Psychopharmacology of Sleep Disorders

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Sleep disorders

• **Insomnias**
  – Insomnia, psychiatric/medical disorders, RLS, medications

• **Hypersomnias**
  – Sleep apnea, medications, Periodic leg movements of sleep

• **Parasomnias**
  – Sleepwalking, sleep terrors, REM sleep behavior disorder

• **Circadian rhythm disorders**
  – Shift work sleep disorder, Delayed sleep phase disorder
DSM-5 Insomnia disorder

• Dissatisfaction with sleep quality or quantity associated with (at least one of):
  – difficulty initiating sleep
  – difficulty maintaining sleep
  – early morning awakening

• Distress or dysfunction related to sleep disturbance

• Minimum of 3x/wk for 3 months

• The insomnia does not co-occur with another sleep disorder

• The insomnia is not explained by coexisting mental disorders or medical conditions
Roughly 30% of sleep problems last > 1 year

Roth et al, Biol Psych 2006
Chronic Insomnia Requires a Thorough Evaluation

Symptoms → Differential Diagnosis

Treatment ↯ Diagnosis
Sleep quality is only as strong as the weakest link and many insomniacs have many sleep-related issues.

All contributing factors must be treated to achieve maximum benefit.
Our understanding of the regulation of sleep informs insomnia treatment approaches

Two processes control sleep timing, quality and quantity

1. Homeostatic Drive
   - Increases with the duration of waking and dissipates with sleep

2. Circadian Rhythms
   - Confines sleep and waking to different phases of the 24-hour day
   - Entrained to the light-dark cycle
   - Sleep-independent
Insomnia tips the scales of sleep

High Arousal
(physiological/psychological)
eg pain, worry, dyspnea

Low Homeostatic drive
To treat insomnia:

1) increase sleep drive and decrease arousal

Arousal
(physiological/psychological)
eg pain, worry, dyspnea

Homeostatic drive
To treat insomnia:
2) match time in bed to optimal circadian time for sleep
Chronic Insomnia Requires a Thorough Evaluation

Symptoms → Differential Diagnosis

Treatment ← Diagnosis
Differential diagnosis of chronic insomnia

- Primary psychiatric disorders
- Medications
- Substances
- Medical disorders
- Restless Legs Syndrome (RLS)
- Sleep schedule disorders
- Obstructive sleep apnea
All psychiatric disorders produce insomnia

Mania > Schizophrenia > Depression and Anxiety Disorders
However, psychiatric disorders are present in only 30-40% of those with insomnia.

Independent treatment of insomnia in MDD improves depression treatment outcome
Sleep disturbance is the most common persistent symptom in treated MDD

**25% had treatment-emergent onset of nocturnal awakenings (Nierenberg et al, 2012)**

MDD = Major depressive disorder.
Persistent insomnia in treated MDD: sleep disorder or mood disorder?

- Fatigue
- Loss of interest
- Sleep disturbance
- Depressed mood
- Impaired concentration
- Worry
- Agitation
- Irritability
- Suicidality

- inadequately treated MDD
- treatment-induced insomnia
- pre-existing independent (or primary) insomnia
- combination of above
• PTSD is a disorder with an essential difficulty maintaining states of decreased vigilance

• PTSD will therefore nearly always interfere with sleep

• Specific questions as to the circumstances of traumatic episodes (eg night, bedroom) may shed light on sleep disturbance

• Treatments:
  - education as to relationship of PTSD to sleep disturbance
  - safety of sleep environment
  - judicious use of hypnotics
  - prazosin or Image Rehearsal Therapy for nightmares
Insomnia related to medications

- Antidepressants
- Stimulants
- Steroids, bronchodilators
- Decongestants
- Dopaminergic antagonists (akathisia)
No evidence of any distinctions between SSRIs in degree of benefit or worsening of sleep complaints in patients treated for depression

Fava et al., 2002
Stimulant pharmacokinetics are not kind to sleep
Insomnia in the elderly is not related to age, but to medical illness

- **Cardiac**: angina, PND
- **Pulmonary**: COPD, coughing
- **GI**: Nocturnal reflux
- **Musculoskeletal** pain
- **Endocrine**: Hypo/hyperthyroidism, diabetes, menopause
- **Neurologic**: Dementia, Parkinson’s, CVA, migraine
- **Urinary**: Nocturia, renal failure
Licit substances

- Caffeine
  - Sleepiness can overcome stimulant effects, but awakenings are common
- Alcohol
  - Produces 3-4 hours of good sleep, followed by increased wakefulness in 2nd half of night
Treatment of RLS

• Modify reversible causes
  – Iron Deficiency (keep Ferritin > 50)
  – Medication-Induced (SRIs, DA antagonists, antihistamines)

• Pharmacologic approaches
  – Dopaminergic agonists (pramipexole, ropinirole, rotigotine patch) but watch for iatrogenic worsening of RLS
  – Alpha 2 delts ligands (gabapentin, pregabalin)
  – Opioids (oxycodone, methadone)
Sleep schedule disorders

• Delayed Sleep Phase Syndrome
  – Most common in adolescents
  – Initial insomnia and difficulty awakening in AM
  – Daytime sleepiness

• Advanced Sleep Phase Syndrome
  – Most common in the elderly
  – Early AM awakening
Insomnia is more common than daytime sleepiness in those with sleep apnea (AHI>15).

All patients while untreated (n = 705)

- No insomnia = 32%
- Late insomnia = 28%
- Initial insomnia = 15%
- Middle insomnia = 59%
- Late insomnia and Initial insomnia = 7%
- Middle insomnia and Initial insomnia = 4%
- Late insomnia and Middle insomnia = 5%
Physical exam (kind of) predicts likelihood of sleep apnea
Berlin questionnaire (kind of) predicts sleep apnea

1. Complete the following:
   height ________ age ______
   weight ________ male/female ______

CATEGORY 1

2. Do you snore?
   □ Yes
   □ No
   □ Don’t know

If you snore:
3. Your snoring is?
   □ Slightly louder than breathing
   □ As loud as talking
   □ Louder than talking
   □ Very loud...can be heard in adjacent rooms

4. How often do you snore?
   □ Nearly every day
   □ 3-4 times a week
   □ 1-2 times a week
   □ 1-2 times a month
   □ never or nearly never

5. Has your snoring ever bothered other people?
   □ Yes
   □ No

6. Has anyone noticed that you quit breathing during your sleep?
   □ Nearly every day
   □ 3-4 times a week
   □ 1-2 times a week
   □ 1-2 times a month
   □ never or nearly never

CATEGORY 2

7. How often do you feel tired or fatigued after your sleep?
   □ Nearly every day
   □ 3-4 times a week
   □ 1-2 times a week
   □ 1-2 times a month
   □ Never or nearly never

8. During your wake time, do you feel tired, fatigued or not wake up to par?
   □ Nearly every day
   □ 3-4 times a week
   □ 1-2 time a month
   □ Never or nearly never

9. Have you ever nodded off or fallen asleep while driving a vehicle?
   □ Yes
   □ No

   If yes, how often does it occur?
   □ Nearly every day
   □ 3-4 times a week
   □ 1-2 times a week
   □ 1-2 times a month
   □ Never or nearly never

CATEGORY 3

10. Do you have high blood pressure?
    □ Yes
    □ No
    □ Don’t know

    BMI = _____

Scoring Questions: Any answer within highlighted box outline is a positive response
Scoring Categories: Category 1 is positive with 2 or more positive responses to questions 2-6
                  Category 2 is positive with 2 or more positive responses to questions 7-9
                  Category 3 is positive with 1 or more positive responses and/or a BMI>30
Final Results: 2 or more categories indicate a high likelihood of sleep disordered breathing
Indications for polysomnography

- Suspicion of sleep apnea (loud snoring *PLUS one of the following*):
  - daytime sleepiness
  - witnessed apneas
  - refractory hypertension

- Abnormal behaviors or movements during sleep
- Unexplained excessive daytime sleepiness
- Refractory sleep complaints, particularly repetitive brief awakenings
OSA treatments

Positive Airway Pressure (PAP)

Auto-PAP is allowing both diagnostic and titration to be performed in the home (no sleep lab necessary)

Weight loss, upper airway surgery, positional treatment
Common cognitive and behavioral issues which can produce/worsen insomnia

- Inconsistent bedtimes and wake times
- “Dozing” in evening before bed
- Excessive time in bed
- Sleep-related anxiety (“insomnia phobia”)
- Unrealistic expectations of total sleep time, sleep onset and number of awakenings
- Clock watching
- Use of electronics in bedroom
- Inappropriate attributions of daytime issues to sleep
Many people with insomnia, regardless of the cause, develop negative associations and anxiety regarding sleep initiation ("insomnia phobia") which perpetuate insomnia.
Treatment of Conditioned Insomnia

• Improve sleep-related habits and beliefs
• Cognitive Behavioral Therapy (CBT-I)
• Hypnotics, intermittently or chronically, if CBT-I fails
<table>
<thead>
<tr>
<th>Component</th>
<th>Intended Effect</th>
<th>Specific Directions for Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep restriction</td>
<td>Increase sleep drive and stabilize circadian rhythm</td>
<td>Reduce time in bed to perceived total sleep time (not less than 5–6 hours), choose specific hours on the basis of personal preference and circadian timing, increase time in bed gradually as sleep efficiency improves</td>
</tr>
<tr>
<td>Stimulus control</td>
<td>Reduce arousal in sleep environment and promote the association of bed and sleep</td>
<td>Attempt to sleep when sleepy, get out of bed when awake and anxious at night, use the bed only for sleep or sexual activity (e.g., no watching TV in bed)</td>
</tr>
<tr>
<td>Cognitive therapy</td>
<td>Restructure maladaptive beliefs regarding daytime and health consequences of insomnia</td>
<td>Maintain reasonable expectations about sleep; review previous insomnia experiences, challenging perceived catastrophic consequences</td>
</tr>
<tr>
<td>Relaxation therapy</td>
<td>Reduce physical and psychological arousal in sleep environment</td>
<td>Practice progressive muscle relaxation, breathing exercises, or meditation</td>
</tr>
<tr>
<td>Sleep hygiene</td>
<td>Reduce behaviors that interfere with sleep drive or increase arousal</td>
<td>Limit caffeine and alcohol, keep bedroom dark and quiet, avoid daytime or evening napping, increase exercise (not close to bedtime), remove bedroom clock from sight</td>
</tr>
</tbody>
</table>
CBT-I (online) effective for ISI, sleep latency, WASO, but not for total sleep time

Ritterband et al, 2017
Predictors of CBT-I lack of success

- Poor adherence to CBT-I (Dong et al, 2018)
- Total sleep time at baseline <6 hours (Bathgate et al, 2017)
- Childhood onset of insomnia (Edinger et al, 2017)
CBT-I treatment of insomnia with medical and psychiatric comorbidity

Wu et al. JAMA Int Med 2015
Psychiatric outcomes using CBT-I for insomnia

<table>
<thead>
<tr>
<th>Source by Comorbid Diagnosis Type</th>
<th>Measure</th>
<th>Hedges g</th>
<th>Standard Error</th>
<th>Variance</th>
<th>95% CI</th>
<th>z Value</th>
<th>P Value</th>
<th>Favors Control/Comparison</th>
<th>Favors CBT-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol dependence: Arnedt et al, 2011</td>
<td>Combined</td>
<td>2.48</td>
<td>0.85</td>
<td>0.72</td>
<td>0.82 to 4.15</td>
<td>2.92</td>
<td>&lt;.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol dependence: Currie et al, 2004</td>
<td>BDI</td>
<td>0.66</td>
<td>0.35</td>
<td>0.12</td>
<td>-0.03 to 1.34</td>
<td>1.88</td>
<td>.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression: Manber et al, 2008</td>
<td>HRSD</td>
<td>0.29</td>
<td>0.38</td>
<td>0.14</td>
<td>-0.45 to 1.02</td>
<td>0.77</td>
<td>.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression: Wagley et al, 2013</td>
<td>PHQ-9</td>
<td>0.76</td>
<td>0.39</td>
<td>0.15</td>
<td>-0.00 to 1.52</td>
<td>1.95</td>
<td>.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression: Watanabe et al, 2011</td>
<td>HRSD</td>
<td>0.83</td>
<td>0.34</td>
<td>0.11</td>
<td>0.17 to 1.49</td>
<td>2.46</td>
<td>.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypnotic dependence: Morgan et al, 2004</td>
<td>Abstinent d/wk</td>
<td>0.69</td>
<td>0.17</td>
<td>0.03</td>
<td>0.35 to 1.03</td>
<td>4.02</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTSD: Margolies et al, 2013</td>
<td>Combined</td>
<td>0.96</td>
<td>0.40</td>
<td>0.16</td>
<td>0.18 to 1.74</td>
<td>2.40</td>
<td>.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTSD: Talbot et al, 2014</td>
<td>Combined</td>
<td>0.26</td>
<td>0.31</td>
<td>0.09</td>
<td>-0.34 to 0.86</td>
<td>0.85</td>
<td>.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTSD: Ulmer et al, 2011</td>
<td>PCL-M</td>
<td>1.89</td>
<td>0.56</td>
<td>0.32</td>
<td>0.79 to 3.00</td>
<td>3.36</td>
<td>.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>0.76</td>
<td>0.15</td>
<td>0.02</td>
<td>0.46 to 1.05</td>
<td>5.03</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Wu et al. JAMA Int Med 2015
CBT-I non-response and medication initiation

- Ritterband (SHUTi, 2017): non-responder rate: 50% at 9 weeks, 40% at 6 months, and 30% at 1 year follow-up
- Presumably, these are individuals for whom it is appropriate to consider a medication trial
- Whether to start medication depends on the severity of the persistent insomnia, comorbidities, and previous response to hypnotics
“A story? Honey, wouldn’t you rather a mild sedative?”
The complex neurochemistry of sleep provides many treatment options.
Pharmacologic Treatments for Insomnia

- Benzodiazepine receptor agonists (BzRAs)
- Melatonin agonists
- Orexin antagonist
- Sedating antidepressants
- Anticonvulsants
- Dopaminergic antagonists (eg antipsychotics)
- Miscellaneous (eg prazosin, clonidine, hydroxyzine)
# Benzodiazepine-Receptor Agonists (BzRA)
Commonly Used as Hypnotics

<table>
<thead>
<tr>
<th>Agent (brand name)</th>
<th>Dose range</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>0.25 -1.0 mg</td>
<td>40 hr</td>
</tr>
<tr>
<td>Temazepam (Restoril)*</td>
<td>7.5-30 mg</td>
<td>4-18 hr</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>0.5-2.0 mg</td>
<td>10-20 hr</td>
</tr>
<tr>
<td>Oxazepam (Serax)</td>
<td>10-30 mg</td>
<td>5-10 hr</td>
</tr>
<tr>
<td>Eszopiclone (Lunesta)*</td>
<td>1-3 mg</td>
<td>5.5-8 hr</td>
</tr>
<tr>
<td>Triazolam (Halcion)*</td>
<td>0.125-0.25 mg</td>
<td>2-3 hr</td>
</tr>
<tr>
<td>Zolpidem (Ambien)*</td>
<td>3.75-12.5 mg</td>
<td>2-3 hr (CR extends duration of action)</td>
</tr>
<tr>
<td>Zaleplon (Sonata)*</td>
<td>5-10 mg</td>
<td>1-2 hr</td>
</tr>
</tbody>
</table>

*FDA approved for insomnia.
Do z-drugs work for insomnia?

Effects modified by higher dose, younger age, female sex

<table>
<thead>
<tr>
<th>Primary outcome-sleep latency</th>
<th>Weighted mean raw differences in effect of Z drugs (treatment) or placebo on insomnia</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weighted mean differences (95% CI)</td>
<td>Homogeneity of effect sizes $I^2$ (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Within groups</td>
<td>Between groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No* Treatment Control</td>
<td>No* Treatment v control Treatment v Control</td>
<td></td>
</tr>
<tr>
<td>PSG</td>
<td>14 $-42 (-60 \text{ to } -23)$ $-20 (-28 \text{ to } -11)$</td>
<td>14 $-22 (-33.00 \text{ to } -11.00)$ 96 (94.75 to 97.15) 41 (0 to 68.68) 94 (91.66 to 95.83)</td>
<td></td>
</tr>
<tr>
<td>Subjective</td>
<td>2 $-24.99 (-30.06 \text{ to } -19.92)$ $-19.43 (-26.61 \text{ to } -12.25)$</td>
<td>2 $-6.90 (-26.00 \text{ to } 12.37)$ 0 (0 to 100) 0 (0 to 100) 27 (0 to 72.41)</td>
<td></td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wake after sleep onset (PSG)</td>
<td>2 $-20 (-59 \text{ to } 18)$ $-13 (-34 \text{ to } 7.89)$</td>
<td>2 $-7.14 (-33.00 \text{ to } 18.23)$ 65 (0 to 91.96) 63 (0 to 91.62) 0 (0 to 99.98)</td>
<td></td>
</tr>
<tr>
<td>No of awakenings (PSG)</td>
<td>2 $1.24 (-6.34 \text{ to } 3.89)$ $-0.94 (-12 \text{ to } 9.99)$</td>
<td>2 $-0.47 (-5.12 \text{ to } 4.17)$ 94 (81.24 to 98.13) 0 (0 to 99.98) 0 (0 to 99.90)</td>
<td></td>
</tr>
<tr>
<td>No awakenings (subjective)</td>
<td>2 $2.88 (-7.15 \text{ to } 1.39)$ $-1.05 (-4.86 \text{ to } 2.76)$</td>
<td>2 $-1.77 (-4.61 \text{ to } 1.07)$ 0 (0 to 100) 0 (0 to 99.95) 0 (0 to 99.81)</td>
<td></td>
</tr>
<tr>
<td>Total sleep time (PSG)</td>
<td>2 $49.15 (-60 \text{ to } 16)$ $35.10 (-34 \text{ to } 10)$</td>
<td>2 $14.05 (-31.00 \text{ to } 58.72)$ 63 (0 to 91.45) 61 (0 to 91.07) 0 (0 to 99.68)</td>
<td></td>
</tr>
<tr>
<td>Sleep efficiency (PSG)</td>
<td>1 $4.27 (2.01 \text{ to } 6.52)$ $0 (-2.52 \text{ to } 2.52)$</td>
<td>1 $4.47 (2.08 \text{ to } 6.86)$ — — —</td>
<td></td>
</tr>
</tbody>
</table>

Huedo-Medina et al, BMJ, 2012
Do benzodiazepines work for insomnia?

Buscemi et al, JGIM, 2007

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Number of Studies</th>
<th>Point Estimate (95% CI)</th>
<th>Heterogeneity (I²) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep onset latency (WMD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>11</td>
<td>-10.0 min (-16.6, -3.4)</td>
<td>72.6</td>
</tr>
<tr>
<td>Polysomnography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Diary</td>
<td>26</td>
<td>-19.6 min (-23.9, -15.3)</td>
<td>55.5</td>
</tr>
<tr>
<td>Non-benzodiazepines</td>
<td>12</td>
<td>-12.8 min (-16.9, -8.8)</td>
<td>39.3</td>
</tr>
<tr>
<td>Polysomnography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Diary</td>
<td>34</td>
<td>-17.0 min (-20.0, -14.0)</td>
<td>64.8</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>4</td>
<td>-7.0 min (-10.7, -3.3)</td>
<td>34.1</td>
</tr>
<tr>
<td>Polysomnography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Diary</td>
<td>2</td>
<td>-12.2 min (-22.3, -2.2)</td>
<td>0</td>
</tr>
<tr>
<td>Wakefulness after sleep onset (WMD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>5</td>
<td>-16.7 min (-25.3, -8.1)</td>
<td>0</td>
</tr>
<tr>
<td>Polysomnography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Diary</td>
<td>4</td>
<td>-39.9 min (-71.0, -8.8)</td>
<td>68.2</td>
</tr>
<tr>
<td>Non-benzodiazepines</td>
<td>3</td>
<td>-7.0 min (-14.6, 0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Polysomnography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Diary</td>
<td>12</td>
<td>-15.0 min (-22.3, -7.7)</td>
<td>66.5</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>2</td>
<td>-12.2 min (-17.5, -7.0)</td>
<td>0</td>
</tr>
<tr>
<td>Polysomnography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Diary</td>
<td>1</td>
<td>-7.1 min (-19.1, 4.9)</td>
<td>NA</td>
</tr>
</tbody>
</table>
Response (ISI Δ6) and remission (ISI<11) with BZRAs in clinic patients

Figure 3—Response and remission rates, stratified by medical/psychiatric comorbidity. Med = medical; Pscy = psychiatric; Com = comorbidity. *p < .05.

Pillai et al 2017
“Are sleeping pills addictive?”

“Substance use disorders occur when their recurrent use causes clinically and functionally significant impairment, such as health problems, disability, and failure to meet major responsibilities at work, school, or home.”- DSM 5

• Tolerance
• Physiological dependence
• Psychological dependence
• Non-medical diversion
The Current Status of BzRA Risks in the Treatment of Insomnia

- Motor vehicle accidents in elderly: long $T_{1/2}$ agents
- Hip fractures in elderly: long $T_{1/2}$ agents?
- Anterograde amnesia: $T_{1/2}$ dependent
- Abuse: unusual outside of other substance abusers
- Tolerance: no evidence from 12- and 26-week studies
- Rebound insomnia: depends upon dose, duration of use, and speed of taper

Benzodiazepines do increase risk for dementia

Table 3 | Risk of Alzheimer’s disease associated with benzodiazepine use (variables assessed five to up to 10 years before diagnosis) in people with Alzheimer’s disease (cases) and controls

<table>
<thead>
<tr>
<th></th>
<th>No (%) of cases (n=1796)</th>
<th>No (%) of controls (n=7184)</th>
<th>Univariable odds ratio (95% CI)*</th>
<th>Multivariable odds ratio (95% CI)Model 1†</th>
<th>Multivariable odds ratio (95% CI)Model 2‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepine ever use:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-users</td>
<td>902 (50.2)</td>
<td>4311 (60.0)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Users</td>
<td>894 (49.8)</td>
<td>2873 (40.0)</td>
<td>1.52 (1.37 to 1.69)</td>
<td>1.51 (1.36 to 1.69)</td>
<td>1.43 (1.28 to 1.60)</td>
</tr>
<tr>
<td>Benzodiazepine density exposure (No of prescribed daily doses):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-users</td>
<td>902 (50.2)</td>
<td>4311 (60.0)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1-90</td>
<td>234 (13.0)</td>
<td>1051 (14.6)</td>
<td>1.08 (0.92 to 1.27)</td>
<td>1.09 (0.92 to 1.28)</td>
<td>1.05 (0.89 to 1.24)</td>
</tr>
<tr>
<td>91-180</td>
<td>70 (3.9)</td>
<td>257 (3.6)</td>
<td>1.33 (1.01 to 1.75)</td>
<td>1.32 (1.01 to 1.74)</td>
<td>1.28 (0.97 to 1.69)</td>
</tr>
<tr>
<td>&gt;180</td>
<td>590 (32.9)</td>
<td>1565 (21.8)</td>
<td>1.85 (1.63 to 2.09)</td>
<td>1.84 (1.62 to 2.08)</td>
<td>1.74 (1.53 to 1.98)</td>
</tr>
<tr>
<td>Benzodiazepine elimination half life:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-users</td>
<td>902 (50.2)</td>
<td>4311 (60.0)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Short half life (&lt;20 h)</td>
<td>585 (32.6)</td>
<td>1996 (27.8)</td>
<td>1.43 (1.27 to 1.61)</td>
<td>1.43 (1.27 to 1.61)</td>
<td>1.37 (1.21 to 1.55)</td>
</tr>
<tr>
<td>Long half life (≥20 h)</td>
<td>309 (17.2)</td>
<td>877 (12.2)</td>
<td>1.72 (1.48 to 1.99)</td>
<td>1.70 (1.46 to 1.98)</td>
<td>1.59 (1.36 to 1.85)</td>
</tr>
</tbody>
</table>

*Matched for age, sex, and follow-up length.
†Adjusted for high blood pressure (diagnosis or treatment), myocardial infarction (diagnosis), stroke (diagnosis), platelet inhibitors or oral anticoagulant treatment, diabetes mellitus (diagnosis or treatment), hypercholesterolaemia (diagnosis or treatment), comorbidity (diagnosis).
‡Further adjusted for anxiety, depression, and insomnia diagnosis.

Billioti de Gage et al, BMJ, 2014
Benzodiazepines do not increase risk for dementia

Gray et al, BMJ, 2016
Do benzodiazepines increase mortality risk?

**Paterno et al BMJ 2017:** Conclusions This large population based cohort study suggests either no increase or at most a minor increase in risk of all cause mortality associated with benzodiazepine initiation. If a detrimental effect exists, it is likely to be much smaller than previously stated and to have uncertain clinical relevance. Residual confounding likely explains at least part of the small increase in mortality risk observed in selected analyses.
Melatonin leads to small benefits for insomnia

**Figure 1. Efficacy of Melatonin in Reducing Sleep Latency.** Forest plot depicting reduction of sleep latency in melatonin compared to placebo. Meta-analysis demonstrated a significant benefit of melatonin in reducing sleep latency. WMD = weighted mean difference; CI = confidence interval.

**Figure 2. Efficacy of Melatonin in Increasing Total Sleep Time.** Forest plot depicting change in total sleep time with melatonin compared to placebo treatment. Meta-analysis demonstrated a significant benefit of melatonin in increasing total sleep time. WMD = weighted mean difference;

**Figure 3. Effect of Melatonin on Sleep quality.** Forest plot depicts sleep quality with melatonin compared to placebo. Meta-analysis demonstrated a significant benefit of melatonin in improving sleep quality. SMD = standardized mean difference; CI = confidence interval.
Orexin antagonist in the treatment of insomnia

*Suvorexant*

- Advantages: little abuse liability, 1-year efficacy data (at 40 mg), few side effects
- Disadvantages: unclear efficacy vs BzRAs, prior authorization
Antidepressants in the treatment of insomnia

*Mirtazapine, Trazodone, Amitriptyline, Doxepin*

- Advantages: little abuse liability
- Disadvantages: probably not as effective as BzRAs, daytime sedation, weight gain, anticholinergic side effects, switch into mania in bipolar disorder
### Association of Incident Dementia and Alzheimer’s Disease with 10-year Cumulative Anticholinergic Medication Use

<table>
<thead>
<tr>
<th>TSDD&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Follow-up time (person-years)</th>
<th>Number of Events</th>
<th>Unadjusted&lt;sup&gt;ad&lt;/sup&gt;</th>
<th>Adjusted&lt;sup&gt;de&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>5618</td>
<td>136</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>1-90</td>
<td>7704</td>
<td>203</td>
<td>0.96</td>
<td>0.77-1.20</td>
</tr>
<tr>
<td>91-365</td>
<td>5651</td>
<td>172</td>
<td>1.31</td>
<td>1.04-1.65</td>
</tr>
<tr>
<td>366-1095</td>
<td>2626</td>
<td>102</td>
<td>1.39</td>
<td>1.07-1.82</td>
</tr>
<tr>
<td>&gt;1095</td>
<td>4022</td>
<td>184</td>
<td>1.77</td>
<td>1.40-2.23</td>
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<td>Alzheimer’s Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5618</td>
<td>112</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>1-90</td>
<td>7704</td>
<td>168</td>
<td>0.96</td>
<td>0.75-1.24</td>
</tr>
<tr>
<td>91-365</td>
<td>5651</td>
<td>128</td>
<td>1.21</td>
<td>0.93-1.58</td>
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<tr>
<td>366-1095</td>
<td>2626</td>
<td>83</td>
<td>1.38</td>
<td>1.03-1.85</td>
</tr>
<tr>
<td>&gt;1095</td>
<td>4022</td>
<td>146</td>
<td>1.73</td>
<td>1.34-2.24</td>
</tr>
</tbody>
</table>

TSDD Total Standardized Daily Dose; HR Hazard Ratio; CI Confidence Interval; ACT Adult Changes in Thought

<sup>a</sup>Observations with missing adjustment variables are excluded from the model (n=115; 3.3%).

<sup>b</sup>TSDD example; the minimum effective daily dose for oxybutynin is 5 mg daily (=1 TSDD); a person would fall into the following TSDD category if they were using 5 mg daily for 45 days (TSDD 1-90); 5 mg daily for 180 days (TSDD 91-365); 5 mg daily for 720 days (TSDD 366-1095); 5 mg daily for 4 years (TSDD>1095)

<sup>c</sup>Age adjustment via the time-axis.

<sup>d</sup>Test for trend P value <0.001 for an association between exposure categories and each outcome

<sup>e</sup>Adjusted for ACT cohort, age (via the time-axis), age at ACT study entry, sex, education, body mass index, current smoking, regular exercise, self-rated health, hypertension, diabetes, stroke, coronary heart disease, Parkinson’s disease, history of depressive symptoms, and current benzodiazepine use.

Gray et al, JAMA Int Med, 2015
Atypical antipsychotics in the treatment of insomnia

Quetiapine

- Advantages: anxiolytic, mood stabilizing in bipolar disorder, little abuse liability
- Disadvantages: less effective than BzRAs, daytime sedation, weight gain, risks of extrapyramidal symptoms and glucose + lipid abnormalities
Anticonvulsants in the treatment of insomnia

Gabapentin

- Advantages: little abuse liability, efficacy in ETOH
- Disadvantages: less effective than BzRAs, cognitive impairment, daytime sedation, dizziness, weight gain
Issues with non-BzRA hypnotics in the treatment of insomnia
(eg antidepressants, anticonvulsants, antipsychotics)

• Paucity of short-term efficacy data
• Absence of long-term efficacy data
• Assumptions of lack of tolerance and rebound insomnia are unsubstantiated
• Anecdotally less effective hypnotics than BzRAs
• May have deleterious side effects
Severe primary insomniacs on BZRA x 19 yrs
At 7 weeks:
  * Small improvements in sleep latency, WASO; large reductions in total sleep time
  * Substantial improvements in ISI
Medication tapering + CBT modest superiority to either alone
Sleep disorders

• Insomnias
  – Insomnia, psychiatric/medical disorders, RLS, medications

• Hypersomnias
  – Sleep apnea, medications, Periodic leg movements of sleep

• Parasomnias (4%)
  – Sleepwalking, sleep terrors, REM sleep behavior disorder

• Circadian rhythm disorders
  – Shift work sleep disorder, Delayed sleep phase disorder
Differential diagnosis of hypersomnia

• “Tired”:
  – excessive daytime sleepiness (EDS)
  – fatigue
  – apathy

• If EDS:
  – inadequate sleep time
  – impaired sleep quality
  – excessive sleep drive
Treatment of parasomnias

- **Night terrors/sleepwalking**
  - Short-acting benzodiazepines (e.g., triazolam)

- **REM behavior disorder**
  - Discontinue serotonergic antidepressant (if present)
  - Benzodiazepines (short, long)
  - Melatonin (6-10 mg)
  - +/- pramipexole

- **Sleep-related eating disorder**
  - Treat RLS, if present
  - SSRRI or topiramate