Addressing Sleep: A Strategy for Symptom Reduction & Suicide Prevention

Wilfred R. Pigeon, PhD
Professor of Psychiatry & Public Health Sciences
University of Rochester Medical Center

Executive Director, Center of Excellence for Suicide Prevention
U.S. Department of Veterans Affairs
Acknowledgements & Disclosures

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• National Institutes of Health: R01 NR013909; R01 CA175053; R21 AG041942; K23 NR010408; F32 NS049789; R21 AG023956; L30 MH087269
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• VA Center of Excellence for Suicide Prevention
• American Sleep Medicine Foundation

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No conflicts to report.

Disclaimer:
The views or opinions expressed in this talk do not represent those of the Department of Veterans Affairs or the United States Government.
1. Sleep Disturbance (e.g., insomnia) exacerbates and causes medical and psychiatric morbidity

Poor Sleep/Sleep Duration associated with:

- All-cause mortality
- Metabolic syndrome
- Diabetes/glucose control
- Hypertension
- Coronary heart disease
- Depression
- Neurobehavioral performance decrements
1. Sleep Disturbance (e.g., insomnia) exacerbates and causes medical and psychiatric morbidity.

**Sleep Deprivation in the Rat:**

Totally sleep deprived rats died within 11-32 days ... with lesions & weight loss despite higher caloric intake than yoked controls that remained healthy.

*Emerson, Bergmann & Rechtshaffen, SLEEP, 12(1) 1989*
1. Sleep Disturbance (e.g., *insomnia*) exacerbates and causes medical and psychiatric morbidity

2. The efficacy, effectiveness and limited AE profile of *Cognitive Behavioral Therapy for Insomnia* (CBT-I) ‘should’ make Rx of hypnotics rare

**Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians**

**Recommendation 1:** All adult patients receive CBT-I as the initial treatment for chronic insomnia disorder.

**Recommendation 2:** Clinicians use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to add pharmacological therapy in adults with chronic insomnia disorder in whom CBT-I alone was unsuccessful.
An Outline in Four Premises

1. Sleep Disturbance (e.g., *insomnia*) exacerbates and causes medical and psychiatric morbidity

2. The efficacy, effectiveness and limited AE profile of CBT-I ‘should’ make Rx of hypnotics rare

3. Treating insomnia improves more than sleep

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Single Arm 8-Session CBT-I for Combat Veterans (N=15)

An Outline in Four Premises

1. Sleep Disturbance (e.g., insomnia) exacerbates and causes medical and psychiatric morbidity
2. The efficacy, effectiveness and limited AE profile of CBT-I ‘should’ make Rx of hypnotics rare
3. Treating insomnia improves more than sleep
4. CBT-I is an anti-depressant with suicide preventing side effects

Single Arm 8-Session CBT-I for Combat Veterans (N=15)

1. Insomnia & Morbidity: (a) PTSD

- Disrupted sleep mediates relationship between PTSD and medical morbidity
- Nightmares respond to PTSD Tx; Insomnia, not so much.
- The presence of insomnia reduces PTSD remission rates

Prevalence (%) of Nightmares & Insomnia among Vietnam Era Combat Veterans

<table>
<thead>
<tr>
<th>Without PTSD</th>
<th>With PTSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nightmares</td>
<td>0%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>100%</td>
</tr>
</tbody>
</table>

Clum, Nishith & Resick, J Nerv Mental Dis. 2001;189:618-22
1. Insomnia & Morbidity: (a) PTSD

6-Month Observational Study of Iraq/Afghanistan Veterans (N=72)

- Disrupted sleep mediates relationship between PTSD and medical morbidity
- Nightmares respond to PTSD Tx; Insomnia, not so much.
- The presence of insomnia reduces PTSD remission rates

- Insomnia predicts 6 Mo PTSD severity (ANCOVA; p=.005)
- Baseline insomnia associated with higher rate of PTSD (38%) vs, No insomnia (5%)

Clum, Nishith & Resick, J Nerv Mental Dis. 2001;189:618-22

1. Insomnia & Morbidity: (b) Depression

Incidence of Subsequent Depression
No Insomnia 4.0%
Baseline Insomnia 13.1%

OR = 2.1 [95% CI: 1.9-2.4]

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Ford and Kamerow 1989 [79]
Vollrath et al. 1989 [70]
Kennedy et al. 1991 [73]
Dryman and Eaton 1991 [69]
Hohagen et al. 1993 [76]
Livingston et al. 1993 [77]
Bredau et al. 1996 [68]
Weismann et al. 1997 [71]
Roberts et al. 2000 [78]
Livingston et al. 2000 [72]
Perlis et al. 2006 [76]
Paffenbarger et al. 1994 [80]
Chang et al. 1997 [82]
Mallon et al. 2000 [81]
1. Insomnia & Morbidity: (b) Depression

Insomnia as Prodrome to MDD Episodes

Insomnia blunts Depression Tx Response

Adjusted Odds Ratios of Remaining Depressed (SCID MDD) for Persistent Insomnia Compared to No Insomnia

Odds ratios adjusted for intervention arm, baseline depression severity and number of chronic illnesses.

Perlis et al., *J Affective Disorders*, 1997

1. Insomnia & Morbidity: (c) Suicide

Relative Risk of Ideation, Attempts & Suicide in the Presence of Any Sleep Disturbance (relative no sleep disturbance)

- Unadjusted RR (95% CI)
- Adjusted RR (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted RR</th>
<th>Adjusted RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ideation (k=33)</td>
<td>2.95</td>
<td>1.86</td>
</tr>
<tr>
<td>Attempt (k=15)</td>
<td>3.13</td>
<td>2.01</td>
</tr>
<tr>
<td>Suicide (k=8)</td>
<td>1.95</td>
<td>1.96</td>
</tr>
<tr>
<td>All (k=56)</td>
<td>2.79</td>
<td>1.91</td>
</tr>
</tbody>
</table>

1. Insomnia & Morbidity: (c) Suicide

Relative Risk of Ideation, Attempts & Suicide in the Presence of Insomnia (relative no insomnia)

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted RR (95% CI)</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ideation</strong> (k=18)</td>
<td>2.79 (1.80-3.96)</td>
<td>2.00 (1.30-3.15)</td>
</tr>
<tr>
<td><strong>Attempt</strong> (k=8)</td>
<td>3.54 (2.12-5.86)</td>
<td>2.40 (1.70-3.38)</td>
</tr>
<tr>
<td><strong>Suicide</strong> (k=6)</td>
<td>2.43 (1.60-3.69)</td>
<td>1.94 (1.40-2.70)</td>
</tr>
<tr>
<td><strong>All</strong> (k=32)</td>
<td>2.84 (2.20-3.69)</td>
<td>2.15 (1.90-2.45)</td>
</tr>
</tbody>
</table>

Unadjusted RR (95% CI): Relative Risk of Ideation, Attempts & Suicide in the Presence of Insomnia (relative no insomnia). Adjusted RR (95% CI): Relative Risk of Ideation, Attempts & Suicide in the Presence of Insomnia (relative no insomnia).
1. Insomnia & Morbidity: (c) Suicide

Insomnia & Ideation among Veterans referred to Behavioral Telehealth (N=654)

Multiple Regression analysis controlling for age, gender, etoh, depression  \( p < .01 \)


Time to Death among Veteran Suicide Decedents (N=381)

Premise 2: Why CBT-I and Not Sedative-Hypnotics

1. CPGs, meta-analyses, comparative meta-analyses & head-to-head trials


Premise 2: Why CBT-I and Not Sedative-Hypnotics

1. CPGs, meta-analyses, comparative meta-analyses & head-to-head trials

2. Humans engage in sleep-interfering behaviors and cognitions

“Sleep is the most moronic fraternity in the world, with the heaviest dues and the crudest rituals.”

---Vladimir Nabokov
Premise 2: Why CBT-I and Not Sedative-Hypnotics

1. CPGs, meta-analyses, comparative meta-analyses & head-to-head trials
2. Humans engage in sleep-interfering behaviors and cognitions
3. Limited adverse events

“We suggest that clinicians not use trazodone as a treatment for sleep onset or sleep maintenance insomnia (vs. no treatment) in adults.”

“We harm outweighs benefits.”

Premise 2: Why CBT-I and Not Sedative-Hypnotics

1. CPGs, meta-analyses, comparative meta-analyses & head-to-head trials
2. Humans engage in sleep-interfering behaviors and cognitions
3. Limited adverse events

Table 6: Adjusted Incidence of Suicide Attempts by Index Prescription: Zolpidem versus Trazodone

<table>
<thead>
<tr>
<th>Agents</th>
<th>N</th>
<th>Suicide Attempts per 100,000 person yrs</th>
<th>Adjusted HR Suicide Attempt (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trazodone</td>
<td>76,215</td>
<td>76.3</td>
<td>1.61 (1.07-2.43)</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>76,215</td>
<td>50.9</td>
<td></td>
</tr>
</tbody>
</table>
Premise 2: Why CBT-I and Not Sedative-Hypnotics

1. CPGs, meta-analyses, comparative meta-analyses & head-to-head trials
2. Humans engage in sleep-interfering behaviors and cognitions
3. Limited adverse events
4. Wide effectiveness

CBT-I efficacy has been demonstrated in a wide range of populations including in patients with:

- Depression, Anxiety & PTSD
- Chronic Pain
- Cancer (post-chemo/radiation therapy)
- Bipolar Disorder
- Delusions & Hallucinations

### Premise 2: Why CBT-I and Not Sedative-Hypnotics

1. CPGs, meta-analyses, comparative meta-analyses & head-to-head trials
2. Humans engage in sleep-interfering behaviors and cognitions
3. Adverse events
4. Wide effectiveness
5. **You can do it here or there**
Premise 3: Treating insomnia improves more than sleep

A. In Patients with Chronic Pain

Baseline Assessments
Self-report battery
Screening Polysomnography

Randomization (N=28 @ 2:1)

8 wk CBT-I (n = 19)
Attention CTRL (n = 9)

Post-Tx, 3 Mo & 6 Mo Assessments

NIH Support: R21 NR009080

Jungquist, et al., Sleep Medicine, 2010; 11(3):302-09.
3: CBT-I improves more than sleep: (a) Pain-1

Adults with Chronic Neck or Back Pain

Effect Sizes (Hedges $g$): CBT-I vs. CTRL

Baseline Assessments
Self-report battery
Screening Polysomnography

Randomization (N=28 @ 2:1)

8 wk CBT-I
(n = 19)

Attention CTRL
(n = 9)

Post-Tx, 3 Mo & 6 Mo Assessments

3: CBT-I improves more than sleep: (a) Pain-2

Adults with Chronic Neck or Back Pain

Baseline Assessments
Self-report battery
Polysomnography
Blood Draws

Randomization (N=22)
CTRL    CBT-P Only    CBT-I Only    CBT-P + CBT-I

Insomnia Severity Pre-Post

CTRL    CBT-P    CBT-I    CBT-I/P

NIH Support: F32 NS049789

3: CBT-I improves more than sleep: (a) Pain-2

Effect Sizes (Hedges $g$): CBT-I vs. CTRL

- Insomnia Severity: 1.64
- Pain Disability: 0.27
- Depression: 3.86
- Fatigue: 0.78

NIH Support: F32 NS049789
3: CBT-I improves more than sleep: (a) Pain-3

Heffner, et al., Clinical J Pain. 2018; 34(12):1133-1140

NIH Support: R21 AG041942
3: CBT-I improves more than sleep: (a) Pain-3

NIH Support: R21 AG041942
3: CBT-I improves more than sleep: (b) PTSD/MDD

A. In Patients with Chronic Pain

B. In Patients with PTSD & MDD

A Randomized Clinical Trial of CBT-I for Survivors of Interpersonal Violence

Inclusion: Exposure to IPV in past yr; + PTSD + MDD + Insomnia

1. Will CBT-I improve insomnia, PTSD and depression Sxs?

2. Does sequential delivery of CBT-I and Cognitive Processing Therapy (CPT) improve PTSD & depression, compared to CPT alone?

3. Does sequential treatment enhance response rates achieved by CPT alone?

Recruitment: Family Court & DV Shelter

<table>
<thead>
<tr>
<th>Process</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approached</td>
<td>2,572</td>
</tr>
<tr>
<td>Screened</td>
<td>797</td>
</tr>
<tr>
<td>Consented</td>
<td>220</td>
</tr>
<tr>
<td>Eligible</td>
<td>138</td>
</tr>
<tr>
<td>Randomized</td>
<td>110</td>
</tr>
</tbody>
</table>

CBT-I (56)  CTRL (54)

Screened Sample  % or $M(SD)$

**Insomnia**
- Absent (0-7) 18.6 (6.0) 5%
- Mild (8-14) 17%
- Moderate (15-21) 43%
- Severe (22-28) 35%

**PTSD (PCL)**
- ≥ 45 cutpoint 59.6 (14.2) 84%

**Depression (PHQ)**
- None-mild (0-9) 15.7 (5.6) 15%
- Moderate (10-14) 22%
- Severe (15-24) 63%

CBT-I improves more than sleep: (b) PTSD/MDD

### Demographic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>37.3 (10.8)</td>
</tr>
<tr>
<td>Hispanic/Latina</td>
<td>12%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>49%</td>
</tr>
<tr>
<td>Black/AA</td>
<td>38%</td>
</tr>
<tr>
<td>Other/Multi</td>
<td>13%</td>
</tr>
<tr>
<td>Income</td>
<td></td>
</tr>
<tr>
<td>Under $20,000</td>
<td>63%</td>
</tr>
<tr>
<td>20,000-60,000</td>
<td>28%</td>
</tr>
<tr>
<td>60,000+</td>
<td>9%</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>&lt; High School</td>
<td>15%</td>
</tr>
<tr>
<td>High School</td>
<td>15%</td>
</tr>
<tr>
<td>Some College</td>
<td>44%</td>
</tr>
<tr>
<td>Bachelors+</td>
<td>26%</td>
</tr>
</tbody>
</table>

### Clinical Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISI Score</td>
<td>20.3 (4.1)</td>
</tr>
<tr>
<td>HAM-D Score</td>
<td>24.2 (5.1)</td>
</tr>
<tr>
<td>CAPS Score</td>
<td>75.2 (15.4)</td>
</tr>
<tr>
<td>Fear of Sleep</td>
<td>36.2 (19.8)</td>
</tr>
<tr>
<td>Suicidal Ideation</td>
<td>32%</td>
</tr>
<tr>
<td>Antidepressant Rx</td>
<td>17%</td>
</tr>
<tr>
<td>Court Order of Protection</td>
<td>89%</td>
</tr>
<tr>
<td># Traumatic Life Events</td>
<td>5.2 (2.4)</td>
</tr>
</tbody>
</table>
3: CBT-I improves more than sleep: (b) PTSD/MDD

Interventions

- **CBT-I:**
  - Four (4) Individual Sessions over 5 weeks

- **CPT:**
  - Twelve (12) Individual Sessions over 12-16 wks

NIH Support: R01 NR013909
3: CBT-I improves more than sleep: (b) PTSD/MDD

Results following CBT-I vs. CTRL

- **Insomnia Severity**
  - p < .001; ES = 1.08

- **Depression Severity**
  - p < .001; ES = 0.99

- **PTSD Severity**
  - p < .01; ES = 0.47

NIH Support: R01 NR013909

3: CBT-I improves more than sleep: (b) PTSD/MDD

Results following; CBT-I + CPT vs. CTRL + CPT

**Depression (HAM-D):** $p < .01; ES = 0.82$

**PTSD Severity (CAPS):** $p = .06; ES = 0.53$

NIH Support: R01 NR013909
3: CBT-I improves more than sleep: (b) PTSD/MDD

Results following: CBT-I + CPT vs. CTRL + CPT

**Depression Response Rate:** $p < .05$

![Depression Response Rate Chart](chart1.png)

**PTSD Response Rate:** $p < .051$

![PTSD Response Rate Chart](chart2.png)

Premise 4: CBT-I will Reverse Climate Change
Premise 4: CBT-I = Suicide Prevention

# 4: CBT-I = Suicide Prevention

<table>
<thead>
<tr>
<th>An RCT of Brief CBT-I vs. TAU in VA Primary Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=50 Randomized:</td>
</tr>
<tr>
<td>• Veterans in VA PC endorsing SI (without intent) + Insomnia + MDD and/or PTSD;</td>
</tr>
<tr>
<td>• identified from electronic medical record DXs</td>
</tr>
<tr>
<td>• recruited by introductory letter from their PCP</td>
</tr>
<tr>
<td>• assessed and treated in a co-located PC office</td>
</tr>
<tr>
<td>• progress notes co-signed by PCP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Brief = Two 30-40 min. sessions + Two 15-20 min. phone sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Insomnia Severity Index (ISI)</td>
</tr>
<tr>
<td>• Patient Health Questionnaire (PHQ-9)</td>
</tr>
<tr>
<td>• PTSD SX Checklist-Military Version (PCL-M)</td>
</tr>
<tr>
<td>• Columbia-Suicide Severity Rating Scale (C-SSRS)</td>
</tr>
<tr>
<td>– Suicidal Ideation (0-5 categorical scale)</td>
</tr>
<tr>
<td>– Intensity of Ideation (5 items, 1-25 continuous scale)</td>
</tr>
<tr>
<td>– Suicidal Behaviors</td>
</tr>
</tbody>
</table>

VA Support: I21 HX001616
CBT-I vs. Treatment-as-Usual: N=50 Veterans w/ Suicidal Thoughts

- **Insomnia Severity**
  - $p < .001$; $ES = 1.79$

- **Depression Severity**
  - $p < .01$; $ES = 1.13$

- **PTSD Severity**
  - Not Significant

VA Support: I21 HX001616
4: CBT-I = Suicide Prevention?

Wow!

ρ = 0.153; ES = 0.44
Brief CBT-I delivered in primary care reduced Sx severity by 50-60% for:

- Insomnia
- Depression
- Suicidal Thoughts

Compared to 1-25% for Treatment as Usual

VA Support: I21 HX001616
Summary

1. Sleep Disturbance (e.g., insomnia) exacerbates and causes medical and psychiatric morbidity

2. The efficacy, effectiveness and limited AE profile of CBT-I ‘should’ make Rx of hypnotics rare

3. Treating insomnia improves more than sleep

4. CBT-I is an anti-depressant with suicide preventing side effects

“The best bridge between despair and hope is a good night's sleep.”

-- E. Joseph Cossman
Thank You.... Closing Thoughts/Discussion
Insomnia & Depression: A parallel process model

Figure 3. Etiology and pathophysiology of insomnia and depression. The box delineating the homeostatic and circadian factors is highlighted because the neurobiological control mechanisms are not detailed.

Cognitive–behavioral domain

- Psychosocial stress
- Stress-related problem solving and worry
- Problems with SL & WASO
- Reduced TST
- Sleep/depression related worry
- Selective attending to sleep/depression-related stimuli
- Attentional bias to daytime consequences of insomnia
- Behavioral adaptation
- Extended sleep opportunity
- Remain in bed awake
- Altered exposure to light during the sleep period
- Conditioning effects
- Depression

Acute insomnia
Subchronic insomnia
Chronic insomnia

Adaptive insomnia
Maladaptive insomnia

- ▲ Monoamines
- ▲ Acetylcholine
- ▲ Cortisol
- ▲ Orexin
- ▲ Adenosine
- ▼ 5-HT
- Acute change within one or both branches of the auras and/or the VLPO
- Acute cortical hyperarousal
- Homeostatic and circadian dysregulation
- Chronic changes within one or both branches of the auras and/or the VLPO
- Chronic cortical hyperarousal
- Depression

Neurobiologic–Neurocognitive Domain

5-HT: serotonin; SL: sleep latency; TST: total sleep time; VLPO: ventrolateral preoptic area of the hypothalamus; WASO: wake after sleep onset.

Pigeon & Perlis; Int J Sleep Dis; 2007; 1:82-91
Future Directions

- Bishop Apnea
- Adolescents – C. Glenn
- Stecker---
- Combined/sequential Txs
- Sleep as a ‘Mechanism’ in Cancer
- Sleep as a mechanism in early dementia
Please enter your questions in the Q&A box and be sure to include your email address.

The lines are muted to avoid background noise.
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- **Attendance**: Join via TMS and listen to the lecture.
- **Evaluation**: Posttest is no longer required for this lecture. Return to TMS and complete evaluation. Search “My Learning” to find it.
- **Certificate**: Print certificate from “My History” section of TMS.

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# UPCOMING TOPICS

**SAVE THE DATE: Third Wednesday of the Month from 2-3PM (ET)**

<table>
<thead>
<tr>
<th>Date</th>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 18</td>
<td>Treating Comorbid PTSD and Borderline Personality Disorder</td>
<td>Melanie Harned, PhD, ABPP</td>
</tr>
<tr>
<td>January 15</td>
<td>Dissociation, Somatization, and Other Challenging Presentations of PTSD</td>
<td>Abigail Angkaw, PhD</td>
</tr>
<tr>
<td>February 19</td>
<td>Concurrent Treatment of PTSD and SUDs using Prolonged Exposure (COPE)</td>
<td>Sudie Back, PhD</td>
</tr>
</tbody>
</table>

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