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# Practical Recommendations for Hypnotic Switching in Insomnia Management: A Canadian Expert Clinical Framework

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## Background

Insomnia disorder is a complex condition in which patients experience difficulties with sleep initiation, sleep maintenance, or early morning awakening. Chronic insomnia is defined as dissatisfying sleep quality or quantity, occurring at least three times per week, that has persisted for at least three months.[1]

Insomnia is common, with a higher incidence in certain subpopulations, including older adults (≥65 years of age) and patients with psychiatric and physical comorbidities, such as depression, anxiety, dementia, restless leg syndrome, obstructive sleep apnea, chronic pain, and alcohol or substance use disorders.[2-4] Individuals experiencing insomnia often have disrupted sleep architecture, with polysomnography showing reduced time spent in the rejuvenating slow wave and rapid eye movement (REM) sleep stages.[5] As such, insomnia can seriously impair daytime functioning, cognition, and quality of life.[6] Further, insomnia may result in a higher risk of various conditions, including cardiovascular disease, obesity, and diabetes, though the association between insomnia and these comorbidities is likely bi-directional.[7, 8] Unfortunately, for a variety of reasons, the diagnosis is often missed or trivialized in medical practice.[6] Given the profound impact of chronic insomnia, a proactive diagnosis and successful treatment is essential.

The primary non-pharmacologic treatment option available for insomnia is cognitive behavioural therapy for insomnia (CBT-I), which focuses on sleep hygiene techniques, sleep restriction, circadian rhythm therapy, and cognitive therapy. Although CBT-I is the first-line treatment for insomnia and should always be recommended, it may not always be available in a timely manner, it can be costly and not every patient can afford it, some patients choose to opt out, and may not be sufficient as a single therapy approach. Thus, in many cases, pharmacotherapy may be needed in addition to or instead of CBT-I to treat insomnia and improve daytime functioning and associated cardiovascular and metabolic risks.[6] Of note, patients also often self-medicate with over-the-counter medications, including cannabis products.[9]

Currently, commonly prescribed medications for insomnia include benzodiazepine receptor agonists (BZDs; e.g., lorazepam, clonazepam) and Z-drugs (e.g., zolpidem, zopiclone, eszopiclone).[10] In addition, despite their risks, antidepressants (e.g., trazodone, mirtazapine), and antipsychotics (e.g., quetiapine) have also been used to treat insomnia despite being off-label and promoting sleep indirectly.[10]

Dual orexin receptor antagonists (DORAs) are a newer class of agents for insomnia with a novel mechanism of action.[11] The orexin system plays a central and unique role in the regulation and stabilization of the sleep-wake cycle by promoting wakefulness and arousal.[12] Rather than promoting sedation, DORAs inhibit orexin receptors 1 (OX1R) and 2 (OX2R) to reduce wakefulness, which aids in initiating and maintaining sleep, while improving sleep architecture, unlike many of the above

mentioned older medications.[12]

Due to the high incidence of insomnia, primary care physicians often are the main healthcare providers to manage this disorder for patients. A recent publication identified significant concerns with commonly prescribed medications to treat insomnia and the need to provide better guidance for clinicians regarding the appropriate use of medications for the treatment of insomnia.[13] To support confident, rational prescribing when medication is indicated, evidence-based guidance regarding initiation, titration, switching, and otherwise managing insomnia treatment is critically important. Thus, we discuss the safety of various treatment classes to highlight the importance of considering both starting and switching from commonly prescribed medications to safer, sleep-promoting medication with better daytime functional outcomes. Finally, we provide a clinical framework for the successful switching of hypnotic medications for the treatment of insomnia.

## Efficacy and Safety of Insomnia Pharmacotherapeutics

BZDs and non-BZDs (Z-drugs) sedative-hypnotics are some of the most prescribed treatments for insomnia. However, higher doses and longer-term use of these medications are associated with next-day sedation, cognitive dysfunction, risk of falls and fractures, motor vehicle accidents, respiratory depression, withdrawal, and the development of tolerance and/or dependence.[10,14] All of these agents are indicated for short-term use only, though eszopiclone and zolpidem have long-term data. For instance, for zopiclone, the label states treatment should usually not exceed 7-10 days, with re-evaluation needed after 2-3 weeks, and ideally should not be prescribed in quantities for more than 30 days.[15] Long-term safety concerns regarding BZDs, Z-drugs, and other agents used off-label for sleep, such as antidepressants, atypical antipsychotics, and over-the-counter antihistaminergic agents, include risk of falls, next-day sedation, cognitive/functional impairment, and even extrapyramidal symptoms (EPS) and weight gain.[10]

Because of the long list of adverse effects and safety issues associated with the insomnia treatments listed above, it is generally recommended that these be used in limited circumstances and, in some cases, avoided. For instance, BZDs should be used to support sleep in limited circumstances (e.g., lorazepam to aid sleep in bipolar mania or hypomania) and for short-term treatment.[10] Further, it is recommended to deprescribe BZDs and Z-drugs in people with insomnia aged 65 years and older, if possible.[16] Sedating antipsychotics are often associated with significant weight gain and can cause EPS, and even tardive dyskinesia, with longer-term use. Patients should be made aware of these risks and, in general, these drugs should not be used as a primary insomnia treatment.

The American Academy of Sleep Medicine (AASM) has acknowledged that those with chronic severe refractory insomnia may require long-term treatment. However, any treatment should be initiated with caution based on careful assessment and monitoring. Safer options with better long-term data among pharmacologic treatments, such as DORAs, should be considered first line for long-term use, because there are no time duration limitations associated with their on-label use. Significant additional quantitative and long-term safety and efficacy data are available for these newer agents compared to BZDs and Z-drugs.

## Efficacy and Benefits of DORAs

In clinical trials, lemborexant (5 or 10 mg)[17] significantly improved objective sleep onset parameters as measured by polysomnography at nights 1 and 2 and at the end of one month of treatment, compared with placebo.[18] Lemborexant also improved sleep efficiency and wake after sleep onset as compared to placebo, and wake after sleep onset in the second half of the night was also better for both doses of lemborexant as compared to zolpidem tartrate extended-release (6.25 mg).[18] Further, a Phase 3 study demonstrated that the benefits of lemborexant observed on sleep onset and sleep maintenance in the first 6 months as compared to placebo were sustained to at least 12 months, suggesting lemborexant can be used effectively long-term.[19] An evaluation of data from nine clinical studies showed that postural stability in the morning, driving performance, and alertness were not impaired with lemborexant (5 or 10 mg), suggesting next-day functioning is not affected with this medication.[20]

Daridorexant (25 or 50 mg)[21] was shown to improve sleep outcomes (wake time after sleep onset and latency to persistent sleep)[22], and daytime functioning (50 mg), as compared to

- **Is there a need to stop or switch medication?**
- **Is the patient stable on current medication?**
- **How is the daytime functioning of the patient?**
- **How severe is the insomnia?**
- **How long has the patient been using their current insomnia medication?**
- **Does the patient have comorbidities that are also treated with the current insomnia medication?**

**Box 1.** Considerations and key questions to ask before considering switching of insomnia medication

placebo.[23] Further, long-term analysis (up to 1 year) suggested maintained improvements in sleep and daytime functioning, including the exploratory outcomes of self-reported total sleep time (sTST) and decreased Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) scores, with the 50 mg having the most profound effect on both.[24]

A systematic review of 69 studies of various insomnia medications found that DORAs were more effective in terms of various sleep parameters, compared to Z-drugs and placebo, with a favourable tolerability profile. DORAs showed an overall superior efficacy and safety in this indirect comparison study.[25] This further reinforces that DORAs could also be considered as first-line therapy for the chronic treatment of insomnia.

## Safety of DORAs

In clinical trials, DORAs are well tolerated, with most reported treatment-related adverse events (TEAEs) being mild or moderate. In a 12-month trial for lemborexant, the most common TEAEs were somnolence and headache in the first 6 months. A higher percentage of patients in the 10 mg group discontinued due to a TEAE than those receiving 5 mg or placebo.[26] The incidence of the most common TEAEs decreased during the second half of the study, and included nasopharyngitis, somnolence, and headaches. No new safety signals or increases in suicidal ideation/behaviour or self-injurious behaviour were reported in this long-term study.[19] Earlier safety studies testing doses up to 200 mg of lemborexant did not show respiratory depression, nor seizure activity at the 75 mg dose.[27]

To assess the potential effects of discontinuing lemborexant, a 2-week follow-up period showed no signs of withdrawal symptoms or rebound insomnia after abrupt discontinuation following a 6- or 12-month period of lemborexant (5 or 10 mg). Fewer than 20% of patients experienced significant worsening of insomnia symptoms compared to screening. For most patients, sleep outcome improvements were maintained in the 2-week off-treatment period.[28] These data suggest that long-term use of lemborexant is safe, and the potential risk of withdrawal symptoms and rebound insomnia reported with other insomnia medications is minimal.

Similar rates of TEAEs were detected in studies assessing daridorexant (25, or 50 mg) and placebo groups, with a somewhat higher rate of TEAEs in the group treated with zolpidem (10 mg).[21] Nasopharyngitis and headaches were the most reported adverse events. In phase 3 trials, the incidence of serious TEAEs was <5.5% in all groups. Two serious TEAEs were reported: orthostatic intolerance (daridorexant 25 mg) and depression/suicidal ideation (placebo); most TEAEs were mild or moderate in nature. In analyses with use up to 1 year, daridorexant was not associated with tolerance, dependence, or rebound insomnia.[23,24]

Sedative hypnotics may affect next-day functioning such as driving performance, and use of BZDs is associated with a higher risk of car accidents.[10] A systematic review of studies assessing driving performance after the use of insomnia medication found that zopiclone impaired driving performance and was most frequently the

cause of premature test termination. Lemborexant, on the other hand, on average did not affect driving performance as assessed by the standard deviation of lateral position (SDLP), and none of the individuals required premature test termination during on-road driving tests, either after one dose or after 8 days of treatment.[29] For daridorexant, next-morning driving performance was assessed 9 hours after intake in a driving simulator. On the morning after the first dose, daridorexant impaired the driving performance as assessed by SDLP, and the effects were stronger in those receiving 100 mg compared to those taking 50 mg. After 4 days of treatment, impairment was not observed for either tested dose. Thus, patients prescribed daridorexant should be cautioned against driving until they are familiar with how the medication affects them.[22]

Further, it should be noted that in a small percentage of patients, DORAs can result in vivid dreaming and/or sleep paralysis due to an increase in REM sleep. These potential events should be explained to patients before initiation of a DORA.[17,22,30]

## Special Populations

### *Older Adults*

Insomnia becomes more common with aging, and older adults may be more prone to adverse events from sedative hypnotics, due to their association with an increased risk of falls, cognitive impairment, car accidents, and impaired response to auditory stimuli.[31]

In this subpopulation, lemborexant improved several sleep parameters, with effects maintained at 12 months. Falls and cognitive deficits were not commonly reported and there was no evidence of withdrawal symptoms following lemborexant discontinuation, suggesting similar efficacy and safety to those in the general adult population.[32]

Further, an analysis of data from three clinical trials showed that lemborexant improved various sleep parameters in the population aged ≥65 years, as compared to placebo or zolpidem extended-release. No impairments in postural stability at wake time or memory were detected. One of the studies assessed the subject's ability to awaken to auditory stimuli, and no difference was detected vs. placebo. However, there was a difference in the percentage of participants wakening from the maximum tone of 105 dB with lemborexant 5 and 10 mg, resulting in 11.1% and 3.7% not wakening, respectively, vs. 18.5% of those taking zolpidem (extended-release, 6.25 mg) not wakening. Next-day driving performance was also not affected by lemborexant, compared to placebo.[33]

In an assessment of sleep architecture in adults ≥55 years of age taking lemborexant (5 or 10 mg) or zolpidem (extended-release, 6.25 mg), lemborexant improved REM and non-REM sleep and was more effective than zolpidem.[34] Finally, postural stability was assessed after the use of zolpidem (extended-release, 6.25 mg) or lemborexant (5 or 10 mg). While middle-of-the-night cognitive performance was poorer in the 10 mg lemborexant and 6.25 mg zolpidem groups, morning body sway and cognitive performance did not differ from placebo in both lemborexant groups, while body sway was higher in the zolpidem group.[35]

In the population aged ≥65 years with insomnia, one study showed that daridorexant efficacy was highest at a dose of 50 mg, with improved daytime functioning. There was no increased risk of TEAEs or residual effects the next morning for this population, suggesting good tolerability.[36]

### *Comorbidities*

Obstructive sleep apnea (OSA) commonly co-occurs with insomnia. Early research showed that lemborexant was safe in people with mild OSA[37], and a crossover study compared the use of lemborexant 10 mg with placebo in adults aged 45-90 years with moderate or severe OSA. While the incidence of TEAEs was higher for lemborexant treatment than placebo, there were no serious TEAEs, and no adverse respiratory effects were detected, suggesting this treatment is safe for this subpopulation.[38] Daridorexant was studied in a crossover study at a dose of 50 mg for five days in people with mild to moderate OSA. While daridorexant induced more respiratory events, this could be explained the longer total sleep time induced by daridorexant, and there were no differences in apnea and hypopnea duration or number of awakenings, suggesting safe use in this subpopulation.[39] A separate crossover study in people with severe OSA, daridorexant use for five days was also found to be safe. With both DORAs, due to study limitations, clinically meaningful respiratory effects in OSA cannot be excluded.[17, 22]

### *Hospitalized Patients*

A retrospective study that investigated the risk of falls with hypnotics in patients hospitalized in Japan found that the use of sedative hypnotics was associated with a higher risk of falls. In

| Switching Strategies | Strategy Description | When to Use | Example Protocol |
|---|---|---|---|
| Cross Taper | Introduce new drug first, then gradual dose reduction and increase dose of new drug | BZDs → other class<br>Trazodone → other class<br>Mirtazapine → other class<br>TCAs → other class<br>Quetiapine → other class | **Zopiclone (15 mg) to lemborexant**<br>**Week 1:** add lemborexant 5 mg<br>**Week 2:** decrease zopiclone to 2×5 mg<br>**Week 3:** increase lemborexant to 10 mg<br>**Week 4:** decrease zopiclone to 5 mg |
| Harm Reduction Tapering | Gradual dose reduction but do not discontinue drug while introducing new drug | Hypnotic agent is required for comorbidities, but dose reduction can be achieved with introduction of DORA | **Eszopiclone (3 mg) to lower dose**<br>**Week 1:** add lemborexant 5 mg<br>**Week 2:** decrease eszopiclone to 2 mg<br>**Week 3:** increase lemborexant to 10 mg<br>**Week 4:** decrease eszopiclone to 1 mg |
| Slow Taper | Gradual dose reduction (often over 4 weeks) to discontinue drug | BZDs → other class<br>Trazodone → other class<br>Mirtazapine → other class<br>TCAs → other class<br>Quetiapine → other class | **Lorazepam (2 mg) to discontinue**<br>**Week 1:** lorazepam 1.5 mg,<br>**Week 2:** lorazepam 1 mg,<br>**Week 3:** lorazepam 0.5 mg,<br>**Week 4:** lorazepam 0 mg, introduce new drug |
| Taper & Wait (1-2 days) | Slow taper but withhold new drug for 1-2 days after taper | Zolpidem → other/same class<br>Eszopiclone → other/same class | **Zolpidem (10 mg) to another drug**<br>**Week 1:** zolpidem 5 mg<br>**Week 2:** zolpidem 5 mg every other day,<br>**Week 3:** stop zolpidem, introduce new drug 1-2 days later |
| Direct Switch | First drug is stopped and new drug is introduced next day | BZDs → same class<br>Zaleplon → other/same class<br>DORAs → other/ same class | **Lemborexant to daridorexant**<br>**Day 1:** last dose of lemborexant<br>**Day 2:** first dose of daridorexant |

**Figure 1.** Switching strategies for insomnia medication; *courtesy of Fiore Lalla, MD, Alan Lowe, MD, Walter Chow, MD, Atul Khullar, MD, MSc, FRCPC, DABPN, Serge Lessard, MD, and Diane McIntosh, MD*

*Time period and dosing for switching depends on many factors and clinicians should be flexible in their approach to switching and to consider patient comorbidities and length of time on current therapy as well as comorbidities.

**Abbreviations: BZDs:** benzodiazepine receptor agonists; **DORA:** dual orexin receptor antagonist; **TCAs:** tricyclic antidepressants.

contrast, the use of DORAs (suvorexant and lemborexant) in this population significantly lowered the risk of falls.[40]

## Optimization and Challenges With Switching

A focused initial evaluation is essential when determining the best treatment choice for patients with insomnia disorder; however, the authors felt that DORA drugs should be first-line therapy. This is also recommended by insomnia experts in Japan who recommended lemborexant as first-line for sleep initiation insomnia, and lemborexant and suvorexant as first-line for sleep maintenance.[14] Treatment personalization requires the consideration of several important factors, including the patient's sleep, medical, and psychiatric history, their adherence to currently prescribed medication, and their use of alcohol or recreational substances. The choice of drug should be further individualized depending on factors such as age, the presence of another serious psychiatric disorder, or other medical comorbidities, and the potential negative impact of adverse events, such as an older adult's risk of falls.[6] Furthermore, patient preferences and the availability of treatment should be thoughtfully considered. The most important characteristics of a prescription medication for chronic insomnia as noted by practitioners in a survey were a lack of causing dependency, safe for long-term use, and ability to improve daytime functioning.[9]

A Canadian study found that in 52.5% of adults (<65 years) and 69.5% of seniors (≥65 years), insomnia medications were not prescribed appropriately. Most commonly reported was the long duration of use of BZDs or Z-drugs, which, as described above, might be associated with safety risks.[41]

In situations where a switch to another, potentially safer, insomnia treatment is deemed warranted, several factors should be considered. The sudden discontinuation of a typical sedative hypnotic, whether a BZD, Z-drug, or antidepressant/antipsychotic with antihistaminergic effects, can result in rebound insomnia or discontinuation symptoms. In some cases, rebound insomnia is worse than the original insomnia. Negative sleep experiences, whether associated with rebound or discontinuation symptoms, are often falsely attributed to the new treatment, making a switch even more challenging.

Few studies have assessed the abrupt transitioning between various insomnia medications. One study evaluated switching from zolpidem to lemborexant.[42] Adults with insomnia disorder who were intermittent or infrequent (3-4x per week) zolpidem users (median duration of zolpidem use was 5.6 [SD: 2.9] years) were switched to lemborexant 5 mg, while frequent (≥5x per week) zolpidem users (median duration of zolpidem use 4.7 (SD: 4.4) years) were switched to lemborexant 5 or 10 mg.[42] The switching was successful in 81.1% of patients. More patients reported that lemborexant helped with returning to sleep after waking than while using zolpidem. Lemborexant was well tolerated, with most adverse effects being mild or moderate (somnolence and abnormal dreams were most commonly reported). None of the adverse effects reported in this study suggest there was rebound insomnia or withdrawal effects due to the abrupt stopping of zolpidem. However, according to the clinical experience of the authors, significant rebound insomnia is observed following the abrupt discontinuation of most Z-drugs, except eszopiclone.

In a study that evaluated the characteristics of patients who were able to switch from a BZD to lemborexant, it was found that those prescribed a lower BZD dose or those taking the BZD for a shorter duration could more easily switch.[43] Therefore, the success rate of switching may be lower in patients who have had a long history of sedative hypnotic treatment, especially those prescribed higher doses of BZDs or Z-drugs. Another consideration is that while lemborexant was shown to have additional benefits, the sensation of falling asleep on a DORA may differ from typical sedative hypnotics, and the symptoms of insomnia might be temporarily aggravated during the switch. It is important to discuss this with the patient before switching is attempted.

### *Recommendations for Switching*

Although current studies indicate that direct switching from a sedative hypnotic to a DORA can be done successfully, the authors have found that in clinical practice, adding a DORA first for 3-6 weeks, followed by a cross-taper of the sedative hypnotic, is practical and successful to avoid withdrawal and rebound insomnia **(Figure 1)**. This is preferable if the patient has been on a BZD or Z-drug long-term at high doses.[44] Adding a DORA onto an existing sedating medication regime for the purposes of cross-tapering other agents down or off without

worsening sedation and withdrawal from other agents may be possible because of their unique and different mechanisms of action compared to older GABAergic agents. There may even be beneficial augmenting effects, as observed in those treated for chronic severe refractory insomnia, but more studies are needed.

The response to switching and the time it takes will depend on many factors, such as the type of insomnia (difficulty falling asleep, difficulty maintaining sleep, and/or early awakening), its severity (mild, moderate, severe), and duration (acute or chronic), as well as the presence of comorbidities. It may, for instance, take 2-4 weeks or longer to make stepwise incremental adjustments in doses during cross-titration and patience and motivation are required with frequent monitoring **(Figure 1)**. However, being able to lower or stop the use of an existing BZD or Z-drug that has been required long-term can be rewarding for both clinician and patient, especially when the new agent is a safer with long-term use and also effective.

In certain situations, it may not be possible to completely discontinue the existing insomnia treatment, especially if the patient has underlying anxiety, severe initial insomnia for which a GABAergic agent may still be helpful, or in cases in which the insomnia is severe, chronic, and refractory. Additionally, in some patients, harm reduction tapering should be considered, in which a sedative hypnotic agent may be required for comorbidities other than insomnia (e.g., anxiety, depression) but the dose can be lowered when a DORA is added for insomnia treatment.

When aiming to reduce or stop the use of BZDs by switching to other medications, a Japanese report suggested lemborexant and suvorexant as first-line recommendations.[14] These guidelines were released before the approval of daridorexant in Japan. In the recently released Canadian Delphi consensus recommendations for chronic insomnia management, it was stated that DORAs have a side effect profile that may be more favourable compared to benzodiazepines, Z-drugs, and some commonly prescribed pharmacotherapies for insomnia.[45,46]

Please consult **Box 1** for considerations and key questions to determine whether to switch between drug classes. **Figure 1** provides more information on types of switching to consider for various drug classes; furthermore, it is recommended that physicians also refer to switchrx.com for specific information on the best method of switching for their patient's particular case.

There is little data to guide and inform the clinical approach to switching from a BZD, Z-drug, or an antidepressant or antipsychotic used for insomnia to a DORA. Although off-label, according to the clinical experience of the authors, drugs that pose the greatest risk of rebound insomnia should always be considered for a cross-taper switch. Most experienced clinicians recommend starting the DORA at the lowest therapeutic dose and, once tolerability is assured, initiate a slow taper of the older medication. The speed of the taper is based on the type, dose, and duration of use, as well as any anxiety or sensitivity the patient may experience. The anxiety associated with not sleeping can be a powerful predictor of the success of the switch, so preparing the patient is critical; discuss the reason for the switch and the likely benefits, and ensure the journey is as smooth as possible.

If rebound insomnia occurs, return to the last tolerable dose of the older agent and titrate the DORA, if possible, to a higher dose. Once again, establish tolerability and, if the patient is sleeping well, initiate the taper of the older medication again. Sometimes, the taper of a BZD or Z-drug may require weeks at each dose. Taking your time and engaging regularly with your patient increases the likelihood of success.

## Conclusion

Insomnia disorder often requires pharmacotherapy to improve a patient's daily functioning and quality of life. Traditional sedative hypnotics can have long-term safety issues. Newer first-line treatment categories, such as DORAs, offer options that can be used long-term, with an improved tolerability profile, including safety in older adults and other at-risk populations. Here, we presented data on the safety and efficacy of DORAs in patients with chronic insomnia, with particular attention to special populations. Although DORAs should be considered first-line therapy, we have provided a framework based on our clinical experience on how to best switch to a DORA (from other insomnia medication categories), and what factors to pay attention to when making decisions on switching in clinical practice.

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