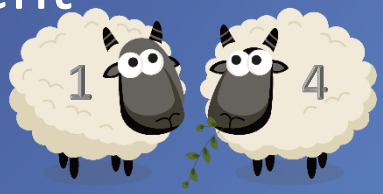
Can you just refill my zopiclone?

…….and other bedtime stories

Learning Objectives

1. Recall important aspects of sleep physiology
2. Review the differential diagnosis of insomnia
3. Describe non-pharmacological strategies for treatment of insomnia (CBT-I, sleep hygiene, progressive muscle relaxation)
4. Review evidence for total sleep time and sleep onset latency for select pharmacological treatments of insomnia
5. Highlight useful patient and practitioner resources regarding insomnia management



Faculty/Presenter Disclosures

- **Faculty:** Dr. Grace Frankel
- **Relationships with commercial interests:**
  - **Consulting fees:** Elsevier Canada (Book editor – Drug Reference)
  - No Bias Identified

- **Faculty:** Dr. Karen Toews
- **Relationships with commercial interests:**
  - **None**

https://www.sleepadvisor.org/do-cats-dream/

Why do we sleep?

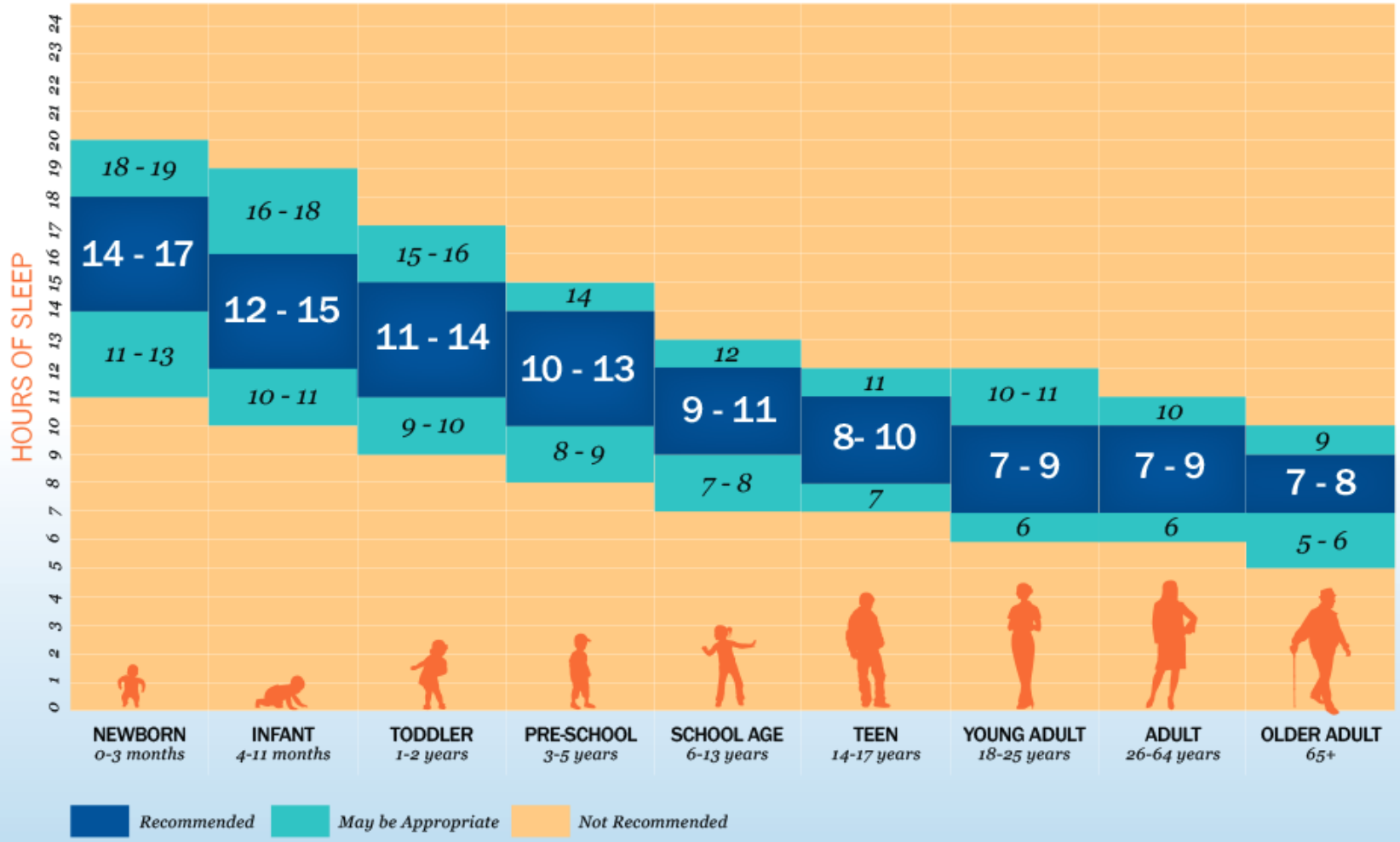
https://blogs.scientificamerican.com/observations/why-do-we-sleep/

Audience Question: LIVE

How many hours of sleep do you get (on average) per night?

NATIONAL SLEEP FOUNDATION

SLEEP DURATION RECOMMENDATIONS



https://www.sleepfoundation.org/sites/default/files/2018-10/NSF_sleep_duration_recommendations_chart.png

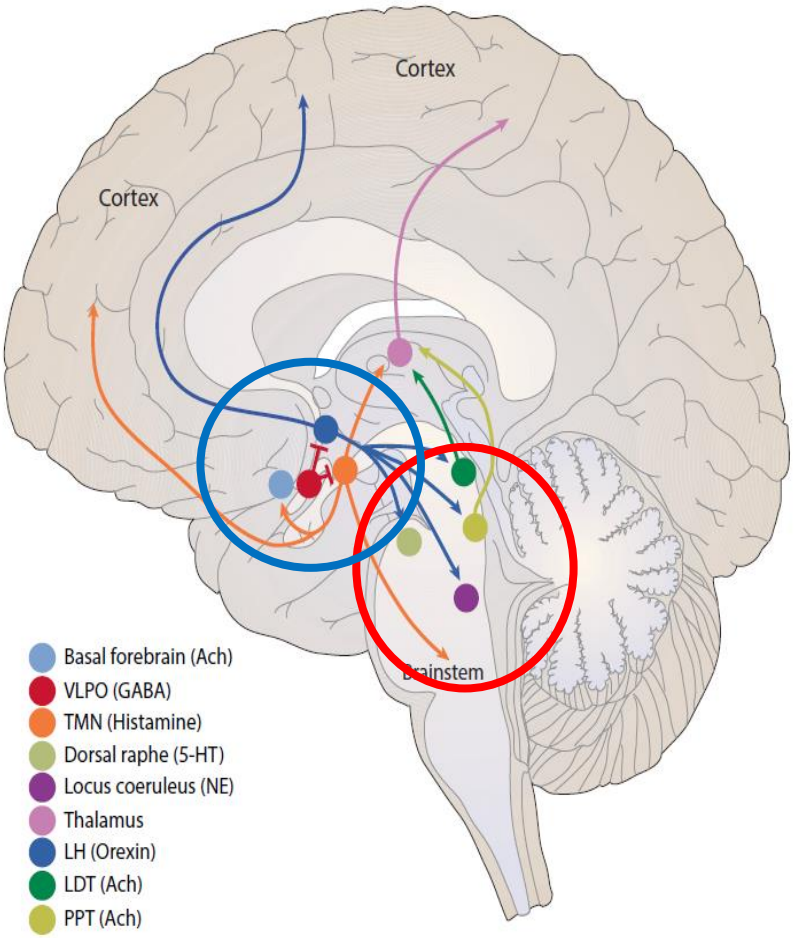


Figure 1. Main CNS nuclei that influence sleep.

Brainstem

↑NE and 5-HTP	↓NE and 5-HTP
↓Ach	↑Ach

Hypothalamus and circadian centres

↑ Orexins	↓ Orexins
↑ Histamine	↓ Histamine
↓ GABA	↑ GABA

J Syst Integr Neurosci 2016;2(2);doi: 10.15761/JSIN.1000125

WHEN SLEEP GOES WRONG

https://myfox8.com/2015/09/25/its-not-just-the-duff-making-homer-simpson-sleepy-he-has-narcolepsy/

- Narcolepsy
- Kleine-Levine Syndrome (Sleeping Beauty Syndrome)
- Fatal Familial Insomnia
- Exploding head syndrome
- Sleep paralysis
- Restless Legs Syndrome/Periodic Limb Movement Disorder

INSOMNIA

Audience Question: slido

Which of the following statements is **NOT included** in the diagnosis of chronic insomnia?

a) Must cause distress or impairment in functioning
b) Occurs at least 3 nights per week
c) Lasts for at least 3 months
d) Is not substance related
e) Must not be related to a co-morbid condition (depression, chronic pain)

Audience Question: slido

List *causes* of disrupted sleep

Risk factors/comorbidities of chronic insomnia

Psychiatric conditions

- depression, anxiety, bipolar disorder, panic, PTSD, schizophrenia

Medical Problems

- pulmonary, rheum, neurologic, cardiovascular, urinary, GI, chronic pain, DM, malignancy

Neurological conditions

- neurodegenerative disorders, FFI, MS, TBI

Medications and Substances

- steroids, diuretics, caffeine, alcohol, nicotine, opioids, cocaine, amphetamines

Other sleep disorders

- RLS, sleep apnea, jet lag

Audience Question: slido

I have a TV in my bedroom

TRUE

Or

FALSE?

Behavioural Therapies:
Sleep Hygiene

Behavioural Therapies:
Stimulus control

Behavioural Therapies: **Relaxation**

Behavioural Therapy:
Sleep restriction

Cognitive Behavioral Therapy

http://www.sleepreviewmag.com/2019/09/brain-forget-dream-sleep-rem/

Interpreting Efficacy on Sleep: Definitions from Studies

Sleep latency onset (SLO) - **The length of time that it takes to transition from full wakefulness to sleep; normally to the lightest of the non-rapid eye movement (REM) sleep stages**

Total sleep time (TST) - **The amount of actual sleep time in a sleep episode; equal to total sleep episode less awake time.**

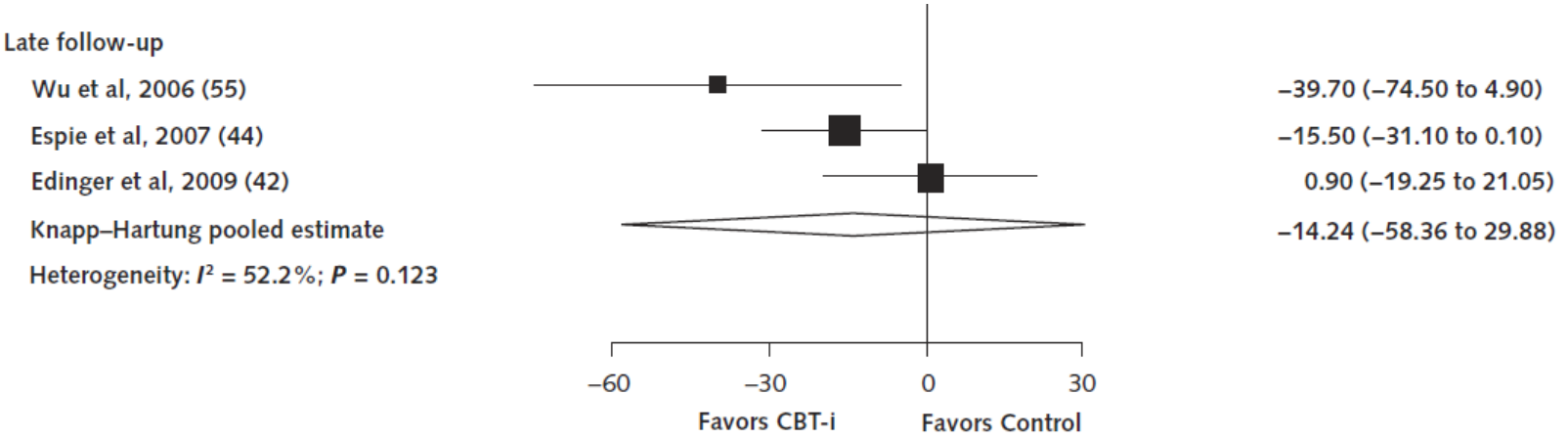
Wake after sleep onset (WASO) - **Periods of wakefulness occurring after defined sleep onset**

Sleep efficiency (SE%) - **Refers to the percentage of total time in bed actually spent in sleep**

CADTH TECHNOLOGY REVIEW
Clinical Evaluation of Interventions for the Management of Insomnia: A Review of Reviews

Falling asleep

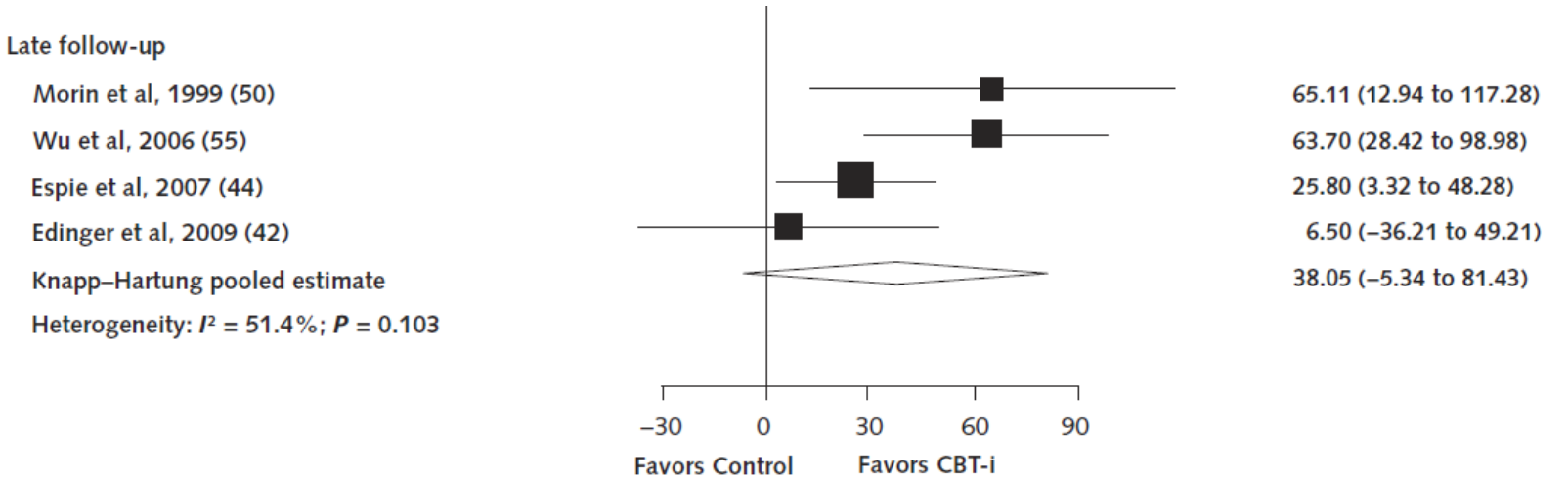
Figure 2. Meta-analysis of the effect of CBT-i on SOL.



CBT-i = cognitive behavioral therapy for insomnia; SOL = sleep onset latency.

Staying asleep

Figure 4. Meta-analysis of the effect of CBT-i on TST.

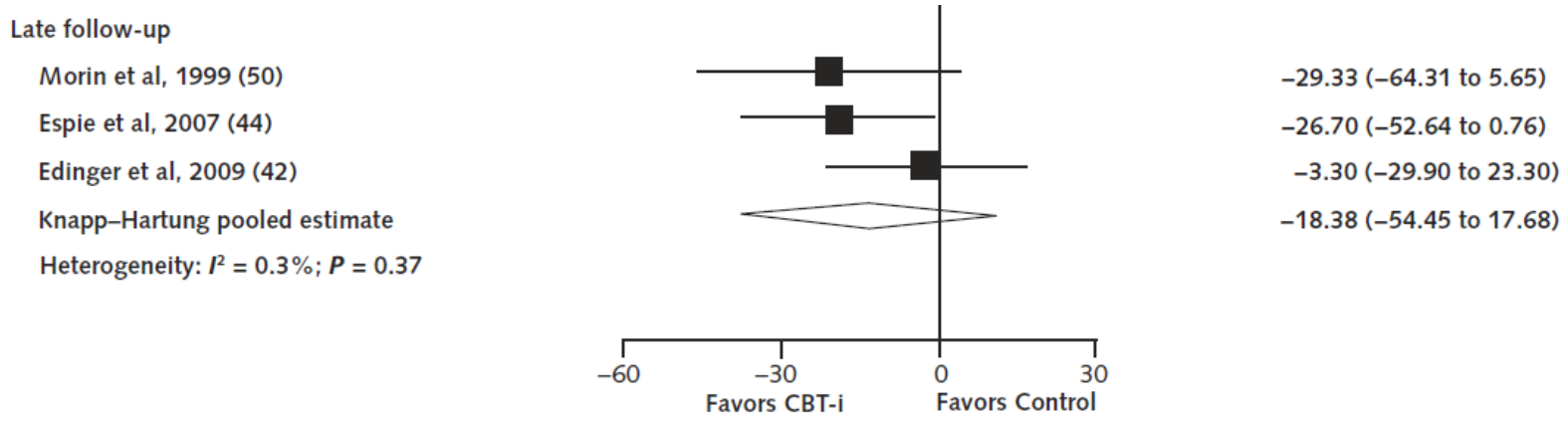


CBT-i = cognitive behavioral therapy for insomnia; TST = total sleep time.

Ann Intern Med. 2015;163:191-204

Waking up in the night

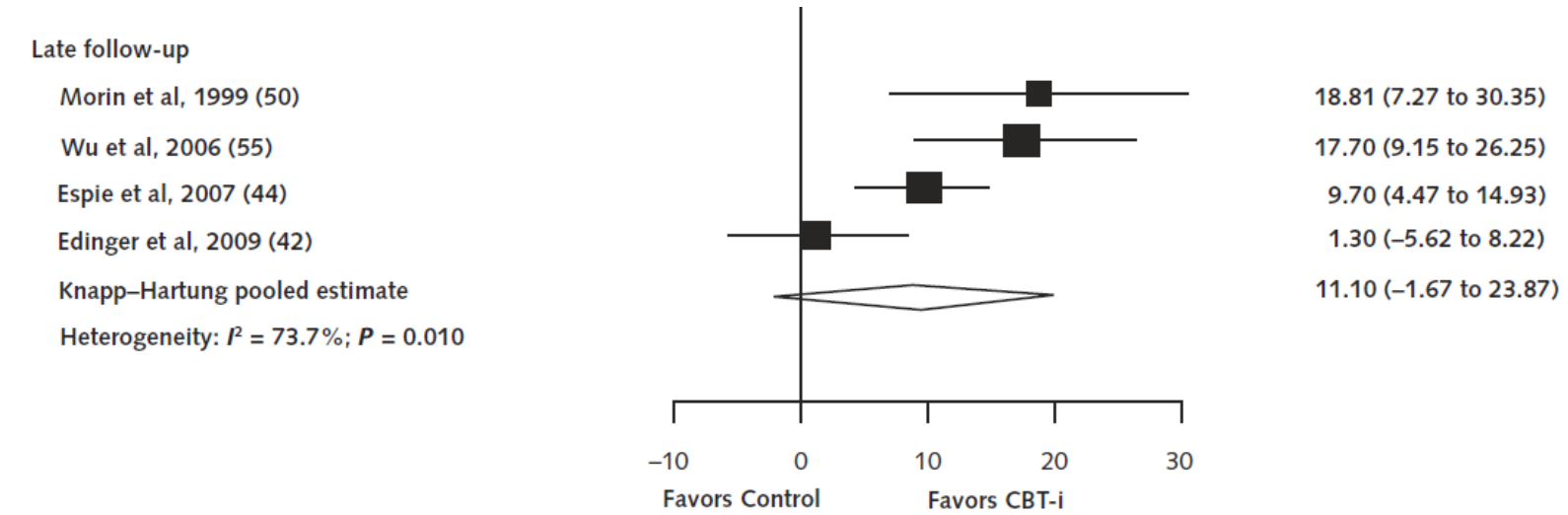
Figure 3. Meta-analysis of the effect of CBT-i on WASO.



CBT-i = cognitive behavioral therapy for insomnia; WASO = wake after sleep onset.

% time in bed asleep

Figure 5. Meta-analysis of the effect of CBT-i on SE%.



CBT-i = cognitive behavioral therapy for insomnia; SE% = sleep efficiency.

Ann Intern Med. 2015;163:191-204

Audience Question: slido

Zopiclone increases total sleep time by _____ as compared to placebo.

a) 5 hours
b) 30 minutes
c) 60 minutes
d) 2 hours

	Sleep Laten… On… (SLO…	…l Sleep Time (TST)[1]	Used for:[2]
Zolpidem or Zopiclone	**-…** (-…	**…utes** …ns)	**Sleep-onset** ?Maintenance
Benzos (flur/tem/triaz)	**-2…** …4 to -11 mins)	**…minutes** (Max 60 mi…	**Maintenance** …iazolam – sleep …t)
Suvorexant	**-5 minutes** (-10 to -4 mins)	**+15 m…** (Max 25…	**… onset …intenance**
Doxepin	**-5 minutes** (-8 to +1 min)	**+30 mins** (Max 70 mins)	**Maintenance**
Trazodone	**-12 minutes** (-22 to -2 mins)	Not reported (mixed results)	**Maintenance**
Quetiapine*	**-40 min** (-96 to -22 mins)	**+50 minutes?** (Max 80 mins but one study **lost sleep**)	NO NO NO!!!
Melatonin	**-5 mi…**	**+5 minutes** (Max 25 mins)	**Sleep onset**
Diphenhydrami…		**…18 minutes?** …ax 40 mins, several no difference)	**Sleep onset Maintenance**
CBT-I (multi-component)	(…	**+8 minutes** (max ~20 mins, some no difference)	**Sleep onset** ?Maintenance

What the heck is this?

Don't see this often….

But look how well it works!

*Very low quality evidence, very small sample sizes
All versus placebo or inactive controls

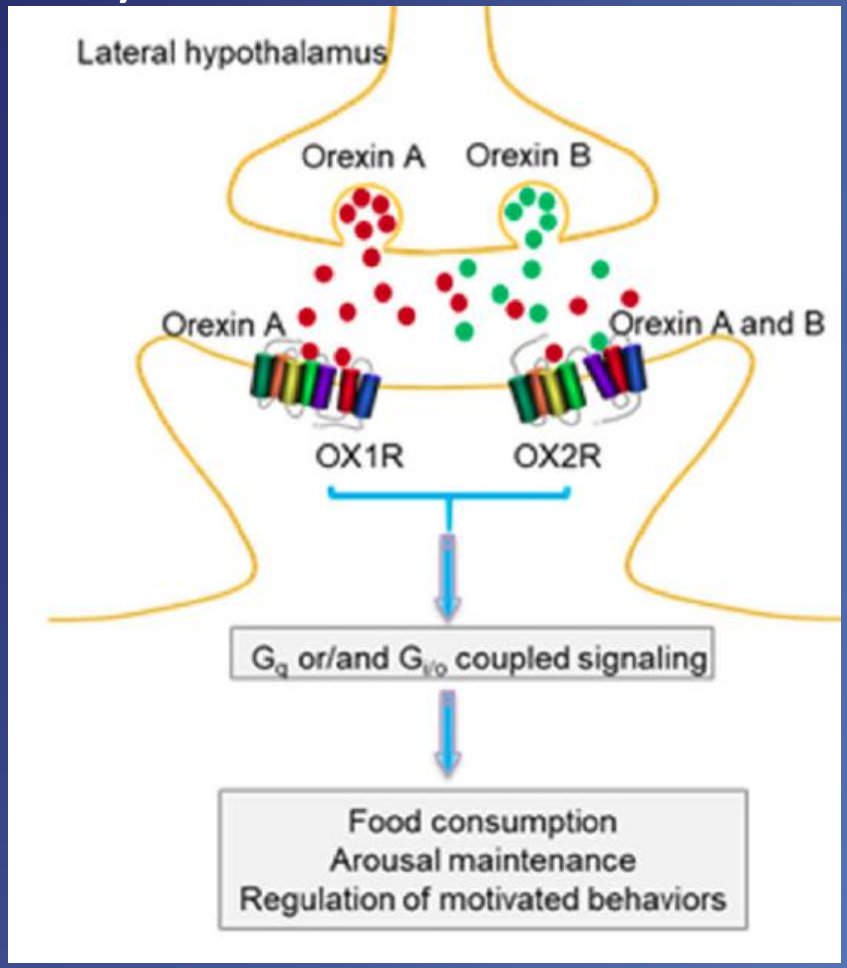
1. https://www.cadth.ca/sites/default/files/pdf/HT0003-OP0527_Insomnia_Cinical_Review.pdf
2. Clin Ther. 2016 Nov;38(11):2340-2372

Suvorexant (Belsomra®) What the heck is this?

Pharmacology: Orexin receptor antagonist

N = 3076 4 RCTs	1 month	3 months	12 months
Sleep Onset Latency	-9.2 mins	-9.5mins	-4.4 mins (NS)
Total Sleep Time	+20 mins	+19 mins	+16 mins

Sleep Medicine Reviews 35 (2017) 1e7



Neurosci Bull. 2019 Nov 28. doi: 10.1007/s12264-019-00447-9

Dose: 5-20mg HS (empty stomach)

Risks: rebound insomnia, cataplexy, risky behaviors while not fully awake

Cost: ????? On DPD, not in catalogue

Coverage: not covered by Pharmacare

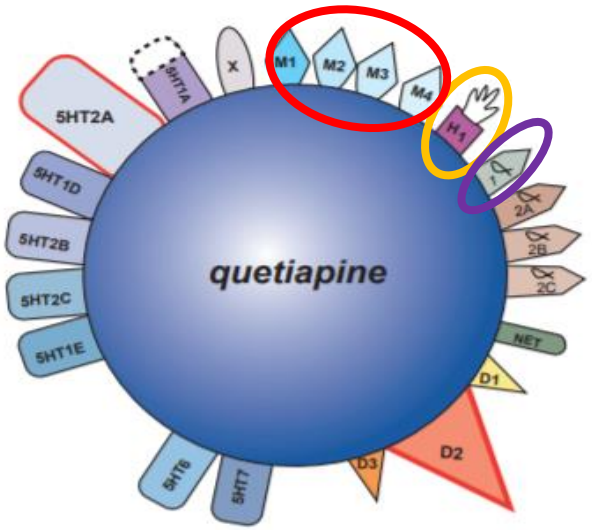
QUETIAPINE 👏 is 👏 NOT 👏 A 👏 SLEEP 👏 AID 👏

Why it could work for sleep: H1 blockade, antimuscarinic, alpha-1 blockade and 5-HT2A antagonism (all produce sedation)

Risks:

- Side effects begin *even at LOWEST dose*[1]
  - Anticholinergic, orthostatic hypotension, EPS, metabolic adverse effects (lipids, weight, BG)

- Very few patients have been studied (~40) without comorbid psychiatric disorders
- Studies lack objective testing (polysomnography)



Stahl's Essential Psychopharmacotherapy, 4th ed.

1. Tidsskr Nor Laegeforen. 2019 Sep 16;139(13) 2. Am J Health-Syst Pharm. 2014; 71:394-402

You won't let me use Z-drugs, benzos, or Seroquel® -now what?

Trazodone (Off-label use) $0.23/tab for 50mg (Part 1 Pharmacare benefit)

- Dose 25-50mg HS (alpha blocker, histamine blocker) – SARI higher doses
- Useful: Aggressive behaviour/agitation in Dementia and sundowning [Curr Treat Options Neurol. 2019 Jun 24;21(7):30]
- Risks: hypotension, GI symptoms, longer half-life in elderly

Doxepin (Silenor®) $0.66/tab 3mg, $1.33/tab 6mg (not covered),
(Sinequan®) 10-50mg $0.37-$0.86/capsule (Part 1 Pharmacare)

- 3mg-6mg HS (histamine blocker)
  - 3mg TST +12 mins, WASO 10 mins, 6mg TST 17mins, WASO 14 mins[1]
- Separate at least 3 hours from meals (delayed absorption), 30mins prior to bedtime
- Risks: anticholinergic (mild), headache, increased BP

Innov Clin Neurosci. 2017;14(7–8):24–34
RxFiles : Sleep/Insomnia Drug Comparison Chart [Accessed Jan 23/2020]

You won't let me use Z-drugs, benzos, or Seroquel® - now what?

Melatonin Age-Related Insomnia

- DOSE IS 0.3mg-1mg (*physiologic*)
- Hormone: wearing off (eventually), rebound insomnia and concerns regarding puberty in children[1]

Ramelteon (Rozerem®) not in Canada ☹

- Melatonin receptor agonist (M1+M2) higher affinity than melatonin

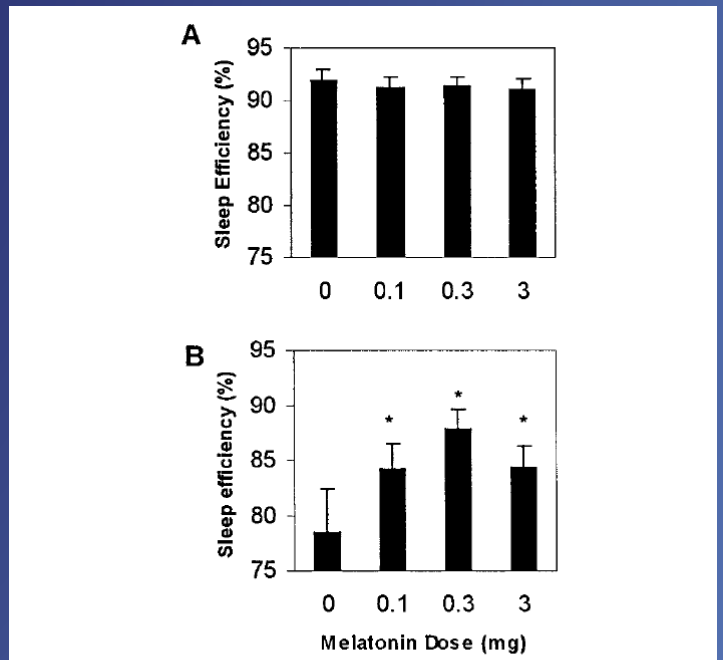


FIG. 1. Sleep efficiency in subjects with normal sleep (A) and age-related insomnia (B) following melatonin or placebo treatment. *, $P < 0.05$.

[J Clin Endocrinol Metab. 2001 Oct;86(10):4727-30]

Exploit sedative effects of other medications (comorbid disorders)

- Depression – TCAs, paroxetine, mirtazapine, trazodone
- Neuropathic pain/FM – TCAs, gabapentin, pregabalin

1. Journal of Paediatrics and Child Health **51** (2015) 584–589

Audience Question: slido

Name a drug that disrupts sleep

Drugs that disrupt sleep

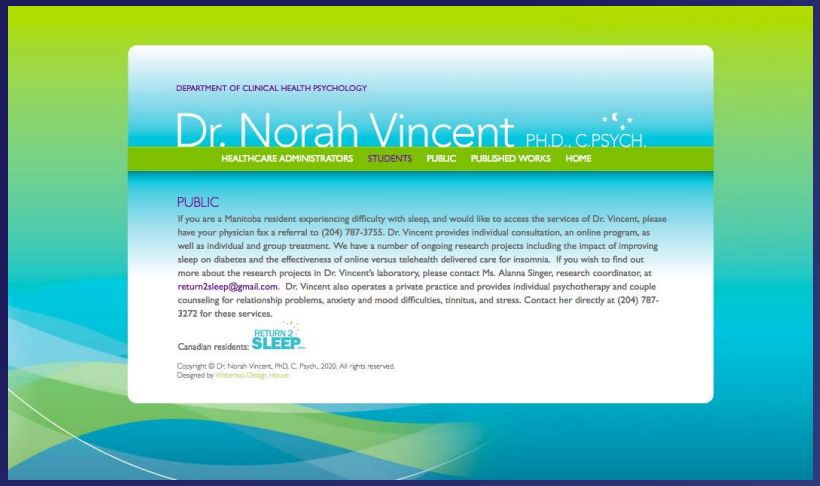
Steroids	Antidepressants	Bronchodilators
Diuretics	Stimulants	Alcohol
Nicotine	Thyroid	Dopamine analogs/agonists

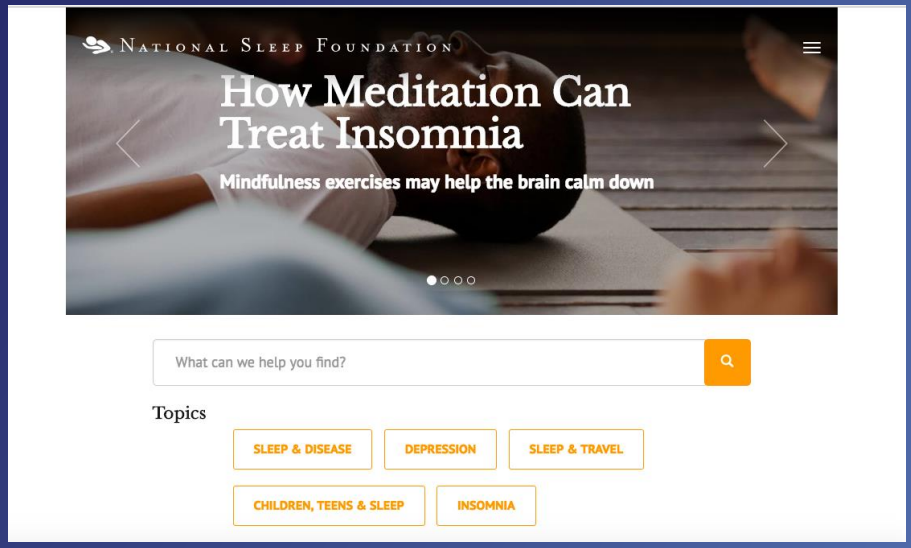
Resources

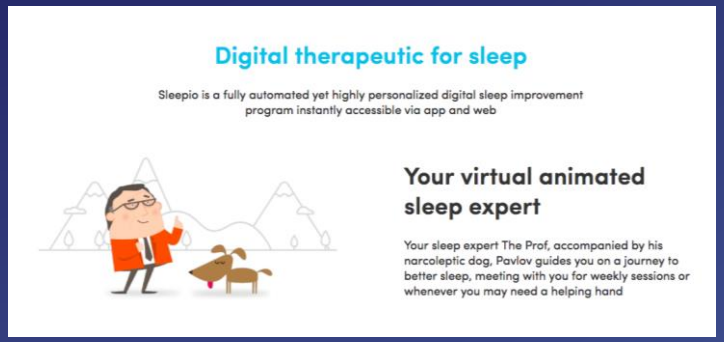
CEP | Providers

Management of Chronic Insomnia

This clinical tool guides primary care providers to assess and manage chronic insomnia and pharmacological options in the general adult population. An estimated 3.3 million Canadians aged 15 years or older (about one in every seven Canadians) have difficulty going to sleep or staying asleep.[1] This can impact both daily functioning and quality of life. Appropriate management options, such as cognitive behaviour therapy for insomnia (CBT-I) and pharmacotherapy regimens, are discussed in the tool to support primary care providers in their approach.[2,3,4] Considerations and instructions for initiating a benzodiazepine taper are also addressed within the tool.








Sleep Well
Any questions?