Dual Orexin Receptor Antagonists – An Alternative to Traditional Hypnotics for Insomnia in the Elderly Population

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University of St. Thomas
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Current Concepts in Sleep & Epilepsy, Tampa FL
What can we learn about insomnia treatment from Elvis?

“Elvis Presley: Head Trauma, Autoimmunity, Pain, and Early Death” by Forest Tennant, MD, DrPH
Diazepam, methaqualone, phenobarbital, ethchlorvynol, and ethinamate were below or within their respective ranges. Codeine 10x higher.

How much have sedative/hypnotics improved since Elvis’ “Knock-out” packets 40 years ago?
Learning Objectives

• Discuss limitations of traditional sedative/hypnotic medications

• Describe the role of the orexin signaling system in maintaining wakefulness

• Contrast Dual Orexin Receptor Antagonist medications with sedative/hypnotics for the treatment of insomnia
Insomnia is the #1 Sleep Disturbance in the elderly.

Elderly patients show longer sleep latency, decreased TST, REM sleep fragmentation, increased WASO, and decreased SWS.
Sleep disturbance* from worries about the family, work, loneliness, and money by age

* at least 3 times a week  

Source: Women’s Sleep in the UK Survey
### Insomnia in the Elderly: STEP 1

**DETAILED SLEEP HISTORY**

- Confirm that the patient had insomnia
- Identify the symptom (onset, duration, pattern, and severity)
- Evaluate 24-h sleep/wakefulness patterns
- Review 1 to 2-wk sleep diary
- Interview the bed partner
- Review the family history of sleep disorders
- Identify the cause(s)

- Sleep disorders, Medical & Psychiatric Illnesses
- Behavioral & Environmental sleep disrupters
- Medication side effects
# Management Insomnia in the Elderly

**Comprehensive physical examination**

**Evaluate the personal/social impact of the sleep disorder**

**Treatment**

- Discuss the expectation with the patient
- Effective treatment of the primary problem
- Sleep hygiene measures
- Nonpharmacologic measures
- Pharmacologic intervention
- Referral to sleep specialist if necessary

*The American Journal of Medicine 2006 119, 463-469*
What controls when we sleep?

- Homeostatic Drive
- Circadian Rhythm
- Zeitgebers
- Psychoactive substances
Forebrain areas key to the neuropsychology of dreaming

Prefrontal cortex:
- Ventromedial
- Dorsolateral

Anterior limbic structures:
- Amygdala, anterior cingulate, ventral striatum

Posterior cortices:
- Inferior parietal
- Visual association

Thalamocortical control of NREM sleep rhythms, EEG activation and deactivation

Hippocampal–cortical control of memory consolidation

Origin and expression of circadian rhythms
- Hypothalamic nuclei:
  - Suprachiasmatic
  - Subparaventricular
  - Dorsomedial

Diencephalic control of sleep onset
- Hypothalamic nuclei:
  - Ventrolateral preoptic
  - Lateral
  - Tubermammillary
  - Basal forebrain

Pontine control of the REM-NREM cycle
- Mesopontine nuclei:
  - Laterodorsal tegmental
  - Pedunculopontine
  - Dorsal raphe
  - Locus coeruleus
## FDA Approved Insomnia Medications

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Nonbenzodiazepines (Z drugs)</th>
<th>Non-GABA Receptor Targeted Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triazolam</td>
<td>Zaleplon</td>
<td>Ramelteon</td>
</tr>
<tr>
<td>Estazolam</td>
<td>Zolpidem</td>
<td>Suvorexant</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Eszopiclone</td>
<td>Doxepin</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>Zolpidem ER</td>
<td></td>
</tr>
<tr>
<td>Quazepam</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Commonly Prescribed Insomnia Medications

Sedatives
• Benzodiazepines
• Antipsychotics

Hypnotics
• Antihistamines
• Zolpidem
• Benzodiazepines

Anxiolytics
• Benzodiazepines (acute)
• Antidepressants (chronic)

Antidepressants
• SSRI’s
  • Trazodone
  • Serzone
  • Mirtazapine

• TCA’s
  • Amitriptyline
  • Doxepin
Most Sedative/Hypnotics Increase the function of the GABAA Receptor

How well do the sedative hypnotics actually work, particularly for the elderly?
Meta-analysis of Hypnotic treatment in the elderly

- Subjective sleep quality 1-7 scale: 3.7 vs. 3.8
- 25 min increase in TST, 0.6 reduction in awakenings
- No difference between bz and z drugs

Meta-analysis of AE in Hypnotic treatment in the elderly

- Increase in Negative Cognitive Side Effects [4.78]
- More problems with falls, balance
- No difference between bz and z drugs
- And these were just the published studies

Medications Associated with Delirium
(2012 AGS Beers Criteria: Potentially Inappropriate Medications for Elderly)

- All tricyclic antidepressants
- Anticholinergics (eg, diphenhydramine)
- Benzodiazepines
- Corticosteroids
- $H_2$-receptor antagonists
- Meperidine
- Sedative hypnotics
- Thioridazine/chlorpromazine
Risk of pneumonia associated with incident benzodiazepine use among community-dwelling adults with Alzheimer disease

Heidi Taipale PhD Pharm, Anna-Maija Tolppanen PhD, Marjaana Koponen MSc Pharm, Antti Tanskanen Phil Lic, Piia Lavikainen PhD, Reijo Sund DsocSc, Jari Tiilinen MD PhD, Sirpa Hartikainen MD PhD

Cite as: CMAJ 2017 April 10;189:E519-29. doi: 10.1503/cmaj.160126


Hypnotics and the Occurrence of Bone Fractures in Hospitalized Dementia Patients: A Matched Case-Control Study Using a National Inpatient Database

Hiroyuki Tamiya1, Hideo Yasunaga2, Hiroki Matusi2, Kiyohide Fushimi3, Sumito Ogawa1,*, Masahiro Akishita1

BMC Geriatrics

Research article
Are sedatives and hypnotics associated with increased suicide risk of suicide in the elderly?
Anders Carlsten*†1 and Margda Waern†2

4x inc in. suicide risk
Association Between Benzodiazepine Use and Epilepsy Occurrence

A Nationwide Population-Based Case–Control Study

Tomor Harnod, MD, PhD, Yu-Chiao Wang, MSc, and Chia-Hung Kao, MD

Abstract: We conducted a retrospective case–control study to evaluate the association between the risk of benzodiazepine (BZD) use and epilepsy occurrence by using data from the Taiwan National Health 100 units, the epilepsy risk increase by 1.03-fold (95% CI = 1.01–1.04, P = 0.003). The annual BZD exposure day ranges were significantly associated with epilepsy (2–7 days: aOR = 1.67; 8–35 days:

Meta-Analyses of Hypnotics and Infections: Eszopiclone, Ramelteon, Zaleplon, and Zolpidem


Scripps Clinic Sleep Center, La Jolla, CA

Study Objectives: Recent meta-analyses raising concern about risks of hypnotics suggest a need for more clarification of these risks. Methods: Because of preliminary suggestions that eszopiclone or zolpidem individually were associated with reported infections,
Sedative Hypnotic Medication Use and the Risk of Motor Vehicle Crash

Ryan N. Hansen, PharmD, PhD, Denise M. Boudreau, PhD, Beth E. Ebel, MD, MSc, MPH, David C. Grossman, MD, MPH, and Sean D. Sullivan, PhD

Sedative hypnotic medications are commonly prescribed for treatment of insomnia. Residual sedation is common with sedatives, especially the class of short-acting GABA-agonists commonly referred to as “z-hypnotics” (zolpidem, zopiclone, and zaleplon), and sedation in itself is a usual factor for many.

Objective. We sought to estimate the association between sedative hypnotic use and motor vehicle crash risk.

Methods. We conducted a new user cohort study of 409,171 adults in an integrated health care system. Health plan data were linked to driver license and collision records. Participants were aged 21 years or older, licensed to drive in Washington State, had at least 1 year of continuous enrollment between 2003 and 2008, and were followed until death, disenrollment, or study end. We used
“..risk ratios demonstrated lead to estimated U.S. deaths associated with hypnotic usage of the same order of magnitude as those associated with cigarette use, around 300,000–500,000 per year.”
American Geriatric Society Recommendations—Beers Criteria

- 2012—Avoid benzodiazepines (any type) for treatment of insomnia, agitation, or delirium.\[a\]
- 2015—The nonbenzodiazepine, benzodiazepine receptor agonist hypnotics (eszopiclone, zaleplon, zolpidem) are to be avoided without consideration of duration of use because of their association with harms balanced with their minimal efficacy in treating insomnia.\[b\]

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Is there another pharmacological option?

“In people over 60, the benefits associated with sedative use are marginal and are outweighed by the risks, particularly if patients are at high risk for falls or cognitive impairment.”

Orexin receptor antagonists as therapeutic agents for insomnia
Hypocretin/Orexin Promotes Wakefulness

“If you think about a normal day, 98% of the time is spent either awake or asleep,” Saper says. “There is a very short transition period between the two. The brain seems to have a flip-flop switch that changes the state from wakefulness to sleep, and orexin acts like the thumb that keeps this switch in the ‘on’ position.”
Orexin receptor antagonists as therapeutic agents for insomnia
Phase III clinical trials of Suvorexant

• 19 min increase TST after 3 months of use
• Little adverse side effects
• Safe in geriatric populations
• Primary complaints: ineffective, nightmares, headaches
• No significant effects on next day memory or balance in elderly subjects

## Adverse Drug Events After Suvorexant vs. Placebo

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 Adverse event</td>
<td>20.1%</td>
<td>17.7%</td>
<td>19.7%</td>
<td>30.5%</td>
<td>36.1%</td>
</tr>
<tr>
<td>≥1 Drug-related event</td>
<td>6.8%</td>
<td>4.8%</td>
<td>6.6%</td>
<td>20.3%</td>
<td>23%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0.4%</td>
<td>1.6%</td>
<td>4.9%</td>
<td>10.2%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Sedation</td>
<td>0.4%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3.3%</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3.4%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>0.8%</td>
<td>1.6%</td>
<td>0</td>
<td>0</td>
<td>4.9%</td>
</tr>
<tr>
<td>Headache</td>
<td>2.4%</td>
<td>0</td>
<td>1.6%</td>
<td>5.1%</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

DORAs aren’t yet on the radar as alternatives to sedative/hypnotics.

### Prescription sleeping pills: What's right for you?

Sleeping pills help when stress, travel or other disruptions keep you awake. If you have chronic insomnia, a better approach may be to find and remove the cause.

*By Mayo Clinic Staff*

<table>
<thead>
<tr>
<th>Sleep medication</th>
<th>Helps you fall asleep</th>
<th>Helps you stay asleep</th>
<th>Can lead to dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxepin (Silenor)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Estazolam</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Eszopiclone (Lunesta)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ramelteon (Rozerem)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Zaleplon (Sonata)</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Zolpidem (Ambien, Edluar, Intermezzo, Zolpimist)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Zolpidem extended release (Ambien CR)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

[Article on Mayo Clinic](http://www.mayoclinic.org/diseases-conditions/insomnia/in-depth/sleeping-pills/art-20043959)
A recent analysis of more than 1,000 safety reports submitted to the Food and Drug Administration about the sleeping pill suvorexant (Belsomra), found that it was associated with side effects such as agitation, disturbed sleep, and next-day drowsiness—or that it simply didn't work at all. Those and other effects are listed in the FDA's approved drug label for suvorexant or were already found in clinical trials. But because suvorexant is the first of a new type of sleeping pill with limited evidence supporting its safety, Consumer Reports has been closely monitoring the effects of the drug in real-world conditions.
Why is treating insomnia so important?

Eiko Ojala
Sleep Drives Metabolite Clearance from the Adult Brain.
Xie et al. (2013) Science
Can the DORA drugs help slow Neurodegeneration in those with MCI/AD?

Neurodegeneration: Paying It Off with Sleep

A new study in fruit flies suggests modulation of neural activity links sleep and Alzheimer’s disease. Both sleep loss and amyloid beta increase neural excitability, which reinforces the accumulation of amyloid beta and shortens lifespan.

Alex C. Keene¹,² and William J. Joiner²

Alzheimer’s disease (AD) is a progressive, irreversible brain disorder between clearance and production of Aβ results in toxic amyloid aggregates within neurons or as plaques between neurons that initially damage synapses and later cause...
Sleep disruption leads to Beta-amyloid deposits in mice

- Results showed that increase in sleep time slowed the production of Aβ and sleep deprivation increased the amount of Aβ pathology in the brain.

Sleep Disturbance

Changes in lifestyle, activity, medication use

Reduced glymphatic clearance

MCI / AD symptoms

ISF Aβ accumulation
Can DORAs help?

Blocking Sleep-Wake Protein Orexin May Treat Alzheimer’s

DECEMBER 4, 2014    BY ADMIN    IN ALZHEIMER’S NEWS, NEWS.
Amyloid-β Dynamics are Regulated by Orexin and the Sleep-Wake Cycle

![Graph A](image)

- **ISF Aβ (average of 1st day)**
  - Light
  - Dark
  - Orexin

![Graph B](image)

- **ISF Aβ during light (d1)**
  - NoT
  - Orexin

![Graph C](image)

- **Total minutes awake during light (d1)**
  - NoT
  - Orexin

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Kang et al.
DORA infusion reduces ISF Aβ levels
Takeaways

• Traditional hypnotics, usually GABA agonists, are minimally effective at improving subjective and objective sleep.
• The negative side effects of sedative/hypnotics usually outweigh the benefits, particularly in the elderly population.
• Hypnotic use is estimated to contribute to >300,000 deaths in the US per year.
• Dual Orexin Receptor Antagonists (DORAs) offer an entirely distinct pharmacological approach for treating insomnia.
• DORAs’ impact on sleep is comparable to sedative/hypnotics, but side effects are better tolerated in healthy geriatric population.
• Orexin over expression increases beta amyloid production, and DORA infusion prevents this.

• Ergo, DORAs likely offer an improved insomnia treatment option to sedative/hypnotics, particularly for elderly with or without MCI.
Dual Orexin Receptor Antagonists – An Alternative to Traditional Hypnotics for Insomnia in the Elderly Population

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