Cradle to Grave: It’s 1/3 of Your Life

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Disclosures

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- Past recipient of an unrestricted educational grant from Sepracor.
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Objectives

• By participating in this session, you will be able to:

• Describe normative changes in sleep across the lifespan.

• Explain common sleep disorders across the lifespan.

• Apply evidence-based approaches to the pharmacological management of common sleep disorders across the lifespan.
**Sleep Across the Lifespan**

<table>
<thead>
<tr>
<th>Infants</th>
<th>Up to 2 months</th>
<th>10 – 18 hours per day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 - 12 months</td>
<td>Approximately 15 hours per day</td>
</tr>
<tr>
<td>Children</td>
<td>12 – 18 months</td>
<td>13 – 15 hours</td>
</tr>
<tr>
<td></td>
<td>18 months – 3 years</td>
<td>12 – 14 hours</td>
</tr>
<tr>
<td></td>
<td>3 – 5 years</td>
<td>11 – 13 hours</td>
</tr>
<tr>
<td></td>
<td>5 – 12 years</td>
<td>10 – 11 hours</td>
</tr>
<tr>
<td>Adolescents</td>
<td>May vary across the developmental period</td>
<td>9 – 10 on average</td>
</tr>
<tr>
<td>Adults/Elders</td>
<td>May vary across the developmental period</td>
<td>7 – 9 hours</td>
</tr>
</tbody>
</table>

**Sleep and Age**

Sleep Architecture

- NREM: 75% of total sleep
  - Stage 1: 5-10%
  - Stage 2: 45-50%
  - Stage 3: 12%
  - Stage 4: 13-15%
  - $\Delta$ sleep = stages 3 + 4
- REM: 25% of total sleep time

Sleep-Wake Cycle

Edgar DM et al. (1993), J Neurosci 13(3):1065-1079
Sleep & Psychiatric Illness

• Approximately 26.2% of Americans over 18 live with some form of psychiatric illness.

• 1 in 10 children/adolescents have mental illness severe enough to yield impairment

• Prevalence rates of sleep disturbance vary: 60% to 91% of those referred to or hospitalized on inpatient facilities.

Sources: Niet De, 2008; Sateia, 2009;
http://www.surgeongeneral.gov/topics/cmh/cmhreport.pdf

Sleep in Infants
Sleep in Infants

- Irregular sleep patterns first two months; AM exposure to light helps to entrain the infant to the environmental day/night cycle.
- Sleep influences: hunger and comfort needs.
- REM/NREM ratio is about 50/50.
- As the first year progresses, sleep consolidates, naps reduced to 1-2/day by the end of the first year.

National Sleep Foundation, 2013; www.sleepfoundation.org

Sleep Transition to Toddlerhood

- Critical period to establish good sleep hygiene/sleep habits.
- Following a bedtime routine with limit setting on sleep time/wake time.
- Encourage independent sleep onset.
- Move from crib to bed.

National Sleep Foundation, 2013; www.sleepfoundation.org
Developmental Tasks in Sleep: Infants to Toddlers

- Newborns sleep on back (SIDS precaution) with scheduled ‘tummy time’
- Establish sleep/wake patterns
- Self soothing during night time

Sleep Problems: Infants

- Infants: Sleep disruption and insufficient sleep, often schedule-based.
  - Impairs cognitive development, regulation of affect, attention, health outcomes and quality of life.
  - Left uncorrected or treated, sleep problems from infancy are likely to become chronic; powerful implications for those with predisposition to psychiatric illnesses.
Sleep Problems: Toddlers

• Toddlers: Frequent night time awakenings are seen in 20-30% of children.

• Approach to the awakenings predicts outcomes.

• Bedtime refusal (behavioral insomnias of childhood; limit setting type).

• Difficulties with falling asleep (behavioral insomnia of childhood; sleep onset association type).


Approaches to Sleep Problems: Infants and Toddlers

• Evidence base powerfully points to behavioral approaches/recommendations:
  ▪ Behavioral interventions are critical.

  ▪ Unmodified extinction with parental presence and preventive parental education (Standards); strongest evidence

  ▪ Graduated extinction, bedtime fadings, scheduled awakenings are effective but with less certainty than unmodified extinction.

  ▪ Teddy Bear, Curious George et al are great at this age!

Sleep in Children

- Napping usually ends by 5 years of age.
- Sometimes night time fears emerge.
- Children in this age bracket need about 11 to 13 hours of sleep a night.
- Challenges can be with competing things such as DVDs, electronic games.

National Sleep Foundation, 2013; www.sleepfoundation.org
Helpful Approaches to Preschoolers

- Set a routine and stick with it!
- Bedtime resistance is very common in this age group.
- Use of comfort measures such as reading to the child every night help routinize bedtime.
- Cool, dark and comfortable room

National Sleep Foundation, 2013; www.sleepfoundation.org

Sleep in School Age Children

- Sleep problems are common in this age group, best approximations are around 37%.
- One of the most common parental concerns addressed in pediatric medical practices.
Sleep in School Age Children

- Sleep issues may be transient but when not addressed become chronic.
- Sources of difficulties are varied:
  - Circadian preference
  - Cognitive or language delays
  - Medical or psychiatric comorbidity
  - Parental variables.

Common Sleep Problems in Children

- Sleep terrors
- Sleepwalking
- Sleep talking
- Nightmares
Common Sleep Problems in Children

- Often transient and benign
- Intervention with these parasomnias is generally focused on safety.
- With night terrors, remain with the child but do not try to comfort. The child will have no memory of the event; best not to focus on it.
- Persistent nightmares may be indicative of prior trauma.

Sleep Problems Requiring Evaluation

- Snoring
- Sleep apnea
- Insomnia
- Restless legs syndrome
- Narcolepsy
Sleep in Special Populations of Children

- In children with developmental and intellectual disabilities, sleep problems occur in 30-80%.
- Sleep pattern disruptions occur in 50-70% of children with autism.
- Virtually all children diagnosed with psychiatric illnesses have sleep disturbances.

Owens, J. Journal of Clinical Sleep Medicine, 1(4), 454-458

Sleep in Special Populations of Children

- Children with ADHD usually have sleep onset difficulties.
- Children who have been victims of trauma universally have significant disruptions in sleep.
- Medical comorbidities carry an equally high risk of sleep pattern disruption.
- Sleep and psychiatric illness share a bidirectional relationship.

Owens, J. Journal of Clinical Sleep Medicine, 1(4), 454-458
Recent Findings: Sleep & Children

- In children with ADHD, there is an increased association with sleep-related movement disorders such as restless legs syndrome, periodic limb movements, sleep apnea and a number of parasomnias:
  - Sleep walking
  - Sleep terrors
  - Confusional arousals


Treatment of Children with Sleep Disruption

- Behavioral measures and environmental adjustments are essential as first line measures:
  - Sleep hygiene
  - Sleep scheduling
  - Sleep practice with basic routine
  - Dietary restrictions: caffeine use, timing of meals

National Sleep Foundation, 2013. www.sleepfoundation.org
Pharmacology and Sleep in Children

• Medications: adjuncts to behavioral measures!

• Many medications are prescribed based on clinical experience, often with adults and all of the agents are used in off label ways.

• Examples of medications used: antihistamines, barbiturates, phenothiazines, soporific antidepressants, benzodiazepines, alpha agonists and melatonin.

Pharmacology and Sleep in Children

• Despite lack of evidence base, some guidelines have been developed for sleep promotion for children with psychiatric disorders.

• Two major recommendations:
  • Improving sleep hygiene and use of relaxation techniques for long sleep latency.
  • In children 6-12 who have ADHD and/or developmental disabilities, melatonin is used to improve sleep onset and duration.

Resources for Sleep in Children

- The National Sleep Foundation has a wealth of tools, quizzes, games and sleep hygiene resources for children.

- Check out www.sleepfoundation.org

Sleep in Teenagers
Common Trends with Sleep & Teenagers

- Phase delay (later sleep onset and later wake onset)
- Teens need 9-10 hours/night and 85% of teens in the USA get less than required regularly.
- Poor sleep habits and irregular sleep patterns are common.
- Daytime sleepiness is common.

National Sleep Foundation, 2013. www.sleepfoundation.org

Sleep & Teenagers

- Common consequences of poor sleep and daytime sleepiness:
  - Impaired social, behavioral and cognitive functions
  - Poor school performance
  - Reduced capacity for problem solving
  - Tardiness/absence from school
Sleep in Teenagers with Psychiatric Illnesses

- Sleep deprivation/poor sleep quality heightens the risk for:
  - Depression/other mood pathologies
  - Hyperactivity
  - Emotional volatility with risk for violence
  - Increased likelihood to engage substance abuse
  - Daytime sleepiness = drowsy driving

Sleep Interventions with Teenagers

- Sleep ONE additional hour/day for risk reduction
- Avoid naps
- Avoid high caffeine/taurine energy drinks
- Exposure to light on awakening
- Exercise but not close to bedtime

National Sleep Foundation, 2013. www.sleepfoundation.org
Pharmacotherapy for Sleep with Teens

- Similar circumstances as with children
- Hypnotic use in those with psychiatric illnesses needs to be carefully assessed but appropriately applied.
- In light of the obesity epidemic in the USA, screen for sleep apnea.
- Untreated sleep disruption will impact medication effectiveness.

Referral to a Sleep Specialist: Children & Teens

- When sleep apnea is suspected (snoring, overweight, daytime sleepiness, poor treatment outcomes)
- Sleep-related breathing disorder (chronic asthma, cystic fibrosis, pulmonary hypertension, chest wall abnormalities)
- Restless legs syndrome, periodic limb movement disorder, sleep-related violence (REM sleep behavior disorder)

Sleep in Adulthood

Insufficient Sleep by State

CDC 2008; MMWR 58(42);1179-1179
Cost Burden

- In the United States, recent estimates of costs related to sleep disorders (including insomnia):
  - $92.5 billion (Direct costs)
  - $107.5 billion (Indirect)

Reeder, Franklin and Bramley, 2007

Cost Burden

- In 2010 in the United States 57,287,000 prescriptions were written for sleep medications.
- This number represents a 7% increase from the pharmacoeconomic data available from 2007.

American Academy of Sleep Medicine, 2010
### Major Themes: Sleep Disruption & Adults

- Loss of work/life balance
- Increase in medical comorbidities with obesity, diabetes, hypertension, CV disease
- Psychiatric comorbidities
- 24 hour society
- Gender differences in sleep

### Psychiatric Disorders Associated with Sleep Disturbance/Insomnia

- Depression/Bipolar illness
- PTSD/anxiety disorders
- Substance related disorders
- Psychotic conditions
- ADHD/cognitive disorders
- Predominantly secondary insomnia

Sources: Bryant, Creamer, O'Donnell et al., 2010; Putnins, Griffin., Fitzmaurice et al., 2012; Krystal, Thakur, & Roth, 2008.
Sleep in Elders

Sleep and Elders

- As everyone ages, there is a greater sensitivity to variables impacting sleep.

- Sleep efficiency declines with advancing age (time in bed/time asleep).

- The ability to get continuous and consolidated sleep is reduced with age.

- Sleep disruption is common in nearly 50% of elders.

- While teens phase delay, elders phase advance.

National Sleep Foundation, 2013
Sleep Problems with Advancing Age

• Insomnia increases with age.
• Snoring is diminished as one ages.
• The risk of sleep apnea is reduced.
• Increased risk of restless legs syndrome.

National Sleep Foundation, 2013

Risk for Medical Illness with Aging

• All associated with sleep problems:
  ▪ Menopause
  ▪ Stroke
  ▪ Heart failure
  ▪ Cancer
  ▪ Other cardiovascular conditions
  ▪ Pain
  ▪ Dementia
<table>
<thead>
<tr>
<th>Sleep Quality-Related Risks in Elders</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tendency to remain in bed awake, trying to get more sleep rather than getting up.</td>
</tr>
<tr>
<td>• Napping is more common.</td>
</tr>
<tr>
<td>• Poor sleep quality and associated anxiety over sleep create the perfect storm for ongoing problems.</td>
</tr>
<tr>
<td>• Substance use for sleep is common.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sleep Interventions in Elders</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cognitive and behavioral approaches to sleep are essential among elders.</td>
</tr>
<tr>
<td>• Judicious use of medications due to changes in metabolism and risk for drug/drug interactions in light of other medications for comorbidities.</td>
</tr>
<tr>
<td>• Heightened sensitivity to side effects with potential increase for falls.</td>
</tr>
</tbody>
</table>
Nonpharmacological Treatment

• Patients may need to change reinforcing behaviors and thoughts for their chronic insomnia to improve.

• Specific behavioral and cognitive strategies may be beneficial for chronic insomnia: CBT-I is the gold standard approach.

• Sleep hygiene, stimulus control, relaxation, sleep restriction, cognitive behavioral therapy aimed at perceptual distortions and sleep.

Pharmacological Approaches to Insomnia Treatment
What Do People Take To Try To Improve Their Sleep?

- Alcohol
- Herbals
- Melatonin
- Dietary supplements
- OTC sleep aids
- Antihistamines
- Antidepressants
- Assorted psychotropics
- Sedative-hypnotics

Dietary Supplements and Herbal Preparations

- Evidence base is poor in terms of efficacy of the various agents.
- Pediatric population is not included in any of the available studies.
- Many studies have significant limitations.
- Commission E (Germany).

Medications Prescribed for Insomnia

- Antihistamines
- Antipsychotics
- Anticonvulsants
- Antidepressants
- Anxiolytics
- Hypnotics

Antihistamines

- OTC or prescription
- Most common: diphenhydramine
  - Benadryl
  - Tylenol-PM
- Mild to moderate sedation
- Tolerance may develop
Antihistamines

• Potential adverse effects
  ▪ Sedation (residual)
  ▪ Dizziness
  ▪ Incoordination
  ▪ Nervousness
  ▪ Tremors
  ▪ Insomnia
  ▪ Anticholinergic

• Potential drug interactions
  ▪ CYP2D6 inhibition

Atypical Antipsychotics for Insomnia

• Quetiapine (Seroquel), olanzapine (Zyprexa), risperidone (Risperdal)

• Advantages
  ▪ Mildly to highly sedating
  ▪ Useful for comorbid psychiatric disorders
  ▪ Anxiolytic
  ▪ Minimal abuse potential

• Disadvantages
  ▪ Limited effectiveness
  ▪ Residual daytime sedation
  ▪ Multiple potential acute and chronic adverse effects
Antidepressants for Insomnia

- Minimal efficacy data for insomnia treatment
- Tricyclic antidepressants
  - Amitriptyline (Elavil), doxepin (Sinequan), trimipramine (Surmontil)
- SSRIs
- Miscellaneous sedating antidepressants
  - Trazodone (Desyrel)
  - Nefazodone
  - Mirtazapine (Remeron)

Tricyclic Antidepressants

- Possible adverse effects
  - Hypotension
  - Cardiac
  - Sexual
  - Weight gain
  - Anticholinergic
  - Seizures
  - Residual sedation
- Multiple potential drug-drug interactions
Trazodone

- **Pharmacokinetics**
  - Elimination half-life: approximately 5-12 hours
  - Residual sedation common

- **Hepatic metabolism**
  - CYP3A4 substrate
  - Metabolite: meta-chlorophenylpiperazine (m-CPP)
  - Individual variation—slow metabolizers

- **Pharmacodynamics**
  - $5\text{HT}_{2A}$ receptor antagonist (strong)
  - $5\text{HT}_{1A}$ and $5\text{HT}_{2C}$ partial agonist
  - Serotonin reuptake inhibitor (weak)
  - $\alpha_1$ receptor antagonist
  - Histamine $H_1$ receptor antagonist

James SP, Mendelson WB, J Clin Psychiatry 65(6):752-755

Sedative-Hypnotics for Insomnia
Sedative-Hypnotics

- Hypnotics are indicated for the treatment of insomnia and have the strongest evidence base; recommended as 1st line in the treatment of insomnia.
- All are Schedule IV
  - Abuse liability
- 8 medications
  - 5 benzodiazepines
  - 3 nonbenzodiazepines


FDA Approved Hypnotics

- Benzodiazepines
  - Estazolam (ProSom)
  - Flurazepam (Dalmane)
  - Quazepam (Doral)
  - Temazepam (Restoril)
  - Triazolam (Halcion)
- Nonbenzodiazepines
  - Eszopiclone (Lunesta)
  - Zaleplon (Sonata)
  - Zolpidem (Ambien)

Sedative-Hypnotic Pharmacodynamics

- Compounds interacting with GABA<sub>A</sub> receptor complex
  - Benzodiazepine receptor agonists
  - Barbiturates
  - Neurosteroids

- Benzodiazepine receptor agonists are positive allosteric modulators of GABA at the GABA<sub>A</sub> receptor complex

Möhler H et al, J Pharmacol Exp Ther 300(1):2-8; Rowlett JK et al., CNS Spectr 10(1):40-48

Sedative-Hypnotic Approximate Elimination Half-Lives

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaleplon</td>
<td>1</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>2.5</td>
</tr>
<tr>
<td>Triazolam</td>
<td>1.5-5.5</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>6</td>
</tr>
<tr>
<td>Temazepam</td>
<td>3.5-18.4</td>
</tr>
<tr>
<td>Estazolam</td>
<td>10-24</td>
</tr>
<tr>
<td>Quazepam</td>
<td>39</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>47-100</td>
</tr>
</tbody>
</table>

Sedative-Hypnotic Summary

- Demonstrated efficacy
  - Shortened sleep onset latency
  - Total sleep time, number of awakenings
    - Except very short half-life medications
- Mechanism of action through enhancing GABA inhibitory function
- Minimal abuse potential, but all DEA Schedule IV


National Institutes of Health State-of-the-Science Conference Statement: Manifestations and Management of Chronic Insomnia in Adults. Draft Statement, June 15, 2005

Resources

- National Sleep Foundation [www.sleepfoundation.org](http://www.sleepfoundation.org)
- Sleep Education [www.sleepeducation.org](http://www.sleepeducation.org)
Conclusions – Part 1

- Sleep disruption can occur at any point across the developmental spectrum.
- It may be related to a primary sleep disorder.
- More commonly sleep disruption is related to a psychiatric and/or medical comorbidity.
- Cognitive and behavioral approaches are primary and need to be included in all treatment plans.

Conclusion – Part 2

- No hypnotics are indicated for children.
- Sleep-inducing and maintaining medications are used with children adolescents (off label) but commonly used with adults and elders.
- Many off label applications of medications are used for sleep due to fears of dependency with benzodiazepine receptor agonists.
- Use the evidence base to guide practice.
Questions