Treatment of Insomnia:
“the use and misuse of hypnotic agents”

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  – Anthem Insurance, Multiple Energy Technologies

• Patents: None

Revised 2/29/16
Learning Objectives

• The participant will be able to describe the benefits of hypnotics
• The participant will be able to describe the risks of hypnotics
• The participant will be able to describe the alternatives to hypnotics
True/False Active Learning Exercise

- The diagnosis of insomnia disorder requires sleep laboratory confirmation  T/F ?

True/False Active Learning Exercise

• The diagnosis of insomnia disorder requires sleep laboratory confirmation

False!

What is Insomnia? Per DSM-5

• Insomnia symptoms:
  – trouble falling asleep, staying asleep, or waking too early (note there is no time dimension to the sleep complaints)

• Insomnia Disorder (per DSM-5):
  – Insomnia symptoms, associated with distress or impairment (i.e., irritability, fatigue, concentration problems, etc.)
  – At least 3 nights per week, for at least 3 months

• Note there is no lab testing required!

Some Forms of Chronic Insomnia Do Fit the Medical Model:

• Insomnia due to:
  – Respiratory:
    • Nocturnal asthma
    • COPD
    • CHF(with Cheyne Stokes)
  – Pain
  – Neurological
    • RLS
Even the Primary (idiopathic) forms of insomnia seem to have some physiologic basis:

- Brain areas that fail to show the expected decrease in PET activity in the transition from wake to sleep in insomniacs

DSM-IV Diagnoses in Chronic Insomnia

Percent of Patients

- Mental Disorder: 50%
- Primary Insomnia: 20%
- DSPS: 5%
- OSAS: 3%
- Medical Disorder: 2%

N=216

DSPS=delayed sleep phase syndrome
OSAS=obstructive sleep apnea syndrome

Why do we care about insomnia??

Insomnia as a Precursor to Psychiatric Disorder

• Unresolved insomnia ↑ the odds of new Ψ disorder over one year (especially major depression episode (MDE) and panic disorder)¹

• Unclear whether preceding insomnia is an early symptom of MDE or a modifiable risk factor

¹. Ford and Kamerow JAMA 1989
Persistent Insomnia and Subsequent Psychiatric Disorders

At 1-Year Follow-Up

- Resolved Insomnia
  - Any Psychiatric Disorder: 12.7%
  - Major Depression: 0.6%
  - Anxiety Disorders: 7.4%
  - Alcohol Abuse: 2.5%

- Unresolved Insomnia
  - Any Psychiatric Disorder: 33.6%
  - Major Depression: 14%
  - Anxiety Disorders: 25.6%
  - Alcohol Abuse: 3.4%

Adapted from Ford DE and Kamerow DB, 1989.
Why do we care about insomnia??

Insomnia During MDE

• Insomnia is an independent contributor towards poor quality of life in depressed patients\(^1\)

• Insomnia predictive of suicide\(^2\)


2. McCall WV. Insomnia is a risk factor for suicide – what are the next steps? Sleep 2011;34:1149-1150
Evidence linking Insomnia to Suicide

- Relative risk up to 2.4
- Includes 5 prospective studies of completed suicide
- Nightmares may represent an independent risk separate from insomnia
Why is insomnia a risk factor for suicidal thinking, suicidal behavior, and suicide death? – Psychological factors

DOI: 10.1017/S0033291703008092 Printed in the United Kingdom

**BRIEF COMMUNICATION**

Problem-solving in suicide attempters

L. R. POLLOCK\(^1\) AND J. M. G. WILLIAMS

From the Institute of Medical and Social Care Research, University of Wales, Bangor; and University of Oxford, Department of Psychiatry, Warneford Hospital, Oxford

- Compared with a non-suicidal psychiatric control group, on psychological tests, suicidal patients produce more passive and more ineffectual responses when presented with a problem to solve
Patients with MDD (N=215) received a fixed dose of fluoxetine 20 mg for 8 weeks. Presence of residual symptoms not predicted by baseline demographic characteristics or Axis I and Axis II comorbid conditions.

Non-pharmacologic Treatment of Insomnia

- Generally reserved for chronic insomnia
- Includes changes in diet and activity such as elimination of caffeine and alcohol
- Includes specific behavioral therapies such as sleep restriction and stimulus control therapy
- Are efficacious in controlled clinical trials of primary insomnia, with some evidence for efficacy in psychiatric insomniacs

Active Learning Exercise

• 1. The principal advantage of hypnotic medications over non-pharmacologic strategies for insomnia is that:
  – Hypnotics increase total sleep time more than non-pharmacologic strategies
  – Hypnotics reduce sleep latency more than non-pharmacologic strategies
  – Hypnotics improve sleep quality more than non-pharmacologic strategies
Active Learning Exercise

• 1. The principal advantage of hypnotic medications over non-pharmacologic strategies for insomnia is that:
  
  – **Hypnotics increase total sleep time more than non-pharmacologic strategies**
  – Hypnotics reduce sleep latency more than non-pharmacologic strategies
  – Hypnotics improve sleep quality more than non-pharmacologic strategies
Short-term Treatment Effects: Behavioral Therapy (BT) vs. Pharmacotherapy (PCT)

Morin et al., 1994; Murtagh & Greenwood, 1995; Nowell et al., 1997; Smith et al., 2002
Active Learning Exercise

2. Six months after the completion of a course of non-pharmacologic therapy for insomnia, the gains made during treatment have typically:
   - Been lost
   - Stayed the same
   - Continued to improve
Active Learning Exercise

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   - Stayed the same
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Durability of Therapeutic Benefits of Behavioral Insomnia Therapies
(Follow up: 6 months)

Pharmacologic Treatment of Insomnia

- Melatonin/Valerian
- Sedating antihistamines and antidepressants
- Benzodiazepines
- Non-benzodiazepine benzodiazepine receptor agonists
- Melatonin-1 receptor agonist
- Low-dose doxepin
- Orexin-1 receptor blockers

Figure 1—Prescription medication commonly used for insomnia (MCUFI), past month: 1999-2010. *Unreliable estimate (n < 30). **P value for trend < 0.001.
Z-meds: eszopiclone, zaleplon, zolpidem.
Melatonin/Valerian

• Melatonin
  – Weak or absent efficacy when used by insomniacs at bedtime.
  – Perhaps more effective for circadian rhythm disorders than for insomnia\(^1\)
  – Concerns about purity of commercially available melatonin
  – L-tryptophan and eosinophilia myalgia syndrome

• Controlled trials of valerian have mixed results\(^2\)
TRZ in insomnia that persists during antidepressant treatment

- Drug of first choice by 78% of psychiatrists treat SSRI-related insomnia\(^1\)
- TRZ has some PSG-proven efficacy in primary insomniacs, but it is associated with memory deficits \(^2\)

1. Dording CM et al., 2002
3. Which of the following is an orexin receptor blocker?
- Ramelteon
- Suvorexant
- Zaleplon
Active Learning Exercise

3. Which of the following is an orexin receptor blocker?
   - Ramelteon
   - Suvorexant
   - Zaleplon
FDA- Approved Hypnotics

- Barbiturates and related compounds:
  - Ethchlorvynol
  - Chlora Hydrate
- Benzodiazepines (BZ)
  - Flurazepam
  - Temazepam
  - Triazolam
  - Estazolam
  - Quazepam
- Non-BZ-BZRA
  - Zolpidem
  - Zolpidem CR
  - Zaleplon
  - Eszopiclone
- Melatonin receptor agonists
  - Ramelteon
- Low dose doxepin
- Orexin1 receptor blockers
  - suvorexant
Benzodiazepine Hypnotics

- Efficacy established in persons with primary insomnia\(^1\)
- Efficacy established with both subjective reports and PSG
- Efficacy established against placebo with nightly use up to 4-5 weeks
- Efficacy independently established in older persons

1. JAMA 1997;278:2170-7
Benzodiazepine Hypnotics

• Problems:
  – Tolerance, dependence, abuse
  – Daytime sleepiness, delayed reaction time
  – Falls, amnesia, behavioral disinhibition
Non-benzodiazepine benzodiazepine receptor agonists

• Zolpidem, Zaleplon, (Es)Zopiclone
• Approved for open-ended use (RCT up to 6 months)
• Hypnotic efficacy medicated through the benzodiazepine receptor
  – More selective for Benzo Type I
• Pharmacokinetic and dynamic differences may explain differences in therapeutic and residual side effects
A Comparison of The Pharmacokinetic Profiles Of Different Hypnotics Following Single Administration Of The Usual Adult Dose
Ambien CR™ Pharmacokinetics

- half-life = 2.8 h
- $t_{max} = 1.5$ h

- Rapid initial absorption
- Extended plasma concentrations beyond 3 hours
  - Ambien CR vs zolpidem immediate-release

Ambien CR Prescribing Information.
Eszopiclone Sleep Onset Effect with Chronic Administration

Adult, pt-reported
N=788

‡

P ≤ 0.0001 vs PBO

Krystal et al. SLEEP. 2003;26;793-799.
6-mos, open-label, extension trial – data on file Sepracor Inc.

‡‡‡ ‡‡
Eszopiclone Sleep Maintenance Effect with Chronic Administration

**P ≤ 0.01, ‡‡P ≤ 0.0001 vs PBO

Kryzstal et al. SLEEP. 2003;26;793-799.
6-mos, open-label, extension trial – data on file Sepracor Inc.
True/False Active Learning Exercise

- Eszopiclone is approved for open-ended duration of use T/F?
True/False Active Learning Exercise

• Eszopiclone is approved for open-ended duration of use
  True!
Eszopiclone (ESZ) as add-on Treatment for SSRI in Depression

- 60 depressed adults with insomnia all given open label FLX 20 mg, and randomized to ESZ 3 mg versus placebo at bedtime for 8 weeks
- Improvement in all subjective sleep measures, and a greater rate of antidepressant response in those receiving ESZ (80%) versus those receiving placebo (38%)

Adults with Chronic Insomnia – 6 Months

Latency to Persistent Sleep (PSG)

Mean Latency to Persistent Sleep (min)

Weeks of Treatment

Baseline 3 6 9 12 15 18 21 24

Placebo (n = 224)
Ramelteon (n = 227)

P < .001  P = .003  P = .021  P = .020  P = .004

EC302.
PSG = polysomnography.
Last observation carried forward (LOCF).
Least-squared mean LPS, with standard error.

Low dose doxepin in older insomniacs

- Low-dose doxepin reduces WASO compared to placebo in 240 elderly primary insomniacs (>65 yo)

![Graph showing sleep efficiency % by hour on night 1 with P-values for 1 mg and 3 mg vs placebo.

Figure 2—Effects of doxepin 1 mg and 3 mg versus placebo across the 8-hour night: sleep efficiency % by Hour on Night 1.

Krystal et al. Sleep 2010; 33:15531561
Orexin receptor blockers

- Suvorexant
Suvorexant 30/40 mg versus placebo for one year in 445 adults with chronic insomnia

<table>
<thead>
<tr>
<th>Diary measures†</th>
<th>Suvorexant, N=298*</th>
<th>Placebo, N=147*</th>
<th>Difference</th>
<th>p value</th>
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<tbody>
<tr>
<td>sTST, min</td>
<td>60.5 (54.0 to 66.9)</td>
<td>33.0 (23.7 to 42.2)</td>
<td>27.5 (16.2 to 38.8)</td>
<td>&lt;0.0001</td>
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<tr>
<td>sTSO, min</td>
<td>-26.6 (-30.5 to -22.7)</td>
<td>-17.0 (-22.6 to -11.4)</td>
<td>-9.7 (-16.5 to -2.9)</td>
<td>0.0055</td>
</tr>
<tr>
<td>sWASO, min</td>
<td>-33.5 (-37.4 to -29.7)</td>
<td>-23.8 (-29.3 to -18.3)</td>
<td>-9.7 (-16.5 to -3.0)</td>
<td>0.0048</td>
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# Newer Hypnotics

<table>
<thead>
<tr>
<th></th>
<th>Ramelteon</th>
<th>Doxepin</th>
<th>Suvorexant</th>
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</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Melatonin agonist</td>
<td>H1 antagonist</td>
<td>Orexin antagonist</td>
</tr>
<tr>
<td>Dose – mg [elderly]</td>
<td>8</td>
<td>3,6 [3]</td>
<td>5-20</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (hours)</td>
<td>0.75</td>
<td>3.5</td>
<td>2</td>
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<tr>
<td>Half-life [elderly] (hrs.)</td>
<td>1-2.6</td>
<td>15.3</td>
<td>12</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>↓</td>
<td>--</td>
<td>↓</td>
</tr>
<tr>
<td>Wake After Sleep Onset</td>
<td>--</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Total sleep time</td>
<td>--</td>
<td>--</td>
<td>↑</td>
</tr>
<tr>
<td>Schedule</td>
<td>None</td>
<td>None</td>
<td>IV</td>
</tr>
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Psychiatric Correlates of Insomnia

Principles of Treatment

• Insomnia is worth treating
• Improvements can be made in insomnia without prescribing a medication
• Hypnotic medication can improve quality of life
• Consider suicide risk (both with and without hypnotic treatment)
Reducing Suicidal Ideation Through Insomnia Treatment: (REST-IT)

Call 706-721-1011 !!
Questions?

Thank You!