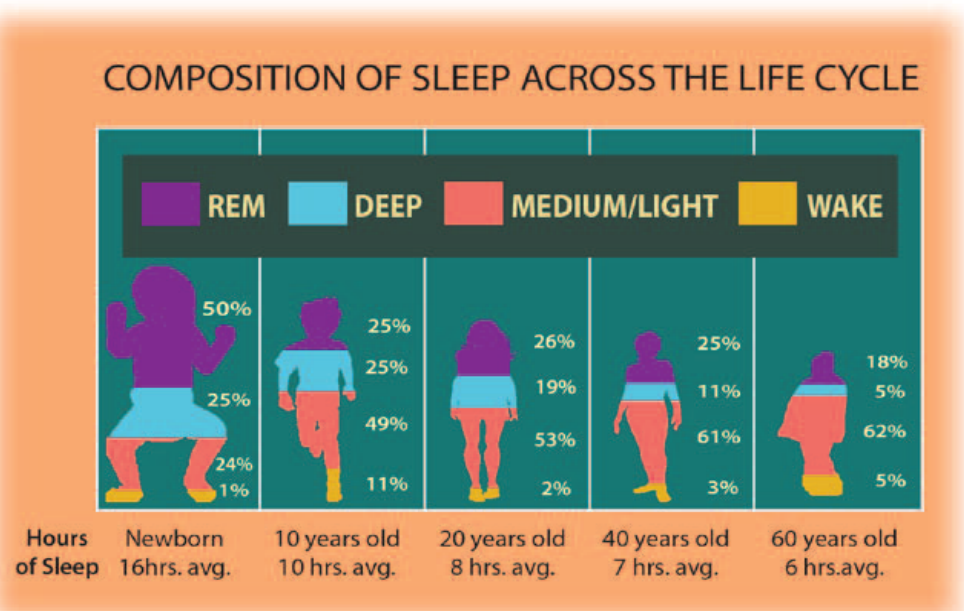


Adult Insomnia

- ❖ Approximately 1 in 7 Canadians have insomnia; may affect daily function & quality of life.¹
- ❖ Patients with insomnia usually have sleep misperception; they underestimate sleep time & overestimate awake time.
- ❖ A sleep diary may give a better picture of the patient's sleep and overcome some of the sleep misperception.
- ❖ Figure 1 reflects the average hours of sleep as people age. Using this figure may help patients understand that sleep changes across their life cycle.

Figure 1: The size of the figure reflects the average hours of sleep²



Assessment & Management^{3,4,5}

Assessment

1. Obtain a thorough history.
2. Suggest clinician use a sleep disorder questionnaire (e.g., Epworth Sleepiness Scale, Insomnia Severity Index, Pittsburgh Sleep Quality Index).
3. Suggest patient complete a sleep diary.
4. Refer to sleep clinic or study for further investigation if necessary (e.g., circadian rhythm disorder, sleep apnea/snoring, movement disorder, or parasomnia).

Management Overview

1. Address and optimize management of any underlying medical, psychiatric or environmental causes.
2. Consider drug causes:
 - Change drug(s) to AM, taper or stop.
3. **Non-Drug Therapy = 1st line therapy**
 - Cognitive Behavioural Therapy for Insomnia (CBT-I)
4. If required, consider sedatives for short-term use only (e.g., < 5 weeks) along with CBT-I.
5. Consider taper and/or discontinue benzodiazepines, Z-drugs or other sleeping pills if taking for a prolonged period of time; risks most likely outweigh benefits.

Common drugs which may cause fragmented sleep, nightmares, nocturia or stimulation⁶

- Ten most common:**
1. Levodopa
 2. Prednisone
 3. Venlafaxine
 4. Fluvoxamine
 5. Rotigotine
 6. Donepezil
 7. Pramipexole
 8. Tolcapone
 9. Varenicline
 10. Sertraline

Drug Class	Examples	{CHANGE DRUG(S) TO AM, TAPER OR STOP}
Antidepressants, antipsychotics	Bupropion, MAOIs (phenelzine, tranylcypromine), SNRIs (des-venlafaxine, duloxetine), SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline), aripiprazole, clozapine	
Cardiovascular	α-blockers (e.g., tamsulosin), β-blockers (e.g., propranolol, metoprolol), diuretics (e.g., furosemide, hydrochlorothiazide), statins	
Decongestants	Phenylephrine, pseudoephedrine	
Opioids	In combination with caffeine (e.g., Tylenol #1, #2, #3)	
Respiratory	Formoterol, indacaterol, olodaterol, salbutamol, salmeterol, terbutaline	
Stimulants	Amphetamine, caffeine , cocaine, ephedrine, methylphenidate, modafinil	
Others	Acetylcholinesterase inhibitors (e.g., donepezil), alcohol (fragmented sleep), antineoplastics, corticosteroids (e.g., prednisone), levodopa, nicotine , medroxyprogesterone, thyroid supplements, SGLT-2 inhibitors (e.g., dapagliflozin, canagliflozin, empagliflozin)	

MAOIs=Monoamine Oxidase Inhibitors, SGLT-2=Sodium-Glucose co-Transporter-2, SNRIs=Serotonin Norepinephrine Reuptake Inhibitors, SSRIs=Selective Serotonin Reuptake Inhibitors

Non-Drug Therapy

- **1st line therapy for chronic insomnia = Cognitive Behaviour Therapy for Insomnia (CBT-I)**^{3,4,5}
 - Compared to sleep hygiene or usual treatment, CBT-I improves:⁷
 - Sleep onset latency by 19 minutes (95% CI 14 to 24).
 - Wake after sleep onset by 26 minutes (95% CI 16 to 37).
 - Total sleep time by 8 minutes (95% CI -0.5 to 16).
 - Sleep Efficiency by 9.9% (95% CI 8.1% to 11.7%).
 - CBT-I is more effective in sleep latency, total sleep time, total wake time & sleep efficiency compared to sedative hypnotics (zopiclone, zolpidem, temazepam, triazolam).⁸
- **Most mental health counselors at the HFHT have training in CBT and/or CBT-I.**
 - **Please consult with the mental health counselor on your team for individual or group therapy if available through the HFHT.**



Components of Cognitive Behavioural Therapy for Insomnia (CBT-I)^{9,10}

Component	Intended Effect
Sleep hygiene	Reduce behaviours that interfere with sleep drive or increase arousal.
Sleep restriction	Increase sleep drive and stabilize circadian rhythm.
Stimulus control	Reduce arousal in sleep environment and promote the association of bed and sleep.
Cognitive therapy	Restructure maladaptive beliefs for daytime/health consequences of insomnia.
Relaxation therapy	Reduce physical & psychological arousal in sleep environment.

Drug Therapy^{3,4,5}

- Pharmacotherapy should be considered as an adjunctive therapy to CBT-I.
- CBT-I combined with medication may produce faster improvements in sleep than CBT-I alone.¹¹
- Guidelines recommend no longer than 5 weeks of therapy because of the risk of patient dependence and tolerance; evidence is limited to short-term treatment.¹²
- Long-term use of hypnotics may be appropriate (e.g., severe or refractory insomnia resistant to CBT-I, medical or mental health comorbidities), in which case, regular follow-up and reassessment are beneficial to ensure that comorbidities, tolerance and/or dependence do not emerge.
- There are no strong randomized control trials (RCTs) or systematic reviews that allow for definitive drug recommendations because most of the evidence is of low-moderate quality.

Balancing Benefits vs. Risks for sedative hypnotics^{13,14}

Benefits	Risks
<p>The number needed to treat (NNT) = 13 (95% CI 7-63) for a sedative to improve sleep quality compared to placebo.</p> <p>Compared to placebo, BZD or Z-drugs improves:</p> <ul style="list-style-type: none"> ➤ Total sleep time by 25 min (95% CI 13-38). ➤ Sleep onset latency by ~ 10 min. ➤ Decrease mean number of awakenings by 0.6 (95% CI -0.5 to -0.8). 	<p>The number needed to harm (NNH) = 6 (95% CI 5-7) compared to placebo.</p> <ul style="list-style-type: none"> ○ Drowsiness, fatigue, headache, nightmares, nausea, GI disturbances and cognitive effects. ➤ Serious adverse effects of falls, fractures or fatal vehicle accidents have been reported. ➤ Fatal vehicle accidents:^{15,16} <ul style="list-style-type: none"> ○ Benzodiazepine, Z-drugs: ~2-fold risk. ○ Opiate use: ~3-fold risk. ○ Cannabis use: ~7-fold risk. ○ Alcohol use: ~17-fold risk.

Treating 13 patients with a sedative hypnotic (BZD or Z-drug) for insomnia will improve sleep quality in 1 patient and there will likely be 2 patients with adverse effects (5 days to 9 weeks).

Table 1: Commonly Prescribed Medications for Insomnia (low-moderate quality evidence) ^{3,4,5,17,18}

	Generic, Brand	Comments, Adverse Effects (A/E) ✓=benefit ✗=risk	Usual Dose	Cost \$ (month)
BZD receptor agonists	Zopiclone Imovane 5, 7.5mg T	✓Indicated for short-term treatment (7-10 days) and symptomatic relief of insomnia by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakenings. ✓Improves sleep onset latency (19 min), total sleep time (45 min), wake after sleep onset (11 min). ⁴ ✗Risk of physical tolerance and dependence. <i>Allow at least 12 hours between bedtime dose & any activity requiring mental alertness/driving.</i> A/E: Metallic after taste, daytime drowsiness, falls, fractures, fatal vehicle accidents	3.75-7.5mg hs Max: 5.0mg in elderly or kidney/liver disease	\$15-30 Not covered on ODB
	Zolpidem Sublinox 5, 10mg S Oral disintegrating tablet; cannot be split	✓Indicated for short-term treatment (7-10 days) and symptomatic relief of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakenings. ✓Improves sleep onset latency (15 min), total sleep time (23 min). ⁴ ✓Less chance of morning hang-over effect (short half-life). ✗Risk of tolerance and dependence. A/E: daytime drowsiness, dizziness/vertigo, amnesia, nausea, headache, falls, fractures, fatal vehicle accidents	Initial dose: Women: 5mg Men: 5-10mg ≥65y: 5mg Max: 10mg	\$60 Not covered on ODB
Antidepressants	Doxepin Sinequan 10, 25, 50, 100mg C Silenor 3, 6mg	✓ Silenor is indicated for insomnia; Sinequan is indicated for depression. ✓Consider doxepin if substance abuse or dependence is a concern. ✓3mg: improve total sleep time (~12 min), wake after sleep onset (~10 min). ⁴ ✓6mg: improve total sleep time (~17 min), wake after sleep onset (~14 min). ⁴ <i>Not to be taken within 3 hours of a meal (delayed absorption) = daytime drowsiness.</i> A/E: Anticholinergic effects (higher doses); less risk of tolerance/dependence.	Sinequan 10-50mg hs Silenor 3-6mg hs	\$18-25 Doxepin 3-6mg not covered on ODB
	Trazodone Desyrel 50, 100mg, 150mg T	✓Trazodone is indicated for depression; ✗Limited evidence for insomnia. ✓ Less chance of morning hang-over effect (short half-life). A/E: orthostatic hypotension, priapism (rare); less risk of tolerance/dependence.	25-150mg hs	\$8-12
BZD	Temazepam Restoril 15, 30mg C	✓Indicated for insomnia; ✗Risk of physical tolerance and dependence. ✓Intermediate half-life carries a low-moderate risk of morning hang-over. A/E: Common: drowsiness, fatigue, headache, nightmares, nausea Serious: cognitive impairment, falls, fractures, fatal vehicle accidents	15-30mg hs	\$8
OTCs	Melatonin 1,3,5 mg tab, 10mg CR tab, 3mg SL, various formulations	✓Improves sleep onset latency (~7 min), total sleep time (~8 min) & sleep quality. ¹⁹ ✓No apparent physical tolerance and dependence. ✗Melatonin has no effect on BZD discontinuation ²⁰ ✗Purity concerns A/E: fatigue, headache, dizziness, irritability, upset stomach, daytime drowsiness	1-3mg 30-90 min before hs Shift circadian rhythm: Take 4-5 hours before hs	\$3-5, OTC
	Valerian Root Herbal Sleepwell , various formulations	✗Limited studies. ✗Purity concerns. A/E: dizziness, nausea, headache, upset stomach, hepatotoxicity (rare)	400-900mg 30-60min before hs	\$6-10 OTC

BZD=Benzodiazepine, C=Capsule, hs=bedtime, ODB=Ontario Drug Benefit, OTCs=Over-The-Counters S=Sublingual tablet, T=Tablet

Others: L-Tryptophan **Tryptan** 500mg-2g qhs, indicated as an adjunct for affective disorders, conflicting evidence for insomnia, \$30-50/month

Magnesium 250mg bid, limited evidence for insomnia²¹, ~\$10/month

Not recommended

The following agents are not recommended for the management of insomnia alone except in cases where the agent is being used specifically to manage a co-morbidity such as depression or pain

<ul style="list-style-type: none"> Acetaminophen, codeine, NSAIDS Antidepressant – mirtazapine, fluvoxamine, tricyclics (e.g., amitriptyline) Antihistamines (e.g., chlorpheniramine, diphenhydramine) Antinausea (e.g., dimenhydrinate) Antipsychotics (conventional or atypical) 	<ul style="list-style-type: none"> Benzodiazepines (e.g., diazepam, clonazepam, flurazepam, lorazepam, nitrazepam, alprazolam, oxazepam, triazolam) Muscle relaxants (e.g., cyclobenzaprine, meprobamate) Pregabalin, gabapentin
---	---



Benzodiazepine (BZD) or Z-Drug Tapering

Communication tips (Choosing Wisely Canada)²²

- Stopping sleeping pills can increase alertness, energy, daily function and can also reduce the risk of falls.
- Sleeping pills can have serious or deadly side effects (e.g., confusion, memory problems, falls and/or hip fractures).
- The drugs can increase the risk of car accidents.
- Sleeping pills can be addictive; Sleeping pills may not help much.

Approach to Tapering

- ❖ Little evidence to support one tapering schedule over another.²⁵
- ❖ Taper slowly (e.g., 10-25% every 2 weeks).
- ❖ Use scheduled rather than PRN doses.
- ❖ Schedule follow-up visits every 1–4 weeks depending on the patient's response to taper & ask patient about the benefits of tapering (e.g., increased energy, increased alertness).
- ❖ Halt or reverse taper if severe anxiety, depression, or withdrawal symptoms occur:
 - **Withdrawal symptoms** = rebound anxiety, restlessness, tremor, sweating, agitation, insomnia, or seizures (particularly when benzodiazepines are used > 8 weeks).
 - Onset of withdrawal symptoms: 1-2 days for BZD with short half-lives, 3-7 days for longer half-lives.
 - May consider switching to diazepam or clonazepam or taper slower (See Table 2 below).
- ❖ Consider use of **cognitive therapy** and/or adjunctive agents to improve success rates.
 - Adjunctive agents have little evidence with tapering.
 - Examples: Anticonvulsants (e.g., carbamazepine, pregabalin, valproate), antidepressants (e.g., SSRIs, mirtazapine, imipramine, trazodone), beta-blockers, buspirone, melatonin

Example of a tapering schedule:^{23,24}

STEP-BY-STEP TAPERING-OFF PROGRAM

We recommend that you follow this schedule under the supervision of your doctor or pharmacist to taper off your sedative-hypnotic medication.

WEEKS	TAPERING SCHEDULE							✓
	MO	TU	WE	TH	FR	SA	SU	
1 and 2	●	●	●	●	●	●	●	
3 and 4	●	●	●	●	●	●	●	
5 and 6	●	●	●	●	●	●	●	
7 and 8	●	●	●	●	●	●	●	
9 and 10	●	●	●	●	●	●	●	
11 and 12	●	●	●	●	●	●	●	
13 and 14	●	●	●	●	●	●	●	
15 and 16	×	●	×	×	●	×	●	
17 and 18	×	×	×	×	×	×	×	

EXPLANATIONS

● Full dose ● Half dose ● Quarter of a dose × No dose

Clinical Pearls

- Taper slowly.
- Dispense every 1-4 weeks (e.g., dosette or blisterpack).
- Can taper with current BZD or Z-drug or switch to diazepam or clonazepam.
- Assess regularly for benefits & withdrawal symptoms.
- Use CBT-I if available.

Table 2: Benzodiazepine Equivalent Table²⁶

Benzodiazepine		Approximate Equivalent Oral Dose (mg)	Half-life (hours)
Long-acting	Chlordiazepoxide (Librium®) 5mg, 10mg, 25mg cap	10	100
	Clorazepate (Tranxene®) 3.75mg, 7.5mg, 15mg cap	7.5	100
	Diazepam (Valium®) 2mg, 5mg, 10mg tab	5	100
	Flurazepam (Dalmane®) 15mg, 30mg cap	15	100
Intermediate-acting	Alprazolam (Xanax®) 0.25mg, 0.5mg, 1 ^x mg, 2 ^x mg tab	0.5	12-15
	Bromazepam (Lectopam®) 1.5mg, 3mg, 6mg tab	3	8-30
	Clobazam (Frisium®) 10mg tab	10	10-46
	Clonazepam (Rivotril®) 0.25mg, 0.5mg, 1mg, 2mg tab	0.25	20-80
	Lorazepam (Ativan®) 0.5mg, 1mg, 2mg tab, SL ^x	1	10-20
	Nitrazepam (Mogadon®) 5mg, 10mg tab	5	16-55
	Oxazepam (Serax®) 10mg, 15mg, 30mg tab	15	5-15
	Temazepam (Restoril®) 15mg, 30mg cap	15	10-20
Short-acting	Triazolam (Halcion®) 0.125mg, 0.25mg tab	0.25	1.5-5

Cap=capsule, tab=tablet, SL=sublingual, X=not covered on Ontario Drug Benefit (ODB) formulary

© Copyright January 2017 – Hamilton Family Health Team

Disclaimer: The content of this information represents the research, experience and opinion of the authors and not those of the Hamilton Family Health Team (HFHT). Neither the authors nor HFHT nor any other party who has been involved in the preparation or publication of this work warrants or represents that the information contained herein is accurate or complete, and they are not responsible for any errors or omissions or for the result obtained from the use of such information. Any use of the information will imply acknowledgement of this disclaimer and release any responsibility of HFHT, its employees, servants, or agents. Readers are encouraged to confirm the information contained herein with other sources. References available upon request

Prepared by Margaret Jin, BScPhm, PharmD, MSc & HFHT Pharmacy Program



References

- ¹ Statistics Canada. The Daily – Study: Insomnia. 2005;November 16. <http://www.statcan.gc.ca/daily-quotidien/051116/dq051116a-eng.htm>
- ² Driver H, Gottschalk R, Hussain M, Morin C, Shapiro C, Van Zyl L. Insomnia in Adults and Children. Joli Joco Publications Inc., 2012. http://css-scs.ca/images/brochures/Insomnia_Adult_Child.pdf Accessed May 16, 2016
- ³ Toward Optimized Practice (TOP) Insomnia Group. 2015 December. Assessment to management of adult insomnia: clinical practice guideline. Edmonton AB: Toward Optimized Practice. Available from: <http://www.topalbertadoctors.org>
- ⁴ Qaseem A, Kansagara D, Forcica M, Cooke M, Denberg T. Management of chronic insomnia disorder in adults: A clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2016;165(2):XXX-XXX
- ⁵ Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med* 2008;4(5):487-504.
- ⁶ Doufias A, Panagiotou O, Panousis P, Wong S, Ioannidis P. Insomnia from drug treatments: evidence from meta-analyses of randomized trials and concordance with prescribing information. *Mayo Clin Proc.* 2016;xxx:1-16
- ⁷ Trauer J, Qian M, Doyle J, Rajaratnam S, Cunnington D. Cognitive Behavioral Therapy for Chronic Insomnia. A systematic review and meta-analysis. *Ann Intern Med* 2015;163:191-204
- ⁸ Mitchell M, Gehrman P, Perlis M, Umscheid C. Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. *BMC Family Practice* 2012.13:40
- ⁹ Winkelman J. Insomnia Disorder. *N Engl J Med* 2015;373:1437-44.
- ¹⁰ Alessi C, Vitiello M. Insomnia (primary) in older people: non-drug treatments. *Clinical Evidence.* 2015;05:2302
- ¹¹ Morin CM, Beaulieu-Bonneau S, Ivers H, Vallières A, Guay B, Savard J, et al. Speed and trajectory of changes of insomnia symptoms during acute treatment with cognitive-behavioral therapy, singly and combined with medication. *Sleep Med.* 2014 Jun;15(6):701-7.
- ¹² Tenni P, Dunbabin D. A guide to deprescribing benzodiazepines. Consultant Pharmacy Services. Australia. May 2016, access online on September 16, 2016
<http://www.primaryhealthtas.com.au/sites/default/files/A%20Guide%20to%20Deprescribing%20Benzodiazepines.pdf>
- ¹³ Glass J, Lanctot K, Hermann N, Sproule B, Busto U. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ* 2005
- ¹⁴ Buscemi N, Vandermeer B, Friesen C, et al. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. *J Gen Intern Med* 2007;22:1335
- ¹⁵ Elvik, R. (2012). Risk of road accident associated with the use of drugs: A systematic review and meta-analysis of evidence from epidemiological studies (in press). *Accid.Anal.Prev*
- ¹⁶ World Health Organization. Facts Road Safety – Alcohol.
http://www.who.int/violence_injury_prevention/publications/road_traffic/world_report/alcohol_en.pdf, accessed January 12, 2017
- ¹⁷ PL Detail-Document, Insomnia Treatments. Pharmacist’s Letter/Prescriber’s Letter. May 2013.
- ¹⁸ Canadian Pharmacists Association. Therapeutic Choices for Minor Ailments. First Edition. 2013. (Chapter 5: Insomnia, pages 33-42.)
- ¹⁹ Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. *PLOS ONE* 2013; 8(5): e63773
- ²⁰ Wright A, Diebold J, Otal J, et al. The effect of melatonin on benzodiazepine discontinuation and sleep quality in adults attempting to discontinue benzodiazepines: A systematic review and meta-analysis. *Drugs Aging.* 2015 Dec;32(12):1009-18
- ²¹ Abbasi B, Kimiagar M, Sadeghnilat K, Shirazi M, Hedayati M, Rashidkhani B. The effect of magnesium supplementation on primary insomnia in elderly: A double-blind placebo-controlled clinical trial. *J Res Med Sci.* 2012 Dec;17(12):1161-9.
- ²² Canadian Geriatrics Society. Insomnia and anxiety in older people. Choosing Wisely Canada. 2014.
<http://www.choosingwiselycanada.org/wp-content/uploads/2014/09/Sleeping-pills-EN.pdf>, accessed September 22, 2016
- ²³ Tannenbaum C, Martin P, Tamblyn R, Benedetti A, Ahmed S. Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: the EMPOWER cluster randomized trial. *JAMA Inter Med.* 2014;174(6):890-8.
- ²⁴ Martin P, Ahmed S, Tamblyn R, Tannenbaum C. A drug education tool developed for older adults changes knowledge, beliefs and risks perceptions about inappropriate benzodiazepines in the elderly. *Patient Educ Couns.* 2013;92(1):81-7.
- ²⁵ Pollman AS, Murphy AL, Berman JC, Gardner DM. Deprescribing benzodiazepines and Z-drugs in community-dwelling adults: a scoping review. *BMC Pharmacology and Toxicology.* 2015;16:19 DOI 10.1186/s40360-015-0019-8
- ²⁶ Benzodiazepine. e-cps. 2015, accessed December 31, 2015