

Canadian Guidelines on Benzodiazepine Receptor Agonist Use Disorder Among Older Adults Title



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ABSTRACT

Background

Benzodiazepine receptor agonist (BZRA) use disorder among older adults is a relatively common and challenging clinical condition.

Method

The Canadian Coalition for Seniors' Mental Health, with financial support from Health Canada, has produced evidence-based guidelines on the prevention, identification, assessment, and management of this form of substance use disorder.

Results

Inappropriate use of BZRAs should be avoided by considering non-pharmacological approaches to the management of late life insomnia, anxiety, and other common indications for the use of BZRA. Older persons should only be prescribed BZRAs after they are fully informed of alternatives, benefits, and risks associated with their use. Clinicians should have a high index of suspicion for the presence of BZRA use disorders. The full version of these guidelines can be accessed at www.ccsmh.ca

Conclusions

A person-centred, stepped care approach utilizing gradual dose reductions should be used in the management of BZRA use disorder.

Key words: benzodiazepine, substance use disorder, older persons

INTRODUCTION

Substance use disorders affect millions of Canadians.⁽¹⁾ While in general the prevalence rates for these disorders are lower among older (65 years of age or greater) persons, clinicians should be aware that these conditions can still occur in this segment of the population and be vigilant for them. Sedative use disorder is of particular concern in this age group, as the prescription rate in Canada for these agents is highest among older persons. About one in six are consuming a sedative.⁽²⁾

The Canadian Coalition for Seniors' Mental Health (CC-SMH), with financial support from the Substance Use and Addictions Program of Health Canada, has created a set of four guidelines on the prevention, assessment, and management of substance use disorders among older adults for alcohol, benzodiazepine receptor agonists (BZRAs), cannabis, and opioids. This article deals with the BZRA use disorder guideline.

This is not intended to provide a comprehensive guide on the prescription and/or consumption of BZRAs. Rather, the goal is to provide useful advice for practitioners on preventing the development of BZRA use disorder, identifying it if present, and assessing and treating older persons who have developed this condition. Practitioners may wish to de-prescribe BZRAs being taken by an older patient. Deprescribing is defined as a process of withdrawal of an inappropriate medication, supervised by a health-care professional, with the goal of managing polypharmacy and improving outcomes.³ Reasons for deprescribing, other than a BZRA use disorder, include the BZRAs may no longer be needed, the risk of side effects, or the presence of a contraindication to their continued consumption. Recommendations made in this guideline on

patient education about the potential risks of BZRA use and how to safely discontinue these agents would be relevant for these purposes.

METHODS

The CCSMH BZRA Guideline Development Working Group was created to lead the process. DC and DH were appointed as co-leads of the group. Group membership was based on willingness to commit to the project, and either possessing the required expertise or having a lived experience perspective. Ensuring diversity of members in age, gender, disciplinary background, and geographic distribution across Canada guided the final composition of the Guideline Development Working Group.

Members volunteered to focus on either the prevention or management of BZRA use disorder. Within these broad areas, they assumed leadership roles in assessing and creating recommendations to deal with specific topics. This process was guided by systematic searches of databases to identify relevant literature that was then reviewed by Guideline Development Working Group members. A series of in-person and videoconferences were held to maintain progress, discuss emerging issues, refine recommendations, ensure consistency, and identify gaps. A modified version of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology was utilized to first assess (and score) the quality of the available evidence for each recommendation (based on consideration of study design and quality of available studies, applicability to the question being addressed, and confidence in the estimate of the effect), and

then to assess its overall strength, which took into account additional factors such as the balance between benefit and harm, patient values and preferences and whether this would be a wise use of the required resources for implementation (see Box 1).⁽⁴⁾ A separate category was created for recommendations that were not primarily based on empirical evidence but represented best clinical practice. They were categorized as consensus recommendations. Members of the guideline Working Group voted on all recommendations. For adoption, a recommendation had to achieve consensus approval (75%+ affirmative vote by the members of the Working Group). We were actually able to discuss until we reached 100% member consensus on each recommendation. Details on the methodology used are available at the following <https://ccsmh.ca/substance-use-addiction/intro/>.

BACKGROUND

BZRA use disorder refers to a problematic pattern of BZRA use leading to clinically significant impairment or distress. According to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5) criteria, BZRA use disorder is manifested by at least two of the following eleven criteria occurring within a 12-month period⁽⁵⁾:

1. The BZRA is being taken in larger amounts and/or over a longer period of time than intended.
2. Presence of persistent desire or unsuccessful efforts to cut down or control BZRA consumption.
3. Excessive time is spent on activities to obtain, use, or recover from the effects of BZRAs.
4. Craving (a strong desire or urge to use a BZRA) is present.
5. Recurrent BZRA use has resulted in the failure to fulfill major role obligations at work, school, or home.
6. There is continued use of the BZRA despite negative consequences in social or interpersonal situations.
7. Valued social, occupational, or recreation activities are given up or reduced because of BZRA use.
8. Recurrent BZRA use is occurring in situations where it is potentially hazardous.
9. There is continued use of the BZRA despite knowledge of having a persistent or recurrent physical or psychological problem likely caused or exacerbated by the medication.
10. Tolerance (defined by either a need for markedly increased amounts of the BZRA to achieve intoxication or the desired effect or a markedly diminished effect with continued use of the same amount of the BZRA) develops. Tolerance is not considered to be present if an individual is taking the agent under medical supervision.
11. A withdrawal syndrome (manifested by characteristic symptoms that include tachycardia, hypertension, tremor, headache, nausea and/or vomiting, paresthesias, insomnia, psychosis, depersonalization, depressive or anxiety symptoms, delirium, and/or seizures that occur one to two days after stopping short-acting BZRAs and up to several

BOX 1. Scoring of the quality of evidence and strength of recommendation (based on GRADE approach)

Quality of Evidence

- High: Further research is unlikely to change confidence in the estimate of effects
- Medium: Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate
- Low: Further research is very likely to have an important impact on the confidence in the estimate of effect and may change the estimate

Strength of Recommendation

- Strong: Indicates high confidence that desirable consequences of the proposed course of action outweigh the undesirable consequences (or vice versa)
- Weak: Indicates that there is either a close balance between benefits and downsides (including adverse effects and burden of treatment), uncertainty regarding the magnitude of benefits and downsides, uncertainty or great variability in patients' values and preferences, or that the cost or burden of the proposed intervention may not be justified

weeks after discontinuing long-acting ones) occurs, or the person takes a BZRA (or a closely related substance such as alcohol) to relieve or avoid withdrawal symptoms.

The number of criteria present determines the severity of the use disorder (i.e., 2–3 = mild, 4–5 = moderate, 6+ = severe).

There are particular challenges in the assessment of BZRA use disorders in older persons. Alterations in social roles or the circumstances of the older person (e.g., retirement from work, living alone) can mask their presentation. Age-related pharmacokinetic and pharmacodynamics changes might render older persons more sensitive to adverse effects from BZRAs. Finally, the presence of co-morbidities can heighten the risks of adverse consequences such as cognitive impairment and falls, as well as masking the presence of a BZRA use disorder.

BZRAs act as allosteric modulators of gamma-aminobutyric acid (GABA) activity by binding to inotropic benzodiazepine receptors at the GABA A receptor complex. BZRAs increase GABA binding and chloride ion channel opening, facilitating inhibitory activity. Some of these drugs have a benzodiazepine chemical structure (e.g., alprazolam, bromazepam, chlordiazepoxide, cobazam, clonazepam, clorazepate, diazepam, flurazepam, lorazepam, midazolam, nitrazepam, oxazepam, temazepam, triazolam), while others do not and are referred to as non-benzodiazepine receptor agonists, novel benzodiazepine receptor agonists, or z-drugs (e.g., zolpidem, zopiclone). In this article, we use the term BZRAs for both. The recommendations made deal with all BZRAs, as they have similar benefits, side effects, and risks.

These drugs have regulatory approval for the management of anxiety and panic disorders, short-term treatment of insomnia, seizures, alcohol withdrawal, sedation, and spasticity. They are also often used in an off-label manner to treat conditions such as anxious depression or the behavioural and psychological symptoms of dementia, which are also referred to as responsive behaviours. Though rates of use are dropping in Canada,⁽⁶⁾ these drugs continue to be frequently prescribed, despite widespread agreement that BZRAs should be avoided whenever possible in older adults.^(7,8) An estimated 9–10% of older adults taking BZRAs meet criteria for substance dependency.⁽⁹⁾

KEY CLINICAL RECOMMENDATIONS

The twenty-three recommendations contained in the guideline are included in Box 2 along with the GRADE score for each recommendation. In this summary, we focus on those felt to be of greatest utility for practitioners; however, all the recommendations are listed in Box 2. These key recommendations, as well as the rationale for them and mention of other supporting recommendations, are reviewed below.

Recommendation #1

Long-term use of BZRAs (> four weeks) in older adults should be avoided for most indications because of their minimal

efficacy and risk of harm. Older adults have increased sensitivity to BZRAs and decreased ability to metabolize some longer-acting agents, such as diazepam. All BZRAs increase the risk of cognitive impairment, delirium, falls, fractures, hospitalizations, and motor vehicle crashes. Alternative management strategies for insomnia, anxiety disorders, and the behavioural and psychological symptoms of dementia (also known as responsive behaviours) are recommended. BZRAs have minimal efficacy for anxiety, insomnia, or responsive behaviours related to dementia. This is coupled with concerns about their associated adverse effects.⁽¹⁰⁾ These drugs commonly appear on lists of medications to avoid in the care of older patients.^(7,8) Age-related pharmacokinetic and pharmacodynamics changes predispose older patients to adverse effects such as the ones listed in Recommendation #1.

Recommendations #2

Appropriate first-line non-pharmacological options for the treatment of insomnia and anxiety disorders include cognitive behavioural therapies (CBTs) provided in various formats. Both the American College of Physicians⁽¹¹⁾ and European Sleep Research Society⁽¹²⁾ recommend CBT as first-line therapy for insomnia, with BZRAs and other sedatives reserved for the short-term therapy of those who fail to benefit. CBT is also effective for anxiety.⁽¹³⁾ Available data also do not support the routine use of benzodiazepines for the treatment of the behavioural and psychological symptoms of dementia.⁽¹⁴⁾ Other than as bridging therapy until more appropriate approaches become effective, BZRAs should only be considered for these indications after the patient has failed an adequate trial of either a non-pharmacological intervention or a more effective and/or safer pharmacological option (**Recommendation #3**). An important consideration is the need to advocate for both access and funding of effective non-pharmacological alternatives for the management of these common conditions (**Recommendation #10**).

Prior to initiating therapy, an assessment of risk for a BZRA use disorder and other potential adverse effects should be conducted (**Recommendation #4**). As well the patient should be informed of both the limited benefits and risks associated with BZRA use and alternatives (**Recommendation #5**). Initiating therapy should be a shared decision, with an up-front discussion of how the BZRA should be used and will be monitored (**Recommendation #6**).

Recommendation #7

Older adults who are receiving a BZRA should be:

- educated and provided the opportunity to discuss the on-going risks of taking BZRAs;
- encouraged to only take the BZRA for a short period of time (two to four weeks or less) at the minimally effective dose;
- monitored during the course of their prescription for evidence of treatment response and effectiveness, current and

BOX 2. Recommendations

Recommendation #1: Long-term use of BZRAs (> 4 weeks) in older adults should be avoided for most indications because of their minimal efficacy and risk of harm. Older adults have increased sensitivity to BZRAs and decreased ability to metabolize some longer-acting agents, such as diazepam. All BZRAs increase the risk of cognitive impairment, delirium, falls, fractures, hospitalizations, and motor vehicle crashes. Alternative management strategies for insomnia, anxiety disorders, and the behavioural and psychological symptoms of dementia (BPSD) are recommended. [GRADE: Evidence: Moderate; Strength: Strong]

Recommendation #2: Appropriate first-line non-pharmacological options for the treatment of insomnia and anxiety disorders include cognitive behaviour therapies (CBTs) provided in various formats. [GRADE: Evidence: Moderate; Strength: Strong]

Recommendation #3: A BZRA should only be considered in the management of insomnia or anxiety after failing adequate trials of non-pharmacological interventions or safer pharmacological alternatives OR for short-term bridging until more appropriate treatment becomes effective. [GRADE: Evidence: Moderate; Strength: Strong]

Recommendation #4: An assessment of risk for BZRA use disorder and other potential adverse effects from these agents should be done prior to prescribing a BZRA. [Consensus]

Recommendation #5: If a BZRA is being considered, the older adult should be informed of both the limited benefits and risks associated with use, as well as alternatives, prior to deciding on a management plan. [Consensus]

Recommendation #6: Initiating treatment with a BZRA should be a shared decision between the prescriber and the older adult (or their substitute decision-maker). There should be agreement and understanding on how the BZRA is to be used (including planned duration of no more than 2 to 4 weeks) and monitored. [Consensus]

Recommendation #7: Older adults who are receiving a BZRA should be:

- Educated and provided the opportunity to discuss the ongoing risks of taking BZRAs [GRADE: Evidence: Moderate; Strength: Strong]
- Encouraged to only take the BZRA for a short period of time (2 to 4 weeks or less) at the minimally effective dose [GRADE: Evidence: Moderate; Strength: Strong]
- Monitored during the course of their prescription for evidence of treatment response and effectiveness, current and potential adverse effects, concordance with the treatment plan, and/or the development of a BZRA use disorder [Consensus]
- Supported in stopping the drug, which may require a gradual reduction until discontinued. [GRADE: Evidence: Moderate; Strength: Strong]

Recommendation #8: Health-care providers and organizations should consider implementing interventions to decrease

inappropriate use of BZRAs in their practice settings. These include medication reviews, prescribing feedback, audits and alerts, multidisciplinary case conferences, and brief educational sessions. Regulators, health authorities, and professional organizations should consult with clinical leaders and older adults to develop and implement policies that aim to minimize inappropriate use of BZRAs. [GRADE: Evidence: Low; Strength: Strong]

Recommendation #9: Health-care institutions, including acute care hospitals and long-term care facilities, should implement protocols that minimize new prescriptions for BZRAs because of the potential for harm and the risk of this leading to long-term use following discharge to the community or other transitions in care. [GRADE: Evidence: Low; Strength: Strong]

Recommendation #10: Health-care practitioners, older adults, and their families should advocate for adequate access and funding of effective non-pharmacological alternatives for the management of insomnia, anxiety disorders, and BPSD. [GRADE: Evidence: Low; Strength: Strong]

Recommendation #11: Clinicians should be aware that BZRAs are prescribed more frequently to women and the potential implicit bias that may lead to inappropriate use. [GRADE: Evidence: Low; Strength: Weak]

Recommendation #12: All older adults should be asked about current and past consumption of substances that might lead to substance use disorders, including BZRAs, during periodic health examinations, admissions to facilities or services, perioperative assessments, when considering the prescription of a BZRA, and at transitions in care. [Consensus]

Recommendation #13: Health-care practitioners should be aware of and vigilant to the symptoms and signs of substance use disorders, including BZRA use disorder. Particular attention should be paid to this possibility when assessing common conditions encountered in older adults, such as falls and cognitive impairment. [Consensus]

Recommendation #14: Assessment of older adults suspected of having a BZRA use disorder should include indication, dose, duration, features indicative of BZRA use disorder, readiness to change, and presence of both medical and psychiatric comorbidities, including any other past or current substance use or misuse. [Consensus]

Recommendation #15:

- Multiple substance use is common and should be considered and inquired about in all older adults with a BZRA use disorder. [GRADE: Evidence: Moderate; Strength: Strong]
- Health-care practitioners should avoid prescribing BZRAs concurrently with opioids whenever possible. [GRADE: Evidence: Moderate; Strength: Strong]
- The combination of a BZRA with alcohol should be avoided. [GRADE: Evidence: Low; Strength: Weak]

Recommendation #16: A person-centred, stepped-care approach to enable the gradual withdrawal and discontinuation of BZRAs should be used. Clinicians and patients should share in: a) planning and applying a gradual dose reduction scheme supported by appropriate education of the patient; b) identifying and optimizing alternatives to manage the underlying health issue(s) that initiated or perpetuated the use of BZRAs; c) developing strategies to minimize acute withdrawal and managing rebound symptoms as needed; and d) establishing a schedule of visits for reviewing progress. [GRADE: Evidence: Moderate; Strength: Strong]

Recommendation #17: Abrupt discontinuation of a BZRA after intermediate to long-term use (> 4 weeks) in individuals with BZRA use disorder should be avoided due to the risk of withdrawal symptoms, substance dependence reinforcement, rebound phenomena, and/or higher likelihood of relapse with resumption of BZRA use. [GRADE: Evidence: Moderate; Strength: Strong]

Recommendation #18: Management of acute BZRA withdrawal symptoms should be monitored carefully and can be guided by a validated tool [e.g. Benzodiazepine Withdrawal Symptom Questionnaire, Clinical Institute Withdrawal Assessment-Benzodiazepine (CIWA-B)] and managed with symptom-driven judicious use of an appropriate BZRA. [GRADE: Evidence: Low; Strength: Weak]

Recommendation #19: Regimens involving multiple BZRAs should be simplified and converted to a single BZRA. [Consensus]

Recommendation # 20: The routine switching of a short half-life BZRA with one having a long half-life to aid in withdrawing BZRAs is not generally recommended in older adults. Switching may have a role in certain situations, such as when withdrawal is being hindered by a limited number of available BZRA pill strengths or when alprazolam is the agent of dependence or misuse. [GRADE: Evidence: Moderate; Strength: Strong]

Recommendation #21: Psychological interventions such as CBT should be considered during efforts to withdraw BZRAs as they can improve the older adult's experiences and increase the likelihood of stopping the BZRA. [GRADE: Evidence: High; Strength: Strong]

Recommendation #22: Substituting a pharmacologically different drug as a specific intervention to mitigate BZRA withdrawal symptoms during gradual dose reduction is not routinely recommended [GRADE: Evidence: Moderate; Strength: Strong]

Recommendation #23: Older adults with a BZRA use disorder whose drug use is escalating in spite of medical supervision, have failed prior efforts to withdraw their BZRA, are at high risk for relapse or harm, and/or suffer from significant psychopathology should be considered for referral to a specialty addiction or mental health service. [Consensus]

- potential adverse effects, concordance with the treatment plan, and/or the development of a BZRA use disorder; and
- d) supported in stopping the drug, which may require a gradual reduction until discontinued.

Pharmacist-led educational interventions, consisting of a patient brochure about the risks of BZRAs and alternatives, an evidence-based opinion recommending discontinuing the agent provided to the prescribing physician, and/or one-time counseling of patients, have been shown to decrease BZRA use among community-dwelling older adults.⁽¹⁵⁻¹⁸⁾ As with all prescribed medications, appropriate follow-up care should be provided. Patients must be monitored for evidence of effectiveness and signs of harm, with drug therapy discontinued if the agent is ineffective or the risks of continued use outweigh the benefits.

Recommendation #13

Health-care practitioners should be aware of and vigilant for the symptoms and signs of substance use disorder, including BZRA use disorder. Particular attention should be paid to this possibility when assessing common conditions encountered in older adults, such as falls and cognitive impairment.

Older adults should be routinely asked about current and past consumption of substances that might be associated with use disorders, including BZRAs, during periodic health examinations, at care transitions (e.g., admissions to facilities or services), preoperative assessments, or when a BZRA is

being considered (**Recommendation #12**). Case finding for a use disorder in those at risk can be done by asking if they have taken a prescription medication for a non-medical reason, made prior efforts to cut down on consumption, and/or have used more than intended over the last year.^(19,20) Practitioners should be aware of the DSM-5 criteria for BZRA use disorder and adept in following up on older patients who require a more in-depth evaluation. This assessment should include inquiring about: indication, dose, and duration of BZRA use; presence of BZRA use disorder criteria; readiness of the patient to change their use of the BZRA; and, presence of medical and psychiatric co-morbidities including any other current or past substance misuse or use disorder (**Recommendations #14 and #15**).

Recommendation #16

A person-centred, stepped-care approach to enable the gradual withdrawal and discontinuation of BZRAs should be used. Clinicians and patients should share in:

- a) planning and applying a gradual dose reduction scheme supported by appropriate education of the patient;
- b) identifying and optimizing alternatives to manage the underlying health issue(s) that initiated or perpetuated the use of BZRAs;
- c) developing strategies to minimize acute withdrawal and managing rebound symptoms as needed; and
- d) establishing a schedule of visits for reviewing progress

A stepped care approach to deprescribing BZRAs would start with brief interventions, and then progress to multicomponent approaches, as indicated.⁽²¹⁾ The involvement of the patient in developing, implementing, and modifying the treatment plan is vital. Gradual dose reduction (GDR), often developed with a pharmacist, and regular planned follow-up meetings to both supervise the withdrawal of the BZRA and manage underlying health issue(s), should be implemented. For the latter, psychological interventions like CBT can be helpful (**Recommendation #21**). Abrupt discontinuation of a BZRA taken longer than four weeks should be avoided because of the risk of withdrawal symptoms, substance dependence reinforcement, rebound phenomena, and/or higher likelihood of relapse with resumption of the BZRA (**Recommendation #17**). The ideal rate of tapering with GDR is uncertain. Initially reducing the dosage by 10–25% every one to two weeks, with slower rates of reduction later on, is a reasonable strategy for many, but the type of BZRA consumed (e.g., alprazolam is considered to have unique properties that increase its misuse properties),⁽²²⁾ dosage used, and duration of therapy will influence this.⁽²³⁾ Management of withdrawal symptoms can be informed by the use of validated tools (**Recommendation #18**).

Other guidance given when deprescribing a BZRA include: simplifying multiple BZRA regimens to a single agent (**Recommendation #19**); not routinely switching short half-life BZRAs to long half-life ones (**Recommendation #20**); and, not routinely using a pharmacologically different drug to mitigate BZRA withdrawal symptoms (**Recommendation #22**).

Recommendation #23

Older adults with a BZRA use disorder whose drug use is escalating in spite of medical supervision, who have failed prior efforts to withdraw their BZRA, who are at risk for relapse or harm, and/or who suffer from significant psychopathology should be considered for referral to a specialty addiction or mental health service.

DISCUSSION

While many older adults with BZRA use disorders can be successfully managed in a primary care setting, there are some who should be referred to a specialty service.

Ethical Challenges

While clinical practice guidelines inform appropriate care, they do not in isolation define it. Proposing the discontinuance of a BZRA may be met with resistance by an older patient who perceives benefit and no significant harm with on-going use. Although avoiding or discontinuing the long-term use of a BZRA is, in general, the recommended course of action, this is not the case for every patient. Discontinuing a medication is an active intervention and should be a shared decision with the patient and governed by professional standards of care for that jurisdiction. Prescribers uncomfortable in continuing to prescribe a BZRA to an older adult where they believe the

risk is greater than any likely benefit do not have a duty to do so, as it is ethically indefensible to provide treatment against sound medical judgment.⁽²⁴⁾ It is emphasized, though, that discontinuing a BZRA being consumed long-term should never be done abruptly, and patients must not be deserted in times of need.

DISCLAIMER

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CONFLICT OF INTEREST DISCLOSURES

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