Chronic Insomnia in Older Adults

Sleep patterns naturally change as one gets older.

Compared to younger people, older adults: [1,2,3]

- 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?[4,5] **difficulty falling asleep, staying asleep, waking up too early, or sleep that is non-restorative. Sleep difficulty, lasting ≥ 1 month** 3 nights/week, **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!* [1,2,3, 6]

- 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. 7.4 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.

Table 1: Sleep Disturbance: Contributing Factors [7]

⇨ MEDICAL CONDITIONS - Optimize therapy of these contributing factors

Anxiety	Dementia	Nocturnal wheezing
BPH	Depression	Parkinson's disease
Cardiovascular disease	Gastrointestinal (e.g. reflux, peptic ulcer)	RLS/nocturnal leg cramps
Chronic kidney disease	Incontinence	Seizure activity
Chronic or acute pain	Malignancy	Sleep apnea
COPD	Nasal Problems	Stroke
HF, nocturnal symptoms		Thyroid disease

⇨ DRUGS - Consider eliminating, or changing dose or timing of these agents; may cause fragmented sleep, nightmares, nocturia, or stimulation

Antidepressants, stimulating	Buproprion, citalopram, duloxetine, escitalopram, fluoxetine, MAOIs, paroxetine, sertraline, venlafaxine
Cardiovascular	α-blockers (tamsulosin), β-agonists (salbutamol) β-blockers (propranolol, metoprolol), statins
Decongestants	Phenylephrine, pseudoephedrine
Diuretics	Chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, indapamide, metolazone, spironolactone; caffeine in combination products e.g. TYLENOL #3
Opioids	Codeine, oxycodone (note if pain, opioid may ↑sleep)
Respiratory	Salbutamol , theophylline, ipratropium
Stimulants	Amphetamine derivatives, caffeine, cocaine, ephedrine derivatives, methylphenidate, modafinil
Others	Acetylcholinesterase inhibitors (e.g. donepezil), alcohol, antineoplastics, corticosteroids, levodopa, nicotine, medroxyprogesterone, phenytoin, thyroid supplements

BPH=benign prostatic hypertrophy **COPD**=chronic obstructive pulmonary disease **HF**=heart failure **MAOI**=monoamine oxidase inhibitor **RLS**=restless leg syndrome

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.

Insomnia in long-term care settings [10]

- 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 benefit[11]). 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).[32]
- 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.[12]

Sleep hygiene education (principles of good sleep habits)

- Insufficient evidence that sleep hygiene alone is effective in the treatment of chronic insomnia.[4] 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 1°& 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 2: Components of CBT

Stimulus-control therapy‡ (reassociate bedroom with sleep onset)
- ⇨Go to bed only when sleepy
- ⇨Use the bed/bedroom only for sleep & sex do not watch TV
- ⇨Do not stay in bed longer than 15-20 minutes if unable to sleep

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)

Relaxation (biofeedback; promotes relaxation & ↓arousal prior to bed)
- ⇨Relax muscles throughout body, breathing patterns, direct attention from everyday thoughts by using a mental focusing device that is neutral & repetitive

‡ generally considered feasible for application in primary care

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]

Pharmacological Options (see also RxFiles Sedatives Chart)

General considerations for the use of sedatives[7]

⇨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)[16]

Benefits: improve short-term sleep outcomes

- Estimate: ↓sleep onset latency by 10 to 20 minutes
- Estimate: ↑ total sleep time by ~30 minutes[17]

***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[18] {~10-30% of chronic benzodiazepine users develop physical dependence, & 50% suffer withdrawal symptoms[28,29]; ↑risk with drugs of 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 (only 2 RCTs: small [n=10-41] & short [15-17 days]).
- 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 & chlordiazepoxide) as well as those that are very short acting (triazolam & alprazolam).

Low-Dose Sedating Antidepressants[20] (off-label for insomnia)

⇨ 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.

- Unknown whether sleep improves in elderly with 1° insomnia.[14]
- There is no single antidepressant or class of antidepressants that is most effective for insomnia in those with depression.[19]

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[rare]. (see online extras for more information)

Mirtazapine: role in major depression with associated insomnia; useful alternative or co-prescription for patients with insomnia induced by other antidepressants (e.g. bupropion, some SSRIs); associated with increased appetite & weight gain; long half-life may cause daytime sedation caution: driving {Anecdotally: the 15mg may be more sedating than higher doses because of increased affinity for anticholinergic receptors at the lower dose.}

[**Doxepin** SILENOR 3,6mg: new ultra-low dose of old TCA indicated for insomnia.]

[16] From the BEERS Criteria 2012:

- Avoid benzodiazepines for the treatment of insomnia; ↑risk of cognitive impairment, delirium, falls, fractures & motor vehicle accidents high quality, strong recommendation
- Avoid chronic use (>90 days): nonbenzodiazepine hypnotics (e.g. zopiclone, zolpidem) – adverse events similar to those of benzodiazepines in older adults; minimal improvement in sleep latency & duration moderate quality, strong recommendation
- TCAs (low dose): avoid tertiary TCAs (e.g. amitriptyline, trimipramine, doxepin >6mg/day) as highly anticholinergic, sedating & cause orthostatic hypotension high quality, strong recommendation {consider nortriptyline if using a TCA in older adults}
- Avoid 1st generation antihistamines (e.g. dimenhydrinate GRAVOL & diphenhydramine BENADRYL, UNISOM, NYTOL). Highly anticholinergic, clearance reduced with advanced age & tolerance develops rapidly moderate quality, strong recommendation.

OTC Antihistamines (diphenhydramine, doxylamine)[4,16,20]

- 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 & lacking 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 (small ↓ sleep latency) – assess after 3 week trial duration.[21,35]

Quetiapine (off-label for insomnia)[22,23,24]

- 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**. {See http://www.ti.ubc.ca/letter79 for Therapeutics Initiative's perspective}
- 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 agonist)]
- AEs include: ↑ risk of stroke, Qt-prolongation, diabetes & death

Evidence for quetiapine use in primary insomnia (very limited)[23,37,38,39]

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 leg movements & 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 & two 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.**

Very little data are available concerning adverse effects of low dose (≤150mg/day) quetiapine

- Case reports suggest akathisia & other EPS, periodic leg movements, RLS & orthostatic hypotension may be of concern
- Unknown whether weight gain & metabolic changes may complicate chronic low dose use
- Retrospective chart review: quetiapine <200mg hs for sleep was associated with an average weight gain of 4.9lbs (p=0.037), & average body mass index (BMI) increase of 0.8 points (p=0.048) after an average exposure of 11.1 months. Quetiapine induced weight gain may not be dose-dependent.
- Reports of weight gain despite the use of low quetiapine doses may predispose some to the metabolic disturbances (e.g., diabetes, dyslipidemia) associated with 2nd generation antipsychotic use.

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 SSRIs=seroronin receptor antagonists OTC=over-the-counter MAOIs=monoamine oxidase inhibitors TCAs=tricyclic antidepressants tx=treatment

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Insomnia in Older Adults[1]

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Approach to Insomnia

❑ **Manage any underlying cause of insomnia or associated comorbidities**

Anxiety	Dementia	Nocturnal wheezing
BPH	Depression	Parkinson's disease
Cardiovascular disease	Gastrointestinal (e.g. reflux, peptic ulcer)	RLS/nocturnal leg cramps
Chronic kidney disease	Incontinence	Seizure activity
Chronic or acute pain	Malignancy	Sleep apnea
COPD	Nasal Problems	Stroke
HF, nocturnal symptoms		Thyroid disease

❑ **Address any drug/substance use that may be worsening sleep** (e.g. Discontinue unnecessary medications; Change the timing of administration of stimulating medications to earlier in the day; Decrease the dose of stimulating medications)

Antidepressants, stimulating	Buproprion, citalopram, duloxetine, escitalopram, fluoxetine, MAOIs, paroxetine, sertraline, venlafaxine
Cardiovascular	α-blockers (tamsulosin), β-agonists (salbutamol) β-blockers (propranolol, metoprolol), statins
Decongestants	Phenylephrine, pseudoephedrine
Diuretics	Chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, indapamide, metolazone, spironolactone
Opioids	Codeine, oxycodone (Note: If pain is present, opioid may ↑ sleep)
Respiratory	Ipratropium, salbutamol, theophylline
Stimulants	Amphetamine derivatives, caffeine, cocaine, ephedrine derivatives, methylphenidate, modafinil
Others	Acetylcholinesterase inhibitors (e.g. donepezil), alcohol (can cause fragmented sleep), antineoplastics, corticosteroids, levodopa, medroxyprogesterone, nicotine, phenytoin, thyroid supplements

❑ **Encourage & facilitate as many non-drug measures as possible** (e.g. sleep hygiene, daytime/night-time routines, light therapy, stimulus control, sleep restriction, relaxation techniques, cognitive behavioural therapy (CBT), etc.)

Stimulus-control therapy (reassociate bedroom with sleep onset)
- ⇨Go to bed only when sleepy
- ⇨Use the bed/bedroom only for sleep & sex Avoid or minimize TV watching, using a laptop or tablet, etc.
- ⇨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)

Relaxation (biofeedback; promotes relaxation & ↓arousal prior to bed)
- ⇨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. Hypnotic therapy 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).[2] Attempt to initiate a slow taper. (If a medication cannot be completely discontinued, a ↓ dose is still a win!)

Harms	Benefits
• Risk of rebound insomnia • Development of tolerance, dependence & withdrawal reactions • Residual daytime sedation • Risk of falls, fractures & cognitive impairment • Motor vehicle accidents	Improve **short-term** (up to 6 weeks) sleep outcomes[3]: o ↓ sleep onset by 10 to 20 minutes o ↑ total sleep time by ~30 minutes

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.
- o Sustained-release melatonin preparations might be better for improving sleep maintenance, & immediate-release preparations might to be more beneficial for decreasing sleep latency.
- o 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.[4]
- o Products with a Natural Product Number (NPN) have some regulation to ↑ chance of quality.

B **Non-benzodiazepine hypnotics:**
- o **Zopiclone** Imovane, Rhovane 2.5 to 3.75mg at bedtime
- o **Zolpidem** Sublinox 5 mg SL at bedtime (shorter-acting)

SB **Intermediate-acting benzodiazepines:**
- o **Temazepam** Restoril 15mg at bedtime
- o **Lorazepam** Ativan 0.5mg at bedtime
- o **Oxazepam** Serax 10 to 15mg at bedtime

What about long-term effects on sleep?
76 middle-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.[1]

Consider the presence of co-morbid conditions to optimize other agents:

- **BPSD – aggression, psychosis, agitation**:
  - o SB **Quetiapine** Seroquel 12.5 mg to 25 mg at bedtime
- **Chronic pain**:
  - o SB TCA: **Nortriptyline** Aventyl 10 to 25 mg at bedtime
  - *(↓anticholinergic activity & hypotension compared to amitriptyline but still requires cautious initiation)*
- **Depression**:
  - o **Mirtazapine** Remeron 3.75 mg (i.e. ¼ 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**:
  - o **Trazodone** Desyrel 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 continued

For more detailed medication information, see the RxFiles Drug Comparison Charts

Drug or Drug Class	When a medication could be problematic for Older Adults[1-4]	Clinical Conern[1-4]
Medications used to treat insomnia & their precautions		
ANTIHISTAMINES, FIRST GENERATION (As single agent or as part of a combination product) Chlorpheniramine CHLOR-TRIPOLON Clemastine Cyproheptadine PERIACTIN **Dimenhydrinate** GRAVOL **Diphenhydramine** (oral) BENADRYL Doxylamine DICLECTIN * **Hydroxyzine** ATARAX Promethazine PHENERGAN Triprolidine * Denotes a combination product	B **≥65 YEARS OF AGE** *QE = High (Hydroxyzine & Promethazine) Moderate (All others); SR = Strong* S **USE FOR >1 WEEK** of 1st generation antihistamines	• 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 XANAX $t_{1/2}$ ~ 12 hours Bromazepam LECTOPAM t1/2 ~ 20 hours Lorazepam ATIVAN t1/2 ~ 15 hours Oxazepam SERAX t1/2 ~ 8 hours Temazepam RESTORIL t1/2 ~ 11 hours Triazolam HALCION t1/2 ~ 2 hours Long-acting: Chlordiazepoxide LIBRIUM $t_{1/2}$ ~ 100 hours Clonazepam RIVOTRIL $t_{1/2}$ ~ 34 hours Clorazepate TRANXENE $t_{1/2}$ ~ 100 hours Diazepam VALIUM $t_{1/2}$ ~ 100+ hours Flurazepam DALMANE $t_{1/2}$ ~ 100+ hours Nitrazepam MOGADON $t_{1/2}$ ~ 30 hours	B For treatment of **INSOMNIA** or **AGITATION** *QE = High; SR = Strong* S Use of **LONG-ACTING AGENT**	• 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) Agents: Chlorpromazine LARGACTIL Fluphenazine MODITEN Haloperidol HALDOL Loxapine XYLAC Methotrimeprazine NOZINAN Perphenazine TRILAFON Pimozide ORAP Pipotiazine PIPORTIL Prochlorperazine STEMETIL Thiothixene NAVANE Trifluoperazine TERFLUZINE Zuclopenthixol CLOPIXOL Second-Generation (Atypical) Agents: Aripiprazole ABILIFY Asenapine SAPHRIS Clozapine CLOZARIL Lurasidone LATUDA Olanzapine ZYPREXA Paliperidone INVEGA Quetiapine SEROQUEL Risperidone RISPERDAL Ziprasidone ZELDOX	S As a **HYPNOTIC**, >1 month	• 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)[7 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 ↘ Zopiclone IMOVANE, RHOVANE $t_{1/2}$ ~ 5 hours Zolpidem SUBLINOX $t_{1/2}$ ~ 2.85 hours*In healthy adults (range: 1.57-6.73 hours)[14] *Note: In one study of 8 subjects >70 years, the mean $t_{½}$ ↑ by 32%.*	B **CHRONIC USE** (>90 days) *QE = Moderate; SR = Strong*	• Adverse events similar to those of benzodiazepines in older adults (e.g. delirium, falls, fractures, MVAs) • Minimal improvement in sleep latency & duration

B =Medication listed in 2012 Beers Criteria; S =Medication listed in STOPP Criteria; ↘=Medication requires tapering upon discontinuation; QE=Quality of Evidence; SR=Strength of Recommendation

Drug or Drug Class	When a medication could be problematic for Older Adults[1-4]	Clinical Conern[1-4]
Medications used for indications other than insomnia, that may cause/worsen insomnia		
DECONGESTANTS Phenylephrine **OTC Combo Products** (Not A Comprehensive List): Phenylephrine: BENYLIN*, DAYQUIL*, DIMETAPP*, DRISTAN*, NEOCITRAN*, NYQUIL*, SUDAFED*, TRIAMINIC* ,TYLENOL (ALLERGY, COLD, FLU, SINUS)* * Denotes a combination product Pseudoephedrine **OTC Combo Products** (Not A Comprehensive List): Pseudoephedrine: ACTIFED*, ADVIL COLD & SINUS*, AERIUS DUAL*, ALLEGRA-D*, BENADRYL TOTAL ALLERGY & SINUS*, BENYLIN*, BUCKLEY'S*, CLARITIN ALLERGY + SINUS*, COACTIFED*, DAYQUIL D*, DIMETAPP*, DRISTAN*, DRIXORAL COLD & SINUS*, ENTEX LA*, NEOCITRAN*, REACTINE ALLERGY & SINUS*, ROBITUSSIN*, SINUTAB*, SUDAFED*, TRIAMINIC* , TYLENOL (COLD, COMPLETE, FLU, SINUS)*	B With **INSOMNIA** *QE = Moderate; SR = Strong*	• Risk of confusion
PHOSPHODIESTERASE ENZYME INHIBITORS, NONSELECTIVE **AMINOPHYLLINE** PHYLLOCONTIN **OXTRIPHYLLINE** CHOLEDYL **THEOPHYLLINE** THEOLAIR, UNIPHYL	B With **INSOMNIA** *QE = Moderate; SR = Strong*	• CNS stimulation (restlessness, insomnia, ↑ heart rate)
STIMULANT DRUGS Amphetamines Amphetamine Mixed Salts ADDERALL XR Dextroamphetamine DEXEDRINE Caffeine Lisdexamfetamine VYVANSE Methylphenidate BIPHENTIN, CONCERTA, RITALIN	B With **INSOMNIA** *QE = Moderate; SR = Strong*	• CNS stimulation (aggression, agitation, anger, anxiety, confusional state, dizziness, drowsiness, emotional lability, fatigue, hypervigilance, insomnia, irritability, lethargy, nervousness, restlessness, stroke, tremor, vertigo)
Medications that pose a significant potential for harm & should be avoided		
BARBITURATES ↘ Butalbital FIORINAL* * Denotes a combination product Phenobarbital	B **≥65 YEARS OF AGE** *QE = Moderate; SR = Strong*	• High rate of physical dependence • Tolerance to sleep benefits • Greater risk of overdose at low dosages (narrow therapeutic window)
♦CHLORAL HYDRATE	B **≥65 YEARS OF AGE** *QE = Low; SR = Strong*	• 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**

B =Medication listed in 2012 Beers Criteria; S =Medication listed in STOPP Criteria; ↘=Medication requires tapering upon discontinuation; QE=Quality of Evidence; SR=Strength of Recommendation

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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 synaptosomal 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 (pooled 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[25]

- 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**

Efficacy in primary insomnia – Walsh et al (1998)[26]

- 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)[27]

- 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.
    - travel behaviors peaked at 7 to 9 PM
    - vocalizations at 5 to 7 PM
    - wandering at 5 to 6 PM
    - maladaptive behaviors at 4 to 8 PM
    - physical aggression from 4:30 to 11 PM
    - overall agitation from 4 to 9 PM
    - 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

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

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