Chronic Insomnia in Older Adults

Sleep patterns naturally change as one gets older.
Compared to younger people, older adults:
- Sleep fewer hours & take longer to fall asleep
- Wake up more often during the night & are more easily disturbed by light, noise, pain, etc...
- May not adapt as quickly to changes, such as a new bed
- Have changes in their sleep cycle, e.g. older adults spend less time in the most restful stage of sleep (less deep sleep)

Result: tend to experience ↑ daytime sleepiness

What is chronic insomnia?• difficulty falling asleep, staying asleep, waking up too early, or sleep that is non-restorative.
Sleep difficulty, lasting ≥ 1 month, occurs despite adequate opportunity for sleep. Insomnia is clinically relevant if associated with significant distress or daytime impairment (fatigue, mood, cognitive, social/work dysfunction, etc...)

Sleep & Aging: Quality is as important as quantity!• Prevalence of insomnia in the elderly is estimated to be 40%.
- Although a mild deterioration in sleep quality may be accepted as normal with aging, a complaint of significantly disrupted nighttime sleep or impaired daytime functioning due to excessive sleepiness should be evaluated.
- Older people do not necessarily require less sleep, but they often get less sleep • 7-8 hrs compared to 8-9 hrs in younger adults.
- The sleep-wake cycle in the elderly may be fragmented with interrupted nighttime sleep & daytime wakefulness interrupted by naps. The deep stages of non-REM sleep (stages 3 & 4) are frequently reduced; REM sleep tends to be preserved.

Anxiety BPH Cardiovascular disease Cognitive disease Chronic or acute pain COPD HF, nocturnal symptoms

Insomnia in long-term care settings
- Difficult to treat insomnia in this setting due to staff providing routine care that can affect sleep (turning bed-bound residents every 2 hours, checking incontinent residents periodically at night, early morning vital sign measurements, etc.)
- Other problems: many residents have a roommate, doubling the interruptions. Residents may have little ability to make behavioural modifications given the environment.
- Efforts to ↓ interruptions & noise in this setting, as well as a commitment to ↑ daytime activities, avoid daytime naps & minimize time awake in bed for residents would help reduce use of sedatives in older, frail adults prone to adverse effects.

Approach to insomnia treatment
- Non-pharmacological methods are essential for long-term success (~75% of those treated will benefit11). Avoid the assumption that patients expect a sedative prescription and are unwilling to modify sleep-related behaviours.30-31
- Cognitive behavioural therapy (CBT) & pharmaco-therapy, followed by CBT alone, may produce the best long-term outcomes (6 week acute phase; 6 month follow-up).12
- Follow-up & reassess, as the relapse rate is high.
- Patient completed at-home sleep diary can be used to identify areas for behavioural modification & for monitoring progress.14

Sleep hygiene education (principles of good sleep habits)
- Insufficient evidence that sleep hygiene alone is effective in the treatment of chronic insomnia. It is best used in combination.
  - Avoid clock-watching!!
  - Set consistent bedtimes & wake times.
  - Environmental control (e.g. stimulus control below).
  - Avoidance of nap, caffeine, nicotine & alcohol - can affect initiation & maintenance of sleep continuity.

Cognitive behavioural therapy (CBT) 7,11,13,14 For 1st & co-morbid insomnia
- Demonstrated efficacy in improving sleep-onset latency & total sleep time (multi-component therapies are more efficacious than individual techniques).
- Efficacy of CBT = benzodiazepines or zopiclone at 6 months
- Benefits of CBT are sustained for up to 2 years whereas pharmacotherapy loses benefit after drug discontinuation.
- Access to trained specialists & cost may be barriers.
- “Brief behavioural” tx (e.g. 45min visit, 30min f/u, & 2 phone-calls) & internet-based CBT show benefit & feasibility in primary care.33,34,36

Table 1: Sleep Disturbance: Contributing Factors

MEDICAL CONDITIONS - Optimize therapy of these contributing factors
Anxiety BPH Cardiovascular disease Cognitive disease Chronic or acute pain COPD HF, nocturnal symptoms

DRUGS - Consider eliminating, or changing dose or timing of these agents; may cause fragmented sleep, nightmares, nocturia, or stimulation
Antidepressants, stimulating
Cardiovascular
Decongestants
Diuretics
Opioids
Respiratory
Stimulants
Others

Alzheimer’s disease (AD) & sleep 8,9 (see online extras for more info)
It’s easy to confuse the nocturnal behaviours of AD with insomnia. These will often present as more severe & exceed the limits of what might otherwise be termed insomnia in a non-demented geriatric population. Behavioural therapy should be tried before medication whenever possible.

Exercise: small trial (RCT), community-based older adults - moderate-intensity (30-40 min, 4x/wk, low-impact aerobics/brisk walking); Self-rated improvements ↓ sleep onset ~15 min, ↑ total sleep time ~45 min.15

References
Pharmacological Options (see also RxFiles Sedatives Chart)

General considerations for the use of sedatives
- Try to reserve for situations where poor quality sleep is negatively impacting daytime functioning.
- Use the lowest effective dose, short-term (ideally ≤ 2 weeks).
- Re-evaluate chronic sedative use for efficacy & potential harm.
- Taper & discontinue gradually if previously used long-term.

Benzodiazepines & Non-benzo “Z-drugs” (e.g. zopiclone, zolpidem) Benefits: improve short-term sleep outcomes
- Estimate: ↓ sleep onset latency by 10 to 20 minutes
- Estimate: ↑ total sleep time by ~30 minutes

Harms – a costly trade-off with the benefits:
- Rebound insomnia when stopped abruptly may be a trigger for chronic use
- Development of tolerance, dependence & withdrawal reactions: continuing long-term may serve only to prevent withdrawal symptoms as effectiveness is progressively reduced
- Risk with shorter duration of action, older patients, daily long-term use, higher doses, alcoholism, etc.
- Hangover effects (varies between agents, strongly dependent on dose & duration of effect).
- Other serious adverse effects: fall risk, fractures & memory or performance impairment. Whether zopiclone or zolpidem is any safer than benzos is uncertain.
- If prescribing a benzo for elderly, short to intermediate-acting agents (e.g. lorazepam, temazepam) are preferred; AVOID those with a very long half-life (flurazepam, diazepam & chlorzoxazone) as well as those that are very short acting (triazolam & alprazolam).

Low-Dose Sedating Antidepressants
- Reserve for when other treatments fail or when insomnia is associated with a co-morbid condition (e.g. depression, pain) or in patients with a history of substance abuse.
- There is no single antidepressant or class of antidepressants that is most effective for insomnia in those with depression.
- Trazodone: sedative dose lower than those used to treat depression; lacks anticholinergic effects but is associated with CV adverse effects (e.g. orthostatic hypotension), next-day sedation (longer half-life in the elderly), & priapism.
- Mirtazapine: role in major depression with associated insomnia; useful alternative or co-prescription for patients with insomnia induced by other antidepressants (e.g. buproprion, some SSRIs); associated with increased appetite & weight gain; long half-life may cause daytime sedation & driving (Anecdotally: the 15mg may be more sedating than higher doses because of increased affinity for anticholinergic receptors at the lower dose.)

**Evidence for quetiapine use in primary insomnia (very limited)**
- 2 published RCTs evaluated quetiapine’s effect on sleep in patients not suffering from other medical conditions or psychiatric illness. Only one studied patients suffering from primary insomnia; the other was in healthy subjects without insomnia.
- The healthy subject study evaluated 14 men using a randomized, double-blind, crossover. Placebo or quetiapine at 25 & 100 mg doses were given on 3 consecutive nights with a 4-day washout period before crossover. Both doses of quetiapine produced statistically significant improvements in objective & subjective ratings of sleep, including total sleep time, sleep efficiency, sleep latency & duration of stage 2 sleep. The 100 mg dose increased periodic movement & decreased REM sleep. Two out of 14 subjects taking quetiapine withdrew from the study because of symptomatic orthostatic hypotension.
- In the primary insomnia study, 25 patients were randomized to quetiapine 25 mg or placebo. Patients were asked to record a sleep diary for one week before & 2 weeks after initiation of treatment. No statistically significant improvements were found in the primary outcomes of total sleep time, sleep latency, daytime alertness & sleep satisfaction.

Evidence for sedative hypnotic use in primary insomnia, AEs & evidence

OCT Antihistamines (diphenhydramine, doxylamine)
- Tolerance to sedative effects occurs after day 3 to 4 of continuous use.
- Avoid especially if glaucoma, asthma, & urinary retention.
- It is unknown if these agents improve sleep quality in older adults; poor evidence of efficacy & long-term safety data.

Herbals (Valerian, kava, passionflower, skullcap) & others
- Evidence lacking for efficacy of herbals in the treatment of insomnia
- Adverse events & drug interactions can occur (limited data)
- Products with a natural product # (NPN) have some regulation
- Some products may contain caffeine & be counterproductive
- Melatonin: reasonable option in terms of safety; but effects are minimal, ~30 minutes – assess after a week trial duration.

Quetiapine (off-label for insomnia)
- A number of sleep studies have found that atypical antipsychotics, as a class, can improve aspects of sleep in normal controls & those with psychiatric disorders. However, quetiapine’s sleep effects in older adults, especially with dementia, are relatively unstudied.
- The pharmacokinetic alterations due to aging may contribute to increased adverse effects; use lowest dose. Extended release agents may not be an optimal choice due to slowed motility of GIT & altered pharmacokinetic parameters
- Many drug interactions are possible. [May ↑ levels/effects of: alcohol, anticholinergics, CNS depressants, methylphenidate, QTc-prolonging agents, quinine. May ↓ levels/effects of: amphetamines, anti-parkinson’s agents (dopamine agonists)]
- AEs include: ↑ risk of stroke, QT-prolongation, diabetes & death

How to Sleep Better: http://helpguide.org/life/sleep_tips.htm (patient friendly!)

AD=Alzheimer’s disease  CBT=cognitive behavioural therapy  CNS=central nervous system  CV=cardiovascular  EPS=extrapyramidal symptoms  f/u=follow-up  REM=rapid eye movement  RLS=restless leg syndrome  SSRI=serotonin receptor antagonists  OTC=over-the-counter  MAO=monoamine oxidase inhibitors  TCA=tricyclic antidepressants  treatment

Produced by RxFiles – a provincial academic detailing service funded by Saskatchewan Health. For more information check our website at www.RxFiles.ca or contact us c/o Saskatchewan City Hospital, 701 Queen Street, Saskatoon, SK. S7K 0M7 Copyright 2013 – RxFiles, Saskatoon Health Region (SHR) www.RxFiles.ca See online extras for disclaimer & more information.
Insomnia in Older Adults

Approach to Insomnia

- Manage any underlying cause of insomnia or associated comorbidities
- Address any drug/substance use that may be worsening sleep
- Encourage & facilitate as many non-drug measures as possible
- Stimulus-control therapy (reassociate bedroom with sleep onset)
  - Go to bed only when sleepy
  - Use the bed/bedroom only for sleep & sex
  - Ideally, do not stay in bed longer than 15-20 minutes if unable to sleep
  - Consider taking the clock out of the bedroom
  - Consider phototherapy; Sit in front of 10,000 lux light box (or a window with sunlight) for 30-40 minutes upon awakening (average indoor lighting is 300-500 lux, average sunny summer day is 100,000 lux)
- Sleep-restriction (limit time in bed that will lead to sleep deprivation to result in ↑ in homeostatic drive & sleep efficiency)
- Cognitive therapy (alters faulty beliefs & attitudes about sleep)
  - Relax muscles throughout body, breathing patterns, direct attention from everyday thoughts by using a mental focusing device that is neutral & repetitive
- Tailor behaviour changes to the individual and use a sleep diary for assessment.
  - CBT interventions are recommended 1st line. Hypnotherapy should be supplemented with CBT whenever possible.

What are the Pharmacologic Options?

Medication should only be used to treat insomnia if poor quality sleep is negatively affecting daytime function. However, this may not be an appropriate or practical measure in LTC. A decrease in participation in activities previously enjoyed or in the level of socialization may be a more appropriate measure.

Use the lowest effective dose, short-term; ideally ≤ 2 weeks. Try intermittent therapy if appropriate (e.g. limit to 3 nights/week).

Re-evaluate chronic sedative use. Potential harms often outweigh benefits (e.g. sedatives NNT=13 > NNH=6). Attempt to initiate a slow taper. (If a medication cannot be completely discontinued, a ↓ dose is still a win!)

<table>
<thead>
<tr>
<th>Harms</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Risk of rebound insomnia</td>
<td>Improve short-term sleep outcomes.</td>
</tr>
<tr>
<td>• Development of tolerance, dependence &amp; withdrawal reactions</td>
<td>o ↓ sleep onset by 10 to 20 minutes</td>
</tr>
<tr>
<td>• Residual daytime sedation</td>
<td>o ↓ total sleep time by ~30 minutes</td>
</tr>
<tr>
<td>• Risk of falls, fractures &amp; cognitive impairment</td>
<td>• Motor vehicle accidents</td>
</tr>
<tr>
<td>• Risk of anticholinergic side effects &amp; cognitive impairment</td>
<td></td>
</tr>
</tbody>
</table>

Melatonin: minimally effective but reasonable option in terms of safety; 1 to 3mg at bedtime (max 5mg) - dosing 2 to 3 hours before bedtime may be most effective.
- Sustained-release melatonin preparations might be better for improving sleep maintenance, & immediate-release preparations might be more beneficial for decreasing sleep latency.
- Some evidence suggests that melatonin might be most beneficial for insomnia in older adults, who experience ↓ levels of melatonin due to advanced age, compared to younger adults or children.
- Neurodegenerative disorders (especially in Alzheimer's disease & other types of senile dementia), type 2 diabetes (among other diseases & disorders) can also ↓ melatonin secretion.
- Products with a Natural Product Number (NPN) have some regulation to ↑ chance of quality.

Non-benzodiazepine hypnotics:
- Zopiclone 2.5 to 3.75mg at bedtime
- Zolpidem 5mg SL at bedtime (shorter-acting)

Intermediate-acting benzodiazepines:
- Temazepam 15mg at bedtime
- Lorazepam 0.5mg at bedtime
- Oxazepam 10 to 15mg at bedtime

What about long-term effects on sleep? 76 mid-aged & elderly chronic insomniacs using low-dose benzodiazepines (LDB), for a minimum of 6 months, were compared with drug-free insomniacs to determine the effect on sleep. Results showed that LDB leads to a complete loss of hypnotic activity & substantial suppression of delta & REM sleep.

Consider the presence of co-morbid conditions to optimize other agents:
- **BPSD – aggression, psychosis, agitation:**
  - Quetiapine 12.5 mg to 25 mg at bedtime
- **Chronic pain:**
  - TCA: Nortriptyline 10 to 25 mg at bedtime (↑ anticholinergic activity & hypotension compared to amitriptyline but still requires cautious initiation)
- **Depression:**
  - Mirtazapine 3.75 mg (i.e. ½ tablet) to 15 mg at bedtime; An inverse relationship exists between dose & sedation (lower dose is more sedating). Can ↑ appetite & weight.
- **“Sun-downing” or evening agitation related to dementia:**
  - Trazodone 25 to 50 mg at bedtime. Sedating without anticholinergic effects. Minimal effect on sleep architecture. Adverse events include: hypotension, especially if there are interacting drugs or comorbidities. Can cause priapism (rare).
# Insomnia in Older Adults

## Medications used to treat insomnia & their precautions

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>When a medication could be problematic for Older Adults[^14]</th>
<th>Clinical Concern[^14]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antihistamines, First Generation</strong> (As single agent or as part of a combination product)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clemastine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine (oral)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxylamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Promethazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triprolidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Denotes a combination product</em>*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Antihistamines, First Generation

- **Chlorpheniramine**
- **Doxylamine**
- **Hydroxyzine**
- **Promethazine**
- **Triprolidine**

**B** ≥65 YEARS OF AGE

**USE FOR >1 WEEK of 1st generation antihistamines**

**Clinical Concern**: Sedation & strong anticholinergic side effects (↑ risk of confusion, dry mouth, constipation, urinary retention in ♂ & other anticholinergic effects/toxicity)

**Clearance ↓** with advanced age & tolerance develops rapidly (i.e. after a few days) when used as a hypnotic[^5]

Note: In a study of healthy men aged 18 to 50 years, tolerance to 50mg of diphenhydramine occurred in 3 days[^6]

### Benzodiazepines

- **Short- & intermediate-acting**: Alprazolam (≥10 hours) & Diphenhydramine (1-2 hours)
- **Long-acting**: Chlordiazepoxide (≥12 hours) & Flurazepam (≥10 hours)

**B** For treatment of INSOMNIA or AGITATION

**USE of LONG-ACTING AGENT**

**Clinical Concern**: Older adults have ↑ sensitivity to benzodiazepines & ↓ metabolism of long-acting agents

In general, all benzodiazepines ↑ risk of cognitive impairment, confusion, delirium, sedation, falls, fractures & motor vehicle accidents in older adults. Benzodiazepines can also lower inhibitions resulting in a possible worsening of some behaviours (e.g. sexual disinhibition, calling out)

### Neuroleptics (Antipsychotics)

**First-Generation (Conventional)**

- Chlorpromazine
- Fluphenazine
- Haloperidol
- Loxapine
- Methotrimeprazine
- Perphenazine
- Pimozide
- Pipotizine
- Prochlorperazine
- Thiothixene
- Trifлуoperazine
- Zuclopenthixol

**Second-Generation (Atypical) Agents**

- Aripiprazole
- Asenapine
- Clozapine
- Lurasidone
- Olanzapine
- Paliperidone
- Quetiapine
- Risperidone
- Ziprasidone

**B** As a HYPNOTIC, >1 month

**Clinical Concern**: Risk of confusion, hypotension, extrapyramidal effects, falls, fractures

- Risk of stroke when used for the behavioural & psychological symptoms of dementia (OR: 1.3-3.1)^[^8]

- Risk of all cause mortality when used for the behavioural & psychological symptoms of dementia (OR:1.2-1.6;AR ≥1%/12 weeks; NNH=87/12wks)^[^9][^10][^11][^12][^13]

- Can be appropriately used short-term for severe aggression & agitation if the behaviour is potentially harmful to the individual themselves, care staff or others who may reside in the same area

### Nonbenzodiazepine Hypnotics

**Zolpidem**

**B** CHRONIC USE (>90 days)

**Clinical Concern**: Adverse events similar to those of benzodiazepines in older adults (e.g. delirium, falls, fractures, MVAs)

- Minimal improvement in sleep latency & duration

---

[^1]: [Medication listed in 2012 Beers Criteria; ][^2]: [Medication listed in STOPP Criteria; ][^3]: [Medication requires tapering upon discontinuation; ][^4]: [Quality of Evidence; SR=Strength of Recommendation]
## Insomnia in Older Adults continued

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>When a medication could be problematic for Older Adults</th>
<th>Clinical Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DECONGESTANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OTC Combo Products</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylephrine: BENYLIN®, DAYQUIL®, DIMITAPP®, DRISTAN®, NEOCITRAN®, NYQUIL®, SUDAFED®, TRIAMINIC®, TYLENOL (ALLERGY, COLD, FLU, SINUS)*</td>
<td>With INSOMNIA</td>
<td>• Risk of confusion</td>
</tr>
<tr>
<td></td>
<td>Pseudoephedrine: ACTIFED®, ADVIL COLD &amp; SINUS®, AERIUS DUAL®, ALLEGRA-D®, BENADRYL TOTAL ALLERGY &amp; SINUS®, BENYLIN®, BUCKLEY'S®, CLARITIN ALLERGY &amp; SINUS®, COACTIFED®, DAYQUIL D®, DIMETAPP®, DRISTAN®, DRIXORAL COLD &amp; SINUS®, ENTEX LA®, NEOCITRAN®, REACTINE ALLERGY &amp; SINUS®, ROBITUSIN®, SINUTAB®, SUDAFED®, TRIAMINIC®, TYLENOL (COLD, COMPLETE, FLU, SINUS)*</td>
<td>QE = Moderate; SR = Strong</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PHOSPHODIESTERASE ENZYME INHIBITORS, NONSELECTIVE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMINOPHYLLINE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THEOPHYLLINE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pseudoephedrine: ACTIFED®, ADVIL COLD &amp; SINUS®, AERIUS DUAL®, ALLEGRA-D®, BENADRYL TOTAL ALLERGY &amp; SINUS®, BENYLIN®, BUCKLEY'S®, CLARITIN ALLERGY &amp; SINUS®, COACTIFED®, DAYQUIL D®, DIMETAPP®, DRISTAN®, DRIXORAL COLD &amp; SINUS®, ENTEX LA®, NEOCITRAN®, REACTINE ALLERGY &amp; SINUS®, ROBITUSIN®, SINUTAB®, SUDAFED®, TRIAMINIC®, TYLENOL (COLD, COMPLETE, FLU, SINUS)*</td>
<td>With INSOMNIA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>QE = Moderate; SR = Strong</td>
</tr>
<tr>
<td><strong>STIMULANT DRUGS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphetamines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphetamine Mixed Salts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caffeine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td></td>
<td>With INSOMNIA</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td></td>
<td>QE = Moderate; SR = Strong</td>
</tr>
</tbody>
</table>

## Medications that pose a significant potential for harm & should be avoided

<table>
<thead>
<tr>
<th><strong>BARBITURATES</strong></th>
<th>2012 Beers Criteria; STOPP Criteria; Requires tapering upon discontinuation</th>
<th>Quality of Evidence; Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butalbital</td>
<td>≥65 YEARS OF AGE</td>
<td>• High rate of physical dependence</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td></td>
<td>• Tolerance to sleep benefits</td>
</tr>
</tbody>
</table>

| **CHLORAL HYDRATE** | ≥65 YEARS OF AGE | • Tolerance occurs within 10 days & risk outweighs the benefits in light of overdose with doses only 3x the recommended dose |
|                    |                  | • Fatal at doses ≥ 4 grams                    |

* = Medication listed in 2012 Beers Criteria; ♦ = Medication listed in STOPP Criteria; ♣ = Medication requires tapering upon discontinuation; QE=Quality of Evidence; SR=Strength of Recommendation
EXTRAS...

Trazodone in Insomnia
No objective studies have been conducted in the treatment of DSM-defined primary insomnia with trazodone. As a result, the existing data do not allow for clear-cut, evidence-based recommendations concerning the use of trazodone in insomnia.

MOA
- Precise mechanism of action is not fully understood. Thought to be a weak but specific inhibitor of synaptic reuptake of serotonin (5-HT). It also has antagonistic action at the adrenoceptors & to a lesser extent α2-adrenoceptors.
- Chemically & pharmacologically distinct from other antidepressants
- Trazodone is well absorbed after oral administration & T_max occurs ~1 hr after dosing when taken on an empty stomach or 2 hrs when taken with food

Dose
- Prescribed off-label for insomnia; limited evidence
- Start low & go slow; e.g. initial dose: 25-50mg
- Usual sedative dose: 50-100mg (lower than antidepressant dose which ranges from 150-600mg in divided doses)
- Half-life ~6.4 hrs in younger adults & 11.6 hrs in elderly

Safety
- Unclear what trazodone’s adverse effect profile is at low doses
- Most common (≥10%) adverse events seen at doses of 75mg/day to 500mg/day include (poored data):
  - drowsiness 29.1% (20-50%)
  - dizziness 21.9% (10-30%)
  - dry mouth 17.7% (2-33.8%)
  - nausea/vomiting
  - constipation
  - headache
  - hypotension
  - blurred vision
- ~25-30% of pts experience difficulty tolerating trazodone at doses higher than 50mg/day (in controlled trials of trazodone used for clinical depression). Drops out rates, are high (25-60%) with ~25-50% of discontinuations due to adverse events.
- Sedation: next-day sedation can be a problem with trazodone, even when administered to depressed patients as a hypnotic at doses between 25-100mg hs.
- Cardiac safety: CV adverse effects (hypotension, orthostatic hypotension with syncope, ventricular arrhythmias, cardiac conduction disturbances, exacerbation of ischemic attack) typically occur at antidepressant doses (100-600mg/day), orthostatic hypotension has been observed in elderly pts receiving lower doses (50-175mg/day) & concomitant antihypertensive therapy. Cardiac arrhythmias were also seen with trazodone dosages ranging from 200-300mg/day.
- Compared with older tricyclic antidepressants, trazodone seems to have a more benign CV risk profile*
- Priapism: FDA found that majority of cases occurred with doses of 50-150mg/day (amounts typically used to treat insomnia). Onset usually occurred within the first 28 days of treatment. Difficult to treat. It has been theorized that trazodone’s α-adrenergic-blocking properties contribute to the induction of priapism.

Advantages & possible adverse effects
- Tolerance development is not expected, permitting long-term use, & there is no abuse or addiction potential
- Trazodone lacks anticholinergic effects, which is an advantage; however, there is a higher risk of orthostatic hypotony & ventricular arrhythmias

Evidence
2005: Review of the evidence for the efficacy & safety of trazodone in insomnia
- 18 studies identified
- Majority of studies are very small → only 5 trials enrolled >30 pts in trazodone arm
- Studies are of limited duration → half of the trials employed an active treatment period of ≤3 weeks; no trials exceeded 6 weeks of active treatment
- Only 3 trials were randomized, double-blind, & placebo-controlled design → of these 3, only 1 employed objective measures (7 depressed patients with brofaromine-induced insomnia & had an active treatment duration of only 1 week)
- 14 studies were performed in depressed populations in which insomnia was either secondary to depression or induced by antidepressants
- 2 studies assessed trazodone’s effect on sleep in healthy subjects
- 2 studies were identified that examined trazodone’s effect in nondepressed subjects with sleep disorders

- Compared hypnotic efficacy of trazodone 50mg & zolpidem 10mg with placebo for 2 weeks in 306 adults (21-65 years)
- Sleep parameters were assessed using a subjective sleep questionnaire (self-reported sleep latency, sleep duration, # of awakenings, wake time after sleep onset) that pts completed each morning & at weekly office visits. There were no objective measurements.
- Results:
  - Week 1: relative to placebo, pts reported significant improvement in subjective sleep latency, sleep duration, WASO & sleep quality with trazodone & zolpidem (p<0.02), & self-reported sleep latency was significantly shorter with zolpidem than with trazodone (p<0.037).
  - Week 2: trazodone group did not differ significantly from the placebo group. However, zolpidem group demonstrated significant improvement compared with placebo for sleep latency (p=0.037) & sleep duration (p<0.02) even though the placebo group demonstrated increases in sleep duration over the 2 week period (25 minutes above baseline during week 1 & 37 minutes during week 2).
  - ?? tolerance to the sedative effect quickly develops

Mashiko et al (1999)
- Primarily concerned with dose finding, & it compared the efficacy of 50mg, 75mg & 100mg/day trazodone doses
- 33 pts (12 ♂, 21 ♀; 42.5 ± 15.6 yrs) depressive state with sleep disorders
- Optimal results achieved with trazodone 100mg/day (premature morning awakening, lack of sound sleep, difficulty initiating sleep)

Roth et al (2011)
- 50 mg nightly vs. placebo, in pts with primary insomnia, n=16
- Short trial (7 days) to evaluate next day impairment associated with nighttime dosing of trazodone
- Significantly decreased number of night-time awakenings. Modest impairments noted in short-term memory, verbal learning, body sway & arm muscle endurance.

Bottom line
Trazodone is not officially indicated for insomnia, but may be considered a treatment option in the elderly if initiated at a low dose (25-50mg hs). Beware of the potential adverse effects & increased half life!
Alzheimer’s disease (AD) & sleep

- Sleep disturbance in Alzheimer’s disease (AD) is very common - Nocturnal sleep disturbance in AD patients is often accompanied by increased daytime napping, frequently in direct association with the extent of dementia.
- Symptom manifestation: sleep onset & maintenance insomnia, sleep fragmentation & disturbed circadian rhythm (↑daytime napping).
- “Sundowning” symptoms may be seen in advanced AD (confusion, delirium, wandering, & agitation).
- Sleep disturbance is related to loss of neurons in suprachiasmatic nuclei & alteration in endogenous melatonin secretion (20% of those of age-matched controls) contributing to disturbed circadian rhythm.
- When behaviours are measured systematically using actual clock time as an independent variable, temporal specificity for the behaviours, rather than random occurrence, is the rule.
  - o travel behaviors peaked at 7 to 9 PM
  - o vocalizations at 5 to 7 PM
  - o wandering at 5 to 6 PM
  - o maladaptive behaviors at 4 to 8 PM
  - o physical aggression from 4:30 to 11 PM
  - o overall agitation from 4 to 9 PM
  - o Taken together, these behaviours appear to be worse around sunset & the nocturnal hours (AKA sundowning). (Not all studies report this kind of temporal specificity). Also found - agitation near time of sunset worse in winter (time-of-day effects less apparent).
- In the later stages of AD, patients may spend up to 40% of their time in bed awake & a significant proportion of their day-time hours asleep. This ↑ day-time sleep consists almost exclusively of stage 1 & 2 sleep & does not replace or even remotely compensate for the night-time losses of slow-wave sleep (SWS) & REM sleep.
- Cholinesterase inhibitors can cause insomnia (+significant dream disturbance & nightmares).

Insomnia Clinical Pearls

Tips for assisting a person who wishes to stop taking benzodiazepines or ‘z-drugs’

- Assess if now is a suitable time in the person’s life to tackle this
- Consideration should be given to whether withdrawal can be appropriately managed in primary care
- Withdrawal may be undertaken with or without switching to diazepam
- A gradual drug withdrawal schedule (dose tapering) that is flexible should be negotiated.
- Reviews should be frequent to detect & manage problems early & to provide advice & encouragement.
- If a person does not succeed on their first attempt, they should be encouraged to try again.

Available from:  http://cks.nice.org.uk/benzodiazepine-&-z-drug-withdrawal!topicsummary

Tips to avoid sleeping issues (Expert Opinion):

- Avoid dosing furosemide & other diuretics in the evening
- Instruct patients to sit or lie down with feet up for 1-2 hours before bedtime
- Use nitro patch at night (i.e. apply at 8pm & remove at 8am)
- Tell patients not to take corticosteroid too late in the day as they are stimulating
- Avoid excessive salbutamol use in the evening (excessive use may be due to an uncontrolled respiratory disorder)
- Avoid exercising within 4 to 5 hours of bedtime; early morning or afternoon is best

Stages of the sleep cycle

<table>
<thead>
<tr>
<th>Stage</th>
<th>Classification</th>
<th>Description/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-REM sleep I</td>
<td>Relaxed wakefulness</td>
<td>Sleep initiation (15-30 minutes)</td>
</tr>
<tr>
<td>Non-REM sleep II</td>
<td>Light, α-wave sleep</td>
<td>Constitutes ~50% of total sleep time; sedative-hypnotic medications typically increase amount of time spent in this stage</td>
</tr>
<tr>
<td>Non-REM sleep III &amp; IV</td>
<td>Deep, δ-wave sleep (AKA slow-wave sleep)</td>
<td>Performs revitalizing &amp; restorative functions; time spent in δ-wave sleep diminishes with age &amp; often becomes nonexistent in persons aged ≥75 years</td>
</tr>
<tr>
<td>REM sleep V</td>
<td>Active sleep</td>
<td>Achievement of REM sleep is crucial for learning &amp; mood regulation; dreams occur &amp; sexual arousal is common; in normal restorative sleep, the sleeper spends roughly 20%-25% in REM sleep</td>
</tr>
</tbody>
</table>
References: RxFiles - Chronic Insomnia in Older Adults

1 Neubauer DN. Sleep problems in the elderly. Am Fam Physician. 1999 May 1;59(9):2551-8, 2559-60.

21 http://www.nice.org.uk/insomnia#scenario/recommendation.1

Other Resources