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

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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 ■ 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 ■ 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: 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		■ 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		■ 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 Columba 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

1. Health Canada Drug Product Database; 2. AHRQ 2005 Systematic Review; 3. College Physicians Surgeons British Columbia Standards; 4. US FDA 2016 opioid respiratory depression sedation; 5. Health Canada 2020 benzodiazepines & benzodiazepine receptor agonists; 6. US FDA 2020 benzodiazepines; 7. Brandt Drugs 2017; 8. Canadian 2019 BZRA Use Disorder Guideline; 9. Drugs@FDA; 10. McKesson Canada

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

1. Health Canada Drug Product Database; 2. AASM 2017 Guideline; 3. US FDA 2010 Review Doxepin; 4. Drugs@FDA; 5. VA DOD 2019 Guideline; 6. McKesson Canada

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

1. Health Canada Drug Product Database; 2. AASM 2017 Guideline; 3. Cochrane 2018 antidepressants; 4. VA DOD 2019 Guideline; 5. AHRQ 2005 Systematic Review; 6. AHRQ 2015 Systematic Review; 7. CADTH 2018 Evidence Review; 8. Choosing Wisely Canada 2020 Psychiatry; 9. Pucci Adverse Drug Reaction Bull 2020; 10. Watt CMAJ 2018; 11. Bronskill J Am Geriatr Soc 2018; 12: Health Canada 2005 atypical antipsychotics dementia mortality; 13: Health Canada 2016 atypical antipsychotics sleep apnea; 14. US FDA 2016 opioid respiratory depression sedation; 15. Health Canada 2016 atypical antipsychotics urinary retention; 16. Coe Ann Pharmacother 2012; 17. Drugs@FDA

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, Cost[1-5]

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

1. Health Canada Drug Product Database; 2. Drugs@FDA; 3. US FDA 2019 Lemborexant Review; 4. US FDA 2016 opioid respiratory depression sedation; 5. McKesson Canada

Medications for Insomnia: Drug Interaction Overview

dose reduction or lower maximum dose of hypnotic is indicated

large > 80% change in drug clearance: avoid or increase clinical monitoring

moderate 50-80% change in drug clearance: increase clinical monitoring

risk: overdose, death (Health Canada 2020 & US FDA 2016)

risk: overdose, death (US FDA 2016)

risk: increased hypnotic, CNS depressant adverse events

■ pharmacodynamic interaction

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**
DECREASE ▼ levels of other drugs: hypnotic induces the metabolism of other drugs via cytochrome P450 induction												
CYP2B6 inducer	bupropion, methadone											**2 fold**

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						■	■	■	■	■	

Health Canada Drug Product Database; Drugs@FDA; Lexicomp; US FDA 2016 opioids respiratory depression sedation; Health Canada 2020 benzodiazepines & benzodiazepine receptor agonists; Indiana University Cytochrome P450 Table; US FDA 2019 complex sleep behaviours warning; US FDA 2019 lemborexant review; US FDA 2020 Drug Development Drug Interactions; Credible Meds. *For complete information, please consult a drug interaction resource.*

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	
CBTi, BBTi	Kelty's Key Vancouver Coastal Health Online Therapy[7] Self help modules keltyskey.com/courses/insomnia/
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]

Tips

- 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 hours[7]
- Book "Say Good Night to Insomnia" (Gregg D. Jacobs)

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	■ 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	■ 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

1.Health Canada 2020 benzodiazepines & benzodiazepine receptor agonists; 2. US FDA 2020 benzodiazepines; 3. College Physicians Surgeons British Columbia Standards; 4. Deprescribing.org; 5. Canadian 2019 BZRA Use Disorder Guideline; 6. Paquin Expert Opin Drug Safety 2014; 7. Ashton Manual Benzodiazepine Withdrawal; 8. Benzodiazepine Information Coalition; 9. Inner Compass Withdrawal Project; 10. BenzoBuddies Community Forum

Medications for Insomnia:

Drug Information to Support Drug Therapy Decisions

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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

Email: PAD@gov.bc.ca Web: www.bcpad.ca

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