Deprescribing benzodiazepine receptor agonists taken for insomnia: a review and key messages from practice guidelines

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KEY WORDS

ABSTRACT

Long-term benzodiazepine receptor agonist (BZRA) use for insomnia is common and highly prevalent in adults in all care settings. Evidence syntheses suggest that the therapeutic benefits of benzodiazepines for insomnia are marginal and very short term. On the harm side, BZRAs are associated with daytime sedation and confusion. Long-term use increases the risk of falls, fractures, cognitive impairment, and motor vehicle accidents. An evidence-based clinical practice guideline has been developed to assist with deprescribing BZRAs. This review highlights the rationale for deprescribing BZRAs used for insomnia and summarizes key messages for clinicians from the new BZRA deprescribing guideline and their supporting evidence.

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Introduction   Benzodiazepine receptor agonists (BZRAs), which include benzodiazepines and the so-called z-drugs (zopiclone, eszopiclone, zolpidem, and zaleplon), are amongst the most commonly prescribed medications for older adults in many countries. Because benzodiazepines are frequently prescribed for the management of insomnia, the prevalence of their use is estimated to be as high as 27% in the community setting, 55% in long-term care, and 69% in the hospital setting.[1,2] Although rates of benzodiazepine prescription have decreased in some countries over the years, this has only led to the unintended increase in the frequency of prescribing z-drugs, trazodone, quetiapine, and melatonin.[3-6]

In many cases, however, the use of these BZRAs is high-risk and potentially inappropriate.[7-9] Nearly 50% to 70% of individuals take these drugs chronically, sometimes for decades.[9,10] Dosing is also frequently higher than outlined in best practice recommendations for safety or maximum doses published in drug monographs.[9,11] Multiple clinical practice guidelines and professional medical societies have recommended that clinicians avoid BZRAs as first-line agents for insomnia, and many have advocated for deprescribing if they are currently being used.[12] These include the recommendations from the STOPP/START criteria, Beers Criteria, several national Choosing Wisely campaigns as well as practice guidelines developed by the American College of Physicians, the American Academy of Sleep Medicine, and the European Sleep Research Society.[13-17]

Deprescribing has been described as the "planned and supervised process of dose reduction or stopping of medication that might be causing harm or no longer providing benefit."[18] In a consensus process involving physicians, pharmacists, and nurse practitioners, BZRAs were selected as the highest priority for a deprescribing clinical practice guideline.[18] Although recent systematic reviews have concluded that deprescribing appears to be relatively safe and feasible, in the case of BZRAs it is particularly challenging.[19,20]

The identified issues include negotiating change and "buy-in" with patients, finding effective alternative approaches to manage insomnia, and advising on how best to intervene and taper the drugs.[2,18] After a systematic review of trials on benzodiazepine deprescribing for insomnia, a new clinical practice guideline has been published to help clinicians safely deprescribe benzodiazepines.[21]

In this paper, we describe the rationale for deprescribing BZRAs used for insomnia, summarize the recommendations and key messages for clinicians from the new BZRA deprescribing guideline (TABLE 1), and review their supporting evidence.

Rationale for deprescribing benzodiazepine receptor agonists for insomnia The overall benefits of BZRAs for insomnia are minimal to moderate at best. Evidence is limited to short-term use and the data suggest that a "placebo response" is a major contributor to their perceived effectiveness.[22] Based on multiple systematic reviews with meta-analyses, 13 patients (95% CI, 6.7–62.9) need to be treated with a benzodiazepine for one to report any improvement in sleep quality.[23] Compared with placebo, the mean decrease in sleep latency (10.0 minutes [95% CI, 3.4–16.6]) and increase in total sleep time (25.2 minutes [95% CI, 12.8- 37.8]) are considerably less than many patients expect of an effective treatment.[23,24] Similar results have been shown for the z-drugs.[22,24,25]

When used beyond a short-time period (ie, ≥2 weeks), benzodiazepines lose their utility in insomnia and the balance of harms outweighs any perceived benefits. Despite initial improvement in sleep parameters, benzodiazepines decrease the amount of deep sleep and thereby disrupt overall sleep architecture.[26] Both dependence (physiologic and psychological) and tolerance to the sedative and antiepileptic effects occur rapidly within 2 to 4 weeks, but the risk of adverse effects continues to persist.[27] In fact, adverse drug events associated with benzodiazepine use are more than twice as likely to occur compared with enhanced quality of sleep. Meta-analyses suggest that only 6 patients (95% CI, 6.7–62.9) need to be treated for 1 patient to experience an adverse drug event.[23]

The harms associated with BZRAs have been well described. In general, all BZRAs increase the risk of falls, fractures, motor vehicle accidents, delirium, and cognitive impairment. Meta-analyses of randomized controlled trials (RCTs) estimate increased odds of daytime sedation of 3.82 (95% CI, 1.88–7.80) and odds of cognitive impairment of 3.78 (95% CI, 1.47–15.47) with benzodiazepines.[23] Meta-analyses of observational studies estimate an increased relative risk of fractures of 1.25 (95% CI, 1.17–1.34) and an increase incident rate ratio of motor vehicle accidents of 1.81 (95% CI, 1.35–2.43).[28,29] Although the z-drugs were originally promoted

and perceived as safer alternatives to benzodiazepines for insomnia because of their more selective activity at the γ-aminobutyric acid type A receptor and shorter elimination half-lives, they appear to be similar in effectiveness as well as their potential for adverse effects, dependence, and abuse.[30] They carry similar risks of daytime sedation, cognitive impairment, falls, fractures, and motor vehicle accidents.[24,31]

The risk of physical and psychological dependence is high with BZRAs, and long-term use is habit forming.[32] It is estimated that dependence develops in nearly half of patients who use benzodiazepines for longer than 1 month.[33] Studies suggest that BZRAs with shorter half-lives are associated with a greater risk.[33,34] In addition, the rebound insomnia and withdrawal symptoms that may occur early with stopping the drugs make it harder to convince patients to stay off them. Older adults are particularly vulnerable to the harms of BZRAs due to age-related changes in pharmacokinetics and pharmacodynamics and an increased prevalence of frailty. This is reflected in strong recommendations for avoiding the use of benzodiazepines as either first-line or long-term treatment for insomnia in validated medication appropriateness criteria such as the STOPP/START and Beers Criteria.[13,14]

From a societal and population perspective, the negative impact of benzodiazepine use is large. Fall-related hospitalization attributable to benzodiazepines is estimated to cost the European Union nearly €1.8 billion annually (which represents 21.1% of total fall-related hospitalization costs).[35] In Canada, inappropriate benzodiazepine use is estimated to cost an extra $3076 per person per year in hospitalization, emergency department, and outpatient visit costs.[36]

2018 benzodiazepine deprescribing guideline: key recommendations and practical application A guideline development team based in Canada has developed a clinical practice guideline on deprescribing BZRAs using the systematic GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.[21,37] A summary figure of their deprescribing algorithm and a patient information pamphlet are available free of charge for clinicians at http://deprescribing.org. In community or long-term care settings where BZRAs are used for insomnia, the guideline recommends slow tapering for all adults aged 65 years or older and for younger adults if the use exceeds 4 weeks. Although it is not possible to draw firm conclusions because of the small number of trials identified and limited number of participants (see further below), this recommendation is supported by evidence of: 1) improved benzodiazepine cessation rates; 2) similar acute withdrawal and long-term insomnia rates; and 3) well-established risks for harm with long-term use. The optimum rate of tapering, though, is a key topic for future study.

TABLE 1 Key messages to remember when deprescribing benzodiazepine receptor agonists

An adverse event with BZRA use is twice as likely as any subjectively reported improvement in sleep quality (NNT = 6 vs NNH = 13).
Long-term use of BZRA is associated with serious harm including an increased risk of falls, fractures, motor vehicle accidents, cognitive impairment, dependence, and addiction.
Avoid starting a BZRA for insomnia, treat the underlying causes of the symptoms, and recommend safer nonpharmacologic alternatives (eg, cognitive behavioral therapy).
Success rates between 25% to 85% can be achieved with gradual taper strategies if patients are properly educated, provided with a clear plan for deprescribing, and informed about potential withdrawal symptoms
Deprescribing regimens should be flexible and individualized to the patient. A gradual dose reduction of 25% every 2 weeks is recommended as an initial tapering schedule based largely on expert opinion.

Abbreviations: BZRA, benzodiazepine receptor agonist; NNH, number needed to harm; NNT, number needed to treat

The need for educating and engaging patients in deprescribing of benzodiazepine receptor agonists Although there is limited evidence on how best to conduct the process of deprescribing, patient involvement and shared decision-making has been identified in multiple reviews of the deprescribing literature as important to facilitate deprescribing.[38,39]

Surveys of older adults in multiple jurisdictions suggest that there is interest and at least an initial willingness to participate in deprescribing interventions.[40-42] In a Canadian survey of community-dwelling older adults, more than half of the participants reported that they would like to reduce the number of medications they were taking, and more than two-thirds reported that they would be willing to cease one or more of their regular medications if their doctor said it was possible.[40]

It is unclear whether this patient interest in deprescribing applies as completely to BZRAs because opinions regarding specific medications were not explored. Genuine willingness may be much lower as patients (and clinicians) typically overestimate the benefits of treatments and underestimate their harms.[43] In the case of BZRAs, potential physical and psychological dependence compounds this problem.

Regardless of a patient's interest level in stopping their BZRA, prescribers have a fiduciary obligation to their patients to prescribe (and deprescribe) medications in a way that promotes optimal health and their best interests. In situations where the potential harms likely outweigh any perceived benefits, starting or continued prescribing of BZRAs without deprescribing could represent a lapse of this obligation. Depending on the BZRA dose or its clinical effect on the individual, continued use may also constitute a reason to reassess their medical fitness to drive given the drug's impact on road safety.[44]

The clinical practice guideline on BZRA deprescribing suggests discussing the rationale for deprescribing with patients and negotiating a shared plan of action through education and motivational interviewing techniques.[21] This involves dialogue on: 1) the loss of therapeutic effect with long-term use; 2) the risks of ongoing benzodiazepine use; 3) the potential benefits of a reduced dose or discontinuation; and 4) the tapering process and anticipated temporary withdrawal effects.

Studies suggest patients are more amenable to deprescribing if there is a clear plan for tapering, and if the patients are supported and know what to expect during the process.[38] In a recent systematic review of interventions to improve benzodiazepine tapering success, a meta-analysis of 3 RCTs (779 participants in total) evaluating tapering combined with patient education demonstrated a significant increase in the odds of BZRA cessation compared with usual care (odds ratio, 5.94; 95% CI, 3.99–8.83).[45]

RCTs have also shown that simple interventions that focus on patient empowerment and self-management have been successful in benzodiazepine deprescribing.[46,47] Interventions can motivate by focusing not only on the risks of continued use, but the potential benefits of stopping (eg, less daytime fatigue). One RCT found that patients who were successful in cessation and able to remain BZRA-free for at least 5 weeks had modestly lower levels of anxiety than before benzodiazepine discontinuation.[48] Although the prevention of future falls and fractures has not been confirmed in RCT meta-analyses and requires further study, a recent systematic review found that deprescribing BZRAs improves cognitive function across multiple domains (mean [SD] weighted effect size, 0.41 [0.22]).[49-51]

Impact of deprescribing interventions on benzodiazepine cessation rates Evidence syntheses suggest that successful benzodiazepine cessation rates ranging between 25% to 85% can be achieved with gradual tapering strategies.[21,52] Based on their systematic review of 10 RCTs involving 763 participants, Pottie and the guideline development team found improved cessations rates at both 3 months (relative risk [RR], 3.45; 95% CI, 1.49–7.99; 2 studies, 107 participants, low-quality evidence) and 12 months (RR, 2.39; 95% CI, 1.08–4.11; 1 study, 102 participants, moderate-quality evidence) with slow taper deprescribing interventions.[21] Although it is expected that deprescribing, compared with continuation, is probably more likely to elicit withdrawal symptoms and sleep problems on a temporary basis, limited data from observational studies suggest no significant difference in withdrawal scores at 3 months or sleep problems at 1 year (very low-quality evidence).[21]

Gradual dose reduction is generally recommended over abrupt discontinuation Although the guideline recommends a deprescribing strategy be offered to long-term benzodiazepine users and older adults, there is no evidence supporting

the superiority of one strategy over another. Switching from short-acting to long-acting benzodiazepines (eg, diazepam) prior to tapering has not been shown to improve rates of successful cessation or reduce the incidence or severity of withdrawal symptoms.[53-55] Most clinical trials have used gradual dose reductions to the lowest available dose of the specific benzodiazepine (eg, dose reduction of 25% every 1 to 2 weeks until drug-free). Lower and slower dose decrement rates have often been used near the end of taper (eg, dose reduction of 12.5% every 2 weeks). This is based on limited observational evidence suggesting that the most difficulty with discontinuation and withdrawal occurs in the second half of the taper because withdrawal symptoms often begin to appear once doses reach 25% of baseline.[53]

A gradual dose reduction is generally recommended over abrupt discontinuation to minimize withdrawal symptoms.[53-57] A recent scoping review found that 80% of studies evaluating BZRA deprescribing strategies have utilized a tapering approach.[58] Limited observational evidence in blinded BZRA deprescribing trials suggests that gradual dose reduction offers the advantage of decreased incidence and severity of withdrawal symptoms for long-term benzodiazepine users when compared to abrupt discontinuation.[48,53] However, very slow tapering does not appear to be superior to faster tapering regimens in terms of successful cessation.[53,59] Expert opinion and clinical experience also suggest that BZRAs can be abruptly discontinued safely in select situations where patients are closely monitored (eg, hospitalization) for adverse effects. In some of these cases, patients have minimal or no ill drug withdrawal effects. Overall, there is no high-quality evidence to guide the ideal period over which tapering regimens should be completed and to either support or refute that gradual tapering is safer or more effective than abrupt withdrawal from low- to usual-dose BZRAs. Studies systematically comparing taper rates are needed.

Experts generally advocate that taper schedules should be flexible and individualized for the patient to maximize the likelihood of success. They can require anywhere from a few weeks to several months depending on the patient's age, comorbidities, benzodiazepine type and dosage, original reason for prescribing, environmental or psychological stressors, available supports, patient readiness, personality type, and previous experiences with deprescribing or withdrawal.[53,60,61] Slower taper rates are generally advisable in patients who have a higher likelihood of relapse or complications.

Consider cognitive behavioral therapy and avoid substituting other medications Cognitive behavioral therapy (CBT) is a multimodal intervention that combines behavioral and cognitive techniques to elicit behavior change. It is the most common nonpharmacological therapy used for the treatment of insomnia and it can be delivered in different formats including individual, group, or self-directed therapy. Based on the results of the guideline development review, the addition of concomitant cognitive CBT did not lead to significant differences in benzodiazepine cessation rates at 3 months (RR, 1.18; 95% CI, 0.87–1.61; low-quality evidence) or 12 months (RR, 1.30; 95% CI, 0.68–2.47; low-quality evidence).

Despite these results, CBT is a reasonable option to consider, particularly if a patient is not ready for a deprescribing trial. Extensively studied as an individual treatment for insomnia, it is recommended as first-line therapy for chronic insomnia by the American College of Physicians.[15] High-quality systematic reviews have suggested clinically meaningful effect sizes with sustained long-term benefits.[62] CBT, however, is not widely available and can be expensive. A number of self-help CBT resources are available either free or at a relatively low cost. These include the CBT-i Coach mobile application developed by the United Department of Veteran Affair (https://itunes.apple.com/ca/app/cbt-i-coach/id655 918 660?mt=8), the Sleepwell website (https://mysleepwell.ca/) developed at Dalhousie University, or the *Overcoming Insomnia* workbook developed by the Duke University Insomnia and Sleep Research Program.[63]

There is no convincing evidence to recommend substitution or use of adjunct melatonin, nonbenzodiazepine hypnotics (eg, zopiclone or zaleplon), antidepressants (eg, trazodone), or anticonvulsants (eg, valproic acid or gabapentin) to improve benzodiazepine cessation rates.[21,59]

Educate patients and manage expectations for potential withdrawal symptoms Despite the knowledge of the potential adverse effects, fear of BZRA withdrawal and symptom relapse amongst both patients and prescribers is one of the most commonly cited barriers to benzodiazepine deprescribing—the so-called risk vs risk scenario.[52]

With BZRA discontinuation, rebound insomnia occurs in about half of patients in whom sleep latency is increased, sleep is more disturbed and shorter in duration.[48,53,64] This unfortunately often leads to the erroneous conclusion that the BZRA had a beneficial pharmacological effect and premature drug resumption is a common response. Clinicians and patients should be aware that these symptoms will improve over time if one persists with the deprescribing plan as these changes are transient and typically do not last a long time (<1 week).

In addition to rebound insomnia, many other potential withdrawal symptoms have been described. It should be noted that this "withdrawal syndrome" is largely based on studies of chronic dependent users taking BZRAs primarily for anxiety and depression and at higher daily dosages than typically used for insomnia.[48,53,65] In these studies, withdrawal symptoms were mostly mild to moderate and time-limited. The most common somatic symptoms were influenza-like

symptoms including headache, generalized weakness, fatigue, myalgias, diaphoresis, nausea, and loss of appetite, while the most common psychological and psychomotor withdrawal symptoms were sleep disturbance, anxiety, restlessness, impaired concentration, irritability, and hand tremors.

Anecdotally, clinical experts report that most of described withdrawal symptoms, with the exception of rebound insomnia and anxiety, are uncommon in people using BZRAs only for insomnia. This is consistent with the limited RCT studies describing withdrawal symptoms in this patient population, which suggest that most participants using BZRAs for insomnia report few withdrawal symptoms during gradual discontinuation and if they do occur, they are temporary and manageable.[66,67]

Increased risk of withdrawal symptoms can occur as quickly as after 2 weeks of continued use and the onset of symptoms is typically predictable based on the half-life of the benzodiazepine used (ie, the shorter the half-life, the earlier the onset of symptoms). If withdrawal symptoms occur, the majority experience mild symptoms of a short, limited duration (4 to 28 days).[68,69] The occurrence of severe withdrawal symptoms when following a planned deprescribing protocol is rare.[52] Gradual tapering of benzodiazepines does not guarantee avoidance of withdrawal symptoms, but serves to reduce the incident risk and severity (if they occur).

Clinicians should spend time to manage patients' expectations of potential withdrawal symptoms, educate them of the usual mild severity and limited duration of symptoms, and develop a shared action plan of what to do if withdrawal symptoms occur. For the occurrence of withdrawal symptoms of a severity that is not tolerated by the patient, the guideline algorithm suggests maintaining the current benzodiazepine dose for 1 to 2 weeks and then resuming the taper at a slower dose reduction rate.

Priority groups for cautious and thoughtful deprescribing

The decision to deprescribe and the process of deprescribing should take into consideration patients' comorbidities, concurrent medications and vulnerability to adverse events. Insomnia is a symptom, not a disease. It may be caused or exacerbated by another comorbid medical or psychiatric illness. Examples include mood or anxiety disorders, heart failure, obstructive sleep apnea, chronic obstructive pulmonary disease, gastroesophageal reflux disease, diabetes mellitus, urinary incontinence, restless leg syndrome, and uncontrolled pain disorders (eg, osteoarthritis). Insomnia can also be a direct or indirect manifestation of an adverse effect profile of a concurrent medication or ingestion. Common examples include alcohol, caffeine, antidepressants, and diuretics. In these cases, optimal treatment or modification of the underlying cause should be confirmed or pursued before benzodiazepine

deprescribing. These contributing conditions and medications should also be considered during the process of deprescribing as they may be causing pseudo-withdrawal symptoms that could easily be misinterpreted.

Known or potential comorbid mental health conditions are also critical to consider. Mood and anxiety-related disorders are common in individuals with insomnia using benzodiazepines.[70,71] Deprescribing benzodiazepines may have the unintended consequence of unmasking a previously undiagnosed or controlled anxiety symptoms and this possibility needs to be incorporated into the evaluation, follow-up, and management plan.

Frailty status may also have implications on both the urgency to deprescribe and the rate of deprescribing. Indicative of one's level of vulnerability (based on cumulative deficits or phenotype), people who are frail experience a higher incidence and severity of adverse drug events and may be more susceptible to harmful effects of BZRAs or their withdrawal syndromes.[72-74] Utilizing a clinically validated frailty scale (eg, Canadian Study of Health and Aging Clinical Frailty Scale or Study of Osteoporotic Fracture Frailty Index), this vulnerability should be taken into consideration as it may warrant a more cautious and slower approach to deprescribing.[75,76]

Proactive avoidance of deprescribing difficulties

Deprescribing difficulties and BZRA-related harm can be avoided by not initiating BZRA in the first place. While benzodiazepines have a few limited applications outside of insomnia in the community (ie, acute treatment of seizures and alcohol withdrawal and adjunctive treatment of anxiety disorders and anesthesia), they are only approved for intermittent short-term use (<2 weeks) for insomnia itself. However, given that adverse events have been estimated to be roughly twice as likely as any reported improvement in sleep quality, it is likely that the global risk-to-benefit ratio is unfavorable even with short-term use and they should not be initiated in any scenario for insomnia (especially in older adults).[23] This also includes the hospital setting where BZRA initiation for short-term hospital-associated insomnia is common but there is a significant risk factor for both new and chronic outpatient benzodiazepine use.[77,78]

In the rare instance that it is deemed clinically necessary to prescribe a BZRA for insomnia, it is important to discuss the risks and benefits of benzodiazepines with patients, set nonnegotiable prescription dosing and duration limits from the start (eg, short-term, limited-duration prescriptions with no refills), and create an expectation for monitoring and future deprescribing.

Conclusions

Deprescribing BZRAs is a top medication safety priority internationally given the serious potential harms and lack of benefit for clinically significant and patient-important outcomes. The new clinical practice guideline provides useful

evidence and direction on how to deprescribe BZ-RAs. Future studies evaluating different tapering strategies, patient engagement approaches, and long-term patient-important outcomes are needed.

CONFLICT OF INTEREST Drs. Farrell and Holbrook were both members of the benzodiazepine receptor agonists deprescribing guideline development team. Dr. Farrell received research funding from the Government of Ontario to develop this guideline and she has received honoraria from the College of Psychiatric and Neurologic Pharmacists, the European Association of Hospital Pharmacists, the Nova Scotia College of Pharmacists, and the Ontario Long Term Care Clinicians Association for speaking engagements related to deprescribing, as well as a stipend from the Institute for Healthcare Improvement for advice related to introducing deprescribing into the US health care system. Dr. Lee has received financial honoraria from McMaster University for speaking engagements related to deprescribing.

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