TRAZODONE IN INSOMNIA COMORBID WITH DEPRESSION: AN AWAKENING LACK OF STRONG EVIDENCE

Gordon Ang, PharmD
Central Texas Veterans Health Care System
1/5/2018

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>GERD</td>
<td>Gastroesophageal reflux disease</td>
</tr>
<tr>
<td>MDD</td>
<td>Major depressive disorder</td>
</tr>
<tr>
<td>PTSD</td>
<td>Post-traumatic stress disorder</td>
</tr>
<tr>
<td>PSQI</td>
<td>Pittsburg Sleep Quality Index</td>
</tr>
<tr>
<td>CBT</td>
<td>Cognitive behavioral therapy</td>
</tr>
<tr>
<td>BzRA</td>
<td>Benzodiazepine receptor agonist</td>
</tr>
<tr>
<td>5HT-2A</td>
<td>Serotonin 2A receptor</td>
</tr>
<tr>
<td>α1</td>
<td>Alpha 1 noradrenergic receptor</td>
</tr>
<tr>
<td>H1</td>
<td>Histamine 1 receptor</td>
</tr>
<tr>
<td>SERT</td>
<td>Serotonin transporter</td>
</tr>
<tr>
<td>ECG</td>
<td>Echocardiogram</td>
</tr>
<tr>
<td>PSG</td>
<td>Polysomnography</td>
</tr>
<tr>
<td>HAM-D</td>
<td>Hamilton Rating Scale for Depression</td>
</tr>
</tbody>
</table>
Which one of the following treatment options would you use first if you had insomnia?

- Sedative hypnotic (BZD, zolpidem, eszopiclone)
- Herbal/supplement (Melatonin, valerian)
- Low dose antidepressant (Trazodone, doxepin, mirtazapine)
- Other prescription drug (suvorexant, ramelteon)
- Non-pharmacologic measures

Trazodone Drug Mentions for Treatment of Insomnia

[Graph showing the number of Trazodone drug mentions from 1987 to 1996]

Objectives

- Review insomnia pathophysiology and evaluation
- Review non-pharmacologic and pharmacologic treatment options for insomnia
- Describe pharmacodynamics and pharmacokinetics of trazodone as a hypnotic
- Analyze literature addressing trazodone for secondary insomnia
Insomnia Background

• Most common complaint in general medical practice
• “Difficulty initiating or maintaining sleep or nonrestorative sleep causing clinically significant distress or impairment in social, occupational, or other important areas of functioning”

Dopp JM, et al. Pharmacotherapy: A Pathophysiologic Approach, 10e

Common Etiologies

Situational
• Environment, life stressors, shift work

Medical
• Chronic pain, GERD, nocturia

Psychiatric
• MDD, anxiety, PTSD, bipolar disorder

Pharmacologic
• Antidepressants, stimulants, steroids, anticholinergic agents

Substance abuse
• Alcohol, caffeine, stimulants

Sleep and Wakefulness Physiology

- Brainstem, hypothalamus, basal forebrain, and midbrain contribute toward promoting wakefulness

<table>
<thead>
<tr>
<th>Neurotransmitters</th>
<th>Acetylcholine</th>
<th>Norepinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin</td>
<td>Histamine</td>
<td></td>
</tr>
<tr>
<td>Glutamine</td>
<td>Orexin</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>[208x667]</td>
<td></td>
</tr>
<tr>
<td>[190x498]Acetylcholine</td>
<td>[107x482]Norepinephrine</td>
<td></td>
</tr>
<tr>
<td>[107x482]Serotonin</td>
<td>[105x467]Glutamine</td>
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</tr>
<tr>
<td>[106x451]Dopamine</td>
<td>[95x325]Orexin</td>
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</tbody>
</table>

Sleep and Wakefulness Physiology

- Preoptic area, lateral hypothalamus, and pons promote sleep

<table>
<thead>
<tr>
<th>Neurotransmitters</th>
<th>GABA</th>
</tr>
</thead>
<tbody>
<tr>
<td>[163x448]GABA</td>
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</tbody>
</table>

**TREATMENT**

### Treatment Goals and Outcomes

<table>
<thead>
<tr>
<th>Primary Goals</th>
<th>Indicators of Sleep Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve sleep quality and quantity</td>
<td><strong>Complaint</strong></td>
</tr>
<tr>
<td>Improve insomnia related daytime impairments</td>
<td>Difficulty falling asleep</td>
</tr>
<tr>
<td></td>
<td>Difficulty maintaining sleep</td>
</tr>
<tr>
<td></td>
<td>Experiencing nonrestorative sleep</td>
</tr>
</tbody>
</table>

Pittsburg Sleep Quality Index (PSQI)

- 7 component, self-rated questionnaire which assesses sleep quality over a one month interval
- Scores range from 0-3 for each component
- Global score maximum of 21 points
- Global score of 5 distinguishes good and poor sleep
- Sensitivity 89.6%, specificity 86.5%

Components

- Sleep quality
- Sleep latency
- Total sleep time
- Sleep efficiency
- Sleep disturbances
- Use of medications
- Daytime function

APA Guidelines

- Only briefly address insomnia secondary to depression/antidepressants
- Listed strategies
  - Use morning dosing
  - Sleep hygiene techniques or CBT
  - Sedative-hypnotics
  - Trazodone
  - Melatonin


American Academy of Sleep Medicine Guidelines

- Evaluation and Management (2008)
  - Recognize importance of treating comorbidities with insomnia such as MDD
  - No preference between psychological/behavioral and pharmacological interventions
  - Insomnia comorbid with depression should follow the same general outline as with primary insomnia

- Pharmacologic Treatment (2017)
  - Recommend against use of trazodone (weak, moderate)
  - Based on trial of zolpidem vs trazodone in primary insomnia

Link Between Depression and Insomnia

- One study showed depressed patient have 2.02 odds increase in development of chronic insomnia at 7.5 years compared to non-depressed patients
- Studies have supported a 4-8 odds increase of developing major depressive disorder among patients with insomnia

Non-pharmacological Treatment

• Stimulus control
• Relaxation training
• Sleep restriction
• Sleep hygiene therapy
• Cognitive Behavioral Therapy for Insomnia (CBT-I)

Pharmacologic Therapy of Insomnia

<table>
<thead>
<tr>
<th>Class</th>
<th>Medications</th>
<th>Sleep Benefits</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamines</td>
<td>Diphenhydramine, doxylamine</td>
<td>Sleep latency</td>
<td>May reduce sleep quality, Residual drowsiness, Antihistaminic effects</td>
</tr>
<tr>
<td>Herbal/supplement</td>
<td>Melatonin, valerian</td>
<td>Sleep latency (valerian)</td>
<td>Daytime sedation, Sleep disruption (melatonin), Hepatotoxicity (valerian)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Triazolam, temazepam</td>
<td>Sleep latency, Total sleep time, Sleep quality</td>
<td>Abuse potential, Tolerance, Daytime sedation, Memory impairment</td>
</tr>
<tr>
<td>Benzodiazepine receptor agonists</td>
<td>Eszopiclone, zaleplon, zolpidem</td>
<td>Sleep latency</td>
<td>Abuse potential, Tolerance, Daytime sedation, Memory impairment</td>
</tr>
</tbody>
</table>
Pharmacologic Therapy of Insomnia

<table>
<thead>
<tr>
<th>Class</th>
<th>Medications</th>
<th>Sleep Benefits</th>
<th>Major Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin agonist</td>
<td>Ramelteon</td>
<td>Sleep latency</td>
<td>Somnolence, minimal</td>
</tr>
<tr>
<td>Orexin receptor antagonist</td>
<td>Suvorexant</td>
<td>Total sleep time</td>
<td>Somnolence, minimal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sleep efficiency</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Doxepin, trazodone, amitriptyline, mirtazapine</td>
<td>Total sleep time Sleep quality</td>
<td>Anticholinergic/ antihistaminic effects Somnolence</td>
</tr>
</tbody>
</table>

Trazodone Background

• Triazolopyridine antidepressant
• Approved in 1982 for depression
  • Dose = 150-600 mg daily
• Off-label insomnia
  • Dose = 50-100 mg nightly

![Trazodone molecule]


Trazodone Binding Affinities

At hypnotic doses

• 100% saturation
  • 5-HT$_{2A}$
• ≥ 50% saturation
  • $\alpha_1$
  • H$_1$
  • SERT

Trazodone Kinetics and Adverse Effects

Absorption
• Tmax: 1-2 hours

Distribution
• Vd: 0.47-0.84 L/kg

Metabolism
• Extensive CYP3A4 metabolism
• mCCP active metabolite

Excretion
• Half-life: 7 hours

Adverse Effects
• Common
  • Drowsiness, “hangover effect”
  • Dizziness, orthostatic hypotension
  • Dry mouth
  • Blurred vision
• Serious
  • QTc prolongation/cardiac arrhythmias
  • Priapism
• SSRI associated
  • Increased bleed risk
  • Hyponatremia

Question

Which of the following would not be attributed to trazodone administration?
A. Increased QTc
B. Decreased blood pressure
C. Increased prolactin
D. Decreased sodium
# Literature Review

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>Participants</th>
<th>Duration</th>
<th>Method</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haffmans and Vos (1995)</td>
<td>Randomized, double-blind, crossover, placebo-controlled</td>
<td>Depressed patients with buspirone-induced insomnia (N = 7)</td>
<td>50 (N = 7)</td>
<td>1 week</td>
<td>PSG</td>
<td>HAM-D</td>
</tr>
<tr>
<td>Mashiko et al (1999)</td>
<td>Dose-finding study, randomized, noncontrolled</td>
<td>Depressed patients with sleep disorders (N = 75)</td>
<td>50, 75, or 100 (N = 75)</td>
<td>6 weeks</td>
<td>none</td>
<td>HAM-D, HAM-A, Self-Rating Depression Scale, Sleep Rating for Sleep Quality Index, Yale-New Haven Hospital Sleepiness Inventory, Pittsburgh Sleep Quality Index, None</td>
</tr>
<tr>
<td>Mouret et al (1985)</td>
<td>Nouranized, noncontrolled</td>
<td>Depressed inpatients (N = 10)</td>
<td>400–600 (N = 10)</td>
<td>5 weeks</td>
<td>PSG</td>
<td>Spiegel and Norris sleep scales</td>
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<tr>
<td>Nierenberg et al (1994)</td>
<td>Randomized, double-blind, crossover, placebo-controlled</td>
<td>Depressed patients with fluoxetine- or bupropion-induced insomnia (N = 17)</td>
<td>50–100 (N = 17)</td>
<td>6.5 days (mean)</td>
<td>none</td>
<td>Pittsburgh Sleep Quality Index, Yale-New Haven Hospital Depressive Symptom Inventory</td>
</tr>
<tr>
<td>Parno et al (1994)</td>
<td>Nouranized, noncontrolled, single-blind</td>
<td>Dysthyemic patients with chronic insomnia (N = 6)</td>
<td>50–100 (N = 6)</td>
<td>6 weeks</td>
<td>PSG</td>
<td>VAS</td>
</tr>
<tr>
<td>Saleu-Zyklarz et al (2001)</td>
<td>Single-blind, crossover, placebo-controlled</td>
<td>Dysthyemic patients with insomnia and healthy controls (N = 22)</td>
<td>100 (N = 11)</td>
<td>1 night</td>
<td>PSG</td>
<td>Self-Assessment of Sleep and Awakening Quality Scale</td>
</tr>
<tr>
<td>Saleu-Zyklarz et al (2002)</td>
<td>Single-blind, crossover, placebo-controlled</td>
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<td>100 (N = 11)</td>
<td>1 night</td>
<td>PSG</td>
<td>Self-Assessment of Sleep and Awakening Quality Scale</td>
</tr>
<tr>
<td>Scharf and Sachais (1990)</td>
<td>Nouranized, noncontrolled, single-blind</td>
<td>Depressed patients with significant sleep disturbances (N = 6)</td>
<td>150–400 (N = 6)</td>
<td>5 weeks</td>
<td>PSG</td>
<td>None</td>
</tr>
<tr>
<td>van Bemmels et al (1993)</td>
<td>Nouranized, noncontrolled, single-blind</td>
<td>Depressed outpatients (N = 8)</td>
<td>300–400 (N = 8)</td>
<td>5 weeks</td>
<td>PSG</td>
<td>None</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Intervention</td>
<td>Participants</td>
<td>Duration</td>
<td>Method</td>
<td>Scale(s)</td>
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</tr>
<tr>
<td>Haffmans and Vos (1999)</td>
<td>Randomized, double-blind, crossover, placebo-controlled</td>
<td>Depressed patients with brofaromine-induced insomnia</td>
<td>50 (N = 7)</td>
<td>1 week</td>
<td>PSG</td>
<td>HAM-D</td>
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<tr>
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<td>Depressed patients with sleep disorders</td>
<td>50, 75, or 100 (N = 75)</td>
<td>6 weeks</td>
<td>none</td>
<td>HAM-D; HAM-A; Self-Rating Depression Scale; Self-Rating for Sleep</td>
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<td>Depressed patients with chronic insomnia</td>
<td>50–100 (N = 6)</td>
<td>6 weeks</td>
<td>PSG</td>
<td>VAS</td>
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<tr>
<td>Saleh-Zyhlarz et al (2001)</td>
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<td>Depressed patients with insomnia and healthy controls</td>
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<td>1 night</td>
<td>PSG</td>
<td>Self-Assessment of Sleep and Awakening Quality Scale</td>
</tr>
<tr>
<td>Scharf and Sachais (1990)</td>
<td>Nonrandomized, noncontrolled, single-blind</td>
<td>Depressed patients with significant sleep disturbance</td>
<td>150–400 (N = 6)</td>
<td>3 weeks</td>
<td>PSG</td>
<td>none</td>
</tr>
<tr>
<td>van Bommel et al (1992)</td>
<td>Nonrandomized, noncontrolled, single-blind</td>
<td>Depressed outpatients</td>
<td>300–400 (N = 8)</td>
<td>3 weeks</td>
<td>PSG</td>
<td>none</td>
</tr>
</tbody>
</table>
TRAZODONE FOR ANTIDEPRESSANT-ASSOCIATED INSOMNIA


Nierenberg 1994

Trazodone for antidepressant-associated insomnia

Objective • Investigate trazodone as a hypnotic for depressed patients who had persistent, exacerbated, or new insomnia while taking either fluoxetine or bupropion

Design • Randomized, double-blind, placebo controlled crossover study
### Nierenberg 1994

#### Inclusion
- Patients with affective disorder treated with fluoxetine or bupropion
- New, exacerbated, or untreated insomnia
  - Sleep duration <75% normal

#### Exclusion
- Cardiac conduction delays or arrhythmia on ECG
- Receiving as needed medications after 5pm
- History of priapism or intolerance to trazodone

#### Methods

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Improvement in sleep defined as PSQI change ≥ 5</td>
<td></td>
</tr>
<tr>
<td>• Change in PSQI between baseline and ends of treatment phases</td>
<td></td>
</tr>
<tr>
<td>• Fischer’s exact test to compare differences in PSQI improvement proportions between treatments</td>
<td></td>
</tr>
<tr>
<td>• Paired student t-tests used to compare change in PSQI between treatments</td>
<td></td>
</tr>
</tbody>
</table>
Nierenberg 1994

Randomization

1 tablet for 1-2 nights

Trazodone 50mg tablets

Placebo tablets

2 tablets for 1-6 nights

Placebo tablets

1 tablet for 1-2 nights

Trazodone 50mg tablets

2 tablets for 1-6 nights

Patient Characteristics

- 15 of 17 recruited patients completed study
- 1 daytime sedation, 1 non-response to placebo
- 9 men, 6 women
- Mean age 41.9 years
- 12 MDD, 3 Bipolar depression
- 13 fluoxetine (mean 26.4 mg/day), 2 bupropion (mean 275 mg/day)
**Nierenberg 1994**

### Results

<table>
<thead>
<tr>
<th></th>
<th>Trazodone</th>
<th>Placebo</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSQI Global Score</strong></td>
<td><strong>Baseline</strong></td>
<td><strong>End</strong></td>
<td><strong>Difference</strong></td>
<td><strong>Baseline</strong></td>
<td><strong>End</strong></td>
<td><strong>Difference</strong></td>
<td><strong>P value</strong></td>
</tr>
<tr>
<td></td>
<td>10.5 (4.0)</td>
<td>5.9 (3.9)</td>
<td>-4.6</td>
<td>9.5 (4.9)</td>
<td>10.3 (3.8)</td>
<td>0.8</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Overall Improvement</strong></td>
<td>67% (CI: 43-91)</td>
<td>13% (CI: 4-30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Phase duration</strong></td>
<td>6.5 days (3.8)</td>
<td>4.6 days (1.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
</tbody>
</table>

### Adverse Effects

- All patients could differentiate treatments
- No differences in daytime sedation observed (other than dropout)
- 1 patient reduced dose due to prolonged erection


### Strengths

- Randomized, double-blind, placebo controlled
- Use of validated sleep scale (PSQI)
- Applicable patient population

### Limitations

- Small patient population, only select antidepressants used
- Patients could differentiate treatment
- No objective evaluation (PSG)


### Conclusion

- Trazodone was more effective than placebo as a hypnotic for stimulating antidepressant-associated insomnia.
- Longer studies with larger, more robust patient populations, and more objective measures are warranted.

INSOMNIA IN DEPRESSION: DIFFERENCES IN OBJECTIVE AND SUBJECTIVE SLEEP AND AWAKENING QUALITY TO NORMAL CONTROLS AND ACUTE EFFECTS OF TRAZODONE


Saletu 2002

Insomnia in depression: Differences in objective and subjective sleep and awakening quality to normal controls and acute effects of trazodone

| Objectives | • Investigate objective and subjective sleep and awakening quality with nonorganic insomnia related to major depressive disorder  
|           | • Determine the necessity of an adaptation night  
|           | • Measure the acute effect of trazodone 100mg, compared to placebo  
| Design    | • Single-blind, placebo-controlled cross-over study  

### Saletu 2002

#### Inclusion
- Drug-free
  - Last dose of psychopharmacologic medication 5 times half-life of medication
- Age 35-75
- Diagnosis of nonorganic insomnia related to a depressive episode or recurrent depressive disorder
- Complaint of sleep disturbance at least 3 times weekly for at least 1 month

#### Exclusion
- Pregnancy/lactation
- Inadequate contraception for females
- Insomnia secondary to other conditions
- History of trazodone hypersensitivity
- Significant medical disorder
- Patients requiring medications that might interfere with study assessments
- Patients who work at night
- Narrow angle glaucoma

### Methods

#### Outcomes

<table>
<thead>
<tr>
<th>Objective Sleep Quantity</th>
<th>Total sleep time (TST)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sleep latency</td>
</tr>
<tr>
<td></td>
<td>Awakenings</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjective Sleep Quality</th>
<th>Self-Assessment of Sleep and Awakening Quality Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biometric planning and evaluation</td>
<td>Sleep efficiency</td>
</tr>
<tr>
<td></td>
<td>Improvement in 4% considered clinically relevant</td>
</tr>
</tbody>
</table>

#### Statistics

<table>
<thead>
<tr>
<th>Within group</th>
<th>Wilcoxon test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intergroup</td>
<td>Mann-Whitney U test</td>
</tr>
</tbody>
</table>
Saletu 2002

Patient Characteristics

- 11 patients (11 matched controls)
- Mean PSQI 13.2 (SD = 4.1)
- Mean Zung Depression Scale showed mild depression (52.1 +/- 10.0)
### Results

<table>
<thead>
<tr>
<th></th>
<th>Placebo (P)</th>
<th>Trazodone (T)</th>
<th>P:T difference</th>
<th>P:T P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep efficiency (%)</td>
<td>77</td>
<td>84</td>
<td>7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total sleep time (hr:min)</td>
<td>5:42</td>
<td>6:15</td>
<td>00:33</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Latency (min)</td>
<td>24</td>
<td>21</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Awakenings</td>
<td>11</td>
<td>4</td>
<td>7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Sleep Quality</td>
<td>43</td>
<td>39</td>
<td>4</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Adverse Effects

- None reported

### Strengths

- Placebo controlled, crossover design
- Objective measurements with PSG

### Limitations

- One night observation for each phase
- No concomitant depression medications
- Sample size
- Sleep dictated by researchers

### Conclusion

A single dose of trazodone has a fair effect on total sleep time and sleep efficiency, most likely due to reduced awakenings. Longer studies assessing larger, more robust patient populations taking psychoactive medications are warranted to define trazodone’s efficacy in nonorganic insomnia related to depressive episodes.
## THE EFFECTS OF TRAZODONE ON SLEEP IN PATIENTS TREATED WITH STIMULANT ANTIDEPRESSANTS


## Kaynak 2004

**The effects of trazodone on sleep in patients treated with stimulant antidepressants**

<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>• To evaluate the effects of trazodone on subjective and objective measures of sleep in depressed insomnia patients treated with SSRIs.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>• Double-blind, placebo-controlled cross-over study</td>
</tr>
</tbody>
</table>
Kaynak 2004

**Inclusion**
- Female, age 20-50 years
- DSM IV diagnosed major depressive disorder
  - HAMD ≥ 18 (moderate)
- Treated with SSRI for at least 3 weeks
- Complaints of new, exacerbated, or untreated insomnia

**Exclusion**
- Concomitant mental illness
- Alcohol abuse or addiction to other drugs
- Pregnancy or lactation
- Insomnia secondary to illness other than MDD
- Cardiac conduction delays or arrhythmia on ECG
- History of intolerable adverse reaction to trazodone


**Methods**

**Outcomes**
- Mean percentage reduction in HAMD between baseline and last treatment night for trazodone and placebo groups
- PSQI scores between baseline and end of study for each study arm
- PSG sleep parameters between baseline and first treatment night for trazodone and placebo groups
- PSG sleep parameters between baseline and last treatment night for trazodone and placebo groups

**Statistics**
- All comparisons used Wilcoxon match pair signed rank test

Kaynak 2004

Patient Characteristics

- 12 females, mean age 42 +/- 9 years
- 10 patients with untreated insomnia, 2 developed insomnia on SSRI
- 5 taking paroxetine (20mg/day), 3 sertraline (50mg/day), 2 fluoxetine (20mg/day), 1 citalopram (20mg/day), 1 venlafaxine (37.5mg/day)
  - Mean SSRI treatment duration 9 weeks +/- 2.7 weeks
- 6 patients in each group
- No statistically significant differences between groups regarding SSRI treatment
Kaynak 2004

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Trazodone</th>
<th>Placebo ( \pm 3.7 )</th>
<th>Placebo ( \pm 4.5 )</th>
<th>Difference between treatments ( \pm 4.5 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAMD Score</td>
<td>23.4</td>
<td>12.2</td>
<td>11.5</td>
<td>0.8 (NS)</td>
<td></td>
</tr>
<tr>
<td>% Decrease from baseline</td>
<td>-</td>
<td>46.3 ( p &lt; 0.005 )</td>
<td>49.2 ( p &lt; 0.005 )</td>
<td>2.9 (NS)</td>
<td></td>
</tr>
</tbody>
</table>

PSQI Scores Between Baseline and End of Study

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Trazodone most recent</th>
<th>Placebo most recent</th>
<th>Difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 ( \pm 2.5 )</td>
<td>5.17 ( \pm 1.17 )</td>
<td>4.83 ( \pm 2.14 )</td>
<td>0.34 (NS)</td>
</tr>
</tbody>
</table>

PSG Sleep Parameters

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Trazodone night 1 ( \pm 58 )</th>
<th>Trazodone night 7 ( \pm 39^* )</th>
<th>Placebo night 1 ( \pm 35 )</th>
<th>Placebo night 7 ( \pm 66 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time</td>
<td>6:22</td>
<td>7:15 ( ** )</td>
<td>7:08 ( * )</td>
<td>6:26</td>
<td>6:23</td>
</tr>
<tr>
<td>(hr:min ± min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep latency</td>
<td>19</td>
<td>17 ( \pm 29 )</td>
<td>14 ( \pm 14 )</td>
<td>24 ( \pm 26 )</td>
<td>33 ( \pm 53 )</td>
</tr>
<tr>
<td>(min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Awakenings</td>
<td>25</td>
<td>13 ( \pm 11 )</td>
<td>12 ( \pm 13^* )</td>
<td>24 ( \pm 11 )</td>
<td>30 ( \pm 18 )</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>80</td>
<td>90 ( \pm 7^* )</td>
<td>89 ( \pm 8^* )</td>
<td>80 ( \pm 7 )</td>
<td>79 ( \pm 14 )</td>
</tr>
</tbody>
</table>

Adverse Effects

- 1 mild acid indigestion, 2 mild daytime sedation while in trazodone phase
Kaynak 2004

Strengths

- Double-blind, placebo controlled, crossover design
- Multiple SSRIs used by patients
- Objective measurements with PSG
- Validated subjective measurement used

Limitations

- Small sample size
- No mention of treatment identification
- Short duration
- Sleep dictated by researchers

Conclusion

Trazodone 100mg improved total sleep time and efficiency, most likely due to reduced awakenings. Parallel groups studies are warranted to assess subjective sleep measurements, along with studies in patients with significantly prolonged sleep latency.

Question

Which of the following sleep parameters would be least likely to improve after starting trazodone based on trial data?

A. Total sleep time  
B. Sleep latency  
C. Awakenings  
D. Sleep quality
### Literature Summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Trazodone Dose</th>
<th>Length of Trazodone</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nierenberg 1994</td>
<td>Randomized, double-blind, placebo controlled cross-over study</td>
<td>Bupropion/fluoxetine - MDD/Bipolar depression - 15 Patients</td>
<td>50-100 mg nightly</td>
<td>Mean 6.5 days</td>
<td>PSQI ↓ 10.5 to 5.9</td>
</tr>
<tr>
<td>Saletu 2002</td>
<td>Single-blind, placebo-controlled cross-over study</td>
<td>Drug free - Depressive episode/recurrence - 11 Patients</td>
<td>100 mg nightly</td>
<td>1 night</td>
<td>↑ TST (66 min) - ↑ Sleep efficiency (7%) - ↓ Awakenings (5)</td>
</tr>
<tr>
<td>Kaynak 2004</td>
<td>Randomized, double-blind, placebo-controlled cross-over study</td>
<td>SSRIs - MDD - 12 Female patients</td>
<td>100 mg nightly</td>
<td>1 week</td>
<td>↑ TST (53 min) - ↑ Sleep efficiency (10%) - ↓ Awakenings (12)</td>
</tr>
</tbody>
</table>

### Summary/Conclusions

- Depression and insomnia have a bidirectional association, each increasing the risk of developing the other
- Treatment of insomnia with comorbid depression is complicated by the absence of efficacious medicine that is safe long term
- Despite the frequency of trazodone use, efficacy is not strongly supported by current evidence
  - Most studies have weak trial designs, low sample size, and/or short durations
  - Designs do not allow for testing latency
- Placebo controlled studies with top tier design will likely never exist
- Even though trazodone lacks evidence for use, a trial combined with non-pharmacologic measures is appropriate for patients with trouble maintaining sleep
TRAZODONE IN INSOMNIA COMORBID WITH DEPRESSION: AN AWAKENING LACK OF STRONG EVIDENCE

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1/5/2018