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# Medication and Substance Use: Keeping Insomnia Treatment Safe

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**Previous issues of *Insomnia Rounds* have discussed approaches to pharmacological and non-pharmacological management of insomnia. Many family physicians are concerned about the possibility of their patient becoming dependent on benzodiazepines or the other hypnotic agents, in some cases refusing to prescribe them. This issue of *Insomnia Rounds* addresses this concern and discusses the use of other substances that patients often use to self-treat their insomnia.**

## How is a Substance Use Disorder Classified?

According to the *Diagnostic and Statistical Manual of Mental Disorders,* 5th Edition, (DSM-V), a substance use disorder is "a cluster of cognitive, behavioral and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems".[1] The DSM-V lists 10 classes of drugs, which includes alcohol, cannabis, caffeine, inhalants, opioids, and the sedative hypnotic anxiolytic (SHA) agents. The diagnostic criteria for a substance use disorder cluster into 4 groups: 1) impaired control over substance use; 2) social impairment due to use; 3) risky use (eg, while driving); and 4) pharmacological criteria (tolerance, withdrawal). Substance use disorders range in severity from mild (presence of 2–3 symptoms), to moderate (4–5 symptoms), and severe (≥6 symptoms).

As stressed in the DSM-V, tolerance and withdrawal symptoms can occur in the context of appropriate medical treatment. As an example, a patient who has been using an opioid analgesic or an SHA as directed may develop physiological tolerance. Therefore, it is important to note that patients whose symptoms occur while using a substance according to directions for medical treatment should not be diagnosed with a substance use disorder solely on the basis of these symptoms. It is also recognized, however, that prescription medications are used inappropriately by some patients. A diagnosis of a substance use disorder can be assigned in the presence of other symptoms of compulsive drug-seeking behaviour (eg, double-doctoring).

## Sedative Hypnotic Anxiolytic (SHAs) Agents

The SHAs – including benzodiazepines (BDZs) and the non-BDZ hypnotic agents commonly referred to as the "Z-drugs": zopiclone, zolpidem, and zaleplon (approved by Health Canada but no longer marketed) – are commonly prescribed for the management of insomnia. According to the Canadian Alcohol and Drug Use Monitoring Survey (CADUMS),[2] 9% of Canadians aged ≥15 years used SHAs in the previous year, likely for a variety of conditions. While the exact mechanism of action may differ from one drug to another, drugs in this class all enhance the inhibitory neurotransmitter gamma aminobutyric acid (GABA) by binding to the alpha-1 subunit of $GABA_A$ receptors. Tan et al[3] demonstrated in animal models that BDZs also increase dopamine release indirectly by weakening the influence of inhibitory interneurons, which normally prevents excessive dopamine levels by downregulating the firing rates of dopamine-producing neurons. This mechanism of action appears to be similar to that of other substances (eg, opioids) and may be the reason why cross-tolerance between the BDZs and other substances occurs.[4,5]

A number of adverse effects may be noted following use of an SHA. These include daytime drowsiness (of particular concern when driving), dizziness, agitation, hallucinations, and sleep-walking. These reactions are particularly noted when SHAs are used with other substances that depress the central nervous system (CNS), such as alcohol or narcotic pain relievers. A Health Canada-endorsed safety statement issued in 2011 by Meda Valeant Pharma addressed the association of zolpidem with rare but potentially serious complex sleep behaviours (eg, driving a car or leaving the house) that are not recalled the following day.[6] More recently, the United States (US) Food and Drug Administration cut in half the maximum dose of zolpidem for women (from 10 mg

to 5 mg) and for extended-release products (12.5 mg to 6.25 mg), and to request that manufacturers' labeling recommend that healthcare providers use the lower dose in men (ie, 5 mg for immediate-release and 6.25 mg for extended-release products).[7]

### *Should I be concerned about prescribing SHAs for insomnia?*

Family physicians are often concerned about the potential for abuse of the SHAs, to the point where some adopt a strict policy of nonprescription under any circumstances. As with many psychoactive substances, including pain medications, over-the-counter (OTC) formulations, alcohol and illicit substances, SHAs involve activation of the brain reward system (eg, by reducing anxiety or inducing sleep) and have the potential to be reinforcing. However, it is important to bear in mind that the majority of patients use SHAs as prescribed. Furthermore, although SHA use should be considered as a short-term intervention and caution should be exercised when prescribing to higher-risk patients (eg, elderly), data are lacking regarding adverse consequences of long-term use. According to the Centre for Addiction and Mental Health,[8] SHAs account for <1% of all admissions to addiction treatment services, and this is usually in people who report abuse of other substances or alcohol. As the DSM-V points out, the occurrence of tolerance and withdrawal in and of themselves are not diagnostic of an SHA use disorder.[1]

The DSM-V contains a significant revision of SHA use disorder (summarized in Table 1),[1] moving away from the focus on addiction that was seen in the DSM-IV-TR. This category includes BDZs, the Z-drugs, carbamates (eg, meprobamate), barbiturates, all prescription sleeping medications and almost all prescription antianxiety medications; the exception is buspirone, which does not appear to be associated with misuse.

### *How prevalent is SHA use disorder?*

The 12-month prevalence of DSM-IV-defined SHA use disorder in the US is approximately 0.3% among 12–17-year-olds and 0.2% among adults aged ≥18 years.[1] Prevalence of this disorder decreases with age and, contrary to the concerns of many physicians, is lowest among older individuals (≥65 years), despite an increase in the rate of prescription with advancing age. The prevalence for SHA use disorders in the Canadian population is less clear. According to the CADUMS,[2] psychoactive pharmaceutical use was 22.9% (females 25.5%, males 20.2%) in 2011 and higher among adults aged ≥25 years (23.9%) than those aged 15–24 years (17.6%). Of those who had used an opioid pain reliever, stimulant, or SHA, 3.2% reported they "abused" such a drug. While the Z-drugs were designed specifically to avoid some primary adverse effects of BDZs, including dependence and withdrawal, there are few data that specifically address the issue of misuse of these medications. In a systematic review of case studies on abuse of/dependence on zolpidem and zopiclone, Hajak et al[9] concluded that reported dependence was similar for the 2 drugs, but was "remarkably lower than that of BDZs".

### *How can I safely prescribe an SHA?*

- Adopt an open and accepting stance in the therapeutic relationship. Your patient is more likely to be honest about increasing use if he/she believes that you are going to work towards helping him/her deal with the issue or with the underlying concern.
- Monitor use by seeing the patient in follow-up on a regular basis to reassess the risks and benefits of treatment. Do not prescribe SHAs for prolonged periods without seeing the patient in the interim.
- Clarify the target symptoms you are seeking to treat; eg, primary insomnia versus an anxiety disorder. Bear in mind that this class of medications is not first-line treatment for anxiety disorders, but may be used briefly if anxiety is severe and until anti-anxiety therapy becomes effective. An antidepressant with sedating effects (eg, mirtazapine, trazodone, sertraline, and amitriptyline) may lessen the need to use an SHA; sedation typically occurs as soon as treatment begins whereas the anxiolytic or antidepressant effect can take weeks.
- Consider alternative or complementary management strategies, including cognitive behavioural therapy (CBT), progressive muscle relaxation, meditation, and counseling for psychosocial issues.[10]
- Ask about a family history of substance use disorders. Genetic factors likely play a role in this disorder so a strong family history may increase the patient's risk.
- Take a thorough medical, psychiatric, and alcohol/drug use history, including the use of, and response to, OTCs.
- Assess psychosocial factors, some of which may contribute to the patient's need to increase the dose or rely on the effects of the SHAs.

**Table 1: Summary of DSM-V classification of sedative, hypnotic, or anxiolytic use disorder[1]**

| ***Definition*** |
|---|
| Sedative, hypnotic, or anxiolytic use that results in clinically significant impairment or distress, and characterized by ≥2 of the following elements over a 12-month period: |
| • Consumption of the substance in higher quantities and/or for a longer duration than intended |
| • A persistent urge or multiple attempts to reduce use |
| • Time and effort devoted to the substance (obtaining, using, or recovering from its effects) |
| • Craving or strong desire to take the substance |
| • Impairment of responsibilities and duties at work, school, or home |
| • Impairment in social situations or relationships |
| • Avoidance or reduced time devoted to important social, work, or recreational activities |
| • Use of the substance in physically dangerous situations (eg, driving) |
| • Consumption of the substance despite awareness that it is likely to have caused or worsened a persistent or recurring physical or psychological problem |
| • Tolerance, as shown by either a significant reduction in effect by the same dose or the need for significantly increasing doses for the desired effect (not applicable in cases where the medication is being taken under medical supervision) |
| • Withdrawal signs and symptoms (see Criteria A and B of the DSM-V criteria set for sedative, hypnotic, or anxiolytic withdrawal), or if the substance is consumed to counter withdrawal symptoms (not applicable in cases where the medication is being taken under medical supervision) |

DSM-V = *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition.

- If the presenting complaint is insomnia, perform a sleep history. Review sleep hygiene issues, such as caffeine consumption, exercise, and napping.[11] Changes in some of these factors can have significant implications for the patient.
- Bear in mind that there may be an organic cause for the complaint, such as sleep apnea, chronic pain, or restless legs. Exercise caution when prescribing SHAs to a patient with a history of chronic obstructive pulmonary disease or sleep apnea since they may result in a worsening of respiration during sleep.[12]
- Since the risk for misuse is greatest with agents that have a rapid entry into the CNS and a more potent effect on CNS receptors (eg, triazolam, lorazepam, and alprazolam), avoid prescribing these substances for insomnia if possible.
- Avoid long-acting BDZs (eg, diazepam), especially in elderly patients in whom the risk for falls and hip fractures may be increased and confusion or worsening of dementia may occur.
- Stress that the medication is intended for short-term use and should be used only as directed. Although there are no empirical data supporting the recommendation, zolpidem and zopiclone are only indicated by Health Canada for 7–10 consecutive days of use,[13,14] and usage beyond this limit must be evaluated and documented regularly.

### *Factors suggesting tolerance to/dependence on an SHA*

When taking a drug with psychoactive effects, patients tend to become tolerant of the *psychoactive* effects (eg, euphoria, sleep inducement), but not the *therapeutic* effects (eg, reduced anxiety). Dose increases by the patient may be an attempt to experience the psychoactive effects to which he/she has developed tolerance by increasing the amount of medication taken at one dose or the frequency that doses are taken. Therefore, check with the patient why he/she needs the increased dose. Since SHA use disorder is often associated with use disorders with other substances, signs that a patient is misusing another agent (eg, withdrawal symptoms or intoxication) should raise concerns that the SHA is also being used inappropriately. Other concerning signs include negotiation with the physician to escalate the dose and resistance to suggestions regarding other interventions. Seeking out multiple physicians to obtain sufficient supplies of the medication is an obvious indicator for concern. Pay attention to changes in cognition, motor coordination, and memory, or for signs of delirium, which can occur at high SHA doses, particularly in an elderly patient. Listen for patients' concerns regarding interpersonal problems (eg, fights with spouse) or difficulties at work.

### *How do I screen for an SHA use disorder in one of my patients?*

Patients do not usually volunteer information about their substance use, and physicians and other healthcare providers tend not to ask about it. One reason why family physicians do not screen for a medication or substance use disorder may be that they are unsure how to support and treat patients with substance use problems. Physicians may also neglect to ask about substance use to avoid causing patients discomfort or embarrassment. Time is often the limiting factor in assessment. A stepped approach is often the most practical: if you have no concerns about a patient and time is limited, simply ask 1–2 questions. If you have clinical reasons to be concerned, a follow-up appointment should be rescheduled for a more thorough substance use history and assessment.

There are a number of useful screening tools, such as the National Institute of Drug Abuse (NIDA)-Modified ASSIST (http://www.drugabuse.gov/nmassist), or the CAGE questionnaire (Cut down, Annoyed, Guilty, and Eye opener) for alcohol abuse.[15] The "5 A's" (Ask, Advise, Assess, Assist, and Arrange),[16] originally developed for smoking cessation intervention, provides a helpful outline for identification and intervention in any substance-abuse case.

### *What are the signs and symptoms of SHA withdrawal?*

While withdrawal symptoms are more common with high doses and prolonged use, they may occur at therapeutic doses. Withdrawal does not indicate dependence or abuse of the SHA. The likelihood of withdrawal is increased by longer duration of SHA use, short-acting BDZs, higher doses, and an underlying (untreated) anxiety disorder. Symptoms (Table 2) can develop within hours or, in the case of SHAs with a long half-life, up to a week after the last dose. According to the DSM-V, the patient should experience ≥2 symptoms within several hours to a few days after the cessation of (or reduction in) the medication.[1] The symptoms cause clinically significant distress or impairment in social, occupational or other important areas, are not due to another medical condition (eg, essential tremor), and are not better explained by another mental disorder (eg, anxiety), or intoxication or withdrawal from another substance (eg, alcohol).

### *How should withdrawal from SHAs be managed?*

Patients who have been using SHA drugs on a regular basis for several weeks should be withdrawn slowly in order to minimize withdrawal symptoms. Ensure that the original complaint (eg, anxiety or primary insomnia) has been treated to remission, otherwise patient distress and the likelihood of relapse will be high. Bear in mind that there may be a re-emergence of the original complaint as part of the withdrawal process; there may even be an emergence of new symptoms, such as anxiety, or recurrence of a remitting-relapsing disorder such as primary insomnia. Patient education is of paramount importance. Inform him/her what withdrawal symptoms may be experienced, how long these may last, and about the possi-

**Table 2: Signs and symptoms of withdrawal from sedative-hypnotic agents**

Within hours to days after cessation, the patient experiences some or all of the following, causing significant distress or impairment in function and not attributable to a general medical condition or a mental disorder:

- Autonomic hyperactivity; eg, perspiration, tachycardia, and hypertension
- Increased hand tremor
- Insomnia
- Nausea or vomiting
- Transient visual, tactile, or auditory illusions
- Psychomotor agitation
- Anxiety and panic attacks
- Grand mal seizures
- Delirium, psychosis, and cardiac abnormalities (select cases)

ble re-emergence or exacerbation of the original complaint. Let the patient know that you will work with him/her to help manage these symptoms. Allowing the patient to retain a degree of control during the process may be helpful. Tapering strategies for outpatients and inpatients are presented in Table 3. If the taper is being done through your office, follow the patient closely during the tapering and anticipate that the process may need to take several months. Emphasize the benefits the patient may be noticing; eg, feeling more alert and engaged in the daytime. Always monitor for an increase in anxiety or a worsening of depression during the taper. In such cases, assess for suicidal ideation, and slow or halt the taper if necessary. Consider community treatment programs, if available in your area, for socially stable patients with less severe psychosocial or substance-use problems. These programs are usually preferable to inpatient withdrawal, as they do not disrupt work or normal living arrangements. They may offer supportive therapy and/or CBT to assist the patient with managing withdrawal symptoms that may arise and rebound anxiety or insomnia. Inpatient treatment is indicated for a patient who is taking the equivalent of 50–100 mg/day of diazepam, especially if he/she is dependent on other drugs, is medically or psychiatrically unstable, or is likely to access SHAs from other sources. Patients who have failed outpatient treatment or live in a chaotic or unsupportive home environment may be appropriate for inpatient withdrawal.

Given that there is little information regarding the risk of a substance use disorder and withdrawal symptoms associated with the Z-drugs, it is more difficult to recommend tapering strategies specific to these agents. The above principles regarding patient engagement and education should be applied. A slow taper is recommended: eg, for a patient who has been taking 7.5 mg, gradually (several weeks or even months, if necessary) decrease to 5 mg, then to 3.75, to 2.5 mg, and then stop.

**Table 3: Benzodiazepine tapering strategies for outpatients and inpatients**

***Outpatient tapering***

- Start by switching the patient to a longer-acting benzodiazepine; eg, diazepam or clonazepam
- Convert to the equivalent dose of diazepam (maximum 80-100 mg/day) in divided doses, adjusting the initial dose according to symptoms
- Taper by no more than 5 mg per week or 5 mg every 3-4 days if the starting dose is >50 mg of diazepam equivalent, adjusting the rate of taper according to symptoms
- Slow the rate of taper once the dose is <20 mg of diazepam equivalent (eg, 2-4 mg/week)
- Depending on patient reliability, consider daily, biweekly, or weekly dispensing

***Inpatient tapering***

- Start the taper at 1/2 to 1/3 the diazepam equivalent, administering in bid–tid doses
- If the patient experiences significant withdrawal on this dose, increase the next day dose by 10–30 mg
- The patient can be given 10–15 mg of diazepam for acute withdrawal symptoms during the taper
- Hold diazepam and decrease the daily dose if the patient experiences sedation or drowsiness
- Taper by 10–15 mg/day
- Once the patient reaches a daily dose of <50 mg, treatment can be switched over to outpatient

### *Cautions in BDZ withdrawal*

Diazepam may not work for patients who are withdrawing from triazolam or alprazolam so they should be tapered from the index drug rather than switching to diazepam.[17] Switching to the equivalent dose of clonazepam may be used as an alternative to diazepam. As well, diazepam may cause excessive sedation in patients who are elderly, have severe liver disease, asthma, or respiratory failure, or have low serum albumin. In such cases, an intermediate-acting BDZ (clonazepam or lorazepam) should be used to taper.

### *Treating sleep difficulties after discontinuation of an SHA*

Patients with a history of alcohol or a substance use disorder, including the SHAs, may experience significant disturbance with their sleep upon discontinuation, sometimes after years of abstinence. Therefore, the treatment of sleep-related difficulties should be considered as part of the overall treatment plan. Ongoing sleep difficulties increase the likelihood of relapse into the use of alcohol or substances as a means to deal with the insomnia. Educating the patient is crucial, informing him/her that sleep difficulties can be expected and they may take time to resolve. Also, assuring the patient that you take this part of their recovery seriously can be encouraging. CBT, relaxation, and mindfulness/meditation techniques should be encouraged to manage emergent insomnia.[10] Attention to sleep hygiene is paramount:

- Limit caffeine
- Develop a regular sleep-wake routine, particularly a regular rising time 7 days a week, and avoid daytime napping
- Increase exercise
- Initially curtail the amount of time in bed

Medication, if warranted, should be presented as a short-term solution. The efficacy of sedating antidepressants (eg, trazodone or amitriptyline) or the atypical antipsychotics in this population is unclear. Concomitant mood or anxiety disorders can be treated with one of the more sedating selective serotonin reuptake inhibitors, such as sertraline or fluvoxamine, or with mirtazapine.

## Other Medications and Substances Commonly Used to Treat Insomnia

### *Alcohol*

Given its sedative effect, alcohol may be used by patients to treat their insomnia.[18] Alcohol decreases the latency to sleep onset; however, it is metabolized quickly and the blood alcohol level quickly falls to zero. Thereafter, sleep tends to be shallow and disrupted and the proportion of rapid eye movement (REM) sleep is increased,

sometimes resulting in vivid dreams and nightmares (alcohol-induced sleep disorder). During acute withdrawal, sleep quality deteriorates and the amount and intensity of REM sleep increase. In people who use alcohol on a nightly basis, the sedating effect is typically lost.

Alcohol increases the likelihood of snoring, upper airway resistance, and apneic events, even in people with no history of obstructive sleep apnea (OSA).[19,20] In patients with OSA, the combined effect of the disorder and alcohol has been shown to increase the risk of daytime motor vehicle accidents 5-fold.[21,22]

A high proportion of patients with an alcohol use disorder experience clinically significant insomnia.[23] Objective studies indicate that sleep in patients with a chronic alcohol use disorder is severely disturbed, with prolonged sleep latencies, decreased slow wave and REM sleep, poor sleep efficiency, and greater sleep disruption.[24] Insomnia is common upon discontinuation of chronic alcohol use, and can occur up to 27 months after abstinence.[25] Chronic sleep disruption in recovering alcoholics increases the risk of relapse and must be vigorously addressed during the recovery period although evidence for a preferred intervention is absent.[23,26]

### *Over-the-counter (OTC) agents*

A number of OTC medications are commonly used in the management of insomnia. Most include a first-generation antihistamine (eg, dimenhydrinate, diphenhydramine, and doxylamine), which induces drowsiness mainly by the inhibition of the histamine-1 (H1) receptor. They also have significant muscarinic anticholinergic effects. The typical duration of action of these agents is 4–6 hours. Studies suggest that these drugs decrease sleep latency and nocturnal awakenings and increase sleep duration and quality,[27,28] but their efficacy has not been well studied. Potential adverse events include daytime sedation, impairment of psychomotor performance,[29] dizziness, and tinnitus. Elderly insomnia patients should be cautioned about the use of OTC sleep aids due to the risk of significant cognitive impairment.[30] A substance-related disorder in association with the OTC agents is rare but does occur. Commonly reported pleasant effects include antianxiety, antidepressant, and euphoria/pleasure, likely due to H1 interaction with the mesolimbic dopamine system.[31] Chronic users of high doses experience significant withdrawal symptoms upon discontinuation, including dysphoria, agitation, nausea, and cravings. Acute intoxication with large doses of antihistamines can result in hallucinations, confusion, and agitation. While withdrawal is not associated with medically serious consequences, patients can experience nausea and anxiety lasting up to 10 days.

### *Cannabis*

The effect of cannabis on sleep remains unclear. A host of factors confound the results of studies, primarily conducted in the 1970s, including the recruitment of experienced users, withdrawal on the study night, varying doses, and different routes of administration.[32] Subjectively, cannabis often induces relaxation and drowsiness, in addition to its other psychotropic effects. Objectively, acute administration appears to decrease sleep latency and REM sleep measures (eg, amount and density) and increases slow wave sleep (SWS).[33] Tolerance to the effect on SWS and sleep onset latency occurs with chronic use, but the changes in REM sleep continue.[34] Higher doses may have an activating effect and increase the latency to sleep onset.[35] Acute discontinuation of cannabis causes rebound of these parameters; ie, a large increase in REM sleep and a decrease in SWS. Users report an increase in sleep difficulties and often experience strange dreams,[36] which may persist for 6–7 weeks after abstinence.[37,38] Ongoing sleep disturbance is cited as one of the reasons for relapse.[39] Therefore, it is important to educate cannabis users and inquire about sleep when discontinuation is planned.

### *Opioids*

The most commonly abused opioids are codeine, morphine, hydromorphone, and oxycodone, which may have been prescribed for a pain condition or may be obtained illegally. Acute opioid intoxication is typically associated with "significant problematic behavioral or psychological changes (eg, initial euphoria followed by apathy, dysphoria, psychomotor agitation or retardation, impaired judgement", along with pupillary constriction and drowsiness/coma, slurred speech, and impaired attention or memory.[1] Most opioids have a relatively short half-life; the exception is methadone, which, along with its lack of euphoric effects, may explain the fact that it is rarely abused. While one of the effects may be sedation (methadone tends to be activating and can cause insomnia), the opioids reduce total sleep time and REM sleep when first administered to a drug-naïve subject. However, tolerance to these effects occurs quickly upon repeated use so escalating doses are required to obtain the desired (including sedative) effects. In patients with a history of opioid use disorder, sleep is maximally disrupted or even suppressed completely during early withdrawal; while this may improve over the course of the next few weeks, sleep disruption often continues indefinitely. Prolonged insomnia is common in patients with a history of opioid use disorders and represents a risk factor for relapse.[32]

## Conclusion

When prescribing or recommending a medication for the management of insomnia, physicians should be aware that, while the SHAs are generally safe and the majority of patients to whom they are prescribed use them appropriately, there is a potential for misuse, particularly in those who suffer from other substance use disorders. Screening for a substance use disorder is an essential part of initial patient evaluation before prescribing treatment followed by regular monitoring of use and maintenance of vigilance for signs of misuse.

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