Understanding Sleep and Antidepressants: Lessons from Research Literature and Clinical Practice

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Disclosure
• The speaker has no conflicts of interests to disclose

Objective 1
• Explore new recommendations for treating sleep disturbances in psychiatric patients
• Review sleep architecture
• Explore concepts of "sedation" and "fatigue"

Objective 2
• Discuss clinical research and clinical experience of the effects of antidepressants on sleep

Objective 3
• Explore what this data means for psychiatric RN/APRNs
• Implement strategies for managing sleep disturbances in patients with psychiatric illness

Naval Health Center New England
Prevalence & Cost of Lost Sleep

- Prevalence (Non-Psychiatric)
  - 6-30% general population
  - 50-70 million Americans
- Gender – more common in women
- Age – elderly report more problems sleeping

Prevalence (Cont’d)

- 20% of U.S population self-medicate with OTC’s
- 40% self-medicate with ETOH
- 30% of Americans are short-sleeping

Costs of Decreased Sleep

Societal Costs
- $100 Billion in lost productivity (2005)
- School performance impairment
- Personal & social distress ($?)

Healthcare Costs
- Estimated healthcare costs: 75% greater!
  - Increased healthcare visits
  - Chronic disease
  - Injury

Healthcare Effects of Impaired Sleep

- Obesity
- Hypertension
- Metabolic syndrome
- Heart disease
- Depression & Mood disorders (suicide)
- Decreased life-expectancy
- Increased injury & accidents
- Decreased pain threshold
- Impaired immune function
- Increased utilization of healthcare resources
- Dementia/Delirium?
Immediate Effects of Sleep Deprivation

- Impaired concentration
- Depressed mood & irritability
- Malaise & fatigue
- Muscle pain
- Increased sensitivity to pain
- Gastrointestinal complaints
- Appetite changes – carbohydrate cravings?
- Impaired emotional regulation
  - Increased activation in amygdala & insular cortex

Sleep Deprivation and Cognition

- Increased distractibility
- Increased effort to attend to tasks (vigilance & motivation)
- Delayed impulse control and delay of gratification
- Decreased Emotional IQ

Sleep Deprivation and Cognition (Cont’d)

- Impaired “divergent” decision-making skills
  - Unexpected, innovation, revising plans, effective communication, competing distractions

Now the Good News!

- Convergent or Constructive Reasoning remains intact!
  - Rote memory
  - Complex rule-based, complex, logical tasks
  - Requiring heightened interest and compensatory effort

Sleep and Psychiatry

- Insomnia affects 80-90% of all hospitalized psychiatric patients
- And 50-70% of psychiatric outpatients
- 4-7 fold risk increase of mental illness if chronic insomnia exists prior

Recommendations

  - Concurrent mental illness and insomnia/sleep disturbances should be treated as co-morbid illnesses
  - What does this mean for providers?
    - Treat mental illness and insomnia
    - Don’t assume insomnia is caused by mood d/o
    - Don’t assume sleep will improve with treatment of mood d/o
Remember

- Sleep is easy to disturb and very difficult to restore

What is Sedation?

- Sedation is NOT fatigue
  - Calming of the CNS
- Sedation is mediated through:
  - Opiod, gaba, orexin, histamine, muscamic, melatonin receptors
- Sedation=anxiolytic?
- Are sedating antidepressants sedating? Or just disturbing restful sleep?

Sleep Across the Lifespan

- Newborns & Infants may sleep up to 23-24 hours a day. Lots of REM sleep.
- Children require 10-12 hours of sleep
- Teens require 9-10 hours of sleep (rarely get it) and fall asleep later in the evenings than adults (Sleep Phase Delay)
- Adults require about 7-8 hours of sleep
- Elderly have decreased deep sleep and more fractured sleep and often fall sleep earlier and wake earlier (Sleep Phase Advance)

Teenagers

- Sleep-Phase Delay
- Night Owls
- Early Morning Light Exposure- use with caution!

Older Adults

- Sleep-Phase Advance
  - Late afternoon light exposure
- Poor Sleep Continuity
- Frequent complaints of insomnia

The Evolution of Sleep
What is Sleep?

- "Alteration in consciousness"
- Essential for life
- Superchiasmatic Nuclei
  - Amygdala, Hypothalamus, Thalamus
- Distinct brain functions
  - REM & Non-REM
  - Active & Inactive states
  - 90 minute cycles

Stages of Sleep

Non-REM Sleep

- Deep Sleep
- Each stage progressively deeper
- Growth hormone release
- Deepest early in the sleep cycle

REM sleep

- "Active" sleep
- Most prominent in late morning
- Dream sleep associated with consolidation of memory
- Shallow sleep

Sleep Architecture in Mood Disorders

- Increased total REM time (shortened REM latency)
- Decreased total non-REM time
- Increased time to sleep onset, increased awakenings
- Fragmented sleep (initial, middle, terminal arousal)
- Non-restorative sleep
- Daytime fatigue

Mechanisms of Sleep

- Homeostasis
- Circadian Rhythms
- Arousal
Homeostasis

Sleep Load

Arousal

Sleep Pressure

- Sleep pressure is cumulative in the short-term
- Long-term sleep deprivation appears to activate noradrenergic system (adrenaline response)

Circadian Rhythm

- Internal Clock – 24.5 hour cycle
  - Light & Hormone-mediated
    - Time, length & intensity of light exposure
  - Core body temperature
    - Temperature nadir
  - Lark vs. Night Owl
    - Sleep phase advance/delay
  - Hormone cascade
    - Melatonin, adenosine, orexin.....

Arousal

- Length of time awake
- Stimulants
  - Caffeine, exercise, TV/Computer, Cell phones
- Light Exposure
  - "Blue Light Special"

Sleep occurs when …

- Sleep drive surpasses the arousal drive (homeostasis)
- Inner clock recognizes time for sleep (Circadian Rhythm)
- Individual arousal characteristics are decreased (Arousal)

Sleep Disorders

- Primary Sleep Disorders
  - Primary Insomnia
  - Sleep Apnea
  - Restless Leg/Periodic Limb Movement
  - Narcolepsy
  - Parasomnias
- Secondary Sleep Disorders
  - COPD, CHF
  - Depression
What is Insomnia?
- Inability to initiate or maintain restful sleep
  - Functional sequela
  - 3-5 days per week
- Symptom & Syndrome?
- Precipitant
  - Precipitant may leave but insomnia remains

Sleep Hygiene: What is It?
- Behaviors to decrease arousal
- Condition sleep response
- Increase sleep load
- Align circadian rhythms

Sleep Hygiene: Decreasing Arousal
- *Bed only for sleep & sex*
- Avoid noise, temp extremes, bright lights
- No caffeine after 3pm
- Exercise regularly but not later than 5-6 hours before bedtime
- No TV or computer in bed
- Keep bedroom cool and dark
- Light carbo snack
- Create "worry period" – away from bedroom

Sleep Hygiene: Conditioning
- Goal: Condition bedtime with positive sleep emotions/response
  - Maintain regular bedtime and awakening time, even on weekends
  - Incorporate relaxing rituals into bedtime
  - Do not remain in bed longer than 10-15 minutes if unable to sleep
  - Bed only for sleep & sex
  - *Break anxiety cycle related to sleep*

Sleep Hygiene: Increase Sleep Load
- Avoid early bedtimes following a bad night’s sleep
  - Sleep restriction
- Increase day-time sunlight exposure
- Exercise
- Avoid napping

Sleep Hygiene: Circadian Rhythms
- Regular bed-time and awakenings
- Properly timed sun-light exposure
- Regular meal schedules
- Avoid naps
- Lark or Night owl
- Medications
Why Avoid Alcohol?

- Alcohol increases desire to sleep but fragments sleep architecture & increases total REM exposure

Joe's Theory of Sleep Hygiene

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<thead>
<tr>
<th>Time awake</th>
<th>Naps</th>
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<td>TV in bed</td>
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<th>Exercise</th>
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<td>Light</td>
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Rx for Insomnia

- **Non-Benzo Sleep Hypnotics**
  - Zolpidem (Ambien)
    - Parasomnias
    - Inhibits fear extinction?
    - Long-term use data
  - Eszopiclone (Lunesta)
    - Metallic taste
    - May enhance antidepressants
  - Zaleplon (Sonata)
    - May enhance antidepressants

- **Benzo's**
  - Alprazolam (Xanax)
  - Temazepam (Restoril)
  - Triazolam (Halcion)
  - Lorazepam (Ativan)
  - Clonazepam (Klonipin)
  - Enhances sleep cycles

Issues with Benzo’s + Non-Benzo’s

- Addiction potential
  - Addiction potential - greater with short-acting benzo’s
  - No addictive behaviors seen with non-benzo’s
- Fall Risk – Elderly?
- PTSD – Impair Fear Extinction
- Tolerance
  - Tolerance not identified with non-benzo’s
  - Tolerance observed in short-acting benzo’s

Non-Benzo Sleep Aids

- Ramelteon (Rozerem)
  - M₁,₂ agonist
  - 7-10 day delay in response
- Orexin (Suvorexant)
- Tasimelatonin
  - Circadian disorder in blindness
Antidepressants and Sleep

What we were taught ....

• Serotonin = feel calm
• Dopamine = feel good
• Norepinephrine = fight or flight

What we were also taught

• Insomnia?
  – Treat the depression and the insomnia will go away ... or will it?

Remember ...

• 5 HT receptors can be both inhibitory and excitatory
• Post-Synaptic receptors are Auto-Receptors
  – 5 HT 1 – Inhibitory (anxiolytic, cognition, sleep?)
  – 5 HT 2A & 2C – Excitatory (sleep, mood, sex, anxiety, weight)
  – 5 HT 3 – Excitatory (GI)

Also Remember ...

• Blocking 5HT-2A potentiates 5 HT-1A inhibitory action
• Blocking 5HT-2A/2C – increases dopamine and norepinephrine (in pre-frontal cortex)
• Blocking Alpha 1 & 2 – increases serotonin levels and decreases noradenergic stimulation
• Blocking Histamine 1 = sedation, decreased appetite suppression

SSRI’s & SNRI’s

• Impair sleep continuity
• Decrease sleep efficiency
• Increase time to sleep onset
• Sleep fragmentation
• Decrease total time asleep
• Decrease total REM and expand time to REM sleep
• Less deep sleep
Yet, patients’ report more restful sleep?

SSRI’s
- Fluoxetine (Prozac)
  - Most activating
- Paroxetine (Paxil)
  - Most histaminic
  - Sedation?
- Zoloft (Sertaline)
- Celexa (Citalopram)
- Lexapro (Escitalopram)

SNRI’s
- Venlafaxine (Effexor)
  - Primarily an SSRI until 200mg
- Duloxetine (Cymbalta)
- Levomilnacipran (Fetzima)

Sleep Neutral Antidepressants (like Switzerland)
- Escitalopram (Lexapro)
- Buproprion (Wellbutrin)
- Levomilnacipran (Fetzima)

TCA’s
- Sedating TCA’s
  - Amitriptyline
  - Nortriptyline
  - Doxepine (approved as Silenor for sleep continuity)
- Stimulating TCA’s
  - Desipramine
    - Most noradenergic
    - Imipramine, trimipramine (?), protriptyline
    - Clomipramine
      - Most serotonergic, strongest REM suppression

SARI’s
- Block reuptake of 5HT and 5HT 2 post receptors
  - Trazodone (Desyrel)
    - Preserves normal sleep architecture yet enhances slow-wave sleep
  - Nefazodone (Serzone)
    - Improved quality & quantity of sleep
    - Liver toxicity & CYP450
Atypicals

- Bupropion (Wellbutrin)

- Mirtazapine (Remeron)
  - Inverse sedation/dose response

MAOI's

- Who cares?

- REM suppression with increased awakenings and diminished sleep efficiency

  - Diet restrictions

Antidepressants with Positive Effects on Sleep

- SSRI’s
  - Escitalopram *

- SARI’s
  - Trazodone
  - Serzone

- TCA’s
  - Amitriptyline/Nortrip
  - Doxepin

- Atypical’s
  - Buproprion *
  - Mirtazapine

New Antidepressant for Sleep?

- Agomelatine

Other Meds

- 1st generation anti-psychotics
  - Enhance sleep but worth the risk of EPS?

- 2nd generation anti-psychotics
  - Enhance sleep but metabolic risks?

- Gabapentin (Neurontin)

- Lamotrigene (Lamictal)

- Pregablin (Lyrica)

OTC’s & Herbals

- Histamines
  - Residual sedation
  - Side-effects from anti-cholinergic

- Valerian

- Kava Kava
Have you heard about Melatonin?

- Regulates circadian rhythm
- Activates T Lymphocytes, monocytes, natural killer cells, granuocytes, interleukin
- Protective from Oxidative Stress & Ionizing radiation
- Oncostatic and cytotoxic effect on cancer cells
- Alzheimers Protection?

So who shouldn’t take melatonin?

- Rheumatoid arthritis?
- Auto-immune disorders?
- Drug interactions?

Drugs that impair sleep

- Beta Blockers
- Stimulants
- Corticosteroids
- Theophyline
- Nicotine
- Thyroid hormone

Summary

- Good
  - Sedating Tricyclics
    - Amitriptyline, Nortriptyline, Doxepine
    - Mirtazapine
    - Trazodone
    - Buproprion
    - Escitalopram
- Bad
  - SSRI's (except Lexapro)
  - SNRI's
  - Stimulating TCAs

Strategies for Sleep and Antidepressants

- Consider insomnia as a co-morbid disorder
- Assess sleep thoroughly
  - Trouble falling, time to sleep onset, sleep behaviors, environment
  - Feelings about sleep, beliefs about sleep
  - Staying asleep, how many arousals, return to sleep
  - Terminal insomnia
  - Sleep hygiene
- Is your diagnosis correct? Anxiety? Depression?
- Consider non-SSRI's first
- Consider rapid augmentation or dual starts
- Educate patients on sleep hygiene
- Educate patients on the effects of sleep

Issues in Treating Sleep

- Sleep Hangover?
- Rebound Insomnia?
- Sedation?
Questions?