Sleep and Insomnia

Everything you wanted to know

Presented by

- Marie Rataj, MSN, APRN, ANP

Objectives

- Develop a basic knowledge of normal sleep and differentiate from abnormal sleep
- Develop basic understanding of insomnia
- Develop basic understanding of insomnia treatments
- Develop a basic knowledge of insomnia medications

Sleep

- Spend one third of our lives asleep
- Dysfunction in sleep causes a decline in quality of life, diminished waking performance, more frequent illness, and increases both morbidity and mortality
- In clinical practice, sleep disorders are rarely addressed or treated

Sleep

Intermediate state between wakefulness and death; wakefulness being regarded as an active state of all the animal and intellectual functions and death as that of their total suspension.

The Physiology of Sleep by Robert NcNishin, 1834

Behavioral Definition of Sleep

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

Sleep States

- Two distinct sleep states
  - NonREM
    - 4 Stages
    - Minimal or fragmentary mental activity
  - REM
    - Activated brain in a paralyzed body

Normal Sleep Progression

- Normal human adults enter sleep through NonREM sleep
- REM sleep does not occur until 80 minutes or longer after sleep onset
- NonREM and REM sleep alternate throughout the night with an approximately 90 minute cycle
- In one night 4-6 sleep cycles are observed
- Average length of the first cycle is 70-100minutes while the following cycles average 90-120 minutes
- Starts with stage 1 for 1-7 minutes, followed by stage 2 for 10-25 minutes, then slow wave sleep (stages 3 and 4) and lasts 20-40 minutes
- REM follows stage 1 and 2 and is short lived in the first cycle of sleep. Duration increases from the first to last sleep cycle with the longest occurring toward the end of normal sleep and may last as long as an hour
- SWS is highest in the first cycle of sleep and REM is more predominant toward the morning hours

Sleep Length

- Varies from person to person and night to night
- Depends on a great number of factors
  - Volitional determinants
    - Staying up late
    - Waking by alarm
  - Genetic determinants
    - Genetic sleep need
  - Circadian rhythms
- Wakefulness in sleep usually accounts for less than 5% of the night

Sleep Stages and Lengths

- Stage 1 – 2-5% of the night
- Stage 2 – 45-55%
- Stage 3 – 3-8%
- Stage 4 – 10-15%
- REM – 20-25%

Factors Modifying Sleep Stage Distribution

- Age
  - Slow wave sleep is highest in young children and decreases markedly with age
  - Slow wave sleep decreases nearly 40% during the second decade
  - By age 60, slow wave sleep may no longer be present especially in men
  - Women appear to maintain SWS later in life than men
  - Arousals during sleep increase markedly with age
    - Extended wake episodes that individuals are aware of as well as brief and unremembered arousals increase with age

Sleep stage Distribution continued

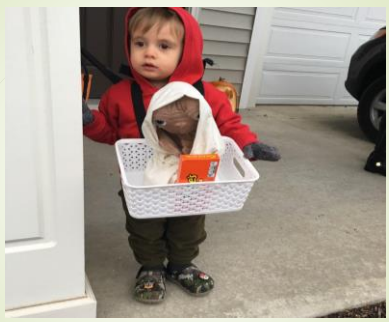
- Prior sleep history
  - One who has experienced sleep loss on one or more nights shows a pattern that favors SWS
  - Chronic restriction of nocturnal sleep, an irregular sleep schedule or fragmented distribution of nocturnal sleep
- Circadian rhythm
  - Shift work
  - Jet lag
- Temperature extremes in sleep environment
  - REM sleep is more sensitive to temperature related disruption than NonREM sleep

Sleep Stage Distribution continued

- Drug ingestion
  - Benzodiazepines suppress REM and has no effect on REM
  - Tricyclic antidepressants, MOA inhibitors and certain SSRI's suppress REM
    - Fluoxetine is associated with REM across all sleep stages
  - Withdrawal from drugs that selectively suppress a stage of sleep tends to be associated with a rebound of that sleep stage
    - Acute withdrawal of Benzo's increase SWS
    - Acute withdrawal of Tricyclic antidepressants increase REM
  - Acute pre-sleep Alcohol increases SWS and REM suppression early in the night which can be followed by REM rebound in the latter portion of the night as Alcohol is metabolized

Sleep Stage Distribution continued

- Pathology
  - Sleep disorders and Non-sleep problems have an impact on structure and distribution of sleep
    - Narcolepsy
    - Sleep Apnea
    - Fragmented sleep due to sleep disorders, medical disorders such as pain, periodic limb movement, chronic fibrositis, Parkinson's, allergic rhinitis, Juvenile Rheumatoid Arthritis



Insomnia

- Defined as a difficulty in initiating or maintaining sleep or of unrefreshing sleep combined with daytime symptoms
- Is a quality of life issue
- Is the most common sleep disorder and is among the most prevalent of all mental health disorders
- Has long been considered a disorder of hyperarousal
- One third of patients with insomnia mention it to their providers and only 5% seek treatment
- 26% of people complain of difficulty falling asleep and 42% complain of difficulty staying asleep at least a few nights a week
- Associated with higher levels of reported cognitive impairment, increased job absenteeism, psychiatric illness, increased accident risks, and higher healthcare costs
- Annual direct costs in the U.S. include $1.97 billion for medications and $11.96 billion for health care services

Diagnostic Criteria

Criteria A-F must be met

A. The patient reports on or more of the following
   1. Difficulty initiating sleep
   2. Difficulty maintaining sleep
   3. Waking up earlier than desired
   4. Resistance to going to bed on appropriate schedule
   5. Difficulty sleeping without parent or caregiver intervention

B. The patient reports one or more of the following related to nighttime sleep difficulty
   1. Fatigue/malaise
   2. Attention, concentration, or memory impairment
   3. Impaired social, family, occupational, or academic performance
   4. Mood disturbance/irritability
   5. Daytime sleepiness

Diagnostic criteria continued

   6. Behavioral problems (e.g., hyperactivity, impulsivity, aggression)
   7. Reduced motivation/energy/ initiative
   8. Proneness for errors/accidents
   9. Concerns about or dissatisfaction with sleep

C. The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (i.e., enough time is allotted for sleep) or inadequate circumstances (i.e., the environment is safe, dark, quiet, and comfortable) for sleep

D. The sleep disturbance and associated daytime symptoms occur at least three times a week

E. The sleep disturbance and associated daytime symptoms have been present for at least three months

F. The sleep wake difficulty is not better explained by another sleep disorder

Duration, Types, Etiologies of Insomnia

- Duration
  - Acute – 1 month or less
  - Intermittent
  - Chronic – 6 months or more
- Types
  - Sleep onset
  - Sleep maintenance
  - Early morning awakening or a combination of both
- Etiologies
  - Primary
  - Comorbid with another condition

Insomnia symptoms

- Needs to include at least one sleep symptom and one wake symptom
- Sleep symptoms
  - Difficulty falling or staying asleep
  - Early morning awakenings
  - Nonrefreshing sleep
- Wake symptoms
  - Daytime sleepiness
  - Fatigue
  - Mood disturbance
  - Cognitive difficulties
  - Social impairment
  - Occupational impairment

Common comorbidities associated with Insomnia

- Psychiatric disorders
  - Anxiety
  - Depression
  - Panic disorders
  - Adjustment disorder
  - Somatoform disorders
  - Personality disorders
- Medical conditions
  - Arthritis
  - Cancer
  - Hypertension
  - Chronic pain
  - Coronary heart disease
  - Diabetes
  - Breathing problems
  - Urinary problems

Medications and other substances known to cause Insomnia

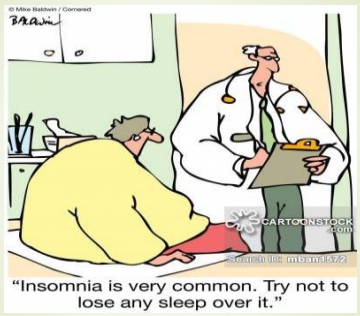
- Adrenergic agonists
- Amphetamines
- Antibiotics especially quinolones
- Anticonvulsants
- Antidepressants especially SSRI's
- Antineoplastic agents
- Beta Blockers
- Bronchodilators
- Decongestants
- Glucocorticoids
- Hypnotics
- Niacin
- Oral contraceptives
- Psychostimulants
- Theophylline
- Thyroid preparations
- Alcohol
- Caffeine
- Nicotine
- cocaine

Demographics and Risk Factors

- Aging
  - Insomnia increases with advancing age
  - May be associated with health complications that can develop as we age
- Gender
  - Women more likely to report symptoms than men
- Ethnicity
  - Middle aged African Americans tend to have a higher rate of symptoms than whites
  - African American women tend to sleep worse than African American men or whites
  - More prevalent in older whites compared to older African Americans
  - More prevalent in middle aged African Americans compared to middle aged whites

Demographics and Risk Factors continued

- Education
  - Those with lower socioeconomic status and education report more difficulty sleeping
  - More education associated with better objective and subjective sleep
- Stress and life events
  - Received mixed support
  - Only mildly related to onset of insomnia
  - People high in anxiety are more likely to develop a sleep disturbance after a stressful life event
- Medical and psychological comorbidities



Insomnia Assessment

- Circumstances surrounding onset
- Type
- Severity, frequency, course
- Daytime consequences
- Past treatments
- Exacerbating factors
- Medical factors
- Pharmacologic considerations
- Psychiatric factors
- Work factors
- Family or social factors
- Comorbid sleep disorders
- Behavioral factors
- Cognitive factors

Medications and how they affect Sleep

- Benzodiazepines
  - Mainstay of treatment for insomnia for many years
  - Suppress REM and decrease slow wave sleep
  - Acute withdrawal can increase slow wave sleep
  - Reduce sleep latency and increases total wake time
- Tricyclic antidepressants, MOA inhibitors and certain SSRI's
  - Amitriptyline and Doxepin
    - Increases total sleep time
    - Decrease wakefulness
    - Suppress REM
    - Increase periodic limb movements
    - Acute withdrawal increase REM
  - Nortriptyline
    - Increases wakefulness but decreases total sleep time

- Alcohol
  - Increases slow wave sleep and suppresses REM early in the night which can be followed by REM rebound in the latter part of the night as alcohol is metabolized
- Marijuana
  - Minimal sleep disruption, slight decrease in REM but chronic ingestion produces long term suppression of slow wave sleep
- Barbiturates
  - Decrease REM
- SSRI's
  - Increase wake time
  - Decrease total sleep time
  - Decrease REM
  - May increase PLM's

Sleep Medication Classes

- Melatonin
- Benzodiazepines
  - Rapidly and completely absorbed
  - Most achieve peak plasma levels in 1-1.5 hours
  - Rapidly enter the central nervous system
- Nonbenzodiazepines
- Sedating antidepressants

Benzodiazepines

- Quazepam
  - Schedule 4 drug
  - Comes in a 15mg tablet
  - Dose: 7.5-15mg
  - Start at 7.5mg at bedtime
  - Side Effects
    - drowsiness
    - headache
    - Complex sleep related behavior
    - Respiratory depression
    - Dependency and abuse

- Estazolam
  - Schedule 4 drug
  - Comes in 1 and 2mg tabs
  - Dose: 1-2mg at bedtime
  - Side effects
    - Somnolence
    - Dizziness
    - Ataxia
    - Confusion

- Temazepam
  - Schedule 4 drug
  - Comes in 7.5mg, 15mg, 22.5mg, and 30 mg capsule
  - Dose: 7.5-30mg
  - Side effects
    - Drowsiness
    - Fatigue
    - Anxiety
    - Confusion

- Flurazepam
  - Schedule 4 drug
  - Comes in 15mg and 30mg caps
  - Dose: 15-30mg
  - Side effects
    - Dizziness
    - Drowsiness
    - Confusion
    - Headache
    - GI disorders

- Triazolam
  - Schedule 4 drug
  - Comes in 0.125mg and 0.25mg tabs
  - Dose: 0.25mg- 0.5mg
  - Side Effects
    - Drowsiness
    - Headache
    - Nervousness
    - Confusion

Nonbenzodiazepines: the "Z" drugs

- Zolpidem
  - Rapidly absorbed
  - Peak concentration after 1.6 hours
  - Absorption slightly decreased when taken on a full stomach
  - Has a mild effect on REM and does not alter slow wave sleep
  - Schedule 4 drug
  - Comes in 5mg, 10mg; ER tab 6.25,g, 12.5mg; SL tab 1.75mg, 3.5mg
  - Dose: 5mg, 6.25mg Max: 10mg, 12.5mg,
    - Middle of the night awakenings: 1.25mg for females, 3.5mg for males
  - Give 5mg or 6.25mg in elderly patients
  - Side effects
    - Headache
    - Drowsiness
    - Performing common natural behaviors while asleep

- Eszopiclone
  - Schedule 4 drug
  - Peak concentration achieved in 1 hour
  - Decreases hyperarousal
  - Elimination half life is 6 hours
  - Found to have effectiveness without tolerance for at least 6 months
  - No limitation or duration of administration by the FDA
  - Comes in 1mg, 2mg, 3mg tablets
  - Dose: 1-3mmg; max is 2mg in elderly
  - Side effects
    - Unpleasant taste
    - Headache
    - Somnolence

- Zaleplon
  - Rapidly absorbed
  - Peak concentration is 1 hour
  - Half life of 1 hour
  - Take immediately before bedtime or after going to bed and experienced difficulty falling asleep
  - Take at least 4 hours before arising
  - Schedule 4 drug
  - Comes in 5mg and 10mg capsules
  - Dose: 5-10mg; maximum of 20mg per night; maximum in elderly is 10mg
  - Side effects
    - Headache
    - Dizziness
    - Somnolence
    - Tremor
    - nightmares

- Suvorexant
  - Is a CNS depressant
  - Is a schedule 4 drug
  - The mechanism by which Suvorexant exerts its therapeutic effect is presumed to be through antagonism of orexin receptors.
  - Peak concentration is 2 hours with a range from 30 minutes to 6 hours
  - Comes in 5mg, 10mg, 15mg, 20mg tabs
  - Recommended dose is 10mg taken within 30 minutes of going to bed. Maximum recommended dose is 20mg
  - Side effects
    - Headache
    - GI disturbance
    - sSmnolence

- Ramelton
  - Is a melatonin agonist and is rapidly absorbed
  - Peak plasma concentration of 0.75-0.94 minutes
  - Half life of1-2.6 hours
  - Decreases sleep latency
  - Efficacy is primarily in decreased sleep latency with little effect on awakenings during the night
  - No dependence producing effects
  - Not DEA restricted
  - Comes in 8mg tablet
  - Dose: 8mg
  - Side effects
    - Headache
    - Dizziness
    - Somnolence
    - Fatigue
    - nausea

Tricyclic antidepressants

- Absorbed moderately quickly
- Maximum concentration of 2-6 hours
- Decrease sleep latency, decrease wakefulness during sleep,
- Increased sleep efficiency reported in depressed patients
- Side effects
  - Dry mouth
  - Constipation
  - urinary retention
  - Seizures
  - Sedation
  - Increased heart rate
  - Decreased electrical conduction
  - QRS prolongation

- Trazadone
  - Tetracyclic antidepressant
  - Rapidly absorbed
  - Peak plasma concentration in 1-2 hours
  - Half life of 5-9 hours
  - Increases stage 3 and 4 sleep, sleep efficiency and total sleep time but has little effect on REM
  - Not controlled by the FDA
  - Comes in 50mg, 100mg, 150mg, 300mg tablets
  - Dose: 25-50mg with a maximum of 200mg
  - Side effects
    - Orthostatic hypotension
    - Weakness
    - Lightheadedness
    - Weight gain
    - Priapism

- Mirtazepine
  - Rapidly absorbed
  - Half life 20-40 hours
  - Decreases sleep latency, nighttime awakenings and stage 1 sleep
  - Increases stages 3 and 4 sleep
  - Not associated with serious toxicity or death in overdose
  - Comes in 15mg, 30mg, 45mg tablets
  - Side effects
    - Sedation
    - Increased appetite
    - Weight gain
    - Dry mouth
    - Less sedating at higher doses

Antihistamines

- All over the counter antihistamines marketed for insomnia include Diphenhydramine or Doxylamine
- First generation have 4-6 hours duration although Hydroxyzine and Meclizine may last up to 24 hours
- Half life of diphenhydramine is 4-8 hours
- Side effects
  - Psychomotor performance impairment
  - cognitive impairment in elderly
  - Dizziness
  - Fatigue
  - Tinnitus
  - decreased appetite
  - nausea, vomiting
  - diarrhea, constipation
  - rhabdomyolysis with resulting kidney failure

Melatonin

- Natural hormone in the body that helps to maintain your sleep/wake cycle
- Dose: 0.3mg to 10mg
- Rapidly absorbed
- Peak levels in 20-30 minutes
- Half life 40-60 minutes
- Secreted by the pineal gland
- Levels are low during the day and begin to increase shortly after onset of darkness and reach peak levels at mid darkness and decrease late in the night to reach daytime levels shortly before light onset
- Inhibited by light
- Side effects
  - Daytime drowsiness
  - Depressed mood
  - Headache or dizziness

Valerian

- Derived from the roots of the plant species Valeriana officinalis
- Dose range 400-900mg
- Mechanism of action unknown
- Decreases sleep latency and improves sleep quality
- Decreases awakenings and stage 1 sleep and increases stage 3 and 4 sleep
- Side effects
  - Headache
  - weakness

Psychotherapy and Behavior Modification

- Goals of psychotherapy
  - Manage stress
  - Develop insight
  - Restructure lifestyle away from complaints of insomnia
- Specific adjuvant measures
  - Treatment of withdrawal states from drugs and alcohol
  - Treatment of medical and psychological causes of insomnia
  - Chronotherapy in sleep phase asynchronies

Cognitive Treatments

- Stimulus-Control Therapy
  - Attempts to re-associate the bedroom environment with healthy sleep
    - Recommendations include
      - Bedtime only when sleepy
      - Using the bed only for sleep and intimacy
      - Curtail time spent awake in bed e.g. if unable to sleep within 15-30 minutes of nocturnal wakening, relax or engage in quiet activity in another room and return to bed when sleepy
      - Avoid clock watching
  - Sleep-restriction therapy
    - Aim to improve sleep onset through sleep deprivation
    - Begin by reducing the time in bed according to estimated time spent asleep
    - Establish a regular wake time and advance bedtime when 90% sleep efficiency is achieved

- Cognitive therapy
  - Reeducates patient's faulty beliefs and attitudes to sleep
  - Correct irrational fears, unrealistic expectations, and excessive concern about the amount of sleep time needed for adequate daytime function
- Relaxation therapy
  - Aims to decrease anxiety and lower arousal threshold
  - Hot bath prior to bedtime (helps relaxation and also increases core temperature to promote sleep during its subsequent decline)
  - Breathing exercises, meditation, modified yoga, guided imagery (may be useful for both sleep onset and sleep maintenance insomnia)
- Progressive muscle relaxation
  - Patient taught to systematically relax each part of the body; (experience needed in conducting PMR)
- Biofeedback
  - Complex procedure, may need many sessions, needs experienced operator

- Sleep hygiene education
  - Often ineffective on its won in chronic insomnia but a necessary component of insomnia management
  - Recommendations include:
    - Adjusting the bedroom environment conducive to sleep (cooler rather than warmer environment)
    - Establish a regular "wind down" routine
    - Avoiding stimulants or activities preventing sleep onset
    - Reduce or eliminate products which interfere with sleep (caffeine, nicotine, alcohol)
    - Avoid napping especially in the evenings
    - No exercising or large meals close to bedtime

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