

# Deprescribing benzodiazepine receptor agonists

## Evidence-based clinical practice guideline

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### Abstract

**Objective** To develop an evidence-based guideline to help clinicians make decisions about when and how to safely taper and stop benzodiazepine receptor agonists (BZRAs); to focus on the highest level of evidence available and seek input from primary care professionals in the guideline development, review, and endorsement processes.

**Methods** The overall team comprised 8 clinicians (1 family physician, 2 psychiatrists, 1 clinical psychologist, 1 clinical pharmacologist, 2 clinical pharmacists, and 1 geriatrician) and a methodologist; members disclosed conflicts of interest. For guideline development, a systematic process was used, including the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. Evidence was generated by conducting a systematic review of BZRA deprescribing trials for insomnia, as well as performing a review of reviews of the harms of continued BZRA use and narrative syntheses of patient preferences and resource implications. This evidence and GRADE quality of evidence ratings were used to generate recommendations. The team refined guideline content and recommendations through consensus and synthesized clinical considerations to address front-line clinician questions. The draft guideline was reviewed by clinicians and stakeholders.

**Recommendations** We recommend that deprescribing (tapering slowly) of BZRAs be offered to elderly adults ( $\geq 65$  years) who take BZRAs, regardless of duration of use, and suggest that deprescribing (tapering slowly) be offered to adults aged 18 to 64 who have used BZRAs for more than 4 weeks. These recommendations apply to patients who use BZRAs to treat insomnia on its own (primary insomnia) or comorbid insomnia where potential underlying comorbidities are effectively managed. This guideline does not apply to those with other sleep disorders or untreated anxiety, depression, or other physical or mental health conditions that might be causing or aggravating insomnia.

**Conclusion** Benzodiazepine receptor agonists are associated with harms, and therapeutic effects might be short term. Tapering BZRAs improves cessation rates compared with usual care without serious harms. Patients might be more amenable to deprescribing conversations if they understand the rationale (potential for harm), are involved in developing the tapering plan, and are offered behavioural advice. This guideline provides recommendations for making decisions about when and how to reduce and stop BZRAs. Recommendations are meant to assist with, not dictate, decision making in conjunction with patients.

### Editor's key points

- ▶ Benzodiazepine receptor agonist (BZRA) prescribing for insomnia is common in both community and long-term care.
- ▶ The efficacy of BZRAs for insomnia can be diminished in as little as 4 weeks.
- ▶ Use of BZRAs is associated with increased risk of falls, motor vehicle accidents, memory problems, and daytime sedation—risks that might be increased in the elderly. Choosing Wisely Canada recommends that BZRAs should be avoided as first-line treatment of insomnia in older persons.
- ▶ A systematic review of BZRA deprescribing in patients demonstrated successful outcomes. The most common withdrawal symptoms were mild, short-term (days to weeks) insomnia, anxiety, and restlessness. There was no evidence of severe withdrawal (eg, seizures) symptoms.
- ▶ This guideline recommends that deprescribing of BZRAs (by tapering) be offered to all adults who take BZRAs, especially those aged 65 and older. Discuss with your patients and their caregivers the harms of continued use, decreased efficacy over time, tapering options, recommendations for monitoring, and potential withdrawal symptoms.

Long-term use of benzodiazepine receptor agonists (BZRAs), including benzodiazepines, zopiclone, and zolpidem, for insomnia is common in adults and the elderly in both community primary care and institutional practice.<sup>1,2</sup> The benefits of BZRAs for insomnia can be briefly summarized by referring to the meta-analysis by Holbrook et al, which found short-term (1 day to 6 weeks) improvements in sleep onset latency of 4 minutes and an additional hour of sleep duration.<sup>3</sup> However, chronic use of BZRAs might lead to physical and psychological dependence. In 2012, more than 30% of Canadian seniors in long-term care facilities and more than 15% living in the community used BZRAs.<sup>4</sup> New evidence has emerged suggesting that the efficacy of BZRAs for insomnia can diminish in 4 weeks, but adverse effects might persist.<sup>5</sup> Benzodiazepine receptor agonists were selected in a Canadian consensus process among family physicians, pharmacists, nurses, and geriatricians as the most important medication class for developing a deprescribing guideline.<sup>6</sup> In an effort to provide evidence-based recommendations and tools to aid clinicians in reducing or stopping medications that might no longer be needed or that might be causing harm, we initiated the Deprescribing Guidelines in the Elderly project ([www.open-pharmacy-research.ca/research-projects/emerging-services/deprescribing-guidelines](http://www.open-pharmacy-research.ca/research-projects/emerging-services/deprescribing-guidelines)).

Our objective was to systematically review the benefits and harms of deprescribing BZRAs, and use patient values and preferences and cost literature to develop evidence-based guidelines that assist clinicians and patients in making decisions about and taking action on reducing BZRA use.

This clinical guideline focuses on long-term use of BZRAs for insomnia. Insomnia, one of the most common complaints in primary care, is characterized by difficulty initiating or maintaining sleep accompanied by impaired daytime function.<sup>7</sup> It is classified by the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, as *insomnia disorder*, which can co-occur with other conditions or occur on its own (previously known as *primary insomnia* in the fourth edition of the manual).<sup>7,8</sup> In Canada, 13% of the population meets the criteria for insomnia, while the prevalence of insomnia is around 11% in the United States and Hong Kong.<sup>9,10</sup> Benzodiazepine receptor agonists and cognitive-behavioural therapy (CBT) have emerged as 2 of the common treatments of insomnia.<sup>11</sup> Guidelines suggest that BZRAs should only be used short term (typically up to 4 weeks) for treatment of insomnia.<sup>12,13</sup> However, in older persons, the Canadian Geriatrics Society and the Canadian Academy of Geriatric Psychiatry Choosing Wisely recommendations and the Beers criteria recommend avoiding BZRAs altogether as first-line treatment of insomnia, and that they should only be used after failure of nonpharmacologic interventions, for as short of a duration as possible.<sup>14-16</sup>

Benzodiazepine receptor agonists attach to a site on the  $\gamma$ -aminobutyric acid type A receptor, but when they

are used over an extended period of time, the receptor can physically change, leaving less potential for sedation but persistent amnesic effects.<sup>17</sup> Studies detect loss of therapeutic effect in a matter of 7 to 28 days.<sup>5</sup> Unfortunately, many patients are unaware of this effect and continue taking these agents indefinitely. This is problematic considering the potential for adverse effects (eg, falls, fractures, cognitive problems), especially in older persons.<sup>18,19</sup> For this reason, reviews have emerged over the past number of years investigating the effectiveness of interventions to stop or reduce use of BZRAs, but none has focused specifically on patients using BZRAs for insomnia.<sup>20-23</sup> While useful, these systematic reviews do not provide practical approaches to stopping or reducing BZRAs. Further, despite the scope of BZRA use, there are currently no evidence-based guidelines to assist clinicians in stopping or reducing use of BZRAs.

Deprescribing is the planned and supervised process of *dose reduction* or *stopping* of medication that might be causing harm or no longer providing benefit. The goal of deprescribing is to reduce medication burden and harm, while maintaining or improving quality of life. Our deprescribing guidelines, from our Deprescribing Guidelines in the Elderly project, use evidence to prioritize medications for deprescribing, to determine benefit and harms of continuing versus deprescribing a medication, and to suggest methods for approaching and implementing deprescribing plans with patients.

Our target audience includes primary care physicians, pharmacists, nurse practitioners, or other specialists who care for patients taking BZRAs for insomnia. The target population includes adults taking a BZRA to treat insomnia disorder: insomnia on its own (primary insomnia) or comorbid insomnia where underlying comorbidities are managed. This includes adults aged 18 to 64 who take BZRAs for most days of the week for more than 4 weeks<sup>12,24</sup> and elderly adults ( $\geq 65$  years of age) who take BZRAs regardless of duration.<sup>14-16</sup> The guideline does not apply to those with other sleep disorders or untreated anxiety, depression, or physical and mental conditions that might be causing or aggravating insomnia. These patients should be appropriately treated for their primary conditions before considering deprescribing of BZRAs or be referred to a psychologist or psychiatrist if appropriate.<sup>12</sup>

## — Methods —

We used Schünemann and colleagues' checklist for a successful guideline enterprise to construct the methods for developing deprescribing guidelines.<sup>25,26</sup>

The Guideline Development Team (GDT) comprised 8 clinicians (1 family physician and guideline chair [K.P.], 2 psychiatrists [R.S., S.D.], 1 psychologist [J.G.], 1 clinical pharmacologist [A.H.], 2 clinical pharmacists with geriatrics expertise [B.F., C.A.S.], and 1 geriatrician [C.B.]) and a GRADE (Grading of Recommendations

Assessment, Development and Evaluation) methodologist (V.W.). Searches were conducted in collaboration with a Canadian Library of Family Medicine librarian, as well as by a pharmacy resident (A.M.), a master's student (W.T.), and a staff member. All GDT members, staff, and investigators of the deprescribing project returned conflict of interest statements at the beginning and at the end of the process. Contributors' expertise, role descriptions, and conflicts of interest are available at **CFPlus**.\*

We used the GRADE system for guideline development (**Box 1**).<sup>27</sup> The GDT formulated the main clinical management question as follows using the PICO (population, intervention, comparison, outcome) approach: What are the effects (harms and benefits) of deprescribing BZRAs compared with continued use in adults with insomnia? We also investigated comparative effects of different deprescribing interventions. The GDT articulated definitions of *deprescribing* that included abrupt discontinuation, tapering, and switching or substituting therapy, among others (**Box 2**).

Before running our search we conducted a scoping review to assess the body of available evidence. We then conducted a systematic review to assess the effects of different approaches to deprescribing BZRAs. The methods and results of the systematic review can be found at **CFPlus**.\*

The systematic review focused on important outcomes relevant to patients, caregivers, and health care providers. Primary outcomes included sleep quality, effect on cognition (improvement or worsening), adverse drug withdrawal events, cessation rate (proportion of patients who completely stop BZRAs), and harms (daytime sedation, balance, motor vehicle accidents, falls, mortality, dependence). Secondary outcomes included BZRA pill burden (average BZRA dose) and patient satisfaction. The GRADE evidence tables that provide a summary of estimates on patient-important and critical outcomes for decision making can be found at **CFPlus**.\*

We formulated clinical recommendations from the evidence tables using confidence in estimated effects and taking into account benefits and harms of BZRA deprescribing, patient preferences and values, harms associated with continued BZRA use, and resource implications. The GDT members met via teleconference to review clinical recommendations and voting was conducted by e-mail. All votes were sent to the project coordinator; unanimous agreement was sought; 80% agreement among the 9 GDT members was considered the cutoff for consensus. All GDT members agreed with the final recommendations.

\*Descriptions of **contributors' expertise, roles, and conflicts of interest; methods and results of the systematic review** and related references; **GRADE evidence tables; ranges of frequency ratios for harms; evidence reviews** and related references; a **patient information pamphlet** on deprescribing of benzodiazepine receptor agonists; and an easy-to-print version of the **algorithm** are available at [www.cfp.ca](http://www.cfp.ca). Go to the full text of the article online and click on the **CFPlus** tab.

### Box 1. Notes on the GRADE framework for guideline development

This guideline was informed by a systematic review and was developed in accordance with the methods proposed by the GRADE Working Group<sup>27</sup>:

- We focused our review and recommendations on outcomes important to patients, such as harms or benefits resulting from deprescribing of BZRAs, harms of continued BZRA use, patient values and preferences, and costs and resource use. Outcomes were proposed by the systematic review team and revised by the Guideline Development Team based on feasibility and the available literature
- Ratings in the evidence profile tables included high, moderate, low, or very low, and depended on our confidence in the estimates of effect. Randomized controlled trials were used, and they started with a high-quality rating, but could be rated down by limitations in any of 4 domains: risk of bias, inconsistency, indirectness, and imprecision. Publication bias could not be rated owing to the paucity of studies
- The GRADE Working Group outlines appropriate wording for recommendations depending on the rating of strength and confidence in the evidence. A strong recommendation with implications for patients (phrased as "we recommend ...") implies that all patients in the given situation would want the recommended course of action, and only a small proportion would not. A weak recommendation (phrased as "we suggest ...") implies that most patients would wish to follow the recommendation, but some patients would not. Clinicians must help patients make management decisions consistent with patients' values and preferences. Implications for clinicians are similar such that a strong recommendation implies all or most patients should receive the intervention. A weak recommendation should prompt a clinician to recognize that different choices will be appropriate for individual patients

BZRA—benzodiazepine receptor agonist, GRADE—Grading of Recommendations Assessment, Development and Evaluation.

## — Recommendations —

The recommendations (**Box 3**) apply to adults aged 18 and older including elderly adults living in the community or in long-term care facilities who take BZRAs for the purpose of treating primary insomnia or comorbid insomnia where all potential underlying comorbidities are effectively managed. These recommendations do not apply to those with other sleep disorders or untreated anxiety, depression, or physical and mental conditions that might be causing or aggravating insomnia.

The rationale for the recommendations is outlined in **Table 1**.<sup>28,29</sup> The algorithm developed for this guideline is provided in **Figure 1**.

In this section of the guideline, we summarize the evidence reviews (ie, systematic review of deprescribing studies, review of reviews of BZRA harms, patient values and preferences, and cost and resource implications literature) that support the GRADE-based

**Box 2. Definitions of BZRA deprescribing**

Deprescribing BZRAs can include the following:

- Abruptly stopping the BZRA (ie, abrupt discontinuation)
- Tapering the BZRA dose (ie, gradually reducing the dose until complete cessation of the BZRA)
- Recommending CBT (ie, a CBT program for insomnia with the aim of stopping or reducing BZRA use in the process)
- Combining tapering and CBT
- Reducing BZRA use with the following approaches:
  - Using a lower dose of BZRA compared with baseline
  - Using BZRAs only as needed
- Providing substitutive therapy (ie, discontinuing the BZRA and replacing it with an alternative agent [eg, melatonin] either abruptly or by cross-tapering)

BZRA—benzodiazepine receptor agonist,  
CBT—cognitive-behavioural therapy.

**Box 3. Recommendations**

For elderly adults ( $\geq 65$  y) who use BZRAs, we recommend the following:

- Taper the BZRA dose slowly (strong recommendation, low-quality evidence)

For adults (18 to 64 y) who have used BZRAs most days of the week for  $> 4$  wk, we suggest the following:

- Taper the BZRA dose slowly (weak recommendation, low-quality evidence)

recommendations. Additional details of the evidence reviews and references can be found at **CFPlus**.\*

Our systematic review results suggest that slow tapering of BZRAs improves cessation rates at 3 and 12 months (compared with continuation or usual care) and does not result in differences in withdrawal symptom scores. **Table 2**<sup>28,30-38</sup> provides examples of tapering. Adding CBT to the tapering intervention improves cessation rates versus tapering alone, but this improvement is not maintained in the long term. Combining CBT and tapering does not appear to ameliorate withdrawal symptoms or affect sleep outcomes more so than tapering alone. Tapering of BZRAs might result in more problems sleeping compared with continuation, but there was no difference between these groups at 12 months. Using melatonin does not appear to improve cessation rates; studies employing zopiclone as a means of tapering from benzodiazepines did not produce usable data to inform recommendations.

Observational studies have shown that BZRAs are associated with various harms. These deserve special note because patients rely on health care professionals to provide them with this information. Associated harms include physical dependence, drowsiness, balance issues, falls, fractures, cognitive impairment, memory disorders (including anterograde amnesia), functional impairment, and motor vehicle accidents. Evidence

demonstrating harms of BZRAs comes largely from older persons, suggesting they might be at higher risk of adverse effects compared with younger adults (however, adverse effects such as dependence and somnolence have also been demonstrated in younger adults). More information on ranges of frequency ratios for harms and the evidence reviews can be found at **CFPlus**.\*

Older persons are often reluctant to consult with a physician about poor sleep owing to fear of receiving medication that they associate with drowsiness or losing control over what they consider to be a natural process. Some patients would like to stop using BZRAs but worry about insomnia, while others state strongly that they would like to continue using BZRAs. Patients tend to rate the benefits of BZRAs higher than physicians do and the risks lower; they commonly state they are reassured that BZRAs are safe because otherwise their physicians would not prescribe them. Those interested in stopping BZRA use see potential improvements in thinking and memory as benefits, as well as obtaining more natural sleep (evidence reviews are available at **CFPlus**).<sup>\*</sup> Spending on benzodiazepines is high; \$330 million was spent on BZRAs in Canada in 2012 to 2013.<sup>29</sup> Using CBT to manage insomnia instead of BZRAs would result in considerable savings owing to decreased risk of falls and related consequences (evidence reviews are available at **CFPlus**).<sup>\*</sup>

Based on the lack of evidence of substantial harm of deprescribing, the evidence of potential harm associated with continuing a BZRA (particularly in the elderly), along with resultant resource implications and the feasibility of tapering interventions, we rated the recommendation to deprescribe BZRAs in older patients as strong. The recommendation to deprescribe a BZRA in the younger population was rated as weak owing to lower risk of adverse effects associated with continuing BZRA use.

**Clinical considerations**

Community and institutional long-term care clinicians at our implementation sites clearly expressed 2 key concerns when applying this deprescribing guideline. First, approaching the patient and getting “buy-in” about reducing BZRA use is challenging. Second, clinicians wanted to know what other approaches could be used instead for insomnia. This section discusses clinically relevant findings on engaging patients, attitudes toward medications, other comorbid conditions, and tapering schedules.

**What patient attitudes should a clinician expect?** Our review of the literature suggests that there are a range of attitudes toward BZRA discontinuation. While some patients show reluctance, other patients appreciate the opportunity to taper and stop BZRA use in order to regain control over sleep and minimize potential for adverse effects. Indeed, our systematic review demonstrates that many patients can successfully discontinue BZRAs, with approximately 60% to 80% of patients able to stop BZRA



**Table 1. Evidence to recommendations table: What are the effects of deprescribing BZRAs compared with continuous use in insomnia for adults  $\geq 18$  y who use BZRAs for insomnia on its own or for comorbid insomnia with underlying comorbidities managed (specifically, adults 18-64 y using BZRAs for most nights of the week for  $> 4$  wk, or adults  $\geq 65$  y taking BZRAs for any duration as first-line therapy)?**

DECISION DOMAIN	SUMMARY OF REASON FOR DECISION	SUBDOMAINS INFLUENCING DECISION
QoE: Is there high- or moderate-quality evidence? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	The QoE for the benefits of deprescribing is low to moderate  The QoE for the harms of deprescribing is low to moderate	Key reason for downgrading is risk of bias  The QoE from RCTs for benefits of deprescribing is low  The QoE from RCTs for harms of deprescribing is moderate (sleep quality)
Balance of benefits and harms: Is there certainty that the benefits outweigh the harms? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	Effects of interventions on cessation rate <ul style="list-style-type: none"> <li>• Tapering or tapering with CBT improves cessation rates compared with usual care; tapering with CBT improves cessation rates compared with tapering alone postintervention (however, improved rate was not maintained at 3 or 12 mo). Behavioural and educational interventions offered as part of tapering advice</li> </ul> Sleep quality outcomes <ul style="list-style-type: none"> <li>• No change in sleep quality with BZRA discontinuation. There was a statistically significant difference in sleep quality with discontinuation of BZRAs compared with continuation of BZRAs at 3 mo in 1 study<sup>28</sup> owing to improvement of sleep in the continuation group; however, sleep quality in the taper group was no different than continuation at 52 wk</li> </ul> Anxiety <ul style="list-style-type: none"> <li>• There was a small decrease in anxiety reported with deprescribing vs continuation</li> <li>• Anxiety might improve within 1 y following deprescribing compared with continuation<sup>28</sup></li> </ul> Other harms of deprescribing (eg, adverse drug withdrawal effects) <ul style="list-style-type: none"> <li>• No difference in withdrawal symptoms (BWSQ score) when discontinuing BZRAs compared with continuation of BZRAs or usual care</li> </ul> Effect of deprescribing on cognition <ul style="list-style-type: none"> <li>• No significant effect noted in controlled trials at 12 mo</li> </ul> Adverse events for the elderly <ul style="list-style-type: none"> <li>• Adverse events for the elderly associated with long-term continued use of BZRAs were also identified: observational evidence shows increased fractures, motor vehicle accidents, functional impairment, respiratory exacerbations (COPD or pneumonia), and memory disturbance</li> </ul>	Is the baseline risk of benefit of deprescribing similar across subgroups? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> <ul style="list-style-type: none"> <li>• There is no evidence at this time to suggest different subgroups benefit from deprescribing</li> </ul> Should there be separate recommendations for subgroups based on risk levels? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> <ul style="list-style-type: none"> <li>• There is no evidence of benefit for any risk level</li> </ul> Is the baseline risk of harm of deprescribing similar across subgroups? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> <ul style="list-style-type: none"> <li>• There is no evidence that harms of deprescribing differ based on subgroup</li> </ul> Should there be separate recommendations for subgroups based on harms of continued use? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> <ul style="list-style-type: none"> <li>• Observational evidence shows risk of harm associated with continued use of BZRAs in older persons</li> <li>• Baseline risk of adverse events with continued BZRA use might be higher for older persons vs younger adults (very low-quality evidence)</li> <li>• Harms from deprescribing are low and not different between groups</li> </ul>
Values and preferences: Is there confidence in the estimate of relative importance of outcomes and patient preferences? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Patients tend to rate the benefits of BZDs higher than physicians do and rate the risks lower. Those patients interested in stopping BZDs see potential improvements in thinking and memory as benefits, as well as obtaining more natural sleep and feeling proud of themselves for having stopped. Factors associated with increased likelihood of stopping BZRA use include higher education level, lower intake or potency of BZDs, and lower anxiety sensitivity scores. Of those who fail BZD discontinuation, many describe having experienced such failure as difficulty in sleeping within a few days of stopping	<i>Perspective taken:</i> Evidence suggests there are patients who wish to discontinue BZRAs to avoid the harms of long-term use. There are others who might be hesitant and might fail owing to difficulty sleeping after stopping <i>Source of values and preferences:</i> Scoping review on subjects including the elderly <i>Source of variability, if any:</i> Education levels, potency of BZRA, and anxiety sensitivity scores Method for determining values satisfactory for this recommendation? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> All critical outcomes measured? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>

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DECISION DOMAIN	SUMMARY OF REASON FOR DECISION	SUBDOMAINS INFLUENCING DECISION
Resource implications: Are the resources worth the expected net benefit? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	<p>Cost implications</p> <ul style="list-style-type: none"> <li>• The <i>Canadian Rx Atlas</i><sup>29</sup> reports that the average Canadian aged <math>\geq 65</math> y spends \$26 annually on a BZD or z drug.</li> <li>• In Holland, tapering alone produced significantly more abstinence vs usual care and with cost benefits (36% vs 15%, NNT = 4.8; <math>P = .03</math>)</li> <li>• Cost-effectiveness studies showed deprescribing led to a reduction in the medication and related costs and adverse events</li> </ul> <p>Physician implications</p> <ul style="list-style-type: none"> <li>• Physicians often anticipate difficulty persuading patients to stop BZDs, concerned about their own workload and how patients will react to being encouraged to stop</li> </ul>	<p><i>Feasibility:</i> Is tapering BZRA intervention generally available? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/></p> <ul style="list-style-type: none"> <li>• Deprescribing readily available but CBT less so (owing to cost and access concerns; online CBT is available)</li> </ul> <p><i>Opportunity cost:</i> Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/></p> <p><i>Economic and preventive benefits for harms:</i> Is there a lot of variability in resource requirements across settings? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <ul style="list-style-type: none"> <li>• Deprescribing through education and tapering was believed to be a low-resource intervention, feasible for primary and long-term care. Studies suggest follow-up medical visits might be needed during tapering.</li> <li>• The addition of CBT to tapering increases the cost</li> </ul>
Overall strength of recommendation in older persons ( $\geq 65$ y): strong Overall strength of recommendation in adults $< 65$ y: weak	<p>There is low-quality evidence that deprescribing interventions improve cessation rates of BZRAs at 3 mo. Compared with continuation of BZRAs, tapering these drugs does not result in any difference in withdrawal symptom scores (low-quality evidence). Those who taper BZRAs might have more problems sleeping than those who continue; however, there is no difference at 12 mo (very low-quality evidence). Our systematic review found that deprescribing of BZRAs did not worsen anxiety. Despite low-quality evidence surrounding deprescribing, our recommendation was rated as strong in older persons owing to evidence surrounding harms of continued BZRA use specifically in older persons (associated increased risk of falls, cognitive impairment, motor vehicle accidents) and resultant resource implications. We also considered literature on patient preferences suggesting patients might value regaining control over sleep and potentially avoiding adverse effects of BZRAs</p>	
<p>BWSQ—benzodiazepine withdrawal symptom questionnaire, BZD—benzodiazepine, BZRA—benzodiazepine receptor agonist, CBT—cognitive-behavioural therapy, COPD—chronic obstructive pulmonary disease, NNT—number needed to treat, QoE—quality of evidence, RCT—randomized controlled trial.</p>		

use as a result of a deprescribing intervention. This is consistent with other systematic review evidence demonstrating a mean success rate of 25% to 80% for BZRA tapering (compared with 10% to 20% cessation rates with usual care when deprescribing is not initiated).<sup>39</sup>

In general, the decision to continue, reduce, or discontinue a medication is based on a balance of knowledge about its indication and effectiveness, as well as risks of use (actual or potential side effects), drug interactions, pill burden, and cost. Patient or family values and preferences play an important role in shared decision making with regard to continuing, tapering, or stopping medications. To facilitate these initial discussions we developed a patient pamphlet, which is available at **CFPlus**.\*

**What is causing insomnia?** When insomnia is caused by a comorbid condition, treatment should first be aimed at optimizing treatment of that condition.<sup>12,24</sup> Insomnia might occur on its own, might be related to a psychiatric illness (eg, an anxiety disorder or major depressive disorder), or might be related to another sleep-wake disorder (eg, sleep apnea or restless legs syndrome).<sup>40-44</sup> Other comorbid medical conditions such as respiratory diseases or pain disorders<sup>45</sup> might also initiate or exacerbate insomnia (such as nocturia, nocturnal pruritus).<sup>46-50</sup> Insomnia might be related to substance use (eg, caffeine,

alcohol) or pharmacologic treatment of other conditions (eg, antidepressants for major depressive disorder).<sup>42</sup> Contributory comorbid mental health conditions need to be considered as part of a comprehensive diagnostic evaluation before initiating treatment or considering deprescribing.<sup>50</sup> Once the reason for insomnia has been clearly determined, appropriate treatment can be instituted and the potential for deprescribing BZRAs considered more clearly.

**How do I engage patients in deprescribing BZRAs?** The GDT members believed that engaging patients in a discussion about BZRAs and their goals and preferences regarding BZRA use was an important first step. The need to engage patients and establish goals and preferences related to BZRA use and deprescribing was also echoed by clinicians at our implementation sites. Ensuring patient values and preferences are incorporated into shared decision making surrounding deprescribing has been highlighted as being critical given the preference-sensitive nature of these decisions.<sup>51</sup> Patients have indicated they would be more amenable to deprescribing if there were a clear plan for tapering and they knew what to expect.<sup>52</sup> The rationale for deprescribing should be clearly explained, a tapering plan should be negotiated, and the following evidence should be discussed:

- risks of ongoing BZRA use (eg, falls, memory impairment, motor vehicle accidents) and potential benefits of discontinuation (eg, reduced fall risk, less daytime sedation, improvement in thinking and memory);
- therapeutic effect of BZRAs might be lost within 4 weeks owing to receptor changes (but amnesic effects persist)<sup>5</sup>; and
- mild, short-term (a few days to weeks) adverse drug withdrawal effects can be expected during tapering.<sup>39</sup>

Our systematic review found that tapering strategies were often accompanied by such brief education interventions informing patients about the withdrawal process, sleep hygiene, and withdrawal symptoms.<sup>28,31</sup> Such engagement strategies (aimed at educating patients regarding BZRA use and involving them in tapering plans) have been employed as part of tapering interventions with success. Randomized controlled trials involving educational and motivational tools about the risks of BZRA use, the benefits of deprescribing, and the tapering process have been shown to be effective in deprescribing BZRAs.<sup>53,54</sup>

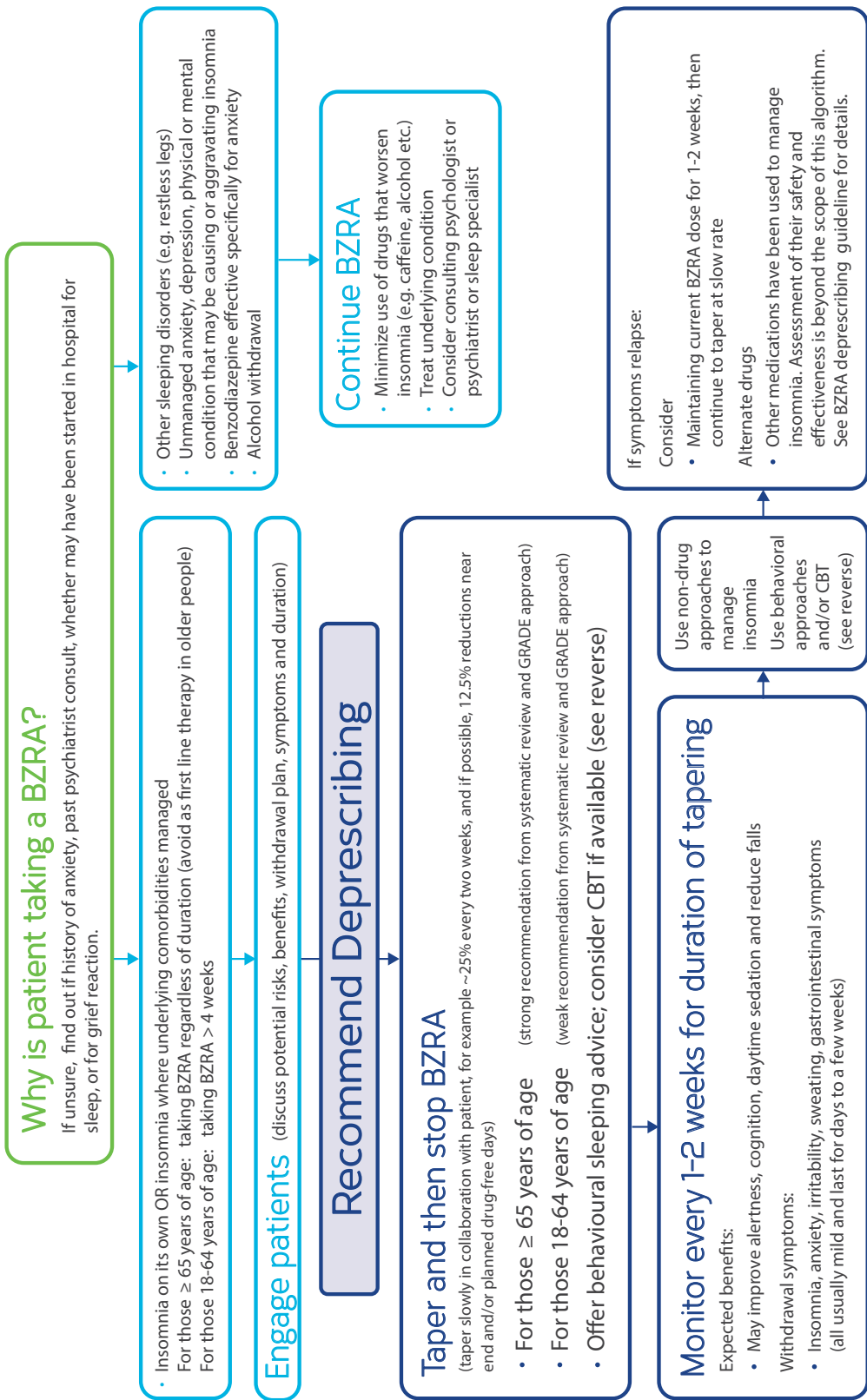
**How should tapering be approached?** A tapering deprescribing strategy should be offered to all eligible patients. However, our systematic review did not identify trials that compared different tapering strategies. Very gradual dose reductions to lowest available doses (eg, 25% reduction every 2 weeks and a slower taper of 12.5% every 2 weeks near the end of stopping), followed by periodic drug-free days were used successfully in clinical trials (Table 2).<sup>28,30-38</sup> Switching to long-acting BZRAs (eg, diazepam) has not been shown to reduce incidence of withdrawal symptoms or improve cessation rates more than tapering shorter-acting BZRAs does.<sup>55,56</sup> Patients using lower doses at baseline and using BZRAs for a shorter duration tend to have greater cessation rates and lower risk of restarting use of their BZRAs.<sup>57-59</sup> Psychological distress and worse general health at baseline appears to increase risk of needing to restart BZRA use.<sup>60,61</sup> When deciding on tapering doses and rates, consider using a slower rate with those more likely to have a higher risk of relapse (eg, long-term use or history of psychological distress). Some clinicians would recommend tapering over several months. Such patients might require closer monitoring and support. It has been the GDT members' experience that other patients might be able to simply stop taking their BZRAs with no or minimal ill effect, and some medical situations might require this, but care should still be taken to monitor for adverse drug withdrawal effects (see monitoring section below for more detail). Some evidence suggests that zolpidem might be less likely than a standard BZRA to cause tolerance, and therefore fewer withdrawal effects upon discontinuation, but there is likely to be a mixture of beneficial effects and adverse effects depending on the patient and duration of treatment.<sup>62,63</sup>

**What withdrawal symptoms can be expected and how should they be dealt with?** Concern over potential for withdrawal symptoms is a key reason why prescribers often do not approach patients about deprescribing BZRAs. Our systematic review found that there was no difference in overall BZRA withdrawal symptom scores for tapering compared with usual care or continuation of BZRAs. The tapering group reported more trouble sleeping at 3 months compared with continuation of BZRAs (mean difference of 16.1 higher on a 100-point scale of "trouble sleeping," 95% CI 15.0 to 17.2), but any difference in reports of trouble sleeping was no longer present at 12 months. In many cases, when withdrawal symptoms occur they are mild and short term (lasting a few days and up to approximately 4 weeks).<sup>39</sup> In studies detailing benzodiazepine withdrawal symptoms, such symptoms tend to appear and peak more quickly (1 to 2 days) and be more severe with abruptly stopping short-acting benzodiazepines compared with after tapering long-acting benzodiazepines (4 to 10 days).<sup>64,65</sup> Gradual taper of short-acting agents does not eliminate withdrawal symptoms but ameliorates their severity, with symptoms beginning to appear once doses are reduced to about 25% of baseline.<sup>55</sup> While common, resulting insomnia is typically mild, and patients should be assured that there is no difference in insomnia compared with usual care or continuation of BZRAs at 12 months. Behavioural management education for insomnia (Figure 1 and patient pamphlet at CFPlus)\* should be offered to patients to address insomnia during tapering. Other common withdrawal symptoms reported in the literature include irritability, sweating, gastrointestinal symptoms, and anxiety.<sup>39</sup> Patients should be reassured that if these symptoms occur they are typically mild and short term (lasting days to weeks), and that discomfort is usually temporary.<sup>39</sup> Severe withdrawal symptoms (eg, seizures) do not appear to occur with tapering but have been reported rarely in patients stopping very high doses without tapering<sup>39</sup> or who have underlying seizure disorders. Patients should be aware of the potential for withdrawal effects and these can be monitored throughout the tapering process (see monitoring section below for more detail).

**What nondrug approaches can be used to help with insomnia?** A variety of behaviour management strategies and interventions such as CBT have been used to help with insomnia and can be considered as nondrug alternatives should insomnia recur during or after deprescribing of BZRAs.<sup>66</sup> Cognitive-behavioural therapy for treatment of insomnia has been widely studied and demonstrates long-term improvements in sleep outcomes.<sup>67-70</sup> Our systematic review found that, when used as part of a deprescribing intervention, CBT combined with tapering improved post-intervention BZRA cessation rates compared with tapering alone. This is consistent with the current evidence base.<sup>21</sup>

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Figure 1 | Benzodiazepine & Z-Drug (BZRA) Deprescribing Algorithm



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**BZRA Availability**

BZRA	Strength
Alprazolam (Xanax®) <sup>T</sup>	0.25 mg, 0.5 mg, 1 mg, 2 mg
Bromazepam (Lectopam®) <sup>T</sup>	1.5 mg, 3 mg, 6 mg
Chlordiazepoxide (Librax®) <sup>C</sup>	5 mg, 10 mg, 25 mg
Clonazepam (Rivotril®) <sup>T</sup>	0.25 mg, 0.5 mg, 1 mg, 2 mg
Clorazepate (Tranxene®) <sup>C</sup>	3.75 mg, 7.5 mg, 15 mg
Diazepam (Valium®) <sup>T</sup>	2 mg, 5 mg, 10 mg
Flurazepam (Dalmane®) <sup>C</sup>	15 mg, 30 mg
Lorazepam (Ativan®) <sup>T,S</sup>	0.5 mg, 1 mg, 2 mg
Nitrazepam (Mogadon®) <sup>T</sup>	5 mg, 10 mg
Oxazepam (Serax®) <sup>T</sup>	10 mg, 15 mg, 30 mg
Temazepam (Restoril®) <sup>C</sup>	15 mg, 30 mg
Triazolam (Halcion®) <sup>T</sup>	0.125 mg, 0.25 mg
Zopiclone (Imovane®, Rhovane®) <sup>T</sup>	5mg, 7.5mg
Zolpidem (Sublinox®) <sup>S</sup>	5mg, 10mg

T = tablet, C = capsule, S = sublingual tablet

**BZRA Side Effects**

- BZRAs have been associated with:
  - physical dependence, falls, memory disorder, dementia, functional impairment, daytime sedation and motor vehicle accidents
  - Risks increase in older persons

**Engaging patients and caregivers**

Patients should understand:

- The rationale for deprescribing (associated risks of continued BZRA use, reduced long-term efficacy)
- Withdrawal symptoms (insomnia, anxiety) may occur but are usually mild, transient and short-term (days to a few weeks)
- They are part of the tapering plan, and can control tapering rate and duration

**Tapering doses**

- No published evidence exists to suggest switching to long-acting BZRAs reduces incidence of withdrawal symptoms or is more effective than tapering shorter-acting BZRAs
- If dosage forms do not allow 25% reduction, consider 50% reduction initially using drug-free days during latter part of tapering, or switch to lorazepam or oxazepam for final taper steps

**Behavioural management**

Primary care:

- Go to bed only when sleepy
- Do not use bed or bedroom for anything but sleep (or intimacy)
- If not asleep within about 20-30 min at the beginning of the night or after an awakening, exit the bedroom if not asleep within 20-30 min on returning to bed, repeat #3
- Use alarm to awaken at the same time every morning
- Do not nap
- Avoid caffeine after noon
- Avoid exercise, nicotine, alcohol, and big meals within 2 hrs of bedtime

Institutional care:

- Pull up curtains during the day to obtain bright light exposure
- Keep alarm noises to a minimum
- Increase daytime activity & discourage daytime sleeping
- Reduce number of naps (no more than 30 mins and no naps after 2 pm)
- Offer warm decaf drink, warm milk at night
- Restrict food, caffeine, smoking before bedtime
- Have the resident toilet before going to bed
- Encourage regular bedtime and rising times
- Avoid waking at night to provide direct care
- Offer backrub, gentle massage

**Using CBT**

What is cognitive behavioural therapy (CBT)?

- CBT includes 5-6 educational sessions about sleep/insomnia, stimulus control, sleep restriction, sleep hygiene, relaxation training and support

Does it work?

- CBT has been shown in trials to improve sleep outcomes with sustained long-term benefits

Who can provide it?

- Clinical psychologists usually deliver CBT, however, others can be trained or can provide aspects of CBT education; self-help programs are available

How can providers and patients find out about it?

- Some resources can be found here: <http://sleepwells.ca/>

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**Table 2. Deprescribing methods from eligible trials in systematic review**

STUDY	TAPERING STRATEGY	NOTES
Baillargeon et al, 2003 <sup>30</sup>	Reduce dose by 25% every 1-2 wk until stopped	Patients followed up weekly; could remain at same dose if they experienced withdrawal symptoms
Belleville et al, 2007 <sup>31</sup>	Reduce dose by 25% every 2 wk until lowest available dosage is reached; then introduce drug-free nights progressively	Drug-free nights planned in advance Rate of taper could vary depending on presence of withdrawal symptoms
Curran et al, 2003 <sup>28</sup>	Reduce dose by 25%-50% every 2 wk until stopped	Rate specific to patient's original dose and BZRA
Garfinkel et al, 1999 <sup>32</sup>	Reduce dose by 50% for 2 wk; then reduce by 25% for 2 wk, and then discontinue	NA
Habraken et al, 1997 <sup>33</sup>	Reduce dose by 25% weekly for 3 wk; then reduce by 12.5% for 2 wk	All participants took lorazepam
Morin et al, 2004 <sup>34</sup>	Reduce dose by 25% every 2 wk until lowest available dosage is reached; then introduce drug-free nights	Drug-free nights planned in advance Specific instructions could vary based on withdrawal symptoms
Pat-Horenczyk et al, 1998 <sup>35</sup>	Reduce dose by 50% for 1 wk; then discontinue	All subjects took zopiclone or flurazepam
Shapiro et al, 1995 <sup>36</sup>	Switch to zopiclone for 4 wk and then recommend abrupt cessation of zopiclone	All patients switched from BZDs through 1 of the following methods: stopping BZD for 3 d and then starting zopiclone; directly switching to zopiclone; or overlapping existing BZD with zopiclone for 3-8 d, and then stopping BZD and continuing zopiclone
Vissers et al, 2007 <sup>37</sup>	Reduce dose by 25% every 2 wk for 6 wk; then reduce by 12.5% for 2 wk and then stop	First converted to diazepam and stabilized for 2 wk
Voshaar et al, 2003 <sup>38</sup>	Reduce dose by 25% weekly for 4 wk; participants could choose to split last step into 12.5% reduction for 4 d	First converted to diazepam and stabilized for 2 wk

BZD—benzodiazepine, BZRA—benzodiazepine receptor agonist, NA—not applicable.

However, the improved BZRA cessation rates following deprescribing were not sustained at 3 months and CBT did not improve clinical outcomes. Deprescribing studies typically employed 4 to 6 CBT sessions delivered by clinical psychologists every 1 to 2 weeks.

Behavioural interventions and CBT for insomnia are reviewed in more detail elsewhere.<sup>67,68</sup> While CBT might be difficult to access for many patients owing to cost and availability, online and self-help options are available.<sup>69,71</sup> Brief interventions and Internet-based CBT have also been shown to be effective in improving sleep outcomes.<sup>67-69,72</sup> The website [sleepwellns.ca](http://sleepwellns.ca) is an example of such an online resource; a link to this site is highlighted in our decision-support algorithm (Figure 1) and patient information pamphlet (CFPlus),\* in which we offer behaviour management advice. With training, various health care professionals can also provide CBT or its components.

**What monitoring needs to be done, how often, and by whom?** Tapering will reduce, but might not eliminate, withdrawal symptoms.<sup>28,34</sup> A monitoring plan should be developed in conjunction with the patient. At each step in the taper (approximately every 1 to 2 weeks for the duration) monitor for severity and frequency of adverse drug withdrawal symptoms (anxiety, irritability, sweating, gastrointestinal symptoms, insomnia), potential benefits

(eg, less daytime sedation, improved cognition, fewer falls), and mood, sleep quality, and changes in sleep. This can be done at a scheduled appointment or through a telephone call (by physician, psychologist, pharmacist, or nurse). If desired, withdrawal symptoms can be monitored using the types of scales used in clinical trials (eg, benzodiazepine withdrawal symptom questionnaire or Clinical Institute Withdrawal Assessment for Benzodiazepines scale)<sup>73</sup> or via clinical assessment. If withdrawal symptoms occur at a severity and frequency that is bothersome for a patient, consider maintaining the current BZRA dose for 1 to 2 weeks before attempting the next dose reduction; then continue to taper at a slower rate.

**What if insomnia returns or persists?** If insomnia persists, consideration should be given to using behavioural management techniques or CBT.<sup>66,67</sup> There are no medications for primary or chronic insomnia in the elderly that are proven to be safe and effective. A 2015 US evidence synthesis by the Agency for Healthcare Research and Quality on management of insomnia disorder reported little to no long-term efficacy evidence for pharmacologic treatments.<sup>67</sup> A 2016 evidence-based guideline from the American College of Physicians strongly recommends CBT for chronic insomnia and includes a weak recommendation for shared decision

making concerning other nonpharmacologic and pharmacologic options.<sup>66</sup>

### Comorbidities

When offering BZRA deprescribing it is essential to be vigilant for pre-existing or incident depression or anxiety disorders. Psychiatric comorbidities are common in insomnia.<sup>74,75</sup> In a 6-year longitudinal study using national data,<sup>76</sup> individuals who both had insomnia and were taking a benzodiazepine had a 5-fold increased risk of developing depression and a 3-fold risk of developing an anxiety disorder compared with individuals who did not have insomnia and did not use benzodiazepines. This increased comorbidity might be due to pre-existing risk factors that initially triggered insomnia but might also relate to a biologic or psychological reaction to the consequences of insomnia or to pharmacologic changes associated with long-term BZRA use.<sup>77</sup>

Depression and anxiety disorders are prevalent in people with insomnia using benzodiazepines. Stopping or reducing a drug with anxiolytic properties (ie, most benzodiazepines) might unmask a previously undiagnosed anxiety disorder. In addition, a change in the behavioural routine of taking a hypnotic medication at bedtime might also provoke a psychological response with anxiety. Cognitive-behavioural therapy might be useful in this instance.<sup>66</sup>

Where depression or anxiety is present, it might be necessary to initiate pharmacologic- or psychotherapy-based treatment. In the context of insomnia, treatment guidelines<sup>13,78</sup> recommend antidepressants that can provide sedation directly.

Where patients exhibit features of an anxiety disorder, a first step would be clinical inquiry for anxiety disorders. In the case of generalized anxiety disorder, a condition dominated by worry in which sleep disturbance is an accessory diagnostic feature, psychological therapy (eg, CBT) or pharmacologic treatment are effective options. First-line medications include serotonin or serotonin-norepinephrine reuptake inhibitors and pregabalin.<sup>79-81</sup> There is still a need for high-quality direct evidence for adjunctive medications in benzodiazepine deprescribing for insomnia.

### Medicolegal considerations

The Canadian Medical Protective Association reported that sedatives were among the most common drugs in the 215 medicolegal cases surrounding medication use between 2005 and 2010 (proportion not reported).<sup>82</sup> Inadequate assessment of adverse effects and not properly evaluating potential effects of drug use in older persons were commonly implicated. Further, 16 of 49 medicolegal cases of opioid-related adverse events involved benzodiazepines.<sup>83</sup> Given the potential for adverse effects with BZRA use, appropriateness and opportunities for deprescribing should be routinely addressed by prescribers on an ongoing basis.<sup>82,84</sup>

### Clinical and stakeholder review

External clinical review of the guideline was conducted by a practising geriatrician and a pharmacist using the AGREE II (Appraisal of Guidelines for Research and Evaluation) Global Rating Scale tool.<sup>85</sup> Relevant stakeholder organizations were invited to similarly review and endorse the guideline. Modifications were made to address reviewer comments. This guideline has been endorsed by the College of Family Physicians of Canada and the Canadian Pharmacists Association.

### How this deprescribing guideline relates to other clinical practice guidelines for insomnia and BZRAs

Guidelines recommending BZRA use for insomnia suggest that attempts to discontinue therapy should be made after 4 weeks.<sup>12,24</sup> Several organizations recommend avoiding BZRAs altogether in older persons as first-line therapy for insomnia.<sup>14-16</sup> The 2016 American College of Physicians evidence-based guideline for treatment of insomnia strongly recommends the use of CBT as first-line treatment of insomnia.<sup>66</sup>

The joint clinical practice guideline from the American Geriatrics Society and the British Geriatrics Society on falls prevention suggests that reduction or withdrawal of sedative hypnotics (such as BZRAs) should be pursued as part of multifactorial falls reduction interventions, along with other components such as exercise and adaptation of the home environment.<sup>86</sup> Systematic reviews and meta-analyses have shown that multifactorial falls prevention strategies (involving medication review or targeted medication [eg, BZRA] withdrawal) reduce fall rates.<sup>87,88</sup>

A BZRA deprescribing guideline works in conjunction with current treatment guidelines because it offers clinicians evidence-based recommendations and clinical considerations to help them deprescribe BZRAs.

### Gaps in knowledge

Insomnia is a common and often complex condition. Practitioners need tools to assist them in both diagnosis and treatment of insomnia, recognizing anxiety and other psychiatric conditions, as well as specific forms of insomnia. Our research provides an estimated strategy for tapering BZRAs. We did not identify studies that compared various tapering regimens head-to-head. There is also limited evidence for optimal shared decision-making approaches related to deprescribing BZRAs. Finally, most studies did not evaluate patient-important outcomes such as quality of life or function. Thus, studies comparing patient engagement approaches and tapering strategies (eg, duration of tapering), and focusing on patient-important outcomes (eg, quality of life and function) are needed to help guide effective deprescribing approaches. There is also a need to study BZRA deprescribing in relation to the potential dependence period at around 4 weeks of BZRA use, as well as the

cost-effectiveness of BZRA deprescribing interventions. More implementation work is needed to improve the process of tapering, as well as consideration of linking it to multifactorial interventions for improving health in elderly adults.

## Next steps

The GDT will provide routine guideline updates as new evidence emerges that might change the recommendations. Prospective evaluation of the effects of this and other deprescribing guidelines will be part of a research strategy in the future.

## Conclusion

The use of BZRAs for insomnia disorder in aging adults has been associated with falls, dementia, motor vehicle accidents, and physical addiction. This guideline outlines these harms and, through a systematic review, demonstrates the efficacy of deprescribing using tapering regimens in patients who were willing to enter deprescribing trials. Many patients are willing to stop taking BZRAs when they can expect improvements in cognition and reductions in other side effects. The tools provided with this guideline—a decision-support algorithm and a corresponding patient information pamphlet—are intended to support clinicians in engaging with patients about this important topic and implementing deprescribing plans with them. A credible guideline developed with a rigorous evidence-based approach arms the clinician with a clear case for discussions about BZRA deprescribing with patients.

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## Contributors

All authors made substantial contributions to the conception and design of the guideline; the acquisition, analysis, and interpretation of data; and drafting the article, revising it critically for important intellectual content, and approving the final version.

## Competing interests

**Dr Farrell** received research funding to develop this guideline; received financial payments from the Institute for Healthcare Improvement and The Commonwealth Fund for a deprescribing guidelines summary; and from the Ontario Long Term Care Physicians Association, the Ontario Pharmacists Association, and the Canadian Society of Hospital Pharmacists for speaking engagements. **Dr Boyd** received funding from Patient-Centered Outcomes Research Institute for a project related to improving patient-centred care for people with multiple chronic conditions and funding from the National Institutes of Health for a project related to medication regimen complexity in home health care. **Dr Sadowski** is the primary investigator on an unrestricted grant from Pfizer Canada related to finding novel strategy to address the underdiagnosed and undertreatment of overactive bladder and urinary tract symptoms and is a member of the Alberta Expert Committee on Drug Evaluation and Therapeutics. None of the other authors has any competing interests to declare.

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