SEVEN FACETS OF INSOMNIA

COLIN SHAPIRO BSc(Hon), MBBCh, PhD, MRCPsych, FRCP(C)
DORA ZALAI MD, PhD, C. Psych
ROYI GILAD MD
NOA GILAD MD, OBGYN specialist (ISR)
CHRIS KIM BSc(Hon), MD
MICHAEL MAK MD, FRCP(C)
ATUL KHULLAR MD, MSc, FRCPC, DABPN (Cert. Sleep medicine), DABOM

SEVEN FACETS OF INSOMNIA

COLIN SHAPIRO BSc(Hon), MBBCh, PhD, MRCPsych, FRCP(Cw
DORA ZALAI MD, PhD, C. Psych
ROYI GILAD MD
NOA GILAD MD, OBGYN specialist (ISR)
CHRIS KIM BSc(Hon), MD
MICHAEL MAK MD, FRCP(C)
ATUL KHULLAR MD, MSc, FRCPC, DABPN (Cert. Sleep medicine), DABOM

Contents

Acknowledgements:
Ilana Rosen, graphic artist and art direction
Monika Rosen, cover illustration and other illustrations in the booklet
Editor: Donna Sherman
Produced by Sleep on The Bay

Foreword

Colin Shapiro
Professor of Psychiatry
Sleep Specialist

Good Sleep is not a given

There are times in life when sleep changes
Idyllic at times- lambs in their mangers
But there are times when sleeping well is a lost skill
And inevitably the sleepless will become ill

Insomnia is often thought of as a consequence
Too much coffee, two little exercise, - are merely an annoyance
For example apnea leading to sleep disruption
And the usual well functioning system suffers a corruption

Thumbs UPPP (see facet three) may help to discern
Which approach to insomnia we try and which to spurn

Disruption of sleep seems to know no boundary
What is thought of as calm and tranquil is no longer flowery
One needs to strategize and one needs to hope
If the old solutions run dry - find another way to cope

Colin Shapiro – February 2025

Introduction – A Broad Perspective of Insomnia

In the last decade, there have been four dramatic changes in the way people have thought about insomnia and its treatment.

The first is the recognition that insomnia is not always a consequence of some other problem, but is often an issue in its own right. This has important implications as it indicates that we need to treat insomnia specifically rather than relying on treating some underlying malfunction that we speculate is the cause of insomnia. This applies to many individuals, but not all.

BMJ

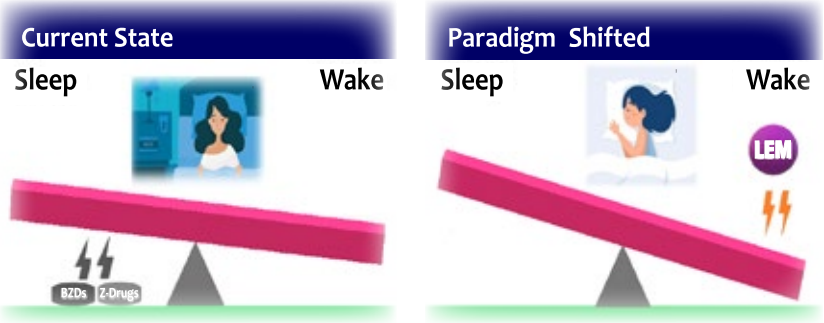
The subject of sleepiness is once more under public discussion. The hurry and excitement of modern life is quite correctly held to be responsible for much of the insomnia of which we hear and most of the articles and letters are full of good advice to live more quietly and of platitudes concerning the harmfulness of rush and worry. The pity of it is that so many people are unable to follow this good advice and are obliged to lead a life of anxiety and high tension.

The reference to the BMJ article being in the 90s is accurate, but it refers to the 1890s, i.e. it is not a recent observation. The notion of stress as the primary cause of insomnia is enduring and incorrect.

The second Facet discusses the role of cognitive behaviour therapy (CBT) in the treatment of insomnia and points out the widespread recognition that this should be the first line of treatment. The rudiments of cognitive behaviour therapy for insomnia (CBT-I) are discussed and while it is widely viewed that in-person treatment – especially if it is short, sharp, and focused – is probably the best way for this to be delivered, there are alternative methods for delivery of CBT and these are referenced. The wide acclaim for CBT-I is encouraging and the figure below shows some of the famous organizations that have come to this conclusion.

For the last 2000 years (and probably longer) we have known of substances that promote sleep, for example alcohol. However, the quality of the sleep is likely impaired and there might be significant withdrawal. In the modern era many people have a negative view of hypnotics and avoid using them. This categorical dismissal ignores the fact that, like all medications, hypnotics have pluses and minuses. The key objective of all of these agents has hitherto been to increase sleepiness level.

However, insomnia can be thought of either as being not sleepy enough or as being too much awake. For the first time, agents which decrease alertness or arousal have become available. This represents a third crucial shift from using agents that increase sleepiness to ones that help to turn down hyper-arousal or alertness. These are still relatively new. Four years ago, in the booklet that was the precursor of this book, only one agent that decreases arousal was available. Now these are three and a detailed and nuanced

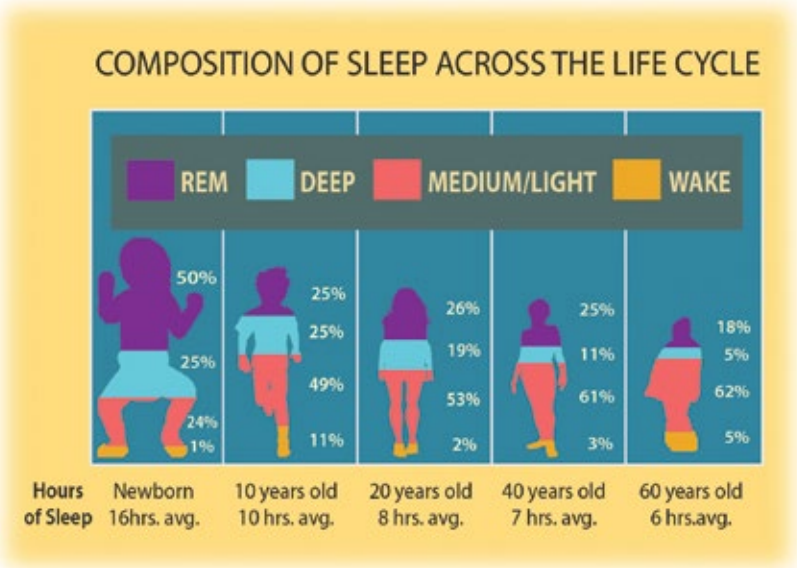


discussion is found in Facet 7. In Facet 3, a description of the Thumps Up scale to detect hyperarousal is given.

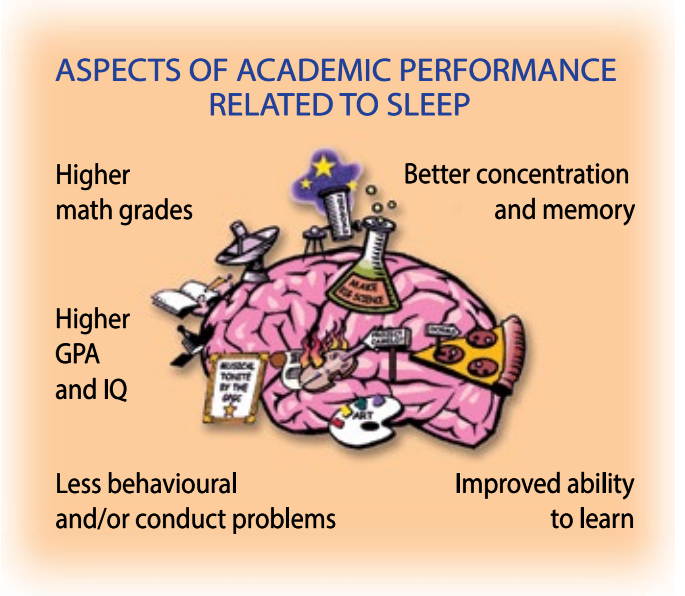
All treatments should be based on an understanding of key drivers of insomnia and insomnia, may come in an acute or chronic form. One would also want to understand what the impact of treatment is beyond hopefully giving one a sense of sleeping well or a sense of oblivion.

There are specific considerations for insomnia in different age groups (see figure on page 7). Facet 4 describes insomnia in children and Facet 5 focuses on sleep issues around menopause. The seventh Facet discusses the impact of sleep promoting treatments on the quality and continuity of sleep. However, there is still relatively little known about the impact of sleep treatments on many of the physiological processes that normally occur during sleep.

One reason to focus on insomnia symptoms, is the observation that these are extremely common complaints.



Insomnia is usually thought as a reduction of time of sleep. However, most people would prefer six hours of solid sleep rather than seven or eight hours of broken sleep, which typically decreases the deep sleep and dreaming sleep stages (which can be thought of as a better quality sleep.)



Finally in this introduction I have included this short table which will facilitate covering the bases in an interview to work out the key issues in insomnia.

Clinical insomnia interview

May include :

SLEEP		ABCDEF	
Stress	e.g. loss of job / marital breakdown / bereavement	**A**ffect	i.e. mood
Lifestyle	e.g. exercise or alcohol too close to bedtime	**B**ehaviours	e.g. spending too much time in bed, irregular wake-up time
Environment	e.g. temperature, noise, light	**C**onsequences	e.g. attention, mood, performances
Exercise	as a promoter of sleep and close to bedtime a disrupter	**D**isorders	sleep apnea, restless legs, body clock problems other medical disorders
Period	i.e. when sleep occurs	**E**cstasy (substances)	substance abuse, over-the-counter agents, medications
		Family History	

FACET 1

Insomnia is the Problem

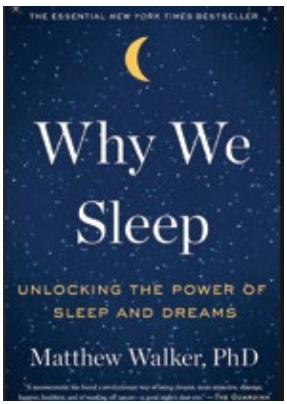
(and Should Be Treated as Such)

With all disorders one instinctively realizes that an understanding of its physiology and pathophysiology is a great help in providing informed interventions.

This applies equally to conditions as diverse as gastric ulcers, diabetes, depression and Parkinson's disease. Unfortunately, the information about the function of sleep (which in the author's view is a necessity if one is to formulate an appropriate approach to managing insomnia) is generally not much appreciated by clinicians.

Fortunately, two books come to the rescue. They share a similar title and look similar but appropriately the first was geared to children, the second to adults.

2016



2018

The Wall of Evidence
for
The Restorative Theory of Sleep

Catabolism/anabolism
The balance tips towards more build-up during sleep

Increased deep sleep
Protects against feeling pain

Growth hormone
Mostly released at night and mostly in deep sleep

ATP concentrations
Increase while oxygen consumption drops during sleep

Oxygen
Use decreases in deep sleep

Pregnancy
Some studies show is associated with increased deep sleep

Sleep loss
Worse performance e.g. driving

Illness
People with illnesses and low energy (e.g. hypothyroidism) have low levels of deep sleep

Exercise
People who exercise have more deep sleep indicating that sleep is restorative

Immunology
Infected animals who are prevented from sleeping are more likely to die

Height
Teenagers get taller during the sleeping period

Cell mitosis
Most cell division is during sleep

Melatonin secretion
Typically peaks prior to sleep onset

Core sleep
When sleep is lost deep sleep is replaced first

Recovery
There is more deep sleep after deprivation

Memory
Growing evidence that certain types of memory need deep sleep

The table on the previous page provides some of the evidence that sleep serves multiple restorative functions

For many patients, long-term insomnia feels like a perennial battle.

Churchill's famous speech in 1940 which uses the highly quoted line "We will fight them on the beaches", and the many other places the "fight" was to take place, lead me to write a poem on the 80th anniversary of Churchill's speech, using Anaphora as the style to describe some of the functions of sleep:

SLEEP FUNCTION

Sleep is that which heals
Sleep is what restores body and soul
Sleep helps to focus the mind
Sleep consolidates memories we have
Sleep changes the inattentive to be focused
Sleep cleans the garbage of the mind
Sleep is a respite from trauma
Sleep helps to modulate pain
Sleep allows for physical growth
Sleep is a cauldron for creative ideas
Sleep allows the athlete to perform at a higher level
Sleep brings down blood pressure
Sleep is at the frontline in the battle with disease
Sleep may allow depression to evaporate
Sleep allows for tranquility and calm

Colin Shapiro – June 4th 2020

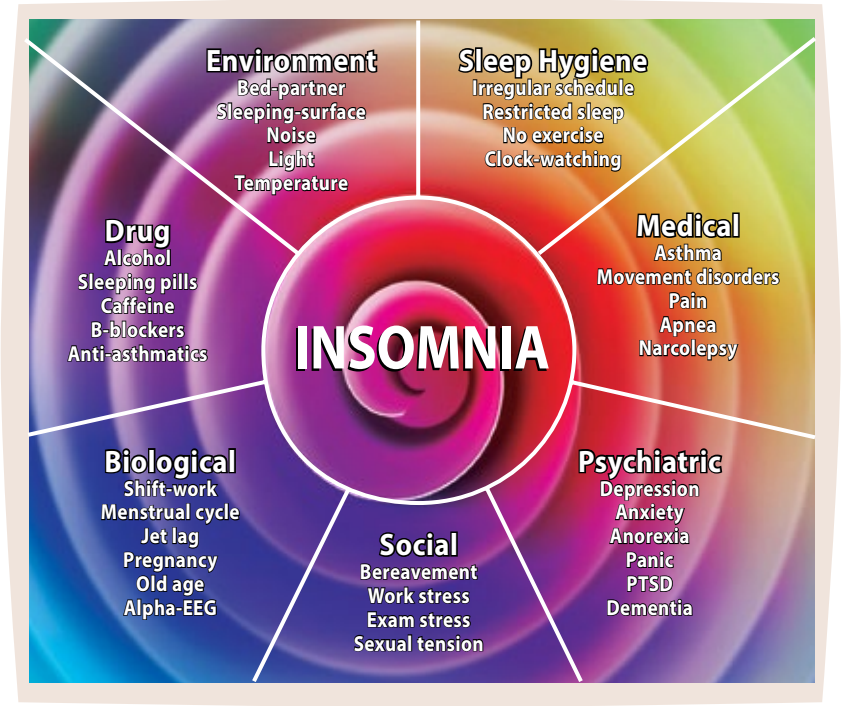
We are fortunate to live in a time of evolving and better treatments for insomnia.

From the 60s up until the last decade, almost all sleep promoting medicines increased sleepiness. This has now changed with the new approaches that have come about both in the use of cognitive behaviour therapy and, more recently, the arrival of pharmacological agents with a different mechanism

of action. The aversion of some experts in sleep medicine to using hypnotics has driven physicians to the inappropriate use of other agents that can be more easily defended. These have included anti-depressant drugs, which may sometimes give the patient a feeling of having better sleep but for which there is little actual evidence. Anti-psychotic agents, for which the side effects are more profound, have also been used in place of hypnotics.

No one would argue that for a patient who is depressed and having sleep difficulties, a drug such as mirtazapine, which has clear anti-depressant and sleep-promoting effects, is a good choice. However, in patients for whom the primary problem is insomnia, the current practice would be to treat with an insomnia-specific intervention as mapped out in the next facets.

Twenty-five years ago, insomnia was generally assumed to be a consequence of some other factor. The figure below shows the range of supposed factors contributing to causing insomnia.



After applying this formula for many years, I came to realize that for many, insomnia was the primary issue. One should then take the view that one needs to deal with insomnia as a stand-alone problem (with all of the impli-

cations that has). Specifically, providing treatment for insomnia either as a temporary aid, or in some cases, on a long-term basis if needed.

Although the notion of long-term management of insomnia has considerable cognitive dissonance for many physicians, the door to this concept was opened more clearly by the change in the conceptualization of insomnia in the DSM-5 (the standard yardstick of the American Psychiatric Association). This was in contradistinction to prior editions of the Manual. For the first time, insomnia was recognized as being *THE STAND ALONE PROBLEM* rather than the handmaiden to some other issue.

Cleopatra and her handmaiden, from the painting by Frederic Arthur Bridgman

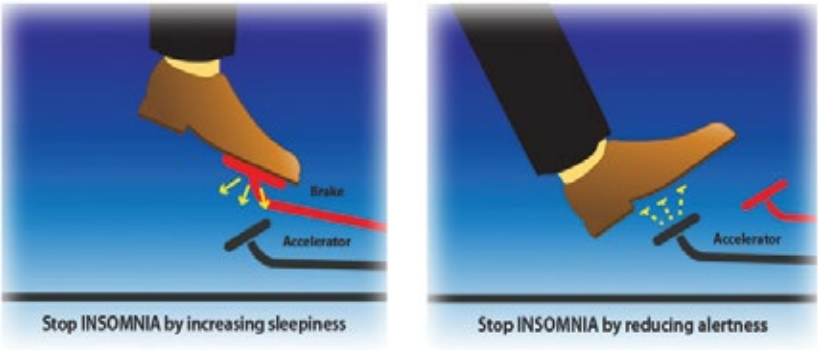
Insomnia disorder, burst out of the role of being the handmaiden of asthma, depression, fractured leg, etc.

While many readers may think that the following analogy is spurious, it is worth stating that no-one says of a person with diabetes that they have taken insulin for long enough, or to a patient with Parkinson's that their dose of L-Dopa has been increasing over the last few years and that they are becoming addicted. Similarly, there is now a shift (by some) that the same applies to insomnia.

For any disease we recognize that it may be long lasting, and for some diseases we recognize that the treatment regime may need to increase over time. For the majority of patients with insomnia, if they have an effective treatment for a limited period and set up a review one month after the end of the treatment regime, an effective and satisfactory solution is arrived at. In a tertiary clinic, up to 20% may need longer treatment and 10% may need a different approach entirely. The advent of distinctly different approaches to insomnia treatment is outlined in Facets 2, 6 and 7.

One would urge readers to no longer think of insomnia as a form of failure, or the need to treat it on an ongoing basis as a failure, any more than we would think of depression as a character flaw (which was once the case).

When one approach is ineffective, the mantra in many other areas of medicine, namely to use a different approach with a different mechanism of action, is a better second choice than using the same type of treatment but with a minor variation. When treating hypertension, if an ACE inhibitor is not effective, then we think of using a drug with a different mechanism of action rather than going to another ACE inhibitor. When treating depression, if an SSRI is not successful, one would not usually think of going to another SSRI but rather to a different category of antidepressant agent. The same philosophy should be taken with the management of insomnia; if a medication that increases sleepiness is not working, then a different approach, such as CBT or an agent to decrease arousal should be tried. Facet 2 describes the benefit of CBT-I (cognitive behavioural therapy for insomnia) usually done by psychologists and Facet 7 focuses on decreasing arousal.



Older sleeping medications increased sleepiness. The new medications decrease wakefulness, a different way to facilitate sleep.

FACET 2

Cognitive Behavioural Therapy

as the First Line Treatment of Chronic Insomnia

What is CBT-I and How Does It Work?

CBT for insomnia is a multi-component psychological treatment that **specifically targets the factors that perpetuate chronic insomnia.**

CBT-I is a short and effective treatment that can be delivered equally effectively in person or via telehealth systems to individuals or in a group format. It has the most robust evidence-base of all insomnia treatments, and it is the only insomnia treatment with a strong recommendation for use by clinical practice guidelines. Research has consistently shown that approximately 70% of individuals who participate in CBT-I experience a significant sleep improvement, and 50% achieve complete remission by the end of the treatment.

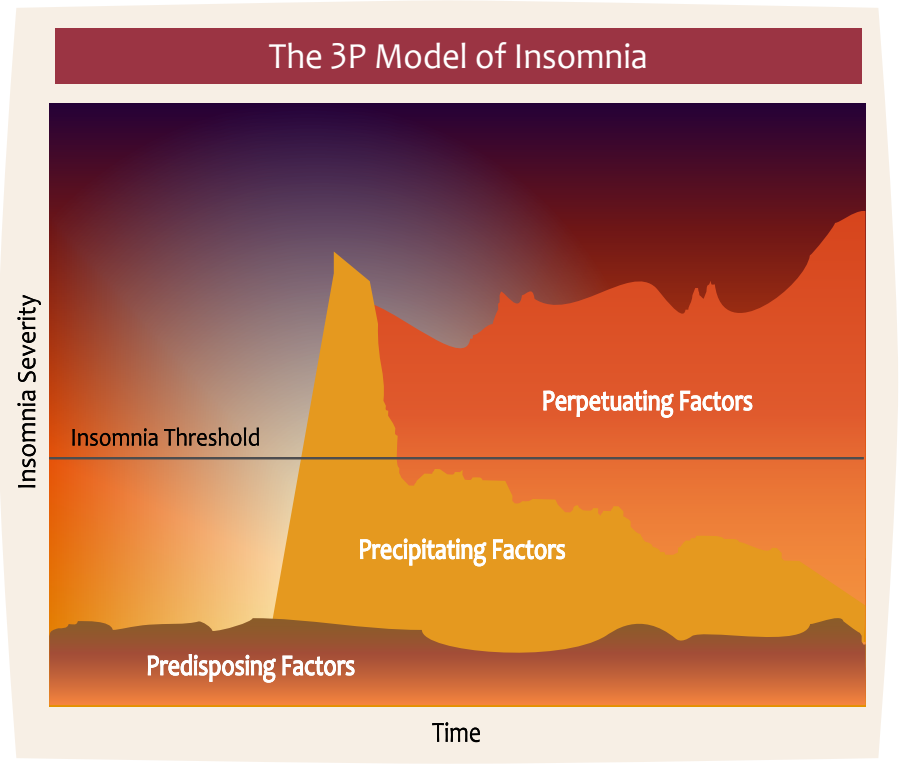
According to both North American and European insomnia treatment guidelines, CBT-I should be recommended to patients as the first line treatment for chronic insomnia

Why Can't I Sleep?

Case Presentation

Violet, age 36, *describes that she has been having poor sleep for at least two years. In retrospect, she realizes that she had sleeping difficulties in the past but never to the extent of her current sleep problem. She still remembers those nights when she could not fall asleep in high school and when she lay awake all night because she felt overwhelmed by the workload at university. At that time, she never thought of her sleep as being problematic because the sleep difficulty was always temporary and did not impact her life. Certainly, she had disrupted sleep when her son was a baby but she simply accepted it as part of parenthood. Violet became increasingly concerned about her sleep after her son reliably slept through the nights and she still spent hours awake in the dark, trying to sleep. She says that she does not understand why she is not able to sleep well when there is nothing that disturbs her sleep. She was told that stress can cause sleep problems and she can identify minor, daily stressors but feels that she can cope well and she does not feel overly distressed or anxious. She describes herself as a happy person and is grateful for having a loving family, a beautiful home and a job that she likes. She had a recent annual check-up with her family doctor and he confirmed that her blood test results were normal and she has no health issues, apart from occasional migraine headaches. She exercises regularly and she eats healthy meals. She also visited a homeopathic doctor who told her that she may have hormonal problems and micronutrient deficiency and recommended that she take supplements. Violet follows the recommendations but she has not experienced a significant improvement in her sleep. She has read on the internet*

that a weighted blanket, magnesium and melatonin can help to sleep and she has tried each of these but none resolved her sleep difficulty. Violet says that she tries everything to promote her sleep: she does not watch TV in the evening, she has a regular bedtime which allows for time to relax in bed before she tries to sleep; she listens to relaxation music and meditation podcasts when she trying to sleep; she uses her weighted blanket; she cools the room for the night; she has blinds and heavy dark curtains to keep the bedroom pitch dark; she uses ear plugs to block out sounds and she knows that her husband would get up and attend their son's needs if her little one woke up at night. Despite of all the "good sleep hygiene" practices, she still finds herself feeling anxious and upset when she is not sleeping and concerned how the lack of sleep would impact her daytime functioning and health. Violet has a prescription for sleeping pills from her family doctor and she used it regularly for a month. She says that she sleeps well after she takes a pill but the sleep difficulty returns as soon as she stops taking the pills. She still takes this medication occasionally when she feels anxious and hopeless about not being able to sleep at night but she does not see it as a long-term solution because she does "not want to be on sleeping pills for the rest of my life." After all these struggles with her sleep, Violet has started to believe that there is something fundamentally wrong with her, as she has lost her natural ability to sleep. She says all she wants is to sleep well again, "naturally, without sleeping aids." She recently heard from a friend that psychotherapy can help insomnia and she would like to learn more about this treatment.



Acute insomnia is part of normal life and can be an adaptive reaction when being awake, alert and ready to act is needed for survival/coping in dangerous situations or when we are facing acute challenging life events. **Predisposing factors** (e.g. female sex, older age, certain personality traits) lower the threshold for insomnia and when **precipitating factors** (e.g. stressful life events or illness) are present, individuals like Violet are more likely to experience temporary sleep difficulties than people who have a lower predisposition for insomnia (see above figure). Acute insomnia may last for a night or for a few weeks and – as Violet experienced previously – it eventually subsides. Violet never saw these sleepless nights as problematic and if she felt distressed, it was because of precipitating factors not because of her sleep. This time, however, things are different. After her son did not wake her, Violet became increasingly preoccupied with and anxious about her sleep. In the past two years, **sleep-related perpetuating factors** have been playing an increasing role in maintaining her insomnia. As these perpetuating factors are becoming the driving force of insomnia, **the relative contribution of the precipitating factors declines and chronic insomnia becomes a condition in its own right.**

Some of the factors that PERPETUATE Violet's sleeping problem:
• Early bedtime relative to her habitual sleep onset
• Excessive time in bed relative to her average sleep time
• Dysfunctional beliefs and attitudes about sleep
• Anxiety about sleep
• Preoccupation with sleep
• Anxiety-driven safety behaviours e.g. over doing bedtime rituals
• High sleep effort
• High arousal (maintained by learned associations between sleep location and wakefulness, dysfunctional beliefs and attitudes about sleep, safety behaviours and sleep effort) in the peri-sleep period and during the night

The perpetuating factors in patients with comorbid medical conditions are the same or similar to those that maintain Violet's sleep problem and ultimately affect the same sleep biological systems (homeostatic sleep drive, circadian rhythm and arousal system) that are relevant in chronic insomnia.

A clear advantage of CBT-I over medication treatments is its long-term effectiveness. Since CBT-I eliminates the perpetuating factors of chronic insomnia, it has enduring effects. In contrast, patients may need to stay on medications if they want to maintain good sleep and the insomnia may return after they stop taking medications if the factors that perpetuate insomnia (see pages 14, 15 and 19) do not spontaneously change while patients are on sleep-promoting medications.

Who Can Benefit from CBT-I?

CBT-I should be offered to every adolescent and adult patient whose sleeping problems meet DSM or ICSD criteria for chronic insomnia. (The diagnostic criteria have changed in the latest edition from one month to three months as a minimum duration of the sleep problem. However, CBT-I is effective even when patients have experienced only a month of poor sleep and

also when the sleep problem has been present for years or decades.) CBT-I is as effective for older adults as it is for younger or middle-aged individuals. Given that chronic insomnia is a condition in its own right that is perpetuated by factors related to sleep, CBT-I is as effective in treating insomnia comorbid with sleep apnea, chronic pain conditions, cancer, chronic obstructive pulmonary disease, mood disorders, PTSD, substance use problems and other medical conditions as it is for insomnia in otherwise healthy individuals.

CBT for insomnia alone leads to improvement in quality of life, fatigue (including cancer-related fatigue), pain and mood, and it boosters the effects of antidepressant medication treatment. When insomnia is present with a mental health problem or chronic pain, the psychologist can combine the CBT treatments to effectively treat more than one condition concurrently.

CBT-I is less effective for a sub-group of patients who have both insomnia and objectively short sleep duration. (Objective sleep duration is measured by polysomnography over multiple nights. There is often a discrepancy between objective and subjective sleep duration in the insomnia population in that the subjectively estimated sleep duration is shorter compared to objective measurement.)

CBT-I for Patients on Hypnotic Medications

CBT-I can be added to the treatment of patients who are on hypnotic medications but continue to have insomnia symptoms in order to help them become symptom free. It is also effectively used to help patients – with or without current residual insomnia symptoms – to come off hypnotic medications. Ultimately, we are implementing a treatment with enduring effects (CBT-I) while we are discontinuing a less optimal treatment for the patient. The process of medication tapering/discontinuation depends on multiple factors, including the type of medication the patient is on, their readiness to reduce/stop taking the medications, their sleep-related self-efficacy and anxiety about insomnia. In the writer's (DZ) experience, the process is typically smooth even when patients are on multiple hypnotic medications and can be completed within the typical time frame of CBT-I. CBT-I for these patients can be especially empowering as they realize that have the ability to sleep well (even if they have comorbid medical conditions) and they can improve their sleep on their own using their newly acquired knowledge and the skills they learn in CBT.

Examples for CBT-I targets and interventions

PERPETUATING FACTORS	INTERVENTIONS
Violet goes bed 1-2 hours earlier than her usual sleep onset and she spends more time in bed than she fills with sleep. Consequently, she spends hours awake in bed, which contributes to conditioned arousal.	Time in bed restriction Strategically timed bedtime and rise time recommendations taking the individual's circadian rhythm into account
Violet engages in wakeful activities in bed (e.g. listening to music and meditation podcasts, lying in bed awake with eyes closed trying to sleep) which contributes to conditioned arousal.	Stimulus control therapy
Violet does not understand why she has not been able to sleep well even though there are no obvious factors that interfere with her sleep; she believes that she has lost her natural ability to sleep; she thinks that will not be able to function at home and at work if she does not sleep all night; she thinks that she will develop health problems because of her sleeping difficulty.	Psycho-education, cognitive therapy and behavioural experiment
Violet invests a great effort into trying to sleep. She engages in anxiety-driven safety behaviours (e.g. wearing ear plugs, checking the time at night when she cannot sleep, taking sleeping pills when she feels anxious about her sleep, and asking her husband to get up when their son calls for them at night).	Behavioural experiments and other cognitive and behaviour strategies to reduce safety behaviours Cognitive, behavioural and mindfulness techniques to decrease sleep effort
Violet exhibits high arousal in the peri-sleep period and during the night.	Stimulus control therapy, cognitive therapy, mindfulness techniques, progressive muscle relaxation

Using CBT-I to Discontinue Hypnotic Medications

1 THE PERSON IS ON MEDICATION FOR SLEEP BUT STILL HAS DIFFICULTIES WITH FALLING/STAYING ASLEEP		2 THE PERSON FALLS SLEEP/STAYS ASLEEP WHEN TAKING SLEEP PROMOTING MEDICATIONS EVERY NIGHT
A	**B**	
Stop the medication (if there is not much benefit and the person is eager to be medication free)	Start CBT-I while the patient is on an agreed-upon nightly dose of medication[1]	Provide psycho-education and decrease medication dose until insomnia symptoms recur
Start CBT-I	After sleep normalizes, taper off/discontinue medication while continuing CBT-I	Implement cognitive and behavioural interventions. After sleep normalizes, taper off/discontinue medication while continuing CBT-I

1. *Medications are tapered off based on an agreed upon plan with the patient to avoid in-the-moment decisions about taking medications based on non-adaptive beliefs about sleep or sleep-related anxiety*
2. *The above outlines the clinical approach of the writer of this facet (DZ)*

CBT-I in a Minute – What Patients Need to Know About CBT-I

Every patient has the right to make an informed decision about their treatment. For this to happen, they need to hear about evidence-based treatment options for their problems. One obstacle in receiving CBT-I is that patients do not receive accurate information about this treatment, or they receive a "diluted" version of ad hoc recommendations, or are directed to apps and books that have not been tested in research. It is akin to telling a patient with bacterial pneumonia to go to the pharmacy and choose an over-the-counter pill with a flavour they like and a pleasing colour. When the patient returns with high fever and dyspnoea and one concludes the pills did not work, one realizes that they need antibiotic medication.

We encourage clinicians to photocopy the following two pages to give to patients.

INFORMATION ABOUT CBT-I IN A NUTSHELL:

- *Cognitive behavioural therapy (CBT) is the number one recommended treatment for the sleeping difficulty you are experiencing.*
- *Approximately 70% of people who complete CBT for insomnia experience a significant improvement in their sleep.*
- *In cognitive behavioural therapy you will learn about your sleeping difficulty and how to sleep well again. It involves keep tracking of your sleep, getting recommendations for a sleep schedule that will help you sleep better, learning what to do when you cannot sleep and how to reduce your anxiety/stress at night.*
- *CBT is a short treatment (typically 3- 5 appointments).*
- *The main advantage of CBT over medication treatment is that it has long-term effects (that is, after you complete the treatment, you can expect that your sleep will remain good) and you will gain knowledge that you will be able to use for the rest of your life.*
- *It is best to do CBT in person or via video-conferencing with a psychologist or treatment provider who has experience in this treatment**.*
- *Therapists who don't work in a hospital are not covered by provincial health insurance but covered by extended health insurance. Ask about the cost and check your coverage – since it is a short treatment, even limited coverage my be sufficient. Also ask about group treatment – it is usually cheaper than one-on-one appointments.*
- *If you don't have coverage and the cost is too high, you can try to use an app that is cheaper and has been tested in research**. *It is best to use the app and at the same time – if it is possible – have short meetings with a psychologist so that they can help you stay on track and provide individually-tailored recommendations.*
- *There are also workbooks that you can try but these are more difficult to do alone – you may need help along the way.*

** See resources at the end of facet.*

The point has been made in the first facet that when a particular therapy does not work for a problem, using a close relative to the original treatment is unwise, whereas using a distinctively different approach is likely to have a better yield. All physicians have had the experience that a treatment with a medication for insomnia did not produce the desired effect. The best option in such a situation is to choose the treatment that is the most different from the original approach. This would almost certainly make CBT-I the "go-to" second choice if it was not the first choice originally.

* Resources

Insomnia Specialty Clinic at Sleep on the Bay

- Comprehensive insomnia evaluation across the lifespan
- Expert-level cognitive behavioural therapy for insomnia, including for pregnant and peri-menopausal women, older adults and individuals with medical and psychiatric comorbidities both in person and via secure tele-health video system everywhere Ontario, Canada
- Information for clinicians concerning insomnia management
- Collaborative, combined psychology and medical treatment plans for patients with sleep disorders and mental health issues
- Refer directly via the website: sleeponthebay.ca

Toronto Metropolitan University Sleep and Depression Lab

- CBT-I for patients who are eligible to and want to participate in research

Local psychology groups with the main orientation of CBT (inquire if they have psychologists who provide CBT-I)

Sleepio: CBT-I App (available in App stores)

Carney, C. E & Manber, R. (2009). Quiet Your Mind and Get to Sleep. New Harbinger Publications, Inc., Oakland, CA: CBT-I book

FACET 3
Assessing Insomnia

Cannot sleep or cannot stop being awake?

In recent years, our understanding of insomnia subtypes has significantly advanced, with growing recognition of the role hyperarousal plays in its pathophysiology. Hyperarousal refers to an inability to lower the vigilance of consciousness, thereby impeding natural sleep mechanisms. This heightened state of arousal or vigilance is particularly common during periods of stress associated with anxiety, mood disorders, post-traumatic stress disorder (PTSD), obsessive compulsive disorder (OCD), and personality disorders. Cognitive Behavioural Therapy for Insomnia (CBT-I), the first-line treatment for chronic insomnia, addresses hyperarousal through techniques such as stimulus control and psychophysiological training. CBT-I also targets sleep homeostasis by employing sleep restriction to increase the drive for sleep.

Despite clinicians' long-standing acknowledgment of hyperarousal – illustrated by patient reports of taking hypnotic medications that induce drowsiness but fail to quiet their "racing minds" and initiate sleep – there were no pharmacological treatments specifically designed to reduce hyperarousal in insomnia until recently. Since 2014, a novel class of hypnotic medications, Dual Orexin Receptor Antagonists (DORAs), has been introduced. Unlike earlier medications such as benzodiazepines and non-benzodiazepine hypnotics (Z drugs), which promote sleep by inducing sedation, DORAs work differently. They inhibit the action of orexin (hypocretin), a neuropeptide that promotes arousal by stimulating other nuclei within the brainstem. For the first time, pharmacological treatments can specifically reduce arousal without solely relying on sedation.

The advent of DORAs has renewed interest in hyperarousal-driven insomnia. To aid in distinguishing between hyperarousal-driven insomnia and "undersleepy" insomnia, we developed the THUMBS-UPPP questionnaire (see page 27). This tool is not intended for diagnosing or assessing insomnia severity (as the diagnosis would already be established). Instead, it provides clinicians with a quick assessment tool to guide treatment decisions for insomnia patients. The questionnaire consists of 10 items, each with four response options ranging from "Never" to "Often."

Responses of "Sometimes" or "Often" are scored as 1 point (with reverse scoring applied to questions 2, 6, and 10). The total score ranges from 0 to 10, with higher scores indicating a stronger hyperarousal component. The hope is that the questionnaire will serve clinicians as a quick office-based tool that can assist in more pathophysiologic-oriented decision making regarding the pharmacological treatment of insomnia.

A commonly used questionnaire to screen for insomnia - provided below

INSOMNIA SEVERITY INDEX (ISI)

Name_____ Date_____

1. Please rate the current (i.e. last 2 weeks) SEVERITY of your insomnia problem(s).

	None	Mild	Moderate	Severe	Very
Difficulty falling asleep:	0	1	2	3	4
Difficulty staying asleep:	0	1	2	3	4
Problem waking up too early:	0	1	2	3	4

2. How SATISFIED/dissatisfied are you with your current sleep pattern?

Very satisfied				Very dissatisfied
0	1	2	3	4

3. To what extent do you consider your sleep problem to INTERFERE with your daily functioning? (e.g. daytime fatigue, ab ility to function at work/daily chores, concentration, memory, mood, etc.)

Not at all Interfering	A little	Somewhat	Much	Very much Interfering
0	1	2	3	4

4. How NOTICEABLE to others do you think your sleeping problem is in terms of impairing the quality of your life?

Not at all Noticeable	Barely	Somewhat	Much	Very much Noticeable
0	1	2	3	4

5. How WORRIED/distressed are you about your current sleep problem?

Not at all	A little	Somewhat	Much	Very much
0	1	2	3	4

Guidelines for Scoring/Interpretation:

Add scores for all seven items (1a+1b+1c+2+3+4+5) = _____ Total score ranges from 0-28

0-7 = No clinically significant insomnia

8-14 = Subthreshold insomnia

15-21 = Clinical insomnia (moderate severity)

22-28 = Clinical insomnia (severe)

THUMBS UPPP

When I try to fall asleep but cannot (either when initiating sleep or trying to resume sleep after waking up in the middle of the night): Respond **Never – Rarely – Sometimes – Often** to the prompts below.
Circle the answer that best applies to you to during most nights.

1. My Thoughts are running wild, and I cannot make them stop

Never Rarely Sometimes Often

2. Even though I am not falling asleep, I feel drowsy, and my Head is "blank"

Never Rarely Sometimes Often

3. I feel an Urge to be engaged in something to distract my mind actively; otherwise, I won't be able to fall asleep (e.g. playing games on phone, social media, sexual activity)

Never Rarely Sometimes Often

4. Without a medication, alcohol, cannabis (or other substance), I will not be able to silent my Mind

Never Rarely Sometimes Often

5. I find myself constantly moving in the Bed or getting in and out of the bed

Never Rarely Sometimes Often

6. I will probably read or watch television until I Spontaneously fall asleep

Never Rarely Sometimes Often

7. While I am sleeping, I frequently experience disturbing dreams, nightmares, or Uncomfortable bodily sensations

Never Rarely Sometimes Often

8. I feel Palpitations, heavy or labored breathing, sweating, hot, cold, or dry mouth in my body

Never Rarely Sometimes Often

9. I feel Pain (in any part of my body)

Never Rarely Sometimes Often

10. I can lie Peacefully in bed until I fall asleep

Never Rarely Sometimes Often

Scoring: answer of Never or Rarely is scored 0 points. Answer of Sometimes or Often is Scored 1 point. Range is 0-10.
Then higher the score the higher the probability for hyperarousal insomnia, the lower the score the higher the probability for "undersleepy" insomnia.
NOTE: Questions 2, 6, 10 are reversely scored

Scoring _____

FACET 4

Insomnia in Children and Adolescents

Insomnia, characterized by difficulty initiating or maintaining sleep, or experiencing non-restorative sleep despite adequate opportunities for sleep, is perceived as a disorder associated with old age and mounting health problems. However, insomnia is a prevalent disorder among children and adolescents. It can significantly affect their physical health, emotional well-being and their academic performance.

In the paediatric population, age plays a crucial role in the different presentation of sleep disruption and a 6-month-old infant would present very differently from a 6-year-old child or a 16-year-old youth.

Understanding the causes, symptoms and management strategies is crucial for promoting healthy sleep habits in this population.

Prevalence and Risk Factors

Prevalence of paediatric insomnia is estimated at about 5% to 20% in general pediatric populations, with a much higher prevalence in children with neurodevelopmental disorders (e.g. attention deficit hyperactivity disorder, autistic spectrum disorder, fetal alcohol spectrum disorder, intellectual disability) ranging from 50%-70% and in some studies, even 90% of children. As in the adult population, children and adolescents that suffer from chronic physical (e.g. asthma, GERD, epilepsy) and mental conditions (e.g. PTSD, mood disorders, anxiety disorders, substance use disorders) have a higher risk for suffering from chronic insomnia.

General risk factors include:

- Biological Factors: Age, developmental stage, temperament, familial/heritability factors, nutrition, sensory hypersensitivity, circadian rhythm pattern, comorbid sleep disorders, chronic medical conditions.
- Psychological Factors: Acute or chronic stress, childhood adverse events and trauma, insecure attachment style.
- Behavioural Factors: Poor sleep hygiene, excessive screen time, irregular sleep schedules, stimulant consumption (e.g. caffeine).
- Environmental Factors: Family stress and unstable parenting, housing instability, noise, excessive nighttime illumination, uncomfortable sleep environments.

Clinical Presentation

Infants and Toddlers

Want to "sleep like a baby"? Think again.

Persistent sleep disturbances in infants and toddlers are estimated to occur in 20%-30% of babies and are termed "behavioral insomnia of infancy". The condition includes sleep difficulties that result from inappropriate sleep associations or challenges in parental limit setting around bedtime routines. The diagnosis of sleep-onset behavioural insomnia relies on the presence of maladaptive and inappropriate sleep associations such as rocking, watching television, using electronic devices and falling asleep only in the parents' bed. The child is usually unable to fall asleep in the absence of these conditions at both bedtime and on waking up during the night. Moreover, the circadian rhythm during early life is not yet consolidated to one or two consistent sleep periods, which makes it more difficult for parents to establish a consistent "sleep routine".

Children

In children 3 to 12 years old, most sleep difficulties revolve around difficulties in initiating sleep and bedtime resistance with refusal to enter bed, crying and temper tantrums when requested to go to bed and ability to fall asleep only with a parent's presence or in the parent's bed. In addition, due to the increase in prevalence of non-REM parasomnias (e.g. sleepwalking, night terrors, confusional arousals) and nightmares, nighttime awakenings are prevalent, sometimes with significant anxiety around the awakening and

inability to resume sleep. Children are less likely to exhibit excessive daytime sleepiness in response to poor sleep quality and will often display irritability, hyperactivity, distractibility, impulsivity, mood lability and temper tantrums.

Adolescents

Sleep in the adolescent population is highly affected by physiological and psychosocial changes during puberty. Sleep disruption in adolescents presents as delayed bedtime both due to physiological factors such as evening chronotype and delayed phase sleep-wake disorder (DPSWD) which is estimated to effect 6%-16% of adolescents, and psychosocial factors such as studying during the night, late extra-curricular (e.g. sport) activities, social gathering and mostly, social media and other electronic use. In addition to the delay in bedtime, adolescents are required to start their school day earlier, which contributes even more to their sleep restriction. Poor sleep quality in adolescents is associated with lower academic achievements, increased drop-out from school, social withdrawal, increase in motor vehicle accidents, depressive and anxiety symptoms, and increase in substance use.

Factors Relevant to Understanding Each Person's Insomnia

1. acute or chronic stressors
2. bedtime routines and habits
3. chronotype
4. chronic physical, mental or neurodevelopmental disorders
5. comorbid sleep and circadian rhythm disorders (e.g. obstructive sleep apnea, restless leg syndrome, periodic limb movement during sleep, delayed phase sleep-wake disorder)
6. family history of sleep and mental health disorders
7. general medical condition and BMI
8. medication use
9. sleep-related behaviours
10. substance use
11. trauma and adversity

Screening for sleep problems in children can be done using BEARS.

	Toddler / Pre-schooler (questions to parent)	School - Aged (questions to parent)	Adolescent (questions to parent)
Bedtime Problems	Problems going to bed or falling asleep?	Problems at bedtime?	Problems falling asleep at bedtime?
Excesive Daytime Sleepiness	Naps or seem over-tired or sleepy a lot during the day?	Difficulty waking in the morning, feels sleepy during the day or takes naps?	Very sleepy during the day? At school? While driving?
Awakenings	Wakes up a lot at night?	Wakes up a lot at night or has trouble getting back to sleep? Sleepwalking or nightmares?	Do you wake up a lot at night or have trouble getting back to sleep?
Regularity and Duration of Sleep	Regular bedtime and wake up time? What are they?	At what time does your child go to bed and get up in school days? Weekends? Is this is enough sleep?	What time do you usually go to bed on school nights? Weekends? How much sleep do you usually get?
Snoring	Snores a lot or has difficulty breathing at night?	Snores loudly or has breathing difficulties at night?	Snores loudly? (question to parent)

Questionnaires to assess the nature and severity of sleep difficulties can be used. These include the Pediatric Sleep Questionnaire (PSQ), Children's Sleep Habits Questionnaire (CSHQ), and the Sleep Disturbance Scale for Children (SDSC).

The use of a sleep diary is recommended in any assessment of a child/adolescent with a sleep complaint.

Other tests, such as Polysomnography, Actigraphy, or Dim Light Melatonin Onset Test (DLMO), are required in patients where a different sleep or circadian rhythm disorder is suspected (e.g. obstructive sleep apnea, periodic leg movement during sleep, delayed phase sleep-wake disorder).

Management and Treatment

Managing insomnia in young individuals requires a multifaceted approach tailored to the child's age, development and specific circumstances.

Behavioural interventions constitute the first-line treatment for insomnia in children and adolescents.

Treatment of behavioural insomnia of infancy is mediated through the patient's parents and focuses on supporting the parents in establishing bedtime routines and gradually creating a disassociation between parent's presence and the ability of the infant to self-sooth and down-regulate his/her arousal to a level that will allow the initiation of sleep. These are commonly achieved through parental guidance and classical behavioural techniques of extinction.

During childhood, behavioural treatment focuses on mutual work with both the child and parents. Parents receive guidance around bedtime routines and hygiene, managing activity and tiredness during the daytime and nutritional and other aspects, while the child receives psychoeducation about sleep hygiene and practices stimulus control and psychophysiological training (e.g. diaphragmatic breathing, progressive muscular relaxation) with the therapist and practices at home with parents. If needed, the therapist will integrate cognitive restructuring regarding any dysfunctional beliefs and attitudes around sleep. Contrary to adult cognitive behavioural therapy for insomnia (CBT-I), sleep restriction is not normally conducted in behavioural treatment for insomnia in children.

In adolescents, the focus shifts to more "typical" individual cognitive-behavioural therapy (CBT) with the adolescent, similar to CBT-I in adults, including integrating sleep restriction to the therapy. The focus of the therapy will be to minimize behaviours that are reducing sleep quantity or quality such

Tryptophan with carbohydrates (and no protein) one hour before bedtime and no protein for 2 hours before bed.

as electronic use, caffeine use, substance use, late night studying, thought rumination, etc.

Pharmacological interventions are reserved for the treatment of insomnia in children suffering from a comorbid neurodevelopmental or mental condition, or for those for whom behavioural therapy was not sufficiently effective or is not possible (for example, due to their developmental/intellectual level or disability, refusal to cooperate in treatment, or other reasons).

In several countries the use of prolonged-release melatonin (PRM) was approved for the use of insomnia treatment from age 2 to 18 for patients with autistic spectrum disorder (ASD) or Smith-Magentis Syndrome with significant success. However, PRM melatonin is a pharmaceutical-grade extended-release melatonin and is not yet approved by Canada Health.

It is important to note that immediate-release melatonin, though an effective treatment for circadian rhythm disorders such as delayed phase sleep-wake disorder, shift work, jet lag, etc., has not been proven effective for the treatment of insomnia in normally developing children. Moreover, the melatonin sold in Canada is not regulated as a prescription drug and its quality is questionable. There have been cases of "over the counter" melatonin being laced with cannabis.

Off-label use of different agents is prevalent in the pediatric population. So far, there is no evidence to support the use of treatments such as Clonidine or Guanfacine, sedating antidepressants such as Mirtazapine, or sedating antipsychotics such as Quetiapine or Olanzapine, unless within the context of treatment of a comorbid psychiatric disorder.

The off-label use of L-Tryptophan is proving effective and safe for the treatment of non-REM parasomnia and insomnia in children and adolescents. The dosing is critical. The consensus is to avoid over-the-counter sedating antihistamines or cannabis-based products.

Benzodiazepine use is reserved for specific patients with neurodevelopmental or mental disorders. Non-benzodiazepines hypnotic (Z-Drugs) and Dual Orexin Receptor Antagonists (DORAs) have not yet been assessed for safety and effectiveness in the paediatric population.

Body Clocks Matter in Teens and at Endopause

The normal secretion of melatonin is to rise when it gets dark at about 7 pm, and to continue rising until approximately 3 am, and then it comes down. In some teens, the rise is late and they have difficulty falling asleep. In some elderly people, there is an endopause. They stop making melatonin which can also disturb the body clock. A dim-light melatonin onset test (DLMO) is extremely useful in both situations and can dramatically change academic performance in teens and quality of life in endopause. (Also see page 46).

Conclusion

Insomnia in children and adolescents is a multifactorial condition requiring a holistic and individualized approach. By addressing underlying causes and promoting healthy sleep practices, caregivers and healthcare professionals can mitigate its impact and support the well-being of young individuals. Early intervention and effective management can significantly improve outcomes. Establishing good sleep habits during childhood fosters lifelong health benefits, including better mental health, improved academic performance and enhanced quality of life.

FACET 5A
Insomnia in Pregnancy
FACET 5B
Insomnia in Menopause

A Insomnia During Pregnancy and the Post-Partum Period

Insomnia, which affects approximately 10% to 20% of the adult population, is much more prevalent (50%) during pregnancy and the post-partum period. This means that every other woman will have difficulty falling asleep, maintaining sleep or having non-restorative sleep.

Factors That Influence Insomnia in the Pregnancy and the Post-Partum Period

1. Hormonal changes

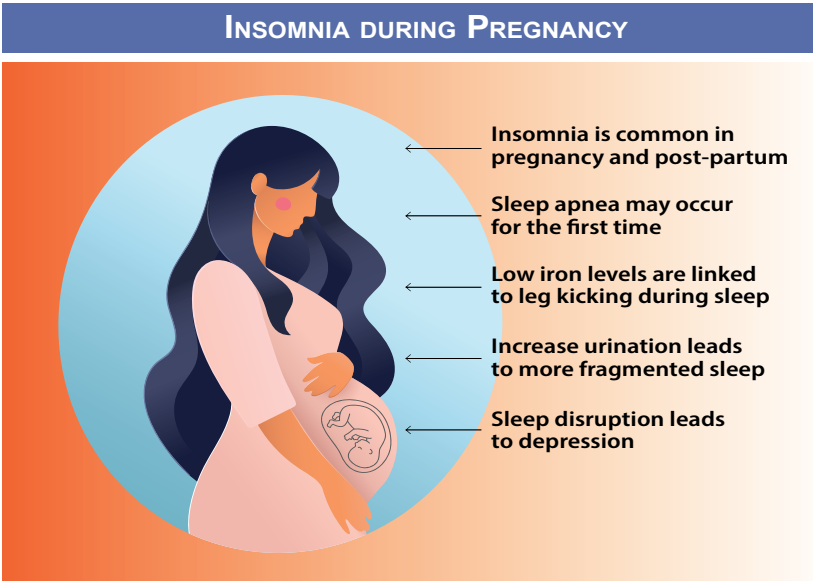
Hormonal variations can cause upper airway changes, including swelling of the cells around the airways, and increase secretions that cause difficulty with breathing. Additionally, regular sleep cycles can be disrupted, resulting in more frequent arousals during sleep.

2. Restless leg syndrome in pregnancy

During pregnancy the growing fetus places high demands on the maternal body, requiring it to supply all the necessities of life. This results in some degree of iron deficiency (anemia) in pregnant mothers. Since low iron storage is a leading cause of restless leg syndrome, this can dramatically interfere with falling asleep and staying asleep.

3. Physiological changes

As the uterus grows with the growing fetus, the diaphragm is pushed upwards causing a 20% reduction in capacity of the lungs, and this is further reduced when the pregnant mother lays down to sleep. The chest wall compliance is also reduced. Together these changes cause the oxygenation of the blood in the lung to be impaired, causing pregnant mothers to wake up spontaneously during the night in order to take a deep breath.



4. Physical discomfort

During pregnancy, physical discomfort caused by nausea and vomiting, contractions, musculoskeletal pain and the need to urinate more frequently during the night, makes falling asleep more difficult, and the sleep is much more fragmented. These disruptions often persist into the post-partum period, as caring for a newborn is demanding. These changes in sleep patterns can continue even after the baby's sleep pattern has regulated and influence the parents' sleep quality for years.

Why Is Insomnia During Pregnancy Important?

1. Pregnancy outcome

Insomnia during pregnancy is associated with obstetric complications including miscarriages, pre-term birth, low birth weight, the need for blood transfusion, sepsis, pulmonary edema, thrombotic events, gestational diabetes and higher rates of caesarean section.

2. Mood disorders

Insomnia is associated with a higher prevalence of anxiety and mood disorders including post-partum depression. Moreover, children of mothers who experience mood disorders post-partum may face mental health challenges and struggle academically in later life.

How to Treat Insomnia Safely During Pregnancy and Post-Partum

Treating insomnia during pregnancy and breastfeeding can be challenging since medications may affect the growing fetus and the newborn. Over-the-counter antihistamines that are sometimes used as self prescribed medication for sleep may impact the quality of sleep and may cause additional fatigue. Other medication should only be use after discussion with an obstetrician, weighing the balance of pros and cons.

The safest and most effective approach is Cognitive Behavioural Therapy (CBT–see Facet 2), a type of therapy that helps improve sleep without medication. With the guidance of a professional therapist, CBT can offer significant relief in a relatively short time, benefiting both the parent and baby. Research has shown that CBT for insomnia during pregnancy not only improves sleep but also reduces symptoms of anxiety and depression. In addition, when CBT is provided for insomnia during pregnancy, it prevents postpartum insomnia. Accordingly, it is important to offer CBT for women with insomnia as early as needed during pregnancy in order to improve sleep in the whole perinatal period.

Take-home message:

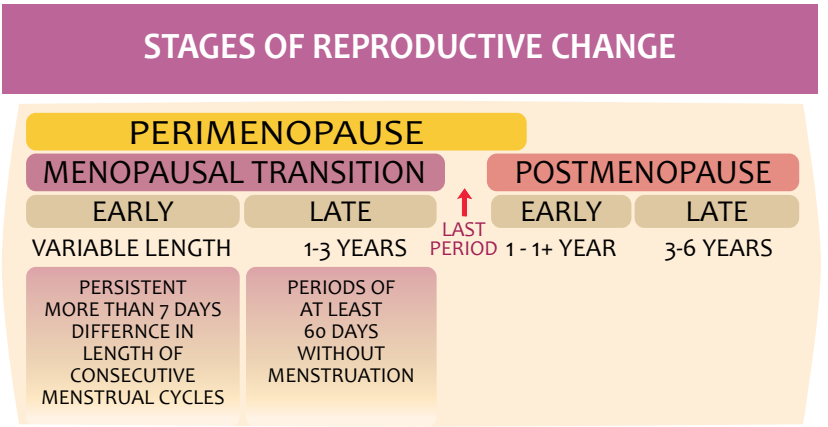
Insomnia is a common issue during pregnancy and post-partum. It is caused by hormonal and physiological changes. It is essential to address this problem, as it can affect both the parents' health and the baby's development. If you're struggling with sleep, reach out to your doctor or a sleep specialist to explore safe and effective treatment options.

B Insomnia in the Perimenopausal Period

Features and Contributing Factors

Perimenopause is a transition from the late female reproductive stage to end of the first year after the last menstrual period. This phase is characterized by noticeable changes in the menstrual cycles as well as fluctuation and eventual cessation of ovarian hormone production.

The interrelated biological, psychological and social changes that women may experience during menopausal transition increase the risk for insomnia via both direct and indirect pathways.



Approximately 50% of women experience insomnia symptoms during perimenopause. The most common features of insomnia during the menopausal transition are difficulty with maintaining sleep and early morning final awakening. Women who have had insomnia in past are more likely experience insomnia symptoms in the perimenopausal period. It is important to take these symptoms seriously because chronic insomnia can impact mood and cognition as well as lower the threshold for joint and muscle aches and pains–issues that are often described as perimenopausal symptoms.

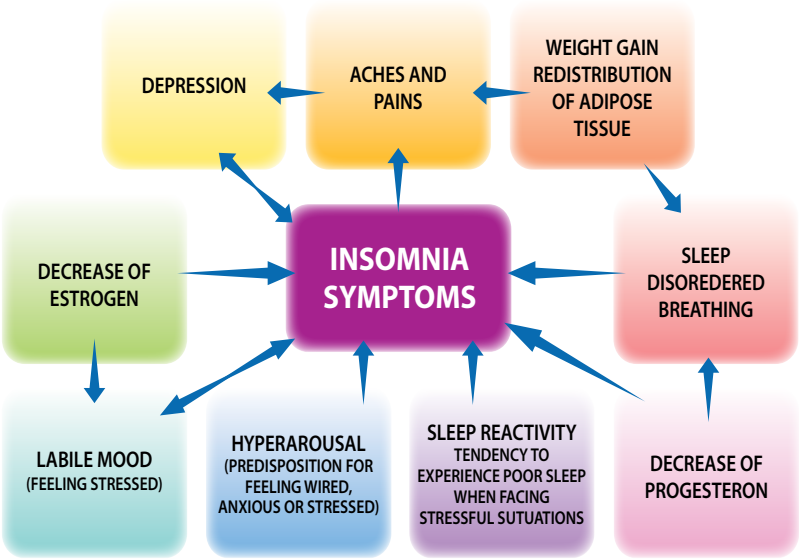
Diagnosis

Insomnia symptoms may be mild and do not significantly disrupt sleep or impact daytime well being. Questionnaires, for example the Insomnia Severity Index, are useful tools to help determine if the insomnia symptoms are clinically significant and likely meet criteria for chronic insomnia disorder (see Facet 3, page 26). Standard sleep diaries (for example, the Consensus Sleep Diary) provide more detailed information and can aid diagnosis.

Biological, psychological and social changes that contribute to insomnia in the perimenopausal period

Biological	Direct	Indirect
Decrease in estradiol	Estrogen binds to receptors in brain areas that are involved in sleep and circadian regulation and it has a sleep promoting effect. Decline in estrogen could impact sleep and the circadian rhythm of sleep-wake cycles.	Estrogen influences neurotransmitter pathways (serotonin, dopamine) that are involved in the pathophysiology of sleep and depression. Estrogen has an important role in thermoregulation and its decline causes vasomotor symptoms which may be distressing and contribute to insomnia.
Decrease in progesterone	Progesterone has a sedative effect via its metabolites facilitating the activity of GABA receptors in the central nervous system. Decline in progesterone may decrease the activity of sleep-promoting neurocircuits.	Progesterone stimulates respiration. Decline in progesterone may contribute to increased risk for sleep apnea, which, in turn can cause insomnia symptoms.
Decrease in melatonin	Decrease of melatonin production and/or the time-nightly melatonin release by the brain can change sleep and wake rhythm .	
Weight gain and/or redistribution of adipose tissue		Increased risk for sleep apnea, which, in turn can cause insomnia symptoms.
Social	**Direct**	**Indirect**
Taking care of teenagers and/or aging parents	Change in bedtime and rise time because of caregiver duties	Stress, worry and/or anxiety can trigger and maintain insomnia
Living alone after children moved out or separation from partner		Feeling lonely and having difficulty coping with this life transition may contribute to depression, which can lead to insomnia.
Psychological	**Direct**	**Indirect**
Stress related to vasomotor symptoms, weight gain, sleep problems, sexual changes, life transitions or other issues	Stress can trigger and maintain insomnia	
Depression	Insomnia can be a symptom of depression	Changes in activities as well as bedtime and rise time can worsen sleep and maintain insomnia when one has depression.
Worry and anxiety	Worry and anxiety can trigger and maintain insomnia	Conditioned arousal (even if there is no acute worry or anxiety) can maintain insomnia.

CONTRIBUTING FACTORS TO INSOMNIA IN THE PERIMENOPAUSAL PERIOD



Habitual early morning final awakening in the peri and post menopausal period can indicate a shift in circadian rhythm. If the sleep diary shows that the typical sleep phase (sleep onset and wake time) is unusually early, it is important to consider the possibility of circadian rhythm sleep wake disorder, advanced sleep phase type, which requires special diagnosis (dim light melatonin onset test) and treatment (see page 34).

The prevalence of sleep related breathing disorders (for example, obstructive sleep apnea) also increases during the menopausal transition. These conditions can cause or worsen nighttime and daytime insomnia symptoms. Screening for sleep apnea is important during medical visits in the perimenopausal period with special attention to snoring, frequent nighttime urination, weight gain, excessive daytime fatigue or sleepiness and mood problems.

Treatment

The first-line recommended treatment for insomnia disorder in the perimenopausal period is cognitive behavioural therapy (CBT) for insomnia (see Facet 2). This treatment is effective even when other medical and psychological issues are present. Importantly, there is a higher rate of insomnia in women who find the vasomotor symptoms distressing – i.e. not only the night sweats but also the distress associated with them can maintain insomnia.

CBT for insomnia helps to mitigate the stress related to night sweats and can be combined with CBT or mindfulness-based treatments to help adjustment to physical, emotional and functional changes in the menopausal transition.

Second line options are sleep medications that are approved for the treatment of insomnia (see Facet 6) taking women's preferences, age, the features of insomnia and comorbid conditions into account.

Menopausal hormone therapy (MHT) is an effective treatment for vasomotor symptoms (hot flashes and night sweats). Research studies testing if MHT improves sleep have shown mixed results: about half of high-quality studies have shown that MHT ameliorates insomnia symptoms, while other rigorous studies did not detect a beneficial effect. There is also insufficient evidence to support that MHT would improve sleep-related breathing disorders in the perimenopausal period.

Referral to an insomnia specialist is warranted if symptoms do not sufficiently improve after evidence-based treatments have been implemented. Furthermore, referral is recommended if there are symptoms that may warrant special consideration, for example, unusually early or late sleep onset and wake time, excessive sleepiness, or other symptoms that may indicate a presence of circadian disorders, sleep apnea or other comorbid sleep disorders.

Resources

The Insomnia Specialty Clinic at Sleep on the Bay (sleeponthebay.ca) offers educational sessions about sleep for women who are going through menopausal transition. The clinic also provides CBT for insomnia, dim light melatonin onset test, as well as treatment of circadian rhythm sleep-wake disorders (see Facet 6).

FACET 6
Pharmacotherapy for Insomnia

According to the International Classification of Sleep Disorders, third edition (ICSD-3), pediatric and adult insomnia have been classified as a single entity as "chronic insomnia disorder". It is generally advisable to rule out other sleep disorders before suggesting behavioural modification therapy. Sleep disorders other than insomnia may precipitate and perpetuate its course. A sleep study is recommended based on the clinical presentation and a thorough patient history. Insomnia may be exacerbated by another sleep disorder such as obstructive sleep apnea (OSA), restless legs syndrome (RLS), periodic leg movement disorder (PLMD) and comorbid medical (including psychiatric) disorders. In the adult population, an estimated 30% to 50% of people with OSA complain of sleeplessness or insomnia. Clinicians may encounter patients with untreated sleep apnea who complain of waking up in the middle of the night gasping for air, leading to sleep disturbance. Patients who have experienced numerous "choking" episodes in sleep may, not surprisingly, become anxious about going to sleep at night. Approximately 30% of older individuals previously diagnosed with insomnia were shown to have significant OSA. In addition, it is important to differentiate sleep disturbance due to Delayed Sleep Wake Phase Disorder (DSWPD) and insomnia – the former presents as insomnia when sufferers are forced to maintain socially acceptable sleep scheduling (i.e. earlier than their natural circadian rhythm). When other medical and sleep disorders have been evaluated, pharmacological intervention may be considered. In general, cognitive behavioural therapy for insomnia (CBT-I) is viewed as the first choice, it is not sufficiently available. We live in an exciting time when newer and safer sedative-hypnotic medications are being developed and have been successfully introduced to the market.

Indications for Pharmacological Management of Insomnia

Insomnia has been linked to a plethora of problems including: obesity, reduced cognitive ability, impaired global executive functioning, emotional

fluctuations as well as negative internalizing and externalizing behaviours (including suicidality). These issues may worsen psychiatric disorders, result in impaired learning, poor work performance, more frequent risky behaviours and negative long-term health consequences. Identifying and treating mental health conditions and other sleep disorders that occur alongside insomnia is the best management strategy.

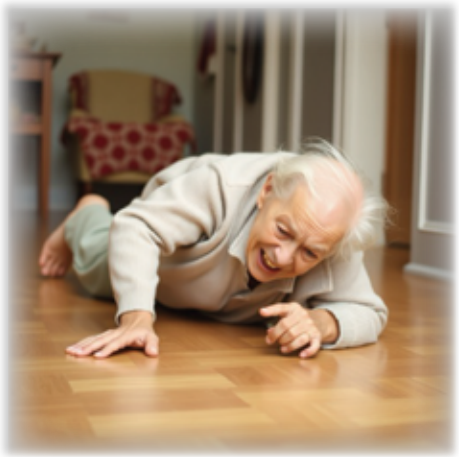
It is important to treat insomnia as a distinct syndrome and to work with patients to develop clear, achievable treatment goals. This includes the use of evidence-based questionnaires, such as the Insomnia Severity Index, Pittsburgh Sleep Quality Index or the Athens Insomnia Scale, to subjectively monitor sleep. Some may choose to objectively monitor and track symptom resolution via activity and sleep trackers, which is considered optional according to American Academy of Sleep Medicine guidelines currently. The primary goals of pharmacotherapy may include improved sleep quality as determined by subjective feelings upon waking, daytime functioning and total sleep time. A sleep diary or actigraphy (a device that looks like a watch and tracks when one is awake and when one is asleep) may be useful in gauging the course of treatment. When selecting a pharmacological option, one may consider the cost, comorbidities, other medications currently taken and potential contraindications. An optimal sedative-hypnotic medication should have a short time to reach therapeutic effect and a half-life that facilitates sleep maintenance, but does not result in next day grogginess. Both the clinician and the patient may work collaboratively with the mnemonic GRAPES: Goals of treatment, Responses of past treatments, Availability of other treatments, Patient preference, Experience of illness and Side effects (see graphic above).

What Pharmacological Options are Available For Insomnia?

Over-the-counter (OTC) Anti-Histamines

Antihistamines are a type of medication that can treat allergies, nausea and prevent motion sickness. First-generation antihistamines were launched in the 1940s and continue to be used today. They traverse the Blood-Brain-Barrier (BBB) and block the histamine receptors in the brain, and thus promote sleepiness. (Note: histamine is wake-promoting.) Antihistamines are not recommended as an insomnia treatment due to their undesirable anticholinergic side effects. Their efficacy is poor. Some of these drugs include: brompheniramine, chlorpheniramine, clemastine, cyproheptadine, dimenhydrinate and diphenhydramine.

Benzodiazepines



Benzodiazepines are the drug names that typically end in "pam". These are potent sedative-hypnotics that bind to a specific benzodiazepine site of the GABA-A receptor. These were widely used in the 60s and 70s, but rarely used as the first-line of treatment for insomnia. This is due to the risks of tolerance and addiction, anterograde amnesia (forgetfulness), cognitive impairment, impairment of balance and falls. Benzodiazepines, if taken for the long-term and at higher doses, should not be withdrawn abruptly due to the withdrawal syndrome which includes rebound insomnia and anxiety, and there is the possibility of death.

Some of the benzodiazepines include flurazepam, nitrazepam, temazepam, triazolam, quazepam, clonazepam, lorazepam, oxazepam, bromazepam and estazolam. Some, e.g. triazolam has triggered inappropriate behaviour that has led to court cases.

The Z-Drugs

Zopiclone, Zolpidem, Zaleplon and Eszopiclone are referred to as the "Z-drugs". Zopiclone is a cyclopyrrolone, which is chemically unrelated to the benzodiazepines and is thought to act on the GABA-A receptor complex at a site distinct from, but closely related to, the benzodiazepine binding site. Some patients may get an unpleasant taste when taking the medication. Milk or orange juice may help (by adjusting the pH in the mouth, one may make it worse and the other may be helpful). Adverse effects are more common with higher doses.

Zolpidem and zaleplon work in similar ways to zopiclone, but for shorter durations. Zaleplon particularly may be useful for shift-workers given that it usually only "works" for four hours. Eszopiclone, an isolated enantiomer of the racemic zopiclone, confers longer total sleep time, higher sleep efficiency and a better safety profile compared to zopiclone.

The Three Dual Orexin Receptor Antagonists (DORAs)

The newest sedative-hypnotic medications on the market are the three Dual Orexin Receptor Antagonists (DORAs). They include suvorexant, lemborexant and daridorexant. These medications for insomnia were recently approved by the Food and Drug Administration (FDA) in 2014, 2019, and 2022, respectively. Suvorexant (Belsomra) is no longer available in Canada. They work by antagonizing both orexin 1 and 2 receptors (OX1R and OX2R). Orexins, also known as hypocretins, are the main controlling neuropeptides that facilitate wakefulness. The DORAs block these receptors to effectively treat insomnia by reducing wakefulness (instead of increased sedation as with other agents). The main advantage of this class of medications is that

they have demonstrated efficacy in insomnia treatment (both in the short and long-term) but are better tolerated than traditional sedative-hypnotics. They do not appear to cause the same risk of falls, tolerance and addiction, cognitive impairment and next day grogginess compared to older agents. This group of medications is covered in more detail in the last "facet" of this book.

Tryptophan and Melatonin

L-Tryptophan is one of the nine essential amino acids (building blocks of protein) for humans and cannot be synthesized i.e. must be consumed. Two enzymatic reactions transform L-Tryptophan into serotonin, and two more enzymatic reactions convert serotonin into melatonin. There is evidence that tryptophan may treat insomnia and is particularly desirable for patients who prefer to take "natural" substances. It is limited by the rather large pill sizing and potential gastric upset. It can be used in children with good results. It needs to be taken with carbohydrates and no protein. Melatonin is a chronobiologic agent that regulates our circadian rhythm (body clock). It does not directly treat insomnia, but rather shifts one's sleep phase timing and stabilizes the sleep-wake cycle. Both tryptophan and melatonin have been used in treating insomnia in children and adults. Using melatonin to treat insomnia is akin to using insulin or thyroid hormone to reduce weight. Melatonin is best suited to treating abnormal shifts in the body clock such as in Delayed Sleep Wake Phase Disorder, where one's natural sleep and wake times are abnormally late. European guidelines suggest trialing extended release melatonin for older adults with insomnia. However, it is important to note that melatonin in Europe is by prescription only, whereas it is over-the-counter (OTC) in North America, leading to problems with potency, and there are brands of melatonin that have cannabis in them (without any indication). Experts in this area do not think melatonin is a good option as a sleeping aid. It is excellent if there is only a body clock problem. The optimal time to take melatonin is 2-6 hours before bedtime.

Precautions With Pharmacotherapy for Insomnia

Insomnia medications are not recommended during pregnancy or breast feeding. Sedative-hypnotics are typically not used in patients under 18 years of age. Patients should be cautioned about risks for falls, cognitive impairment, grogginess and tolerance as appropriate.

The Z-Drugs (Non-Benzodiazepine Hypnotics)

DRUG NAME	MECHANISM OF ACTION	DOSAGE	COMMON ADVERSE EFFECTS
Zolpidem* (Sublinox)	Imidazopyridine hypnotic that is a selective agonist at benzodiazepine-1 (BZ1) receptor resulting in inhibition of action potentials and neuronal excitability.	Immediate release: 5-10 mg. Controlled release: 6.25-12 mg. To be administered immediately before sleep with planned 7-8 h in bed.	Diarrhea, nausea, dizziness, drugged state, somnolence, visual disturbances.
Zopiclone* (Imovane)	A cyclopyrrolone which is chemically unrelated to the benzodiazepines and is thought to act on the $GABA_A$ receptor complex at a site distinct from, but closely related to, the benzodiazepine binding site. Insomnia in the adult population.	**Adults: Oral route:** Usual dose is 7.5 mg. Range is 3.75 to 15 mg. 5 mg tablets available. Administered immediately before bedtime. **Elderly:** Aged over 65 years old. Usual starting dose is one zopiclone low-strength (LS) tablet (3.75 mg) or half a full-strength (7.5 mg) tablet just before bedtime. May be increased to 7.5 mg. **Patients with liver or kidney conditions:** One zopiclone low-strength (LS) tablet (3.75 mg) or half a full-strength (7.5 mg) tablet just before bedtime.	Headache, nausea/emesis, disorder of taste (unpleasant taste), dizziness, somnolence, migraine, increased respiratory infections. Minimal impairment to psychomotor performance and mental alertness the morning after night-time administration. Adverse effects are more common with higher doses e.g. 11.5-15 mg.
Eszopiclone* (Lunesta)	S-stereoisomer of zopiclone. Unknown MoA, but thought to be secondary to its interaction with $GABA_A$-receptor complexes close to benzodiazepine receptors.	**Oral route:** 1-3 mg. To be administered immediately before bedtime.	Headache, nausea/emesis, disorder of taste (unpleasant taste), dizziness, somnolence, migraine, increased respiratory infections.
Zaleplon* (Sonata)	Binds selectively to brain alpha subunit of $GABA_A$ omega-1 receptor.	**Oral route:** Dose range typically 10 mg, range 5-20 mg. To be administered immediately before bedtime or with 4 h of time in bed remaining.	Abdominal pain, nausea, headache, dizziness, somnolence, paresthesia, dysmenorrhea, eye pain.

* Contraindicated in patients with hypersensitivity or those who have experienced complex sleep behaviours after taking zolpidem, eszopiclone or zaleplon. Also contraindicated in patients with myasthenia gravis, severe liver and renal diseases. The Z-drugs are primarily indicated for insomnia in the adult population.

Benzodiazepine Sedative-Hypnotics

DRUG NAME	MECHANISM OF ACTION	DOSAGE	COMMON ADVERSE EFFECTS
Flurazepam* (Dalmane)	Binds to benzodiazepine site of the $GABA_A$ receptor.	**Oral route:** Dose range typically between 15-30 mg daily at bedtime. Indicated for insomnia (short-term treatment) in the adult population.	Metallic taste, ataxia, dizziness, lethargy, sedation, somnolence, apnea, blurred vision. Benzodiazepines should not be withdrawn abruptly**
Temazepam* (Restoril)	Binds to benzodiazepine site of the $GABA_A$ receptor.	**Oral route:** Dose range typically between 7.5-30 mg daily before bedtime. Indicated for insomnia (short-term treatment) in the adult population.	Hypotension, somnolence, blurred vision. Benzodiazepines should not be withdrawn abruptly**
Triazolam* (Halcion)	Binds to benzodiazepine site of the $GABA_A$ receptor.	**Oral route:** Dose range typically between 0.125-0.5 mg daily before bedtime. Indicated for insomnia (short-term treatment) in the adult population.	Dizziness, nervousness, headache, somnolence, lightheadedness. Benzodiazepines should not be withdrawn abruptly**
Clonazepam* (Ceberclon or Klonopin)	A long-acting and high-potency benzodiazepine. Behaves as a $GABA_A$ receptor agonist. It also has serotonergic activity by increasing serotonin synthesis. Has anti-convulsant and anxiolytic effects.	Clonazepam is available as an immediate-release tablet of 0.5 mg, 1 mg, 2 mg, and orally disintegrated tablets (ODT) of 0.125 mg, 0.25 mg, 0.5 mg, 1 mg and 2 mg strength.	Lethargy, fatigue, sedation, drowsiness and motor impairment (impaired coordination, impaired balance, dizziness). Benzodiazepines should not be withdrawn abruptly**

* All benzodiazepines can have teratogenic effects and should not be used in pregnancy.
** Benzodiazepines should not be withdrawn abruptly because it can be dangerous and lead to life-threatening symptoms. Withdrawal symptoms can include: headache, muscle pain, restlessness, stomach pain, trouble sleeping, confusion, psychosis, seizures, rapid heartbeat and sweating. Before starting or discontinuing these medications, please consult with a medical professional.

THE THREE DUAL OREXIN RECEPTOR ANTAGONIST (DORAs) THAT ARE FDA APPROVED TO TREAT INSOMNIA

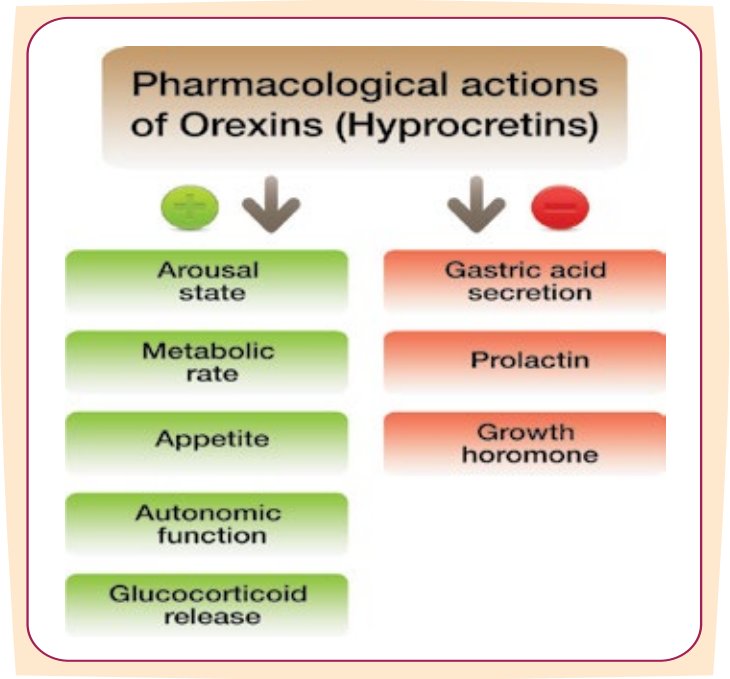
MEDICATION	Suvorexant (Belsomra)	Lemborexant (Dayvigo)	Daridorexant (Quviviq)
General Information and Mechanism of Action	The first agent of its class to gain U.S. FDA approval in 2014. No longer manufactured or available in Canada. Blocks the binding of neuropeptides (orexin A and B) that promote wakefulness. Dual Orexin 1 and 2 Receptors (OX1R and OX2R) antagonist.	Approved for insomnia in December 2019. Binds to both orexin 1 and 2 receptors (OX1R and OX2R), with a greater affinity to OX2R. May be more effective than suvorexant at improving sleep duration and onset. May cause fewer side effects than suvorexant, especially early in treatment.	Approved for insomnia in January 2022. Binds to both orexin 1 and 2 receptors (OX1R and OX2R) at an almost equal affinity. **Lemborexant vs. Daridorexant:** Efficacy: lembo > darido Tolerability: darido > lembo Improves sleep onset, maintenance, WASO, time parameters, daytime functioning in adult and elderly patients. Generally well tolerated.
Half-Life (t1/2)	12 hours	17 to 19 hours	8 hours
Dosing (adult dosing unless specified)	10, 15 or 20 mg once daily, at least 30 minutes before bedtime.	5 or 10 mg taken once daily before bedtime.	25 or 50 mg taken once daily before bedtime. The most effective dose: 50 mg.
Precautions and Contraindications (in general)	May cause abnormal thinking, behavioural changes, amnesia, CNS depressant effects, daytime impairment, complex sleep behaviour, sleep paralysis, hallucinations, cataplexy-like symptoms, worsening depression and suicidal ideation, daytime somnolence, headache, dizziness and abnormal dreams. May increase risk of falls in elderly. Not recommended in patients with severe OSA and COPD.	May cause abnormal thinking, behavioural changes, amnesia, CNS depressant effects, complex sleep behaviour, sleep paralysis, hallucinations, cataplexy-like symptoms, worsening depression, suicidal ideation and daytime impairment. The effectiveness is decreased if taken with food, particularly for sleep onset.	May cause CNS-depressant effects, daytime impairment, sleep paralysis, hallucinations, cataplexy-like symptoms, worsening depression, suicidal ideation, complex sleep behaviours, nasopharyngitis and headache. May have additive effects when used concomitantly with CNS-depressant medications.

* The DORAs do not need to be tapered and can be discontinued abruptly because rebound insomnia and withdrawal symptoms do not occur. Patients considering taking these drugs must consult with experts. They are not recommended during pregnancy or breastfeeding. OSA = obstructive sleep apnea; COPD = chronic obstructive pulmonary disease; CNS = central nervous system; WASO = wake after sleep onset.

FACET 7

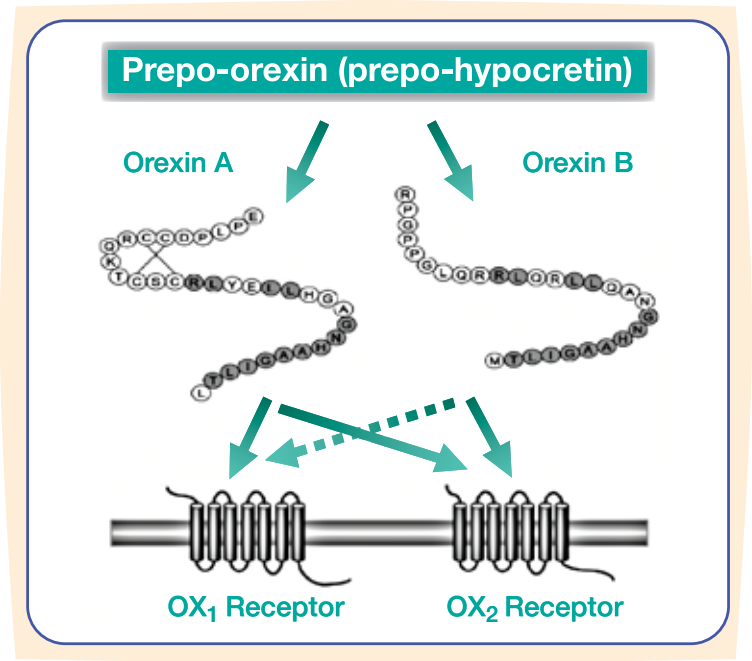
New Medications Orexin Antagonists for Insomnia

Since the orexins (also known as hypocretins) were discovered simultaneously by two different research groups in 1998, extensive studies have demonstrated the anchoring role of the orexin system in numerous basic biological processes. This system projects widely into the entire central nervous system, prominently targeting brain structures involved in the regulation of wake-sleep state, appetite, feeding, pain, cardiovascular function, neuroendocrine regulation and energy expenditure. A summary of its major effects is described in the figure below.



The orexin system consists of neuropeptides orexin A and B (OX-A/B, also called hypocretin 1 and 2) which are produced from a common precursor peptide, prepro-orexin. They are released selectively by a population of neurons localized in a small area of the brain (the lateral hypothalamus). This is a region that is known to orchestrate diverse functions such as sleep, reward processing, food intake, thermogenesis and mood.

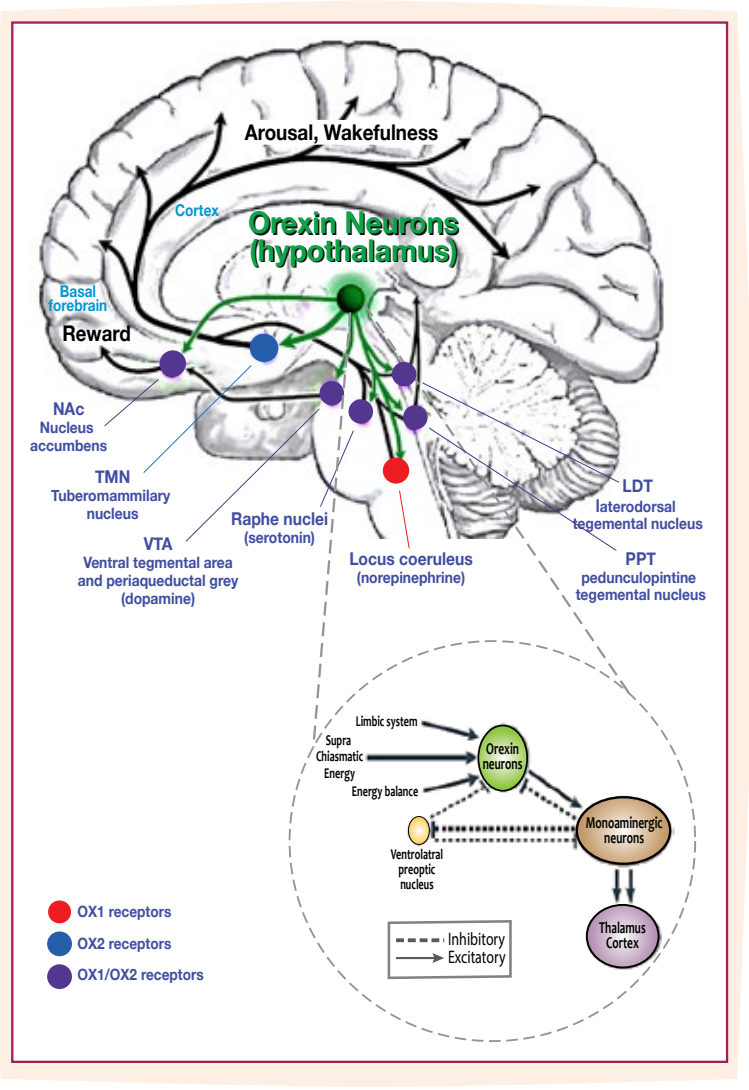
There are also two orexin receptors which the orexin peptides bind to the orexin 1 (OX1R) receptor, which is primarily involved in motivation and reward, and the orexin 2 (OX2R) receptor involved primarily in the modulation of sleep/wake cycle and energy homeostasis. Orexin A exhibits similar affinity for both orexin receptors, whereas orexin B displays a selective affinity for the orexin 2 receptor.



The structure of orexins and their genes are highly conserved throughout mammals, suggesting a strong evolutionary pressure that has maintained these mechanisms. The orexin system appears to have evolved as a system that supports active and purposeful behaviour that is closely related with wakefulness. Orexin neurones are activated during high vigilance states which require increased arousal such as exploratory behaviour and sensory or emotional stimulation. They are also highly active during wakefulness and stop firing during sleep. These neurons also receive direct inputs from

brain areas involved in sleep/wake control, appetite control and reward (see figure below). It is well known that absence of orexin-producing neurons or very low levels of orexin in the cerebrospinal fluid results in a form of narcolepsy, a disorder with a lack of arousal and wakefulness (excessive daytime sleepiness) and disruption in shifts between stages of sleep and wake (the previous booklet in this series is on Narcolepsy).

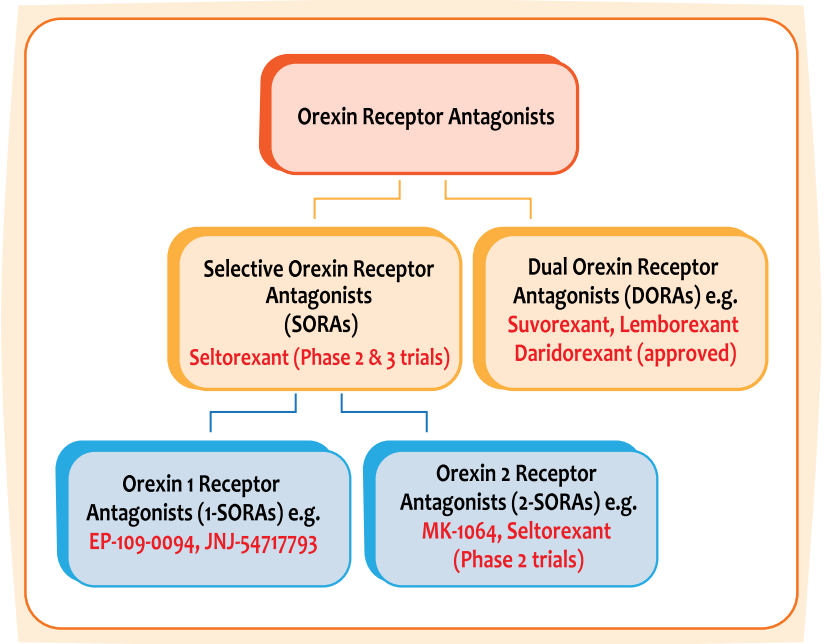
The Interconnections of the Orexin System



Given its central role in a number of biological processes, the orexin system holds much promise as a therapeutic target of treatment for a variety of difficult-to-treat maladies. Obesity, disorders of hyperarousal, substance abuse, migraine headache, pain, neurodegenerative disorders, and depression have all been postulated to have potential treatments through modulation of the orexin system.

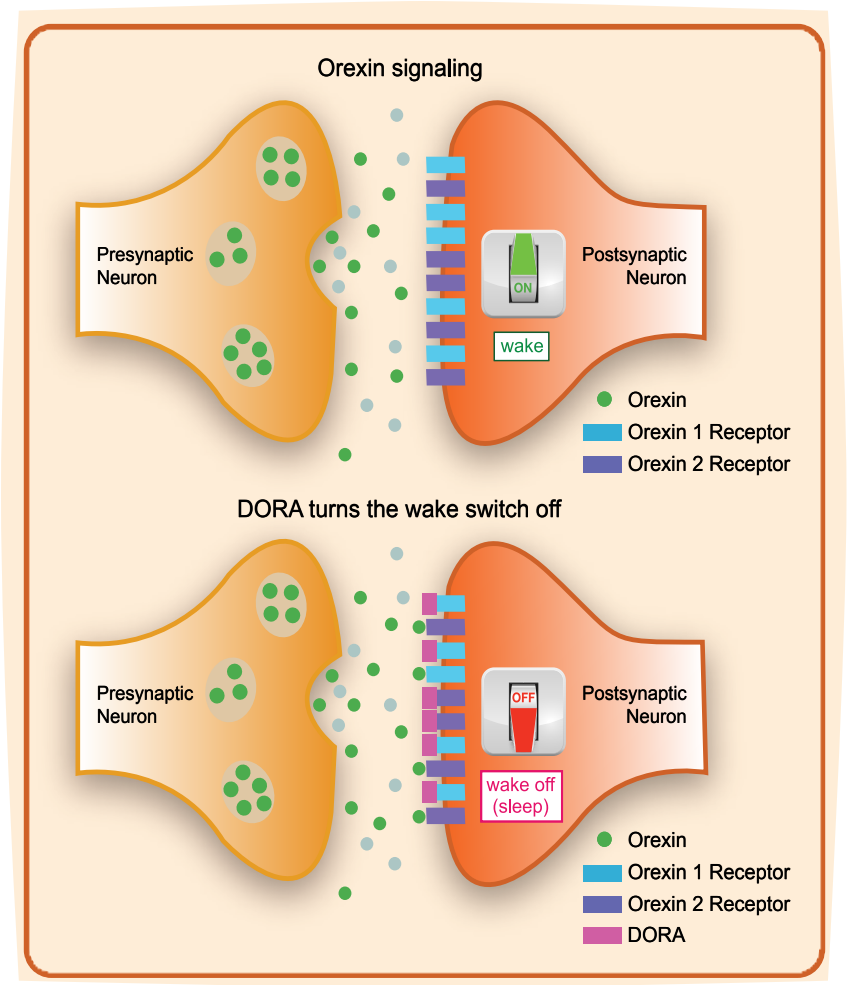
Currently, only the sleep/wake system has been targeted successfully by clinical drug development. There appears to be a greater sleep-promoting effect with antagonism of Ox2R, and Dual Orexin Receptor (Ox1R & Ox2R) Antagonists (DORAs) than with Ox1 antagonists. These antagonists may have a role in obesity, drug addiction and panic disorder, but none are currently on the horizon for treatment.

Three DORA molecules, daridorexant, suvorexant and lemborexant, have been approved for clinical use and are indicated for insomnia treatment. An agent with significant orexin-2 receptor selectivity only (seltorexant) is in the later stages of development and may be commercially available for insomnia or comorbid insomnia and depression treatment soon. The DORAs exert their therapeutic effects by binding to and blocking both orexin receptors for a limited period, thereby temporarily inhibiting the wakefulness promoting effects of the orexin system.



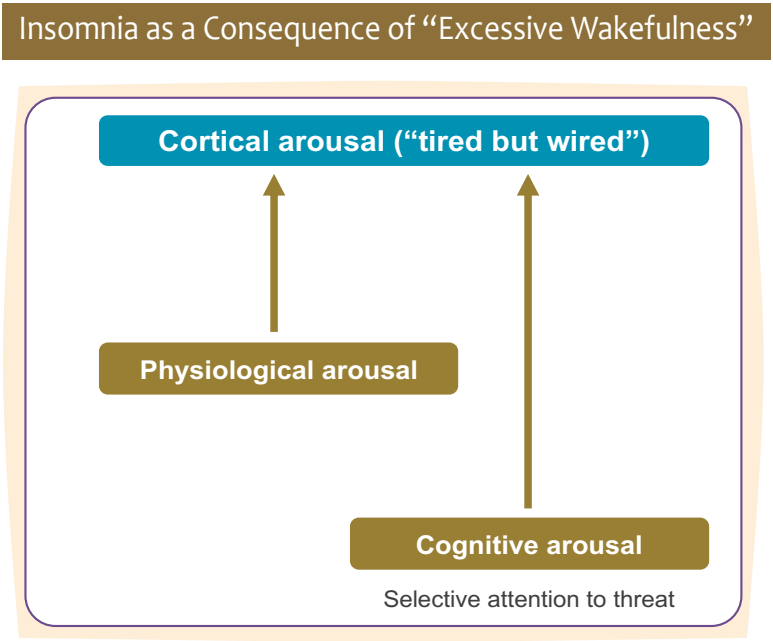
Lemborexant appears to bind more preferentially to OX2 and appears to disassociate from the OX2 receptor quicker than suvorexant. Daridorexant appears to bind in a balanced fashion to OX1 and OX2. This difference in binding could be the genesis of separate response patterns . It also indicates that response to one DORA does not predict response to the entire class. None of the agents appears to affect the myriad of other neurotransmitters involved in sleep and wake, making them unadulterated wake blocking agents.

DORAs agents turn the wake promoting effects of Orexins off

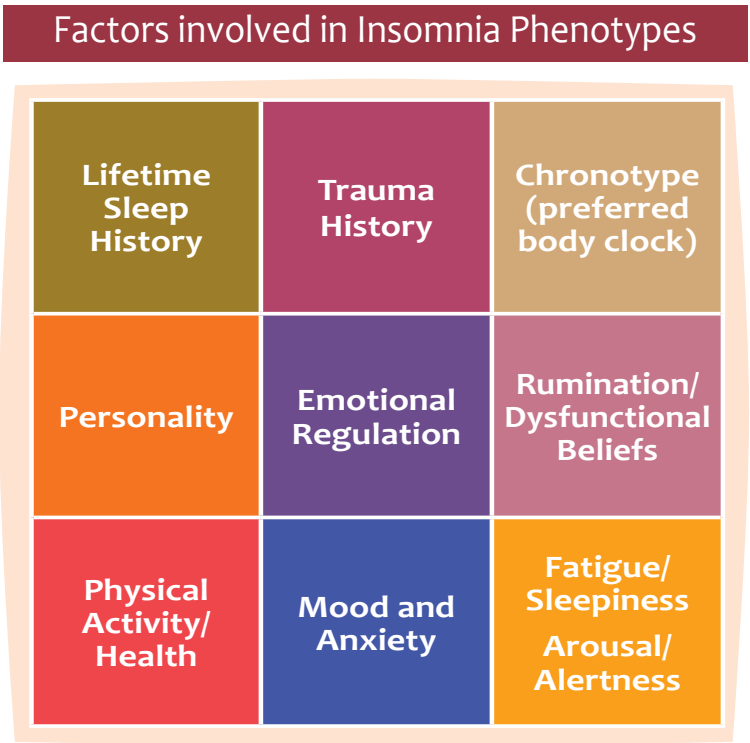


The sleep wake cycle is known to be a complex balance between competing and overlapping neurotransmitter systems. Traditional pharmacological treatments for insomnia, such as benzodiazepines and the partial benzodiazepine agonist Z-drugs, have had their effects through the inhibitory GABA system to promote sleep or "switch on" sleep circuits. They are well known for their potential but somewhat overstated side effect profile of potential addiction, tolerance, memory issues, falls and next day impairment. However, it is important to note that for a certain subset of properly assessed patients with follow up, these drugs can be a reasonable strategy for sleep despite the plethora of bad medical press, stigma and unrealistic draconian prescribing restrictions in some jurisdictions.

This polarized view of these drugs is also missing the larger issue that types of insomnia pathophysiology are simply not being addressed by the limits inherent in the "sleep promotion" paradigm. Evidence is accumulating that hyper-arousal (physiologic and cognitive) may play an equal, if not greater, role in insomnia and reducing this arousal by suppressing inappropriate wakefulness may be critical to helping certain groups of insomnia patients. The underpinnings of CBT-I, the first line treatment for insomnia, are predominantly based around a reduction in hyper-arousal through combined strategies (see Facet 2).

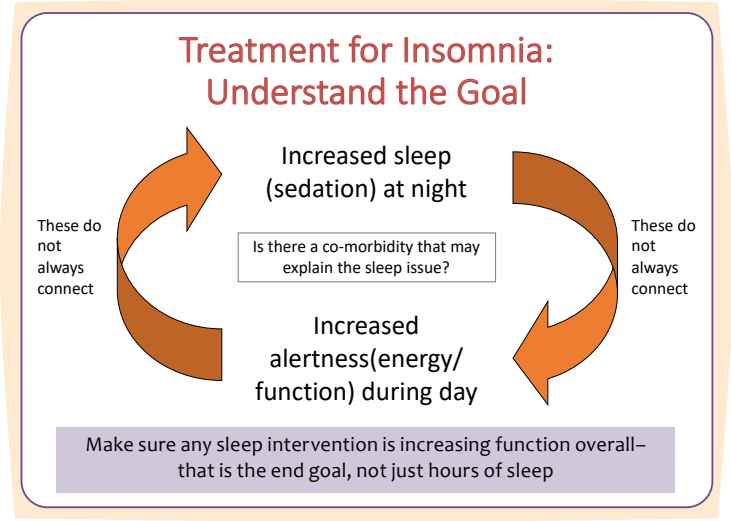


The lack of understanding of hyper-arousal or excessive wakefulness as a mechanism of insomnia stems to some degree from a historically unhelpful view of insomnia as a simple symptom. It is more accurately identified as a disorder with subsequent overlapping comorbidities and not a homogeneous construct. Patients with insomnia have been seen to deviate markedly with respect to a number of factors.

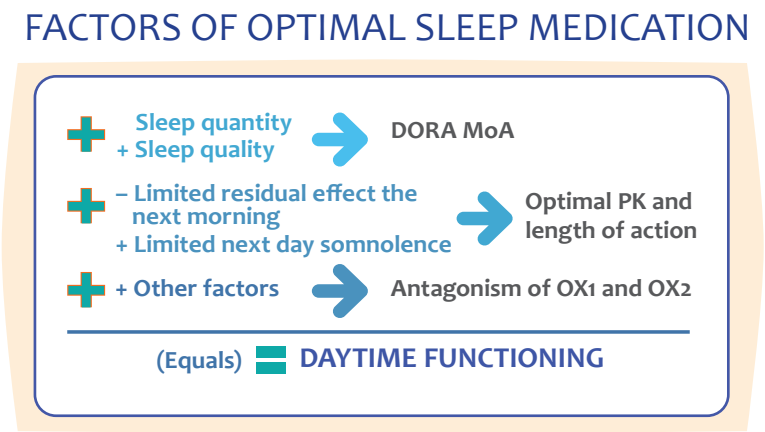


Given this wide variability, more nuanced views of differing insomnia phenotypes must emerge as a paradigm to improve treatment. Further research into subtyping groups and personalizing treatment using targeted behavourial therapies and pharmacological agents is needed. Understanding the concept of modulating wake and arousal versus the promotion of sleep when selecting a treatment is important. Also, any treatment, regardless of type or mechanism, should be assessed for net function the next day and not just for the overall hours of sleep generated. Excessive sedation is of no use if long term function and alertness is compromised. Targeting the wake system by modifying arousal pharmacologically may be a better strategy to target the core pathophysiology in many insomnia patients. Although there is limited data, a combination of mechanisms may also need to be

considered for resistant cases. Vigilance for the evolution of comorbidities should be ongoing as it is well known insomnia can be a risk factor or residual symptom of many disorders. Sleep not leading to increased function and alertness should be a key clinical clue that a comorbidity is present.



Prior to the release of the DORAs, the only approved pharmacological way to block wake was the limited histamine blocking effect of low dose doxepin. However, is likely that some off-label agents (i.e. trazodone, quetiapine) had elements of both wake-blocking and sleep-promotion through their mechanisms on the serotonin, histamine and catecholamine systems. With the DORAs, a much more central wake-inhibition mechanism can be pursued, offering another potentially more precise tool in insomnia treatment.



Suvorexant, lemborexant and daridorexant have all demonstrated significant improvements in multiple parameters of objective and subjective sleep in reasonably sized controlled trials in the short and long term (up to 12 months). Suvorexant was approved by Canadian regulatory bodies, but never commercially released in the country. Its usage is mostly limited to small groups in the US and Japan, hence it is not reviewed here. The differences between the more commonly used lemborexant and daridorexant are outlined in the tables on the next 2 pages.

Pharmacokinetic Properties and Drug Interactions

	LEMBOREXANT	DARIDOREXANT
Time to Peak (hrs)	1-3	1-2
Elimination Half-Life* (hrs)	17-19	8
Metabolism	Extensive: CYP3A	Extensive: CYP3A
Metabolites	M4 (minor, active), M9 (minor, active), and M10 (major, inactive) all P-glycoprotein substrates	M1, M3, and M10 (all inactive)
Elimination	57.4% feces, 29.1% in urine	57% feces, 28% in urine
Older Adults	Despite increased exposure, reported as not clinically impactful	
Pharmacokinetic	Alcohol 35% higher Cmax, 70% higher AUC	Not directly studied
	Strong CYP3A inducers concurrent use not recommended	
	Strong and moderate CYP3A inhibitors concurrent use not recommended	Strong CYP3A inhibitors concurrent use not recommended
Pharmacodynamic	Additive CNS depression - CNS depressants (e.g., hypnotics, alcohol)	

* Likely not directed to duration of action due to possible difference in antagonistic activity and OX1/OX2 binding

Dosing and Safety Considerations

	LEMBOREXANT	DARIDOREXANT
Dose	Initial: 5 mg once nightly Maximum: 10 mg once nightly	Initial: 50 mg once nightly Decrease to 25 mg if drug interactions or sensitivity
Administration	Within 30 minutes of retiring At least 7 hours prior to planned awakening	
In Older Adults	No dose adjustments unless a more cautious approach is needed	
Hepatic Impairment	Mild Liver Dysfunction: No adjustments Moderate Liver Dysfunction: Max 5mg Severe Liver Dysfunction: No data, not recommended	Mild Liver Dysfunction: No adjustments Moderate Liver Dysfunction: Max 25mg Severe Liver Dysfunction: No data, not recommended
Renal Impairment, not on dialysis	No dose adjustments Potential increase in somnolence in severe impairment	No adjustments
Concurrent Medications	3A4 inducers/inhibitors (dose to be adjusted depending on level) Caution with other CNS depressants for next day side effects	
Side Effects	Based on daily administration and at least 7 hours before planned awakening	
Common	Next day somnolence Abnormal dreams	None common from trials but clinically occasional next day somnolence and abnormal dreams
Uncommon	Nightmares	Nightmares
Rare	Sleep paralysis, hallucinations	
Contraindications	Patients with Narcolepsy Hypersensitivity to the drug or any component of the formulation Concurrent CVP3A4 inhibitors depending on potency	

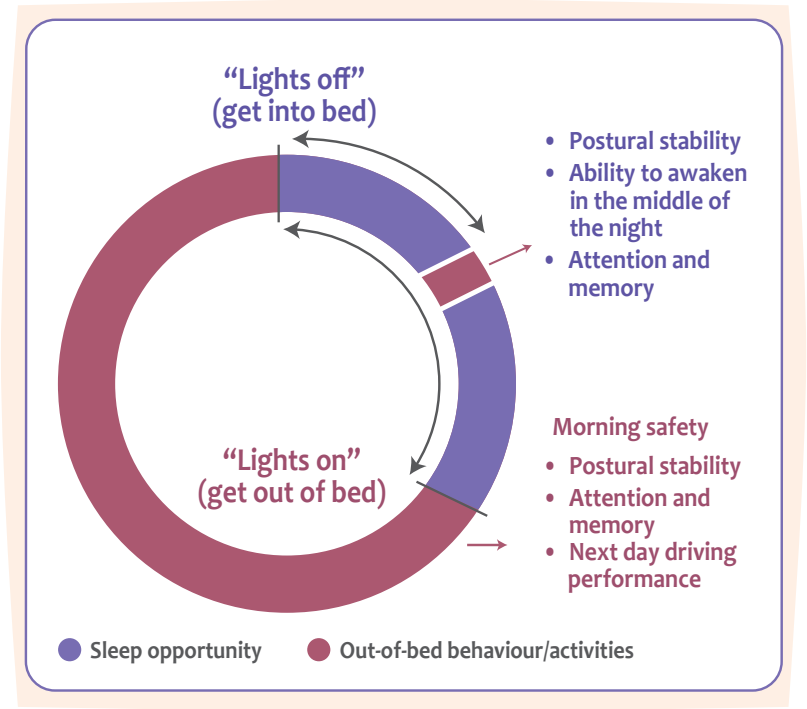
Study designs that included comorbid insomnia patients (up to 75-80% of people have insomnia with at least one significant comorbid condition) make both lemborexant and daridorexant data more clinically relevant. The lack of tolerance, withdrawal and rebound insomnia with both agents is also a key advantage to previous insomnia medications.

There are limited direct head-to-head data for DORAs with other approved sleeping medications. However, in the most recent systematic indirect meta-analysis of approved agents for comparing insomnia treatments, the DORA's demonstrated superior efficacy and tolerability.

Intermittent use of medications for sleep is common for people with milder degrees or residual insomnia. Although there are no documented studies on the intermittent use of DORAs, efficacy after early use has been clearly seen. However, clinical experience with the DORAs indicate that they may function as more of a central sleep-wake stabilizer rather than an acute sedative. Patients may feel differently when they fall asleep in contrast to previous experience with sleep promoting sedatives. A number of days (10-30) may be required with many patients to see the true wake-blocking effect of the DORAs, and it is important to counsel patients about this, especially if they have been on other sleep promoting drugs in the past or have pre-determined expectations

The acute tolerability and safety profile of the DORAs are also advantages compared to traditional sleep promoting agents. Limited self-reported next-day effects were seen in controlled trials with only excess somnolence with lemborexant reported at a consistently greater rate than a placebo. Daridorexant did not show increased somnolence versus placebo in the clinical trials, but has still been seen occasionally in clinical usage. This is unsurprising as any medication that facilitates sleep or blocks wake may cause this excessive sleepiness on occasion in predisposed individuals. Differences in selectivity and dissociation from the OX1R and OX2R receptor may underlie the differences in efficacy and tolerability between daridorexant and lemborexant.

Both DORAs showed no impairment in the ability to awaken from auditory stimuli, which is a proxy for allowing patients to awaken to pertinent nocturnal noise in the environment. Neither DORA marketed has been seen to worsen respiratory depression or sleep apnea but this finding is also noted with therapeutic doses of the sleep promoting Z-drugs. Postural stability and fall risk is a known issue with traditional sleep promoting agents, although the rate is often in keeping with a number of other non-insomnia drugs that are commonly used. Insomnia itself can increase the risk of falls, so a cost-benefit assessment needs to be made with prescribing all sleep promoting medication. Without treatment patients often resort to a myriad



Safety issues can arise from insomnia; they can also arise from OTC products and other substances used to promote sleep.

of OTC sleep agents, cannabis or drink alcohol, leading to even more deleterious side effects. The DORAs are likely advantageous with respect to falls as no signal for an increased fall risk or troublesome postural stability has been seen. On average, measured objective driving safety was not seen to be compromised with either DORAs at 9 hours, but individuals may have issues at higher doses or with shorter time frames.

The Canadian recommendation is to have a 7 hour period for sleep before taking either DORA which contrasts with 8-12 hours for the Z-drugs. The source of broad recommendations based on driving studies are limited as they are usually not done on patients with insomnia. For example, partial mitigation of the Z-drugs on driving performance has been seen over time. Patients must be counseled about these potential safety issues, but again an individual cost-benefit assessment must be done rather than simply not pre-

scribing sleeping medication because the number of hours cannot be always met. More stringency may be needed for professional or commercial drivers in this regard.

Although intuitively a medication with wake-blocking effects could be added to a sleep-promoting drug, this has not been studied and caution is advised when prescribing DORAs with other CNS depressants due to the potential for additive side effects. However, some recently published clinical case series have shown good effect for both DORAs in populations with other psychotropic medications and a large number of people in the DORA trials were on stable doses of concomitant medications. Alcohol is not recommended to be taken with any sedative and increased negative effects on cognition have been seen with addition of alcohol to the DORAs. There has been recent warranted attention on sleep medications (zopiclone and zolpidem) leading to complex sleep-related behaviours such as walking, eating and other activities (especially when combined with alcohol) and although there are warnings for this with the DORAs, no consistent signal and very few case reports have been seen.

In terms of practical prescribing, the DORAs can be taken with or without food around 15-30 minutes before bedtime, but a large meal may delay absorption. Drug interactions are few and mostly centre around the cytochrome P450 3A4 system that metabolizes the DORAs. Moderate to strong inhibitors (verapamil, some anti-fungals, clarithromyicin) and moderate to strong inducers (modafinil, St. Johns wort, Tegretol) of the 3A4 system can potentially increase and decrease the levels of DORAs significantly and should not be used concomitantly. Dose adjustments may be needed if they are used, but higher than recommended doses have been used clinically without any overt deleterious effects. No DORA dose adjustments are needed for people with difficulties with the kidneys, and only a decrease in dose for moderate hepatic impairment (5 mg) with lemborexant. Neither drug was tested in people with severe liver problems.

The potential of abuse for DORAs was assessed to be low in animal models, and no evidence of medication diversion, rebound or tolerance has been seen in any study. There is always the potential of psychological dependence on drugs for insomnia. However, as mentioned previously, DORAs have no evidence of any significant binding on traditional receptors involved in dependence or abuse, hence chances are low that this will emerge chemically. Therefore, in Canada, lemborexant or daridorexant are not controlled substance, but both DORAs are restricted to some degree in the US, where they are considered as schedule IV drugs similar to benzodiazepines. Given the limited data, this categorization was likely a global class effect for sedatives.

There is a bright future for the DORAs, as one more agent is in the late stages of clinical development and there are a number of ongoing clinical trials with daridorexant and lemborexant in insomnia with various comorbidities. These include substance abuse, neurodegenerative disease and trauma-related as well as mood disorders. These trials will likely shed further light on what subtypes of insomnia that arousal reduction or wake-blocking may be useful for. Given the notable short and potential long term cognitive concerns with benzodiazepines and Z-drugs, looking at treating insomnia comorbid with neurodegenerative diseases appears to be a very logical step for the usage of DORAs. Furthermore, insomnia with any comorbidity that has a dysfunction of arousal as part of the disease mechanism (i.e. ADHD, chronic pain) could be a potential target.

The very limited effects on other receptors or neurotransmitter systems of DORAs may also increase clarity on exactly what orexin antagonism and wake-blocking can do in isolation. This will increase understanding of the separate contribution of insomnia to various disease states, as many substances (e.g. CBD/THC) and medications (e.g. quetiapine) used for insomnia may be helping sleep via the effect of actions on other receptors and/or treating comorbid conditions.

In conclusion, it is critical to both understand the importance of DORAs in pushing forward a new paradigm of insomnia while understanding that wake blockade will not be a universal panacea to facilitate sleep. Some patients will continue to be well-served with their current treatment regimens of sleep promoting drugs. Nonetheless, the orexin system and the use of DORAs will be valuable new tools in the clinical armamentarium for improving sleep. The safety and efficacy in current studies indicate that they should be considered first-line in the pharmacological treatment of insomnia. Hopefully this will also shape our understanding of insomnia and its basic physiological processes for years to come.

KEY FACET LEARNING POINTS:

- *Orexins are recently discovered neurotransmitters that play a role in regulating many basic bodily functions including wakefulness.*
- *The first clinical application is the introduction of dual orexin receptor antagonists (DORAs) that can block the wake system, treat insomnia and facilitate natural sleep.*
- *Insomnia needs to be thought of as a heterogeneous condition with multiple phenotypes and comorbidities. DORAs may improve sleep, alertness and function in previously untreatable phenotypes of insomnia that require blocking the wake system versus promoting sleep.*
- *Two DORAs, daridorexant and lemborexant (both available in Canada) have shown good controlled trial data to improve a number of sleep variables in insomnia. Response to one DOES NOT predict response to the other, and both should be sequentially tried.*
- *The DORAs appear to have a superior tolerability profile to traditional sleep promoting drugs, with only somnolence seen as a consistently common side effect. There is minimal daytime impairment, limited drug-interactions and no evidence of tolerance, withdrawal or rebound insomnia and low abuse potential or fall risk.* ***They should be considered potential first-line pharmacologic treatment for insomnia, especially chronic insomnia associated with hyperarousal.***
- *From clinical experience of the DORAs it is important to counsel patients that their experience from previous sedatives and their expectations may not link with the effects of these drugs. Although the DORAs can work quite quickly, a number of days to 3-4 weeks of treatment may be needed to establish their full effect.*
- *The introduction of DORAs does not preclude the fact that a significant proportion of people will still require other agents that facilitate sleep with certain comorbid conditions. These types of drugs should still be considered, especially for as-needed or short-term use. Stable patients who are functioning optimally on sleep promoting agents should be evaluated fully before aggressively switching to wake-blocking agents. Given the potential for rebound and withdrawal with some sleep-promoting drugs, cross tapering agents should be considered.*

Dr. Colin Shapiro has been a sleep researcher on three continents with a strong interest in sleep physiology and sleep disorders. He has published five academic books: CPAP Adherence-Factors and Perspectives; STOP THAT and One Hundred other questionnaires on Sleep; Forensic Aspects of Sleep; ABC of Sleep Disorders and Measuring Human Problems-A Practical Guide. Seven Facets of Insomnia is the 23rd booklet in this series for patients and physicians.

Dr. Dora Zalai had worked as a physician prior to earning her doctoral degree in psychology. She practices in clinical, health and rehabilitation psychology and is an expert in behavioural sleep medicine. She has established an Insomnia Specialty Clinic in Toronto which provides both sleep and circadian evaluation and treatment for people with insomnia symptoms. Her research has led to a new understanding to insomnia after concussion. She currently focuses on sleep issues in the peri-menopausal period.

Dr. Royi Gilad is an assistant professor at the Department of Psychiatry, Schulich School of Medicine & Dentistry, Western University, London, Ontario. He completed training both in psychiatry and child and adolescent psychiatry in Israel and a 3-year clinical fellowship in sleep medicine and neuropsychiatry at the Department of Psychiatry, Temerty Medical School, University of Toronto.

Dr. Noa Gilad completed her medical education and OBGYN residency in Israel, followed by a maternal-fetal medicine fellowship at the University of Toronto. During her fellowship, her primary research focused on sleep quality during pregnancy and the postpartum period, examining its implications for both maternal and fetal health.

Dr. Chris Kim is a clinical practitioner and researcher who works on a number of clinical sleep medicine research projects with the University of Toronto's faculty and staff. He completed clinical electives at Seoul National University in South Korea, the Medical University of Gdańsk in Poland and the University of Manitoba in Winnipeg. He has a keen interest in psychiatry and sleep medicine.

Dr. Michael Mak is a psychiatrist and sleep medicine specialist. He is an Assistant Professor in the Department of Psychiatry at the University of Toronto. He has an interest in the pharmacology of sleep medicine.

Dr. Atul Khullar is a psychiatrist who specializes in the management of sleep, mood/anxiety, obesity and attention deficit disorders. He completed a combined sleep, mood and anxiety fellowship from the University of Toronto. Dr. Khullar is a Fellow of the American Academy of Sleep Medicine, a Clinical Associate Professor at the University of Alberta and the medical director of the Northern Alberta Sleep Clinic.

ISBN 978-0-9950428-7-2

\$25.00