Insomnia as a Root Cause in the Struggle to Obtain Quality Sleep: Epidemiology and Pathophysiology

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Objectives

• Review Insomnia: definition, subtypes, impact, and prevalence
• Discuss overall epidemiology and clinical applications.
• Illustrate pathophysiology of insomnia with specific attention to normal sleep physiology and disruptions in sleep wake mechanisms.
**Insomnia Definition**

- Persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep, and results in some form of daytime impairment.
  - Persistent sleep difficulty
  - Adequate sleep opportunity
  - Associated daytime dysfunction

*International Classification of Sleep Disorders 3rd Ed.*

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**Insomnia**

**Sleep disturbance**
(more than 1 type may be present)

- Sleep initiation
- Sleep maintenance (difficulty returning to sleep)
- Early awakening
- Poor sleep quality

**Next day consequences**

- Mood
- Behavior
- Fatigue
- Cognitive Dysfunction
- Physical
- Performance
**Prevalence Estimates by Definition**

- **Insomnia Sxs Only**
- **Insomnia Sxs + Frequency Criteria**
- **Insomnia w/ Severity Criteria**
- **Insomnia Sxs + Daytime Effects**
- **Sleep Dissatisfaction**
- **Insomnia Diagnosis**

<table>
<thead>
<tr>
<th>Sleep Problem</th>
<th>Age</th>
<th>Prevalence</th>
<th>Med</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Poor Sleepers¹</td>
<td>12-18 yo</td>
<td>12%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Poor sleep²</td>
<td>15-20 yo</td>
<td>13%M</td>
<td>10%</td>
</tr>
<tr>
<td>Sleeping poorly³</td>
<td>8-10 yo</td>
<td>14%</td>
<td>4%</td>
</tr>
<tr>
<td>Sleep difficulties³</td>
<td>8-10 yo</td>
<td>43%</td>
<td>--</td>
</tr>
<tr>
<td>Sleep disturbance⁴</td>
<td>high s.</td>
<td>40.8%</td>
<td>--</td>
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</table>

Increased prevalence of medical disorders in those with insomnia

Community-based population: 772 men/women, aged 20-98 y

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>No Insomnia (N=401)</th>
<th>Insomnia (N=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Disease</td>
<td>*</td>
<td>***</td>
</tr>
<tr>
<td>Cancer</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>HTN</td>
<td></td>
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<tr>
<td>Neuro</td>
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<td>Resp</td>
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<tr>
<td>Urinary</td>
<td></td>
<td></td>
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<tr>
<td>DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Pain</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>GI</td>
<td></td>
<td>***</td>
</tr>
<tr>
<td>Any medical problem</td>
<td>***</td>
<td>***</td>
</tr>
</tbody>
</table>

- * P <0.05
- ** p <0.01
- *** p<0.001

p values are for Odds Ratios adjusted for depression, anxiety, and sleep disorder symptoms.


Insomnia prevalence increases with medical comorbidity

Self-reported questionnaire: 1506 community-dwelling adults ages 55 to 84 years

At-risk Populations for Insomnia

- Gender: (Female: Male, 1.4:1)\(^1\)
- Older age
- Family history \(^2\)
- Comorbid medical illness (esp. respiratory, chronic pain, neurological)
- Comorbid psychiatric illness (especially depression) and substance abuse
- Lower socioeconomic status
- Widowed, divorced
- Work schedules incompatible with sleep
- Night caregiving, sleeping with pets

\(^1\)Zhang B Sleep 2006  \(^2\)Beaulieu-Bonneau Sleep 2007
Other: Morin et al Nature Rev 2015

Prevalence of Insomnia by Age Group

Mellinger GD, Arch Gen Pysch 1985
**Diagnostic Overlap in Insomnia and Psychiatric Diagnoses**

**Insomnia:**
(10-15% of gen population)

**Psychiatric Diagnosis**
- 40-50% those with insomnia report a psychiatric diagnosis
- 80-90% of MDD report insomnia

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**Insomnia: ICSD-3 Classification**

- **Chronic insomnia Disorder (3 months)**
- **Short term insomnia disorder**
- **Other Insomnia Disorder**
- Isolated normal variants:
  - Excessive time in bed
  - Short sleeper

**Sources:**
Ford DE, JAMA, 1989
Ohayon MM, Sleep Med Rev, 2002
Chronic Insomnia - Subtypes

- Psychophysiological insomnia
- Idiopathic insomnia
- Pardoxical insomnia
- Inadequate sleep hygiene
- Behavioral insomnia of childhood
- Insomnia due to (co-morbid with)
  - Drug/substance
  - Medical condition (e.g. GERD pain)
  - Psychiatric condition/mental illness

Psychophysiological Insomnia

- Conditioned sleep
difficulty/heightened arousal; with following:
  - Excessive focus/heightened arousal
  - Difficulty falling asleep with intention; BUT no difficulty without intention.
  - Sleep better away from home
  - Rumination; perceived inability to cease mental activity. Thinking counting… clock!
  - Heightened somatic tension (inability to relax in bed)
Paradoxical Insomnia  
(former name Sleep State Misperception)

- Chronic pattern of little/no sleep, mismatch with objective findings
- **Example:** “I have not slept for 3 weeks” or “I never slept on the sleep study” but you see sleep

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Co-morbid insomnia  
(e.g. Insomnia secondary to mood disorder)

*Timing of insomnia related to onset of psychiatric illness*

## Behavioral Insomnia of Childhood (chronic insomnia)

<table>
<thead>
<tr>
<th>2 types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep association type</td>
</tr>
<tr>
<td>Limit setting type</td>
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</tbody>
</table>

### Behavioral Insomnia of Childhood: *Sleep-onset Association Type*

- Child begins to associate sleep onset with circumstances that are problematic and demanding of the caregiver.
- Child unable to fall asleep without these associations either at initial sleep onset or during nocturnal awakenings.
Behavioral Insomnia of Childhood: Limit-setting Type

- Refusal to go to bed at an appropriate time or following a nighttime awakening
- Insufficient or inappropriate limit setting demonstrated by the caregiver
- Can lead to frequent “curtain calls”

Inadequate Sleep Hygiene

More than just TV

Engagement/ Stimulating activities

Eating late/ other (exercise)

Light (TV/Ipad/etc)

Awake Arousal system

Circadian effects on sleep
**Short-Term insomnia**  
(Adjustment/acute Insomnia)

- **Identifiable stressor**
  - Grief, acute pain, acute stressor
- Usually <few days to weeks ( < 3 months)
- May resolve with resolution of stressor
Hypnotics and Mortality

- Hypnotic prescription use: 4.6 times Mortality hazard (6.1% vs 1.2% in non user deaths in observation period 2.5 years)
  - Dose-response effect: Zolpidem/Temazepam were most prescribed
- Cancer risks higher (35% higher) with >132 pills
- Limitations to data: Epidemiological (not controlled) and other factors

HR 3.60 for 0.4 to <18 pills
HR 4.43 for 18 to 132 pills
HR 5.32 for >132 pills

Kripke, BMJ Open, Feb 2012
Health impact of insomnia

- **Quality of life**\(^1\) on virtually all dimensions of the 36-item Short Form Health Survey of the Medical Outcomes Study (SF-36)
  - (1) physical functioning; (2) role limitation physical; (3) bodily pain; (4) general health perceptions; (5) vitality; (6) social functioning; (7) role limitations emotional; and (8) mental health

- **Mental health**\(^2\)
  - Increase suicide rates (longitudinal and cross-sectional studies)

- **Impairments**\(^1,3\)
  - Higher accident rates, productivity
  - Pain (50% of insomnia; sleep is predictor)

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Insomnia in **Neurological conditions**

- **Stroke**
  - Stroke related Insomnia rates **49-68%** ¹
  - Insomnia post stroke more disability worse QOL
  - **Insomnia: 54%↑** risk of developing stroke ² (adjusted hazard ratio, 1.54; 95% CI 1.38–1.72) Taiwan; 4 year 1st acute stroke hosp (n= 21438 insomniacs vs. 64314 controls)
- **Multiple Sclerosis**: ICSD 25%; clinical sx ≥40% (veuthier)
- **Parkinson’s Disease**: neurodegeneration of sleep wake mechanisms

¹Tang WK et al Topics in Stroke Rehab 2015 ²Ming-Ping Wu et al. Stroke 2014

Schrempf W et al Sleep Disorders in Parkinson’s J of Parkinson’s Disease 2014
Veuthier C and Paul F. Sleep Dis MS relationship fatigue Sleep Med 2014

Insomnia in **Women**

- Higher comorbid psychiatric illness ¹
- **Menopausal transition** insomnia highest incidence, may have onset of mood disturbance and OSA in this population
  - Insomnia associated with more menopausal symptoms
  - nocturnal autonomic hyper arousal across menstrual cycle (HR) → could be a factor in etiology of MTI ²
  - Use of HRT (E) reduces insomnia Santoro Menopause 2016
- **Pregnancy**: over course insomnia rates worsen
- Chronic Insomnia pre-partum predicts increase post partum pain ³

¹Ibrahim,Foldvary ²de Zambotti et al Psychneuroend 2017 ³de ZSivertesen et al Eur J Ob Gyn Repro Bio 2017
**Insomnia in Children**

- **Atopic illness (Eczema, Asthma)** ¹
- **ADHD children/adolescents (5% children):** ² 30-70% have insomnia, highest prevalence in combined type
- **Autistic spectrum disorder** questionnaire studies- higher rate of insomnia compared with other disabilities ³ Sleep problems (44-83%) ⁴
- **Chronic Headaches** (poor sleep in childhood, risk of headaches later, bidirectional relationships) ⁵
- **Chronic illness/chronic pain/psych**


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**Medications and Insomnia**

- Sympathomimetic amines (e.g. xanthines, caffeine, β2 agonists, decongestants)
- Antidepressants (MAO inhibitors, SNRIs)
- CNS stimulants (e.g. Methylphenidate)
- Hormones (steroids → in am, progesterone → use at night)
- Alcohol → middle insomnia
- Nicotine → stimulant
- Opiods → fragmented sleep/apnea
- Diphenhydramine → RLS
- Sleep inducing meds taken during day → naps, consider timing/dosage change
Comorbid Sleep disorders and Insomnia

- **Obstructive Sleep apnea:** many persons may present with insomnia, have comorbid insomnia (up to 50%)
- **RLS/PLMD—** effects sleep onset, possibly sleep maintenance as well

RLS- Restless Legs Syndrome
PLMD- Periodic limb movement disorder
2-Process Model of Sleep regulation

CIRCADIAN RHYTHMS

SLEEP-WAKE HOMEOSTATIS

GENES

EXTERNAL FACTORS (food, stress, social, meds, temp)

Sleep-Wake Cycle

Neurotransmitters in Wake

<table>
<thead>
<tr>
<th>Neurotransmitter (Activating/Arousal Promoting)</th>
<th>Location</th>
</tr>
</thead>
</table>
| Acetylcholine                                  | - Basal forebrain  
                                                | - Pedunculopontine tegmentum (PPT)/laterodorsal tegmentum (LDT) |
| Dopamine                                       | - Ventral periaqueductal gray matter  
                                                | - Substantia nigra |
| Glutamate                                      | - Ascending reticular activating system  
                                                | - Thalamocortical system |
| Histamine                                      | - Tuberomamillary nucleus (TMN)/posterior hypothalamus |
| Hypocretin/Orexin                              | - Lateral hypothalamus |
| Norepinephrine                                | - Locus ceruleus (LC) |
| Serotonin                                      | - Dorsal raphe nuclei (DR), thalamus |

Neurotransmitters in Sleep

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<tr>
<td>Adenosine</td>
<td>Basal forebrain</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Pineal gland</td>
</tr>
<tr>
<td>GABA (located in 30% of all brain synapses)</td>
<td>Ventrolateral preoptic nucleus (VLPO)</td>
</tr>
<tr>
<td>Galanin</td>
<td>Ventrolateral preoptic nucleus (VLPO)</td>
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Sleep Wake Mechanisms

WAKE “Switch”

“Flip-Flop Switch”

SLEEP “Switch”

Brown et al., Physiol Rev 2012

Models for Insomnia Etiology:  
**Hyperarousal**

- Increased basal metabolic rate
- Elevated levels of circulating catecholamines
- Increased hypothalamic-pituitary-adrenal axis activity: Elevated CRH/ACTH/Cortisol
- Increased body temperature
- Reduced parasympathetic tone
- Elevated beta/EEG cortical activation

From Morin et al Nature Review 2015
Models for Insomnia Etiology: Circadian/Homeostatic Dysfunction

Decreased Homeostatic Sleep Drive:
Less total sleep at night but no increased sleepiness on objective testing
Neurophysiologic abnormality

Model for Chronic insomnia
Spielman Model: Three “P” factors

Adapted from Erman MK Primary Psych. 2007
Current research in insomnia

- Paradoxical insomnia
  - Objective measures see “sleep” and patients do not feel it
- Perception of sleep

Where in the brain is insomnia?

Resting State Networks: functional MRI

Insights on relationships b/w functional connectivity and structural connectivity

- RS-fMRI to assist in diagnosis of disorders of consciousness.
  - ADHD, Autism
- Negative correlation between the connectivity of the DMN and level of consciousness impairment

Surface plots of RSN: A: Default mode; B: Somatomotor network; C: Visual; D: Language E: Dorsal attention; F: Ventral attention; G: Frontoparietal control network. Lee and Shimony 2013 Am J Neuroradiol
Conclusions from PET Studies

- Default Mode Networks
  - Decreased precuneousum volume

- Executive
  - Decreased grey matter concentration in dorsolateral

Taylor 2012 Social Cognitive affect Neuroscience
CBT to reduce DMN activity

Conceptual model of insomnia 2015 Buysse

Genetic
Other predisposing factors
Precipitating factor
Network Dysregulation
Sleep Disruption
Tx
INSOMNIA
Conceptual Framework of Sleep health

Reciprocal relationships factors

Daniel J. Buysse Sleep 2014

Are you SATED?

- Measuring sleep Health
- Able to measure sleep PRIOR to problems with sleep
- Large scale efforts on wellness

- S: Satisfaction with sleep
- Alertness during waking hours
- T Timing of sleep
- E: Sleep Efficiency
- D Sleep Duration

Daniel J. Buysse Sleep 2014
Summary

- Insomnia is a common disorder especially with comorbid conditions and psychiatric illness
- Attention is needed in high prevalence groups and sometimes evaluation of comorbid sleep disorders is needed
- Comprehensive evaluation of etiology and understanding pathophysiology can guide further treatment

Cleveland Clinic

Every life deserves world class care.

And good sleep