Sleep & Chronic Pain/Depression

Geoffry Phillips McEnany, PhD, PMHCNS, BC
Professor, University of Massachusetts Lowell

Disclosures

- This speaker has no conflicts of interest or commercial support to disclose.
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- Off label use of medications will be discussed in this presentation and will be cited in the presentation content.

Sleep-Related Disclosure from My Classes

Objectives

- By participating in this session, you will be able to:
  - Identify the neurophysiological processes governing sleep and wakefulness
  - Explain the prevalence of insomnia and its association with pain.
  - Clarify the differential diagnosis of secondary insomnia related to pain and a rational approach to its evaluation in clinical settings.

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Sleep

- A reversible behavioral state of perceptual disengagement from, and unresponsiveness to, the environment
- Actively produced, not a result of passive inactivity
- Complex processes involved
- Highly regulated by homeostatic and circadian processes
- Composed of 2 fundamentally different states: REM sleep and NREM sleep
- Involves the entire organism, not just the CNS
- Purpose is not understood; however, it is essential for normal function and life


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Sleep Architecture

- NREM: 75% of total sleep
  - Stage 1: 5-10%
  - Stage 2: 45-50%
  - Stage 3: 12%
  - Stage 4: 13-15%
- REM: 25% of total sleep time

Sleep-Wake Cycle Regulation

- Nighttime sleep
  - First part of night—sleep because we have been awake all day (homeostatic drive high)
  - Second part of night—sleep because circadian alertness is low
- Daytime wakefulness
  - First part of day—awake because we slept at night (homeostatic drive low)
  - Second part of day/evening—awake because circadian alertness is high (although sleep load is high)

Two-Process Model of Sleep Regulation

- Homeostatic factor
  - Sleepiness “builds up” during wakefulness
  - Duration of prior wakefulness determines current level of sleepiness and amount, duration and depth of sleep
- Circadian factor
  - Controlled by biological clock
  - Results in a bimodal distribution of sleep propensity

Normal Sleep Modulation

Insomnia:
Definitions, Prevalence, Associated Impairments and Neurophysiology
**Insomnia Definition**

- Repeated difficulty with:
  - Sleep initiation
  - Sleep duration
  - Sleep consolidation
  - Sleep quality
- Occurs despite adequate time and opportunity for sleep
- Results in daytime impairment

American Sleep Disorders Association (2005), The International Classification of Sleep Disorders: Diagnostic and Coding Manual, 2nd ed. Westchester, Ill.: The American Academy of Sleep Medicine, p1

**Factors in the Genesis and Progression of Insomnia**

<table>
<thead>
<tr>
<th>Insomnia intensity</th>
<th>Perpetuating</th>
<th>Precipitating</th>
<th>Predisposing</th>
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</thead>
<tbody>
<tr>
<td>Predom</td>
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<tr>
<td>Acute Insomnia</td>
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<td>Early Insomnia</td>
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<tr>
<td>Chronic Insomnia</td>
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</tbody>
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**Insomnia: The Disorders**

- Primary insomnia* (“insomnia syndrome”)
  - Insomnia complaint ≥ 1 month
  - Clinically significant distress or impairment
  - No other etiologies to account for insomnia
- Secondary insomnias
  - Insomnia
  - Related to an underlying disorder such as depression or pain.


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**Functional Impairments**

![Graph showing functional impairments]

**Sleep, Pain and Depression: Exploring the Relationships**

- Changes in sleep architecture/changes in sleep homeostasis
- Changes in sleep architecture, particularly with increases in arousal and lower sleep efficiency
- Changes in neurochemical regulation/changes in circadian functions
- Sleep is under powerful humoral control

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**A Couple ‘Lenses’ on Sleep, Pain and Depression**

- No sleep difficulties
- Occasional sleep difficulties
- Frequent sleep difficulties

Sleep Architecture and Pain

- Pain creates fragmentation in sleep architecture evidenced by more arousal in the EEG.
- Reduction in sleep efficiency is common. Sleep efficiency = time asleep ÷ time in bed.
- Poor sleep efficiency is the culprit in enhanced pain perception (even in the absence of depression.)

Haack & Mullington, 2005

Sleep Architecture and Depression

- Reduced sleep efficiency (and the imposed sleep deprivation) are directly related to onset and course of depression as well as risk for relapse. Subjective and objective measures parallel each other.
- The relationship is bidirectional, e.g., sleep impacts mood and vice versa.
- The sleep/depression relationship powerfully impacts pain perception, given the shared relationship with sleep efficiency.

Sleep Loss in Pain & Depression

- 4 hours of sleep loss and specific REM sleep loss are hyperalgesic the following day.
- Pharmacologic treatments and clinical conditions that reduce sleep and REM sleep time may increase pain.
- Sleep deprivation is negatively associated with course/outcome of depression.

Sleep/Wake Neurotransmitters and Modulators

Wake
- Norepinephrine
- Serotonin
- Acetylcholine
- Histamine
- Orexin/hypocretin

Sleep
- Adenosine (caffeine is an adenosine antagonist)
- GABA
- Galanin
- Serotonin/melatonin

Depression/Sleep Neurotransmitters and Modulators

- Norepinephrine Modulates arousal regulation; wake-promoting (as seen in MOA for drugs like modafinil); critical to attention/mood.
- Serotonin Critical to activation and alertness; tight relationship with melatonin in regulating sleep and wake via the circadian system. Mood/anxiety regulation.
- Dopamine Promotes wakefulness (MOA with stimulants). Mood, focus, attention regulation.
**Pain**

**Neurotransmitters and Modulators**

- Substance P, glutamate, bradykinin (pain initiators); substance P increases histamine in pain.
- Histamine is a powerful wakefulness chemical.
- Proinflammatory cytokines are central to pain but are active in depression, influencing the HPA.

**Neurochemistry:**

**The Role of Serotonin in Depression**

- Alterations in 5HT1a receptor levels are noted in depression and in suicide.
- Desensitization of the 5HT1a autoreceptor is believed to be implicated in the 2-3 week lag with antidepressant medication onset.

**Pain**

**Neurotransmitters and Modulators**

- Serotonin, endorphins, enkephlins (pain inhibitors)
- Norepinephrine Inhibitory influence in pain
- GABA Inhibitory influence in pain
- Acetylcholine Inhibitory influence in pain

**Just a Word on Sleep & Immunity**

- Alterations in 5HT1a receptor levels are noted in depression and in suicide.
- Desensitization of the 5HT1a autoreceptor is believed to be implicated in the 2-3 week lag with antidepressant medication onset.

**Neurochemistry:**

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**Other Impacts on Sleep:** Let's Consider the Ripple Effect on Mood and Pain

- Sleep deprivation/lack of sleep is associated with:
  - Reduction in T cells
  - Reduction in natural killer cells
  - Increase in proinflammatory cytokines

SNRI’s impact on pain and immunity is related to the drug’s impact on the inhibition of the inflammatory TNF.

Ohayon, 2009; Smith, 2010
### Medications Associated With Insomnia

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Antihypertensives</th>
<th>Antineoplastics</th>
<th>Anticholinergics</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs (Wellbutrin)</td>
<td>5-Hydroxytryptamine (Protriptyline)</td>
<td>Leuprolide acetate (Lupron)</td>
<td>Ipratropium bromide (Atrovent)</td>
</tr>
<tr>
<td>Buspirone (Buspar)</td>
<td>Albuterol (Ventolin)</td>
<td>Goserelin acetate (Zoladex)</td>
<td>Medroxyprogesterone (Provera)</td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td>Hydralazine (Hydralazine)</td>
<td>Leuprolide acetate (Lupron)</td>
<td>Leuprolide acetate (Lupron)</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>Clonidine (Catapres)</td>
<td>Goserelin acetate (Zoladex)</td>
<td>Ipratropium bromide (Atrovent)</td>
</tr>
<tr>
<td>Citalopram (Cipramil)</td>
<td>Propranolol (Inderal)</td>
<td>Daunorubicin (Cerubidine)</td>
<td>Propranolol (Inderal)</td>
</tr>
</tbody>
</table>

**References**

### Medical and Neurological Conditions Associated With Insomnia

- Alzheimer's disease
- Arthritis: osteoarthritis and rheumatoid arthritis
- Chronic back pain
- Cancer
- Cardiac disease: congestive heart failure, myocardial infarction, nocturnal angina, dyspnea
- Diabetes mellitus
- End-stage renal disease
- Functional bowel syndromes
- GERD
- HIV
- Huntington's disease
- Menopause
- Nocturia
- Migraine: aura
- Chronic pain
- Parkinson's disease
- PLMD
- Progressive supranuclear palsy
- Pulmonary disorders (e.g., COPD)
- RLS
- Sleep apnea syndrome
- Thyroid disease

**References**

### Critical Relationships

- Poor sleep and depression have been shown to be independently associated with a reduced pain threshold.
- So a good question to ask is whether effective management of sleep improves pain and depression?

**References**
- Chiu, Silman, Macfarlane et al., 2005
- Roehrs, 2009

### Persistent Insomnia Predicts Future Psychiatric Disorders

- Any psychiatric disorder
- Major depression
- Anxiety disorders
- Alcohol abuse

**Reference**

### Insomnia and Mood Disorders: Which Comes First?

**Reference**
Evaluation of Insomnia

- History and physical examination
  - Include the following questions on characteristics of insomnia:
    - Functional impact
    - Severity
    - Duration
    - Age of onset

Schenck CH et al. JAMA 289(19):2475-2479

Evaluation of Insomnia (Cont.)

- Sleep log (diary)
  - Completed by patient for at least 7 days
- Sleep questionnaires (examples)
  - PSQI
- Psychological screening (when psychiatric conditions are suspected)
  - BDI
  - Beck Anxiety Inventory
  - Referral to formal psychological or psychiatric evaluation if needed

Schenck CH et al. JAMA 289(19):2475-2479

7-Day Sleep Diary

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
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</thead>
<tbody>
<tr>
<td>Answer the first 6 questions each morning</td>
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<tr>
<td>1. What time did you first go to bed last night?</td>
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<td>2. About how long did it take you to fall asleep?</td>
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<td>3. About how many times, if any, did you awaken during the night?</td>
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<tr>
<td>4. Overall, about how many hours did you sleep?</td>
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<td>5. At what time did you wake up (for the last time) this morning?</td>
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<tr>
<td>6. In general, how did you feel when you woke up?*</td>
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<tr>
<td>Answer these last 3 questions each night</td>
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<td>7. How much time, if any, did you spend napping during the day?</td>
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<tr>
<td>8. Did you consume any of these substances during the day?*</td>
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<tr>
<td>9. On a scale of 1 to 5, how would you rate your overall functioning during the day?</td>
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</table>

*Key to question: 6. ___Very refreshed___Somewhat refreshed___Fatigued
8. ___Caffeine (within 6 hours of bedtime)___Alcohol (within 1 hour of bedtime)
9. ___5 Energetic___4___3___2___1 Lethargic

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.

Nonpharmacological Treatment

Schenck CH et al. JAMA 289(19):2475-2479
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

Medications Prescribed for Insomnia

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

Medications: Depression/Pain/Sleep

- Tricyclic antidepressants
- SNRIs
- Anticonvulsants

Medications: Tricyclic Antidepressants

- Amitriptyline, nortriptyline, doxepin and imipramine are all used; amitriptyline and doxepin are the most soporific.
- Commonly used for treatment of chronic pain, neuropathic pain and postherpetic pain.
- MOA: indirectly modulate the opioid system via serotonergic and noradrenergic neuromodulation

Patients With Insomnia Who Report Self-Medication

- OTC Medications
- Alcohol
- Either

Ancoli-Israel S, Roth T (1999), Sleep 22(suppl 2):S347-S353
Medications: SNRIs

- Duloxetine (Cymbalta) and venlafaxine (Effexor) are used. Duloxetine (Cymbalta) is approved for diabetic peripheral neuropathic pain, fibromyalgia and chronic musculoskeletal pain.
- MOA: 5 HT and NE reuptake inhibition impact on the functioning pain circuitry in the brain.

Evidence Based Approaches to Sleep Pattern Disturbance

Medications: Anticonvulsants

- Carbamazepine (Tegretol), gabapentin (Neurontin), lamotrigine (Lamictal), oxcarbazepine (Trileptal), phenytoin (Dilantin), pregabalin (Lyrica), topiramate (Topamax), valproic acid (Depakene), zonisamide (Zonegran) all have been used.
- MOA: inactivation of the sodium channels involved in the action potential of the pain signal.

Sedative-Hypnotics

- Hypnotics are indicated for the treatment of insomnia
- All are Schedule IV
  - Abuse liability
- 8 medications
  - 5 benzodiazepines
  - 3 nonbenzodiazepines

Sedative-Hypnotic Pharmacokinetics

- Rapid absorption
- Elimination half-lives vary greatly
- Some have active metabolites that extend the duration of action

Medications: Anticonvulsants

- A number of the anticonvulsants are used as off label sedative hypnotics.
- A sedative depresses the activity of the CNS and induces sleep.
- A hypnotic is defined as a drug whose main goal is to maintain sleep.
Sedative-Hypnotic Pharmacodynamics

GABA

- Most abundant CNS inhibitory neurotransmitter
- Primary inhibitory VLPO neurotransmitter
- Effects of medications enhancing GABA
  - Sedative
  - Anxiolytic
  - Muscle relaxation
  - Anticonvulsant
- Multiple GABA receptors (GABA_A, GABA_B)

VLPO = ventrolateral preoptic nucleus; Benca RM (2005), Psychiatry Serv 56(3):332-343; Rowlett JK et al. (2005), CNS Spectr 10(1):40-48

Sedative-Hypnotic Pharmacodynamics (Cont.)

- Compounds interacting with GABA_A receptor complex
  - Benzodiazepine receptor agonists
  - Barbiturates
  - Neurosteroids
  - Alcohol
  - Picrotoxin
- Benzodiazepine receptor agonists are positive allosteric modulators of GABA at the GABA_A receptor complex

Möhler H et al. (2002), J Pharmacol Exp Ther 300(1):2-8; Rowlett JK et al. (2005), CNS Spectr 10(1):40-48

Sedative-Hypnotic Approximate Elimination Half-Lives

- Zaleplon
- Zolpidem
- Triazolam
- Eszopiclone
- Temazepam
- Estazolam
- Quazepam
- Flurazepam


Sedative-Hypnotic Advantages

- Hasten sleep onset
- Decrease number of awakenings
- Increase total sleep time
  - Varies with medication duration of action
- Make sleep more refreshing

Sedative-Hypnotic Disadvantages

- May alter normal sleep architecture
  - Decrease slow wave sleep
  - Decrease REM sleep
- Residual sedation
- Psychomotor and cognitive impairment
- Psychological dependence in vulnerable individuals
- Rebound insomnia

Sedative-Hypnotics FDA-Approved Insomnia Treatment

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

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**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

**Antidepressants for Insomnia**

- Tricyclic antidepressants
  - Amitriptyline (Elavil), doxepin (Sinequan), trimipramine (Surmontil)
- SSRIs
  - Miscellaneous sedating antidepressants
    - Trazodone (Desyrel)
    - Nefazodone
    - Mirtazapine (Remeron)

**Additional Options for Insomnia**

**Atypical Antipsychotics for Insomnia**

- Quetiapine (Seroquel), olanzapine (Zyprexa), risperidone (Risperdal)
- Advantages
  - Mildly to moderately sedating
  - Useful for comorbid psychiatric disorders
  - Anxiolytic
  - Minimal abuse potential
- Disadvantages
  - Limited effectiveness
  - Residual daytime sedation
  - Multiple potential acute and chronic adverse effects

**Drugs to Enhance Wakefulness**

**Wakefulness Promoting Agents**

- Classic stimulants (amphetamines)
- Modafinil and similar drugs
- Activating drugs such as bupropion
- Caffeine
- Energy drinks!
Resources

- National Sleep Foundation
  www.sleepfoundation.org
- Sleep Education
  www.sleepeducation.org

Case Study

- Current medications include 400 mg ibuprofen twice a day for her shoulder, a multivitamin, calcium 1200 mg with 400 IU of vitamin D a day.
- Past psychiatric history reveals that she has had a positive response to citalopram 30 mg a day but it created transient insomnia which she treated with diphenhydramine.
- Strong family support with good relationships. She has a network of friends though she has distanced them in the last couple of months.

Case Study

- 56 year old married woman who presents with a longstanding history of dysthymic disorder and intermittent MDD.
- Current stressors: Caring for mother with advanced Lou Gehrig’s disease.
- Target symptoms include depressed mood, loss of interest, poor appetite, anxiety, insomnia with difficulty falling/staying asleep with daytime sleepiness, mild anhedonia, poor concentration, tearfulness and fears about pain in her shoulder.

Case Study

- She is employed as an accountant for a large urban law firm and generally enjoys her work.
- Lately, her lack of interest and poor concentration has led to a number of careless mistakes which have caused significant consternation with business transactions.
- “The lawyers aren’t happy with me right now and if you ever dealt with lawyers, you’d know what I mean.”

Case Study

- Medically, she is overweight with a BMI of 30. S/P right rotator cuff tear with surgical repair 8 years ago; no sequellae.
- Neuropathic pain in her left shoulder due to a “pinched nerve in my upper back but I don’t want surgery or narcotics.” Pain worsens sleep.
- Husband complains of her loud snoring at night which is worse if she has had a cocktail in the evening (not a regular thing). No other drugs.

Case Study

- Psychiatric Diagnostic Screening Questionnaire, Beck Depression Inventory, Epworth Sleepiness Scale and the Pittsburgh Sleep Disorders questionnaire all screened positively.
- Diagnostic formulation:
  - Axis 1:
  - Axis 2:
  - Axis 3:
  - Axis 4:
  - Axis 5:
Case Study

- Diagnostic formulation:
  - Axis I: MDD; insomnia due to mental disorder
  - Axis 2: None
  - Axis 3: Neuropathic pain, obesity, r/o sleep apnea
  - Axis 4: Serious health problems in family member
  - Axis 5: 55

Case Study

- Treatment plan:
  - Citalopram trial
  - Low dose (100mg) off label use of gabapentin for sleep
  - Urgent evaluation of potential sleep apnea
  - Consultation with PCP and neurologist who treat the patient
  - Psychotherapy
  - Evaluation for home services

Case Study

- Evaluation (6 weeks later)
  - Citalopram 30 mg a day with 80% reduction in target symptoms
  - Diagnosed with moderate OSAS and treated with CPAP; still adjusting to treatment.
  - Gabapentin dose increased to 300 mg QHS with satisfactory control of insomnia (now related to formal sleep disorder as well as depression); done in collaboration with neurologist; abatement of shoulder pain.

Summary

- Sleep, pain and depression are intricately related.
- The shared relationships appear to be bidirectional.
- Effective intervention in sleep offers hopeful directions for the treatment of both depression and pain.