovascular accident (stroke) and mortality in persons with dementia
    - Avoid use for behavioral problems of dementia unless nonpharmacological options have failed and patient is threat to self or others
      - Avoid Moderate Strong

BEERS

- Barbiturates
  - High rate of physical dependence; tolerance to sleep benefits; risk of overdose at low dosages
    - Avoid High Strong
- Benzodiazepines
  - Older adults have increased sensitivity to benzodiazepines and slower metabolism of long-acting agents. In general, all benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents in older adults
    - Avoid for treatment of insomnia, agitation, or delirium High Strong

BEERS

- Nonbenzodiazepine hypnotics/Z-drugs
  - Benzodiazepine-receptor agonists that have adverse events similar to those of benzodiazepines in older adults (e.g., delirium, falls, fractures); minimal improvement in sleep latency and duration
    - Avoid chronic use (> 90 days) Moderate Strong
- Skeletal muscle relaxants
  - Most muscle relaxants are poorly tolerated by older adults because of anticholinergic adverse effects, sedation, risk of fracture; effectiveness at dosages tolerated by older adults is questionable
    - Avoid Moderate Strong
- Oral decongestants
  - CNS stimulant effects
    - Avoid Moderate Strong

BLACK BOX WARNING

- Highest safety-related warning that medications can have assigned by the Food and Drug Administration.
  - Intended to bring the consumer's attention to the major risks of the drug. Medications can have a boxed warning added, taken away, or updated throughout their tenure on the market
    - Over 400 different medications currently have boxed warnings.
    - Atypical Antipsychotics:
      - Increased risk of falls, stroke and death

****Document, document, document….be sure to document that you have discussed the black box warning and/or the risk benefit ratio and that the risk was worth the benefit and agreed upon by the patient/family.*****

CO-MORBIDITIES

- PSG is not indicated for insomnia alone but may be beneficial to assess for other sleep issues : OSA, PLMD etc
- Sleep/sedating medication can worsen OSA
  - Need to be compliant with OSA treatment
- Alcohol abuse
  - Do not mix sleep meds with alcohol
- Other drugs
  - ? Effects with other drugs – Marijuana or other CNS depressants
- Polypharmacy
  - Most meds are affected by CYP3a4 inhibitors that can increase the plasma concentration of the drug increasing sedation and risk of SE
    - Fluconazole

The true insomniac is a sleep doctor's nightmare.

May require a combination of different meds along with behavioral changes and CBT to treat.

Unrealistic expectations.

Start low go slow and add as tolerated.

THE GOOCH & CZAR

QUESTIONS

REFERENCES

- Dopheide JA. Insomnia overview: epidemiology, pathophysiology, diagnosis and monitoring, and nonpharmacologic therapy. Am J Manag Care. 2020 Mar;26(4 Suppl):S76-S84. doi: 10.37765/ajmc.2020.42769. PMID: 32282177.
- Ramakrishnan K, Scheid DC. Treatment options for insomnia. Am Fam Physician. 2007;76:517–526.
- Wade AG, Ford I, Nir T, Zisapel N. Prolonged release melatonin in the treatment of primary insomnia: evaluation of the age cut-off for short- and long-term response. Curr Med Res Opin. 2011;27:87–98.
- Ziegler G, Ploch M, Miettinen-Baumann A, Collet W. Efficacy and tolerability of valerian extract LI 156 compared with oxazepam in the treatment of non-organic insomnia: a randomized, double-blind, comparative clinical study. Eur J Med Res. 2002;7:480–486.
- Food and Drug Administration Consumer advisory: kava-containing dietary supplements may be associated with severe liver injury. Jun 4, 2014.
- American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012 Apr;60(4):616-31. doi: 10.1111/j.1532-5415.2012.03923.x. Epub 2012 Feb 29. PMID: 22376048; PMCID: PMC3571677.
- Benca RM, Cirelli C, Tononi G. Basic science of sleep. In: Sadock BJ, Sadock VA, Ruiz P, editors. Kaplan and Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2009. pp. 362–375.
- Roth T, Roehrs T, Pies R. Insomnia: pathophysiology and implications for treatment. Sleep Med Rev. 2007;11:71–79

REFERENCES

- Buysse DJ, Tyagi S. Clinical pharmacology of other drugs used as hypnotics. In: Principles and Practices of Sleep Medicine, 6th ed, Kryger MH, Roth T, Dement WC (Eds), Elsevier Saunders, St Louis, MO 2016. p.432.
- https://www.uptodate.com/contents/pharmacotherapy-for-insomnia-in-adults/abstract/3
- Quviviq (daridorexant) prescribing information. https://www.idorsia.us/documents/us/label/Quviviq_PI.pdf.
- https://onlinelibrary.wiley.com/doi/epdf/10.1002/ana.25680
- Roth T, Roehrs T, Pies R. Insomnia: pathophysiology and implications for treatment. Sleep Med Rev. 2007;11:71–79.
- Zammit G, Erman M, Wang-Weigand S, et al. Evaluation of the efficacy and safety of ramelteon in subjects with chronic insomnia. J Clin Sleep Med. 2007;3:495–504.
- Ebbens MM, Verster JC. Clinical evaluation of zaleplon in the treatment of insomnia. Nat Sci Sleep. 2010;2:115–126
- Food and Drug Administration FDA drug safety communication: FDA warns of next-day impairment with sleep aid Lunesta (eszopiclone) and lowers recommended dose. May 15, 2014