



Medications for Insomnia:

Drug Information to Support Drug Therapy Decisions

B.C. Provincial Academic Detailing (PAD) Service

December 2020

Learning Objectives:

Participants in this PAD session will have the opportunity to discuss:

- The strength of recommendations for and against specific medications for insomnia in contemporary clinical practice guidelines
- Prescribing principles applicable to medications for insomnia
- Drug information relevant to the prescribing, deprescribing and monitoring of medications for insomnia with a focus on the most commonly prescribed medications



Medications for Insomnia: Evidence to Practice

Clinical practice guidelines make weak recommendations for and against specific medications, reflecting **uncertainty** in the evidence for medication benefits versus harms.

Apply **prescribing principles** that include:

- discussion of goals of therapy
- medication review
- attention to dose & drug interactions
- communication of risk
- review of ongoing use

Many people in British Columbia are prescribed **higher than the recommended doses** of BZRAs, such as zopiclone. To reduce the risk of next day impairment, Health Canada has lowered starting and maximum doses.

BZRAs: benzodiazepine receptor agonists
(zopiclone, eszopiclone, zolpidem)



Medications for Insomnia: Prescribing Principles

Ask patients
“What do you hope
to achieve with
insomnia
treatment?”¹

Review for medications
that can cause
insomnia & consider
the potential for
prescribing cascades.

Implement
non-pharmacologic
strategies.¹⁻³

Use low starting doses
and note changes to the
maximum doses of
benzodiazepine receptor
agonists (intended to
reduce the risk of next
day impairment).⁴

Decisions about
effectiveness can be
made early. The drug
approval process
requires evidence of
efficacy within the first
1 to 2 nights of use.^{5,6}

Limit prescriptions of
benzodiazepines &
benzodiazepine
receptor agonists to
intermittent or
short-term use.^{4,7,8}

Review for interacting
medications that could
narrow the therapeutic
window.

Recognize the harms
associated with
off-label medications
including low doses of
quetiapine and
trazodone.

Revisit ongoing use with
an individualized &
practical plan based on
treatment goals
(eg, dose reduction, less
frequent use, or tapering
& deprescribing).

**benzodiazepine receptor agonists:
zopiclone, eszopiclone, zolpidem**

1. VA DoD 2019 Guideline; 2. AASM 2017 Guideline; 3. ACP 2016 Guideline; 4. Health Canada Drug Product Database;
5. US FDA 2009 Doxepin Review; 6. US FDA 2019 Lemborexant Review; 7. Therapeutics Initiative 1995 Letter 11;
8. Canadian BZRA Use Disorder 2019 Guideline



Insomnia

Benzodiazepine Receptor Agonists, Benzodiazepines

- In British Columbia, BZRAs account for the majority of hypnotic prescriptions with almost 170,000 people receiving a prescription in a recent one year period. Many people receive higher than the maximum approved dose.
- BZRAs are approved by Health Canada for the short-term treatment of sleep onset and sleep maintenance insomnia.¹
- Compared to placebo, BZRAs decrease time to fall asleep by ~18 minutes and decrease awake time after sleep onset by ~13 minutes, leading to roughly a 30 minute increase in total sleep time.^{2,3}

Selected Drug Information: Safety, Dose, Cost^{1,4-16}

zopiclone

Imovane, generics
3.75, 5, 7.5 mg tabs
~\$0.15
BC PharmaCare:
[limited coverage](#)

- short-term treatment (Health Canada): should usually not exceed 7-10 days
- CPSBC: [Safe Prescribing Standards](#)
- respiratory depression, profound sedation: risk increased with concomitant opioids, other CNS depressants, alcohol & in people with severe respiratory impairment

- initial dose: 3.75 mg; maximum: 7.5 mg
 - *lower* ▼ maximum to 5 mg: age ≥ 65, hepatic or renal impairment, strong CYP3A4 inhibitor (see: drug interaction table)
 - contraindicated: severe hepatic impairment
- take just prior to bed & only if full night's sleep planned (8 hours)
- ≥ 12 hours before driving or other activities that require full alertness

eszopiclone

Lunesta
1, 2, 3 mg tabs
~\$1.60
BC PharmaCare:
non benefit

- contraindicated: severe respiratory impairment, significant obstructive sleep apnea, myasthenia gravis
- falls, fractures
- next day impairment & decreased vehicle control
- complex sleep behaviours (eg, sleep walking, driving, other dangerous activities); risk increased with alcohol
- daytime anxiety & restlessness (interdose withdrawal)
- anterograde amnesia, transient global amnesia, confusion, hallucinations

- initial dose: 1 mg; maximum: 3 mg
 - *lower* ▼ maximum to 2 mg: age ≥ 65, severe hepatic or renal impairment, strong CYP3A4 inhibitor (see: drug interaction table)
 - contraindicated: age ≥ 65 plus severe hepatic impairment or age ≥ 65 and taking a strong CYP3A4 inhibitor (see: drug interaction table)
- take just prior to bed & only if full night's sleep planned (7-8 hours)
- ≥ 12 hours before driving or other activities that require full alertness
- onset of effect delayed if taken with high fat or heavy meal

zolpidem

Sublinox, generics
5, 10 mg ODT tabs
~\$1.30
BC PharmaCare:
non benefit

- behavioural changes (eg, decreased inhibition, psychosis)
- hypnotics: monitor for worsening depression, self-harm
- tolerance, rebound insomnia, withdrawal syndrome
- substance use disorder: [Canadian 2019 Guideline](#)

- initial dose: 5 or 10 mg (men), 5 mg (women); maximum: 10 mg
 - *lower* ▼ maximum to 5 mg: age ≥ 65, hepatic impairment
 - contraindicated: severe hepatic impairment
- take just prior to bed & only if full night's sleep planned (7-8 hours)
- ≥ 8 hours before driving or other activities that require full alertness
- onset of effect delayed if taken with food ■ ODT: orally dissolving tablet

1. Health Canada Drug Product Database; 2. AHRQ 2005 Systematic Review; 3. Cochrane 2018 eszopiclone; 4. College Physicians Surgeons British Columbia Standards; 5. US FDA 2016 opioid respiratory depression sedation; 6. Health Canada 2020 benzodiazepines & benzodiazepine receptor agonists; 7. Health Canada 2014 impairment zopiclone; 8. Health Canada 2014 impairment zolpidem; 9. US FDA 2013 impairment zolpidem; 10. US FDA 2014 impairment eszopiclone; 11. Brandt Drugs 2017; 12. Health Canada 2011 complex sleep disorder; 13. US FDA 2019 complex sleep disorder; 14. Canadian 2019 BZRA Use Disorder Guideline; 15. Drugs@FDA; 16. McKesson Canada



Insomnia

Benzodiazepine Receptor Agonists, Benzodiazepines

- Temazepam is approved by Health Canada for the short-term treatment of sleep onset and sleep maintenance insomnia.¹ Oxazepam does not have a Health Canada indication for insomnia.¹
- Compared to placebo, temazepam decreases time to fall asleep by ~12 minutes and decreases awake time after sleep onset by ~24 minutes.²
- Compared to placebo, benzodiazepines increase total sleep time by ~40 minutes (this estimate is derived from a meta-analysis pooling long and shorter acting benzodiazepines).²

Selected Drug Information: Safety, Dose, Cost^{1,3-10}

temazepam

Restoril
15, 30 mg caps
~\$0.25
BC PharmaCare:
benefit

- short-term treatment (Health Canada): should usually not exceed 7-10 days
- CPSBC: [Safe Prescribing Standards](#)
- respiratory depression, profound sedation: risk increased with concomitant opioids, other CNS depressants, alcohol & in people with severe respiratory impairment
- contraindicated: sleep apnea, myasthenia gravis
- falls, fractures
- next day impairment & decreased vehicle control
- anterograde amnesia, transient global amnesia, confusion, hallucinations
- daytime anxiety & restlessness (interdose withdrawal)
- behavioural changes (eg, decreased inhibition, psychosis)
- hypnotics: monitor for worsening depression, self-harm
- tolerance, rebound insomnia, withdrawal syndrome
- substance use disorder: [Canadian 2019 Guideline](#)

- dose range: 15-30 mg
 - *lower* ▼ maximum to 15 mg: age ≥ 65, frailty
- prescribing information provides no guidance on time frame before driving or activities that require full alertness, however mean half-life is longer than that of BZRAs
- no known clinically relevant CYP450 drug interactions

oxazepam

Serax, generics
10, 15, 30 mg tabs
~\$0.05
BC PharmaCare:
benefit

- dose: not determinable for insomnia
- prescribing information provides no guidance on time frame before driving or activities that require full alertness, however mean half-life is longer than that of BZRAs
- no known clinically relevant CYP450 drug interactions



Insomnia

Doxepin

- Low-dose doxepin (3, 6 mg) is approved by Health Canada for sleep maintenance insomnia, but not sleep onset insomnia.¹
- Compared to placebo, low-dose doxepin decreases awake time after initial sleep onset by ~20 minutes.²
- The US FDA review of low-dose doxepin did not find conclusive evidence of an effect on sleep maintenance outcomes in non-elderly adults.³

Selected Drug Information: Safety, Dose, Cost^{1,4-6}

doxepin

Silenor

3, 6 mg tabs

3 mg: ~\$0.70

6 mg: ~\$1.40

BC PharmaCare:

non benefit

- additive sedative effects: other CNS depressants, other sedating antihistamines, alcohol
 - severe sleep apnea: not recommended
 - next day impairment: small decreases in wakefulness, ability to concentrate, sense of wellbeing; no next day driving tests were conducted
 - nausea: increased with 6 mg dose
 - nausea & vomiting upon discontinuation: after discontinuing 6 mg dose
 - consider anticholinergic burden when coprescribed with anticholinergic medications
 - hypnotics: monitor for worsening depression, self-harm
- dose: 3 or 6 mg
 - *lower* ▼ initial to 3 mg: age ≥ 65, hepatic impairment
 - *lower* ▼ maximum to 3 mg: cimetidine
 - take within 30 minutes of bedtime
 - onset of effect delayed & increased potential for next day impairment if taken within 3 hours of a meal



Insomnia

Amitriptyline, Mirtazapine, Trazodone, Quetiapine

- Amitriptyline, mirtazapine, trazodone and quetiapine do not have Health Canada indications for insomnia.¹
- Evidence reviews identify limited evidence for amitriptyline, mirtazapine, trazodone and quetiapine for the treatment of insomnia (no, few, or small trials with methodologic limitations).²⁻⁷
- Choosing Wisely Psychiatry Canada advises “Don’t routinely use antipsychotics to treat primary insomnia in any age group”.⁸
- See previous PAD topics for [amitriptyline](#) and [mirtazapine](#) drug information.

Selected Drug Information: Safety, Dose, Cost^{1,3,8-17}

trazodone generics

- antidepressant with sedative properties, mechanism of action is not clear
- psychomotor impairment
- alpha adrenergic blockade: postural hypotension & syncope
- dry mouth, nausea, vomiting ■ blurred vision ■ hyponatremia
- priapism: case reports, one-third requiring surgical intervention; other psychotropic drugs also implicated
- older adults living in long-term care: risk of fractures & falls not statistically significantly differentiated from atypical antipsychotics or benzodiazepines but lower risk of death compared to atypical antipsychotics (Ontario observational cohort studies)
- Cochrane 2018: statistical improvement in subjective sleep quality, small effect size (3 trials, 370 participants, doses 50-150 mg)

quetiapine Seroquel, generics

- antipsychotic which interacts with a broad range of neurotransmitter receptors
- [Health Canada 2005](#) increased risk of death in older adults with dementia (cardiovascular, pneumonia)
- [Health Canada 2016](#) association with sleep apnea (new or worsening)
- [US FDA 2016](#) risk of opioid respiratory depression, profound sedation increased with coprescription of antipsychotics
- [Health Canada 2016](#) urinary retention
- extrapyramidal symptoms (akathisia, dystonia, rigidity, tremor), tardive dyskinesia: can occur early in course of therapy & at low doses
- dysphagia ■ psychomotor impairment ■ alpha adrenergic blockade: postural hypotension & syncope
- anticholinergic: dry mouth, blurred vision, urinary retention, constipation, intestinal obstruction
- endocrinologic: dyslipidemia, hyperglycemia, weight gain, hypothyroidism, hyperprolactinemia
- hematologic: leukopenia, neutropenia, agranulocytosis ■ venous thromboembolism



Insomnia

Lemborexant (Orexin Receptor Antagonist)

- Lemborexant is approved by Health Canada for sleep onset and sleep maintenance insomnia.¹
- Compared to placebo, the difference in the time to fall asleep was ~4-8 minutes and the difference in awake time after initial sleep onset was ~13-25 minutes (two trials; currently no published, independent systematic review).^{2,3}
- The US FDA review did not identify a consistent dose-response for efficacy (ie, 5 vs 10 mg) but participants were more likely to discontinue the 10 mg dose due to adverse events.³ Serious adverse events occurred more frequently in participants randomized to lemborexant compared to placebo.³

Selected Drug Information: Safety, Dose, Cost¹⁻⁵

lemborexant

Dayvigo

5, 10 mg tabs

5 mg: ~\$1.60

10 mg: ~\$1.80








BC PharmaCare:

non benefit

- CNS depressant effects: risk increased with opioids, other CNS depressants, alcohol; effects may persist in some patients for several days after discontinuing lemborexant
- narcolepsy: contraindicated
- respiratory: not studied in patients with moderate to severe obstructive sleep apnea or COPD
- decreased vehicle control: driving ability was impaired 9 hours after dosing in some patients who received the 10 mg dose
- complex sleep behaviours (eg, sleep walking, driving, other dangerous activities); risk increased with alcohol
- sleep paralysis: inability to move or speak for up to several minutes during sleep-wake transitions
- cataplexy like symptoms (sudden leg weakness): lasting seconds to minutes, either at night or during the day
- hallucinations: vivid & disturbing perceptions during sleep-wake transitions (hypnagogic, hypnopompic)
- middle of the night: impaired attention, memory, postural stability
- hypnotics: monitor for worsening depression, self-harm
- overdose: limited clinical experience
- misuse: rewarding effects similar to zolpidem & suvorexant in recreational sedative users; controlled substance in the U.S.
- recommended dose: 5 mg; maximum dose: 10 mg
 - *lower* ▼ maximum to 5 mg: moderate hepatic impairment, weak CYP3A4 inhibitor (see: drug interaction table)
 - avoid: severe hepatic impairment, moderate or strong CYP3A4 inhibitors, CYP3A4 inducers (see: drug interaction table)
- administer within a few minutes before bed & only if 7 hours planned before awakening
- onset of effect may be delayed if taken with or soon after a meal
- avoid alcohol: large increases in lemborexant maximum concentration & overall exposure, worsened postural stability & memory
- do not prescribe with other hypnotics



Medications for Insomnia: Drug Interaction Overview

	dose reduction or lower maximum dose of hypnotic is indicated		risk: overdose, death (Health Canada 2020 & US FDA 2016)		pharmacodynamic interaction
	large > 80% change in drug clearance: avoid or increase clinical monitoring		risk: overdose, death (US FDA 2016)		
	moderate 50-80% change in drug clearance: increase clinical monitoring		risk: increased hypnotic, CNS depressant adverse events		CYP450 Interaction Table

INCREASE ▲ hypnotic drug levels: hypnotic is a major substrate altered by other drugs via cytochrome P450 inhibition

Enzyme	Examples	ZOPI	ESZO	ZOLP	TEMA	OXAZ	AMIT	DOXE	MIRT	TRAZ	QUET	LEMB
CYP3A4 inhibitor moderate/strong	clarithromycin, erythromycin, azole antifungals, grapefruit juice, diltiazem, verapamil, ritonavir & other antiretrovirals	5 mg max	2 mg max								6 fold	do not use
CYP3A4 inhibitor weak	amiodarone, amlodipine, cyclosporine, fluoxetine, lurasidone, ranitidine, ticagrelor											5 mg max
multiple CYP enzyme inhibitor	cimetidine, ciprofloxacin, fluvoxamine							3 mg max				5 mg max








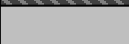
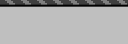
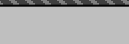
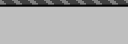
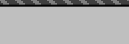
























DECREASE ▼ hypnotic drug levels: hypnotic is a major substrate altered by other drugs via cytochrome P450 induction

CYP3A4 inducer	carbamazepine, phenytoin, rifampin, St. John's Wort										6 fold	do not use
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DECREASE ▼ levels of other drugs: hypnotic induces the metabolism of other drugs via cytochrome P450 induction

CYP2B6 inducer	bupropion, methadone											2 fold
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PHARMACODYNAMIC interactions not mediated by cytochrome P450 enzymes

opioids: additive respiratory depression, profound sedation												
alcohol, other CNS depressants: increased hypnotic adverse events												
anticholinergic medications: additive anticholinergic (antimuscarinic) effects												
cholinesterase inhibitors (donepezil, galantamine, rivastigmine): opposing effects												
clonidine, methyldopa: antihypertensive effect may be reduced												
levodopa, dopamine agonists: antiparkinson effect may be reduced												
QT prolongation: conditional or possible risk crediblemeds.org												



Insomnia

Non-Pharmacologic Strategies for Insomnia

Cognitive Behavioural Therapy for Insomnia (CBTi)¹⁻⁶

- Guidelines strongly recommend CBTi for chronic insomnia.
- Involves cognitive therapy strategies along with behavioural strategies which include sleep restriction and stimulus control with or without relaxation techniques and sleep hygiene.
- Compared to inactive control, CBTi decreases time to fall asleep by ~12 minutes and decreases awake time after sleep onset by ~22 minutes.⁵ Comparisons to drug therapy are limited.^{1,3,6}

Brief Behavioural Therapy for Insomnia (BBTi)²⁻⁶

- Practical techniques if CBTi not possible.
- Involves sleep restriction and stimulus control with or without relaxation techniques and sleep hygiene.

Patient Resources		Tips
CBTi, BBTi	Kelty's Key Vancouver Coastal Health Online Therapy ⁷ Self help modules keltyskey.com/courses/insomnia/	<ul style="list-style-type: none"> ■ Some third party plans provide coverage for CBTi (with in-person or online therapists) ■ Requires time, motivation, and encouragement ■ Recommending sleep hygiene on its own has not been shown to be effective in treating chronic insomnia^{3,4} ■ Sleep restriction: caution in high-risk occupations due to potential for sleepiness during initial phase of sleep restriction;³ time in bed should not be less than 5 hours⁷ ■ Book "Say Good Night to Insomnia" (Gregg D. Jacobs)
Stimulus Control	Establishing the bedroom as a cue for sleep rather than wakefulness ³ Kelty's Key Module 5: Creating a Sleep Sanctuary ⁷ Stimulus Control Patient Fact Sheet (Australia) ⁸	
Sleep Restriction	Limit time in bed to actual sleep time followed by gradual adjustment as sleep efficiency improves ³ Kelty's Key Module 6: Setting Your Sleep Window ⁷ Sleep Restriction Patient Fact Sheet (Australia) ⁸	

1. ACP 2016 Guideline; 2. Alberta TOP 2015 Guideline; 3. VA DoD 2019 Guideline; 4. AASM 2006 Guideline; 5. AHRQ 2015 Systematic Review; 6. CADTH 2018 Evidence Review; 7. Kelty's Key Vancouver Coastal Health Online Therapy; 8. South Australia Drug and Alcohol Services



Insomnia

Benzodiazepine Receptor Agonists, Benzodiazepines: Tapering & Deprescribing

- Tapering is recommended to reduce the severity of withdrawal symptoms & to reduce the risk of seizures when reducing the dose & deprescribing.¹⁻⁵
- A systematic review did not identify trials that compared different tapering strategies: which strategy offers the lowest rate of withdrawal symptoms or greatest likelihood of successful medication discontinuation is not known.^{4,5}
- Published recommendations include:
 - Switching: to a longer half-life benzodiazepine such as diazepam which also has multiple tablet strengths to facilitate more gradual dose reductions.^{6,7}
 - Direct tapering: avoidance of switching to minimize complexity; diazepam has active metabolites which may accumulate in older adults and is susceptible to CYP450 drug interactions.⁴⁻⁶
- The importance of flexibility in the tapering regimen is recognized by regulatory bodies, clinical practice guidelines and patient advocacy groups including: pausing at a dose, returning to a previous dose if important withdrawal symptoms emerge, slowing the rate of taper if necessary.^{1,2,4,5-9}
- Open dialogue is important, patients may seek advice from online support communities.⁸⁻¹⁰

Tapering Guidelines^{4,5}

Deprescribing.org: [Benzodiazepine & Benzodiazepine Receptor Agonist Deprescribing Guideline and Algorithm](#)

Canadian 2019 Guideline: [Benzodiazepine Receptor Agonist Use Disorder Among Older Adults](#)

standard taper	<ul style="list-style-type: none">■ 25% reduction every 1 to 2 weeks, with smaller dose reductions toward the end (taper duration: ~1 to 3 months)■ can be achieved by splitting tablets but more challenging for temazepam capsules, zolpidem oral dissolving tablets
slower taper	<ul style="list-style-type: none">■ 10% reduction every 2 to 4 weeks, with smaller dose reductions toward the end (taper duration: ~3 to 6 months)■ recommended for patients taking high doses, > 6 months of use, history of withdrawal symptoms, substance use disorder■ may require more difficult dose manipulations (eg, compounding); consult a pharmacist to develop a practical & achievable dose reduction plan



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Reference list is available upon request.

Materials are designed to be used in conjunction with an academic detailing session provided by a PAD pharmacist.

For more information, or to schedule an academic detailing session, please contact:

BC Provincial Academic Detailing Service

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