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ASAM Clinical Practice Guideline on Benzodiazepine Tapering
Draft for Public Comment

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Executive Summary

Purpose

To develop and disseminate this *Clinical Practice Guideline on Benzodiazepine Tapering* (hereafter referred to as the Guideline), The American Society of Addiction Medicine (ASAM) has partnered with:

- The American Academy of Family Physicians (AAFP),
- The American Academy of Neurology (AAN),
- The American Academy of Physician Associates (AAPA),
- The American College of Medical Toxicology (ACMT),
- The American Association of Nurse Practitioners (AANP),
- The American Association of Psychiatric Pharmacists (AAPP)
- The American College of Obstetricians and Gynecologists (ACOG),
- The American Geriatrics Society (AGS), and
- The American Psychiatric Association (APA).

The Guideline provides information on evidence-based strategies and clinically informed standards of care for whether and how to taper benzodiazepine (BZD) medications.

Background

Benzodiazepines (BZDs) are commonly prescribed, and FDA approved to treat a wide range of conditions including anxiety and mood disorders, insomnia, and seizures. BZD use is associated with increased risk for adverse events including falls, motor vehicle accidents, cognitive impairment, and overdose (particularly when BZD are used in combination with opioids).[1] The risk-benefit balance may shift over time and, because physiological dependence develops with long-term use, stopping can be challenging. When BZDs are used regularly, abruptly discontinuing or decreasing the dose can lead to serious withdrawal symptoms.

Patients who have been taking BZD for longer than a month should not abruptly discontinue the medication, but rather should gradually taper the dosage over a period of time under clinical supervision. Many patients who have been taking BZD for less than 4 weeks are able to discontinue the medication without a taper. However, physiological dependence can develop in as little as 2 weeks. Depending on medication and patient characteristics, some patients who

have been taking BZD for less than a month may benefit from a taper. This Guideline aims to assist clinicians in helping patients safely taper their BZD medication, while minimizing withdrawal symptoms and associated risks.

Key Takeaways

This Guideline focuses on approaches to tapering BZD medications in patients who have used BZDs for over a month. Recommendations address considerations for tapering, level of care , tapering strategies, withdrawal management, and specific patient populations. The following are 10 key takeaways of this Guideline:

1. Approaches to BZD tapering should always be considered in collaboration with the patient utilizing shared decision-making strategies.
2. Clinical recommendations regarding continued BZD use versus tapering should be based on an ongoing assessment of risks and benefits of continued BZD use. When the risks of BZD medication outweigh the risks, tapering is generally indicated.
    a. More frequent assessment of the risks and benefits of continued BZD prescribing should be conducted for patients who:
        i. Are co-prescribed opioids
        ii. Have a substance use disorder (SUD)
        iii. Have other risk factors for adverse effects
    b. When considering the risks and benefits of continued BZD prescribing in pregnant patients, the maternal fetal dyad should be considered.
    c. Clinicians should taper BZD in most older adults unless there are compelling reasons for continuation.
3. Harm reduction strategies (e.g., naloxone for those co-prescribed opioids or otherwise at risk for opioid overdose) should be employed based on the individual patient's risks.
4. BZD should not be abruptly discontinued in patients who have been taking these medications daily or near daily for longer than one month.
5. While most patients are able to complete BZD tapering in outpatient settings, inpatient or medically managed residential care should be considered when the patient's presentation indicates significant risk that cannot be managed in an outpatient setting.

6. The tapering process should be designed to minimize withdrawal symptoms while balancing the risk of continued BZD use. The initial pace of the BZD taper should generally include dose reductions of 5-25% every 2 to 4 weeks and ***no more than 25% every 2 weeks***
7. Tapering strategies should be tailored to the individual patient and adjusted based on patient response. Patients should be monitored for the emergence of BZD withdrawal signs and symptoms with each dose reduction. If significant signs or symptoms emerge the pace of the taper should be adjusted.
8. Patients undergoing a BZD taper should be offered adjunctive psychosocial interventions (e.g., cognitive behavioral therapy [CBT], sleep hygiene education) to support successful tapering.
9. Patients undergoing BZD withdrawal management in an inpatient or other medically managed setting should be monitored for signs and symptoms of BZD withdrawal regularly – using vital signs and a structured assessment tool – and assessed for seizure risk and managed as appropriate.
10. Concurrent treatment should be provided for any co-occurring substance use or psychiatric disorders.

Summary of Recommendations

Recommendations for Considerations for Tapering BZDs

1. For each patient taking BZD, prescribing clinicians should ideally assess the risks and benefits of ongoing BZD prescribing at least every 3 months (*Clinical consensus, Strong Recommendation*).
    a. At a minimum, risks and benefits should be assessed with each new BZD prescription or BZD prescription refill authorization (*Clinical consensus, Strong Recommendation*).
    b. Prescribing clinicians should review the information in the relevant PDMP as a part of the risk benefit assessment (*Clinical consensus, Strong Recommendation*).
2. When the risks of BZD medication outweigh the benefits for a given patient, tapering is generally indicated (*Clinical consensus, Strong Recommendation*).

a. The clinician should initiate a conversation about tapering, including alternatives for management of the underlying condition (*Clinical consensus, Strong Recommendation*).

3. Clinicians should avoid abruptly discontinuing BZD medication in patients who have been taking BZD daily or near daily (e.g., more days than not) for longer than one month *(Low certainty, Strong Recommendation)*.
    a. While many patients who have been taking BZD for less than 4 weeks are able to discontinue the medication without a taper, clinicians can consider a short taper *(Clinical Consensus, Conditional Recommendation)*.
        i. If the BZD is discontinued without a taper the patient should be counseled to report the emergence of withdrawal and/or rebound symptoms *(Clinical Consensus, Strong Recommendation)*.
            1. If significant symptoms emerge, the clinician can consider medications for symptom management or restarting the BZD and initiating a taper *(Clinical Consensus, Conditional Recommendation)*.

Recommendation for Level of Care Considerations

4. Inpatient care should be considered when:
    a. Patient presentation indicates an imminent risk for significant harm related to continued use of BZD (e.g., overdose, accidents, falls, suicidality or other self-harm) *(Clinical consensus, Strong Recommendation)*;
    b. Patient symptoms and/or co-occurring physical or mental health conditions [e.g., seizure disorder, concomitant use of medications that lower the seizure threshold] cannot be safely managed in the outpatient setting *(Clinical consensus, Strong Recommendation)*;
    c. The patient is experiencing or imminently anticipated to experience severe or complicated withdrawal *(Clinical consensus, Strong Recommendation)*; and
    d. The patient has a history of severe or complicated withdrawal *(Clinical consensus, Strong Recommendation)*.

Recommendation Statement for Partnering with Patients

5. The BZD tapering strategy should be developed in coordination with the patient and/or their care partner(s) in a shared decision-making process, whenever possible *(Clinical consensus, Strong Recommendation)*.

Tapering Process Recommendation Statements

6. Prior to beginning a taper, clinicians should conduct a thorough medication and health review, with particular attention to other psychoactive medications and conditions that may be impacted during the taper *(Clinical consensus, Strong Recommendation)*.
7. When determining the initial pace of the BZD taper, clinicians should generally consider dose reductions of 5-25%. The pace of the taper should not exceed 25% every 2 weeks (See Table 1)*(Clinical consensus, Strong Recommendation)*.
    a. Clinicians should consider current BZD dose and half-life, frequency and duration of BZD use, comorbidities, and patient response to any prior BZD tapering attempts *(Clinical consensus, Strong Recommendation)*.
    b. The overall tapering strategy should be designed to minimize harms, considering the risk for withdrawal symptoms and the risk of harm related to continued BZD use *(Clinical consensus, Strong Recommendation)*.
8. For patients without contraindications (e.g., liver dysfunction, interacting medications), clinicians can consider transitioning to a comparable dose of a longer-acting BZD for the taper *(Clinical consensus, Conditional Recommendation)*.
9. Tapering strategies should be tailored to the individual patient and adjusted based on the patient's response *(Clinical consensus, Strong Recommendation)*.
    a. Patients undergoing tapering should be evaluated for signs and symptoms related to the BZD taper with each dose reduction *(Clinical consensus, Strong Recommendation)*.
    b. For patients experiencing significant symptoms related to the BZD taper, clinicians should consider pausing or slowing the pace of the taper and/or making smaller dose reductions *(Clinical consensus, Strong Recommendation)*.
10. The BZD tapering process can be more difficult for patients as the total daily dose of BZD decreases. Clinicians should proactively consider smaller dose reductions and/or slowing the

pace of dose reductions as the taper progresses *(Clinical consensus, Strong Recommendation)*.

11. If a patient is unable to tolerate further BZD dose reductions, the clinicians can consider – in partnership with the patient and other members of the care team – maintaining the patient on the lower BZD dose with regular risk benefit assessment consistent with Recommendation #1 *(Clinical consensus, Conditional Recommendation)*.

Adjunctive Interventions Recommendation Statements

12. Adjunctive psychosocial interventions should be offered when tapering BZD *(Clinical consensus, Strong Recommendation)*.
    a. Patients undergoing BZD tapering should be offered, or referred for, behavioral interventions such as CBT *(Very Low Certainty, Strong Recommendation)*.
    b. Clinicians should educate patients on lifestyle factors that could support BZD tapering (e.g., sleep hygiene, physical activity as appropriate to ability) *(Clinical consensus, Strong Recommendation)*.
    c. Clinicians can consider recommending complementary health approaches such as mindfulness practices *(Clinical consensus, Conditional Recommendation)*.
    d. Clinicians can consider referring patients for peer specialist services to provide support during the taper *(Clinical consensus, Conditional Recommendation)*.
13. For patients experiencing symptoms that significantly interfere with the taper (e.g., sleep difficulty, anxiety symptoms), clinicians should first consider pausing or slowing the pace of the taper *(Clinical consensus, Strong Recommendation)*.
    a. Clinicians can also consider adjunctive medications to address symptoms interfering with the taper *(Clinical consensus, Conditional Recommendation)*.

Recommendations for BZD Withdrawal Management

14. Patients undergoing BZD withdrawal management in an inpatient or other medically managed setting should be:
    a. Monitored for signs and symptoms of BZD withdrawal regularly using vital signs and a standardized assessment tool *(Clinical consensus, Strong Recommendation)*; and
    b. Assessed for seizure risk and managed as appropriate *(Clinical consensus, Strong Recommendation)*.

15. Tapering with very long-acting agents (e.g., with phenobarbital, chlordiazepoxide) should typically be conducted in an inpatient or medically managed residential setting (e.g., ASAM Criteria Level 3.7). *(Clinical consensus, Conditional Recommendation)*.
    a. Tapering with very long-acting agents may also be conducted in outpatient settings with extended nurse monitoring (e.g., ASAM Criteria Level 2.7) by, or in consultation with, a clinician experienced in the use of these medications for BZD tapering. *(Clinical consensus, Conditional Recommendation)*.
16. Following a physiological taper, discharge planning should include an outpatient follow-up appointment, ideally, within 7 days *(Clinical consensus, Strong Recommendation)*.
17. The follow up clinician should:
    a. Assess the patient for ongoing signs or symptoms related to discontinuation of BZD, including re-emergence of symptoms for which the BZD was originally prescribed *(Clinical consensus, Strong Recommendation)*; and
    b. Consider medications and/or behavioral interventions to address ongoing signs or symptoms related to discontinuation of BZD *(Clinical consensus, Conditional Recommendation)*.
18. Due to risks for refractory seizure, dysrhythmias, and other side effects, for the purpose of BZD tapering, clinicians should avoid rapid BZD reversal agents such as flumazenil *(Clinical consensus, Strong Recommendation).*
19. For the purpose of BZD tapering, clinicians should generally avoid general anesthetics such as propofol or ketamine *(Clinical consensus, Conditional Recommendation)*.

Recommendations for Patients Co-Prescribed BZD and Opioids

20. For patients who are co-prescribed BZD and opioids: Prior to initiating a BZD taper, the clinician should seek to coordinate care with any other clinician(s) who may also be prescribing BZD or opioids *(Clinical consensus, Strong Recommendation)*.
21. Because of the increased risk for respiratory depression with concurrent use of BZD and opioids, the prescribing clinician should assess the risks and benefits of continued BZD prescribing at least every 3 months *(Clinical consensus, Strong Recommendation)*.
    a. Risk benefit assessments should be conducted more often when the patient has other risk factors for adverse events *(Clinical consensus, Strong Recommendation).*

22. Clinicians should provide or prescribe naloxone for all patients co-prescribed BZD and opioids *(Clinical consensus, Strong Recommendation)*.
23. Clinicians should consider additional strategies for mitigating risk, including using lowest effective doses of BZD and opioid medications, and optimizing non-opioid interventions *(Clinical consensus, Strong Recommendation)*.

Recommendations for Patients with BZD Use Disorder and/or Co-Occurring SUD

24. For patients with SUD, clinicians should consider using existing standards for level of care recommendations such as *The ASAM Criteria (Clinical consensus, Strong Recommendation)*.
    a. For patients unlikely to effectively participate in an outpatient taper, clinicians should consider a residential or inpatient setting *(Clinical consensus, Strong Recommendation)*.
25. For patients with BZD use disorder, alcohol use disorder, or opioid use disorder: Clinicians should assess the risks and benefits of continued BZD prescribing at least monthly *(Clinical consensus, Strong Recommendation)*.
26. For patients with other comorbid addictions (e.g., stimulant use disorder, cannabis use disorder, behavioral addictions): Clinicians should consider more frequent assessments of the risks and benefits of continued BZD prescribing compared to the general guidance (Recommendation #1). *(Clinical consensus, Strong Recommendation)*.
27. When tapering BZD in a patient with SUD, the underlying SUD should be managed concurrently with the BZD taper *(Clinical consensus, Strong Recommendation)*.
28. Any medications for SUD treatment, including buprenorphine and methadone, should be continued during the BZD taper *(Clinical consensus, Strong Recommendation)*.
29. Following the taper, clinicians should continue to monitor and treat underlying SUD or refer the patient to an appropriate level of care for continuing care *(Clinical consensus, Strong Recommendation)*.
30. Clinicians can consider using toxicology testing to support the risk/benefit assessment *(Clinical consensus, Strong Recommendation)*.
31. Clinicians should provide or refer for harm reduction services, which may include but are not limited to:
    a. Provision of naloxone and related training *(Clinical consensus, Strong Recommendation)*; and

b. Provision of drug checking or other safe use supplies (e.g., fentanyl test strips, xylazine test strips, sterile syringes) *(Clinical consensus, Conditional Recommendation)*.

Recommendations for patients with co-occurring psychiatric disorders

32. For patients with psychiatric conditions, clinicians should consider using existing standards for level of care recommendations such as The Level of Care Utilization System (LOCUS) *(Clinical consensus, Strong Recommendation)*.
33. Clinicians should consider optimizing evidence-based treatment for any psychiatric disorder prior to the taper *(Clinical consensus, Strong Recommendation)*.
34. For patients with PTSD, clinicians should strongly consider tapering BZD medications *(Clinical consensus, Strong Recommendation)*.
35. Clinicians should monitor sleep closely in patients with mood or psychotic disorders undergoing a BZD taper, particularly for patients with bipolar disorder, as sleep disturbance can trigger episodes of mania *(Clinical consensus, Strong Recommendation)*.
    a. Due to the risk for destabilization, if a patient experiences significant sleep disturbance, clinicians should pause the taper until the symptoms resolve *(Clinical consensus, Strong Recommendation)*.
        i. Clinicians can also consider providing or referring for behavioral interventions (e.g., CBT, sleep hygiene education) *(Clinical consensus, Conditional Recommendation)*.
        ii. Clinicians can also consider consulting with a clinician with psychiatric expertise. *(Clinical consensus, Conditional Recommendation)*.

Recommendation Statement for Older Adults

36. Clinicians should taper BZD in most older adults unless there are compelling reasons for continuation *(Clinical consensus, Strong Recommendation)*.

Recommendations for Pregnant Patients

37. When considering a BZD taper for pregnant patients, clinicians should weigh risks and benefits for the maternal-fetal dyad *(Clinical consensus, Strong Recommendation)*.

38. Clinicians should monitor closely for psychiatric symptoms during the taper as these symptoms may evolve rapidly during the pregnancy and postpartum period and may require treatment *(Clinical consensus, Strong Recommendation)*.
39. Clinicians can consider a referral to or consultation with a healthcare professional with expertise in reproductive psychiatry *(Clinical consensus, Conditional Recommendation)*.
40. For infants with long-term BZD exposure *in utero*, clinicians should:
    a. Encourage breastfeeding, which can reduce neonatal withdrawal symptoms *(Clinical consensus, Strong Recommendation);* and
    b. Communicate with the infant's healthcare provider (with parental consent) regarding exposure to BZD *(Clinical consensus, Strong Recommendation)*.

Introduction

Purpose

The American Society of Addiction Medicine (ASAM) has partnered with:

- The American Academy of Family Physicians (AAFP),
- The American Academy of Neurology (AAN),
- The American Academy of Physician Associates (AAPA),
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to develop and disseminate this *Clinical Practice Guideline on Benzodiazepine Tapering* (hereafter referred to as the Guideline). The Guideline provides information on evidence-based strategies and clinically informed standards of care for whether and how to taper benzodiazepine (BZD) medications.

Background

BZDs are commonly prescribed, and FDA approved to treat a wide range of conditions including common mental health conditions such as anxiety and mood disorders, as well as insomnia and seizure. These medications represent important therapeutic tools; however, data on long-term safety and efficacy are limited, and BZDs are associated with significant risks including potentially life-threatening withdrawal, substance use disorder (SUD), and overdose—particularly when combined with central nervous system (CNS) depressants such as alcohol or opioids.[2] Since 2000, fatal overdoses involving BZDs have increased nearly tenfold, often involving the combination of opioids and BZDs.[1]

While prescribing rates for BZDs have fallen since the most recent peak in 2013, in the 2022 National Survey on Drug Use and Health (NSDUH), 9.1% of US adults reported use of BZD in the past year, with more than 14% of those individuals reporting non-medical use in the past year.[3,4] Between 1996 and 2013, overall BZD prescriptions filled increased from 8.1 million to

13.5 million, while the total BZD prescriptions filled per 100,000 adults more than tripled.[5] Over this time, emergency department visits related to BZDs also tripled, and BZD-related overdose deaths quadrupled.[1,6] Between 2013 and 2023, BZD prescriptions dispensed from outpatient and mail-order pharmacies fell by approximately 35%.[4]

Long-term use of BZDs is common.[7,8] Long-term use is associated with increased risk for dependence and withdrawal and ongoing risk for adverse events such as falls, motor vehicle accidents, and cognitive impairment.[9,10] The risk-benefit balance for continued BZD use may shift over time and, because physiological dependence develops with long-term use, stopping can be challenging. Older adults have the highest BZD prescription rates and are at particular risk of experiencing adverse events related to BZD use. Some have taken BZDs continuously for decades.[7,11,12] In some instances, use has been so prolonged that the original reason for the BZD prescription may be unclear.

Safe tapering of BZDs can be clinically complex since rapid dosage reductions may precipitate acute withdrawal, which can be life-threatening. When BZD are tapered too rapidly, patients are also at risk for recurrence and exacerbation of the symptoms for which BZDs were prescribed (e.g., anxiety, seizures, insomnia) and destabilization. Finally, inadequate tapering strategies may push patients to the ille.g.al drug market, where counterfeit pills laced with fentanyl and other opioids are common, presenting an increased risk for overdose and overdose death.[13] This Guideline aims to guide clinicians in diverse practice settings in determining when and how to taper BZD medications.

Intersection with the Opioid Overdose Epidemic

Co-prescribing of BZDs with opioids quadrupled between 2003 and 2015 in ambulatory care settings, with data from 2014-2016 indicating over one third of BZD prescriptions were co-prescribing with opioids.[11,14] In addition, some individuals may concomitantly take BZDs and opioid to augment the effects of both substances. Given that both BZD and opioids cause CNS depression, co-prescription and combined use increases the risk of adverse events—including fatal and nonfatal overdose.[15-17] In 2021, 13.7% of overdose deaths involving opioids also involved BZDs (with 10,992 deaths involving both substances) and nearly 88% of overdose deaths involving BZDs also involved opioids.[1] This highlights the need for evidence-based

guidance on strategies to safely taper BZDs, particularly in patients who are taking both BZD and opioids.

In their 2022 Guideline for Prescribing Opioids for Chronic Pain, the Centers for Disease Control and Prevention (CDC) stated that[18]:

> *"Although in some circumstances it might be appropriate to prescribe opioids to a patient who is also prescribed benzodiazepines (e.g., severe acute pain in a patient taking long-term, stable low-dose benzodiazepine therapy), clinicians should use particular caution when prescribing opioid pain medication and benzodiazepines concurrently" (pg. 53).*

Note of Caution

As observed upon the 2016 release of the CDC Guidelines for Prescribing Opioids for Chronic Pain, guidelines can have unintended impacts on clinical decision-making.[19] Misapplication of those recommendations led some prescribers to abruptly discontinue pain medications without first developing a plan for safe tapering with their patients.[19] This unintended consequence put patients at risk for withdrawal and transition to illegally obtained opioids while failing to address their underlying pain symptoms.[20,21] Abrupt discontinuation of BZDs confers similar and additional risks: rapid BZD dose reduction can cause life-threatening withdrawal symptoms such as seizures and delirium, as well as potential destabilization of existing mental health conditions, especially in those who have been taking BZDs long-term and at higher doses.[22-24] As highlighted in this guideline, **BZDs should not be discontinued abruptly in patients who have been taking them daily or near daily for longer than one month**..

Scope of Guideline

This Guideline focuses on whether and how to taper BZD medications, including considerations for assessing risks and benefits of continued prescribing, tapering strategies, patient engagement, level of care setting, and withdrawal management. It also includes population specific considerations. Considerations related to initiation of BZDs, ongoing management of BZD prescriptions, and non-BZD sedative hypnotics (e.g., Z-drugs) are beyond the scope of this guideline.

A glossary of terms used in the Guideline can be found in Appendix A. A summary of abbreviations and acronyms can be found in Appendix B.

Intended Audience

The intended audience of this Guideline is clinicians—including behavioral health professionals, physicians, nurse practitioners, physician associates, nurses, and pharmacists—who prescribe BZDs or provide or support treatment for indications for which BZDs are often prescribed. The Guideline is relevant to clinicians who practice in diverse settings such as primary care offices, ambulatory clinics for a broad range of specialty care providers, emergency departments (EDs), hospitals, and outpatient and residential addiction and mental health settings. Some recommendations only apply to specific settings (e.g., inpatient, medically managed) as indicated in the narrative. Palliative care and end of life settings are not the intended audience for this Guideline. The Guideline may also be useful for healthcare administrators, insurers, and policymakers. who implement policies related to medical practice. However, as stated above, the Guideline is not intended to be a source of rigid laws, regulations, or policies related to BZD prescribing. The recommendations contained in this Guideline support flexible, person-centered care.

Qualifying Statement

This Guideline is intended to aid clinicians in their clinical decision-making and patient management. It strives to identify and define clinical decision-making junctures that meet the needs of most patients in most circumstances. Clinical decision-making should consider the quality and availability of expertise and services in the community wherein care is provided. The recommendations in this Guideline reflect the consensus of an independent committee (see Methodology) convened by ASAM beginning January 2023. This Guideline will be updated periodically as clinical and scientific knowledge advances.

Prescribed courses of treatment described in this Guideline are most effective if the recommendations are adhered to by the patient. Because lack of patient understanding and adherence may adversely affect outcomes, clinicians should make every effort to promote the patient's understanding of and adherence to prescribed and recommended treatment services.

This Guideline aims to set the standard for best clinical practice by providing recommendations for the appropriate care of patients tapering from BZDs in diverse settings. Patients should be informed of the risks, benefits, and alternatives to a particular treatment and welcomed as active parties to shared decision-making. In circumstances in which the Guideline is being used as the basis for regulatory or payer decisions, the central goal should be improvement in quality of care. Recommendations in this Guideline do not supersede any federal or state regulations.

Methodology

ASAM's Quality Improvement Council (QIC) and Clinical Practice Guideline Methodology and Oversight Committee (CPG-MOS) oversaw the development of this Guideline. The FDA provided guidance on the content and development of the Guideline but did not dictate the content. The QIC, working with partner medical societies and the FDA, oversaw the appointment of a Clinical Guideline Committee (CGC) comprised of clinicians representing 10 medical and professional societies with broad subject matter expertise across medicine, psychiatry, and pharmacology. A Patient Panel of individuals with lived experience with BZD tapering (the Patient Panel) provided input throughout the development of the Guideline.

The following key clinical questions were addressed in the systematic literature review:

1. What is the efficacy and/or safety of tapering strategies for BZDs?
2. What factors influence the outcomes of BZD tapering and should be monitored?
3. How can shared decision-making and patient-centered health care be utilized to support the effectiveness and safety of BZD tapering?

A systematic literature review was conducted to inform the development of recommendations that considered risks and benefits of BZD tapering, as well as patient values and preferences. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) method was used to develop recommendations in areas with sufficient evidence.[25] Where evidence was lacking, a modified Delphi process was used to develop clinical consensus statements.[26] As very little high quality evidence was found to directly inform the clinical questions, this strategy allowed for the inclusion of guidance in areas for which the evidence is highly limited.

The detailed Methodology can be found in Appendix C. A list of members, their areas of expertise, and conflict of interest disclosures are available in Appendix D. GRADE Evidence to Decision Tables are available in Appendix E.

Patient Engagement and Shared Decision-Making

Patients can experience life-threatening withdrawal symptoms with abrupt or rapid discontinuation of BZDs, and some patients still experience significant symptoms even with a gradual dose reduction.[23,24,27] To this end, it is crucial for clinicians to adopt a patient-centered approach and engage patients in a shared decision-making process when considering BZD tapering.[28,29]

Patients are often reluctant to consider tapering, particularly if they feel that clinicians may underestimate or dismiss their symptoms during tapering.[30] Further complicating the issue is that clinicians often do not discuss tapering with patients and continue renewing prescriptions because of concern for withdrawal, as well as patients' perception of benefits.[31] Clinicians may feel uncomfortable starting these conversations due to the perceived sensitivity and difficulty of the topic. Yet, ironically, many patients indicate they would be open to considering tapering BZDs if their physician discussed it with them.[30,32]

A key step to bridging this gap in understanding is increased communication and education. Engaging patients in discussions about their BZD use serves two important purposes:

1. Clinicians are presented with an opportunity to educate patients on the benefits and risks of both short- and long-term BZD use, alternative pharmacological and nonpharmacological treatment options to manage the condition for which they are taking BZDs, and the tapering process. Discussions on tapering should prepare patients for what they can expect during the process, including potential withdrawal symptoms and how they will be managed.
2. Patients are presented with an opportunity to help clinicians understand how their BZD use impacts them, as well as their treatment goals and preferences. This insight into each patient's experience with BZDs can help inform clinicians' education efforts for a given individual. It also empowers patients to be active participants in their health care by sharing valuable information to help their clinicians better tailor treatment plans, including BZD tapering protocols, to each their unique goals and preferences.

[START BOX]

The recommendations in this CPG should be interpreted in the context of shared decision-making with patients. In other words, when a recommendation says, "clinicians should consider", it should be understood to include "in partnership with the patient".

[END BOX]

Considerations for Tapering BZD

In 2020, the FDA updated the required Boxed Warning for BZD medications to describe the risks of physical dependence, withdrawal, and SUD.[33] The associated Drug Safety Communication encouraged prescribers to carefully weigh the risks and benefits of BZD medications, limit the dose and duration to what is needed to achieve the clinical goal, and monitor patients for BZD misuse and use disorder. When prescribing BZDs, it is important for prescribers to have a thoughtful strategy for medication management that regularly reassesses the risks and benefits of continued prescribing, as well as a patient-centered plan for tapering the medication when the benefits no longer outweigh the risks.

The risks of BZD use continue while a patient continues to take the medication. In addition, the risk for physical dependence and BZD use disorder, particularly in patients who use alcohol or other drugs, increases with time.[34] As such, long-term BZD use is frequently associated with more risks than benefits. Significant risks include oversedation, cognitive impairment, falls, motor vehicle crashes, and nonfatal and fatal overdose.[9] Despite this, clinicians often encounter patients who have been taking prescribed BZD for months or years.

While short-term BZD use is associated with decreased anxiety and insomnia, it is commonly recommended that use not exceed 4 weeks, because at that point clinical benefits often decrease while risks increase.[28,35] Meta-analyses of patients taking BZD for insomnia demonstrated minor improvements in sleep onset, increased duration, and decreased nighttime awakenings.[36,37] However, therapeutic effects diminish in days or weeks due to changes in BZD receptor density and/or affinity resulting from chronic use, while risks continue. A meta-analysis of RCTs comparing BZD to placebo for insomnia in adults over age 60 showed 3.8 -fold increase in daytime sedation, and 4.8-fold increase in cognitive impairment and increased incidence of psychomotor effects (e.g., falls, motor vehicle accidents).[36] Another meta-analysis showed increased risk for fractures associated with current and recent BZD use in older adults.[38] In

addition to its psychomotor effects, BZDs may increase the risk of orthostatic hypotension in older adults, contributing to fall risks.[39]

Because of the risks of regular BZD use, the committee recommended that prescribing clinicians assess risks and benefits of continued prescribing with each new prescription and prescription refill. At minimum this assessment should occur every three months. For patients who have just initiated a prescription for BZD, reassessment of risks and benefits should occur within one month, and ideally much sooner given the potential for rapid development of BZD dependence. The clinician should discuss any adverse effects of BZD use, including those discussed above, and elicit information from the patient on perceived risks and benefits of ongoing use. Clinicians should be mindful of unconscious bias when making decisions regarding initiating a taper.

A new BZD prescription represents an opportunity to proactively review risks and benefits of BZD use, and to provide patient education regarding the importance of limiting the duration of use. Many patients as well as clinicians are unaware that clinical benefits of BZD decrease within a few weeks, while risks continue or increase. Virtual follow-up visits can often be leveraged for this purpose.

Given that polypharmacy is common among patients who use BZDs, clinicians should conduct a thorough medication review as part of the regular risk–benefit assessments and prior to beginning a taper.[14] Prescription drug monitoring programs (PDMP) can be helpful tools for detecting multiple BZD prescriptions, concurrent prescribing of other controlled substances with CNS depressant effects, and other issues related to polypharmacy. While mandates regarding PDMP use vary widely across states, the committee noted that prescribing clinicians should review the information in the relevant PDMP as a part of the risk benefit assessment, with each new BZD prescription and refill authorization.

Combined use of BZDs and opioids increases the risk of adverse events, including fatal and nonfatal overdose, due to the central nervous system (CNS) depression caused by both drug classes.[5,17,40] Other interactions with BZDs include additive sedation with sedating medications (e.g., antihistamines, antipsychotics, opioids), and pharmacokinetic interactions involving P450 (CYP) enzymes (See Appendix F). Excessive sedation has been observed when BZDs have been used with CYP 3A4 inhibitors, which includes common antibiotics like clarithromycin and

erythromycin.[41] Additionally, clinicians should explore patients' consumption of alcohol, a CNS depressant, and grapefruit juice*, a strong CYP 3A4 inhibitor.[41]

If clinical evidence reveals that the medication is no longer benefiting the patient or the medication is causing harms that outweigh benefits, tapering is indicated.[29] Additionally, if the patient exhibits signs of potential BZD misuse, including requesting early refills or continued requests for increased dosage or number of pills, tapering should be discussed with the patient. The patient should be assessed or referred for further evaluation and treatment for potential SUD.

While long-term BZD use should generally be avoided, exceptions do exist. For example, in patients with treatment resistant generalized anxiety disorders or bipolar disorder, long-term use may be indicated.[42-44] Additionally, BZDs have a role in certain medical conditions such as complex seizure disorders and spasticity, or in palliative/end of life care settings.[45,46]

Even when the risk-benefit assessment favors BZD tapering, discontinuation of the medication may present risks.[47] A recent study of a US commercial database indicated that the mortality risk among patients who discontinued BZD use over a six-month period was 1.6 times higher compared to those who had not discontinued use. However, the analysis could not examine the reason for discontinuation and did not account for the rate of the taper or discontinuation.[47] While the findings suggest an association between discontinuation of BZD and mortality risk, this correlation may reflect the underlying reason for BZD discontinuation such as declining health (e.g., liver or kidney dysfunction), falls, or cognitive decline – rather than having been *caused by* the discontinuation. In contrast, major adverse events were not seen in a controlled trial evaluating a patient educational intervention for BZD tapering[48] and only one adverse event was reported among 364 patients after initiating a primary care-based intervention for BZD tapering.[49]

The committee carefully considered the results of this study but, ultimately, do not believe that these findings should outweigh the extensive body of literature characterizing the risks associated with BZD use. However, as discussed throughout this Guideline, the prescribing clinician should carefully consider the risks and benefits of both continued BZD use and tapering

* at least 8 oz or half a grapefruit per day.

for the given patient and should not assume that tapering is the right choice for all patients. For some patients there may be risk associated with stopping the BZD which should be taken into account based on their individual needs and circumstances. Tapering should be undertaken carefully, accompanied by additional research to better understand the potential risks of BZD deprescribing and develop strategies to mitigate them.

Many patients who have been taking BZDs for less than 4 weeks are able to discontinue the medication without a taper. However, physiological dependence can develop in as little as 2 weeks, depending on medication and patient characteristics. In deciding whether to taper in these situations, the dose and type of BZD should be considered. Alprazolam, which is unique in having a very short half-life and no active metabolites, tends to be associated with a more rapid onset of physiological dependence.[50] Therefore, a taper may be appropriate for patients taking this medication daily, even for a short duration.

Further, when determining whether to taper with a patient who has been taking BZD for less than 4 weeks, the clinician should elicit information from the patient regarding any concerns about abrupt discontinuation or preferences for tapering. The clinician should gather information about the patient's risk for withdrawal, including asking whether the patient has experienced withdrawal symptoms if they have missed doses in the past, and any past experiences with withdrawal symptoms associated with tapering BZD, especially adverse events including seizures. It is also important to determine if there is ongoing daily alcohol use, as alternate strategies may be needed in these situations. In such cases, consider consulting an addiction specialist.

If the BZD is discontinued without a taper in a patient who has been using BZD for less than a month, the patient should be educated about and encouraged to report any withdrawal and/or rebound symptoms that may occur. If the patient reports significant symptoms, the clinician can consider initiating a taper.

Recommendations for Considerations for Tapering BZDs

6. For each patient taking BZD, prescribing clinicians should ideally assess the risks and benefits of ongoing BZD prescribing at least every 3 months (*Clinical consensus, Strong Recommendation*).

c. At a minimum, risks and benefits should be assessed with each new BZD prescription or BZD prescription refill authorization (*Clinical consensus, Strong Recommendation*).
d. Prescribing clinicians should review the information in the relevant PDMP as a part of the risk benefit assessment (*Clinical consensus, Strong Recommendation*).

7. When the risks of BZD medication outweigh the benefits for a given patient, tapering is generally indicated (*Clinical consensus, Strong Recommendation*).
    b. The clinician should initiate a conversation about tapering, including alternatives for management of the underlying condition (*Clinical consensus, Strong Recommendation*).
8. Clinicians should avoid abruptly discontinuing BZD medication in patients who have been taking BZD daily or near daily (e.g., more days than not) for longer than one month *(Low certainty, Strong Recommendation)*.
    a. While many patients who have been taking BZD for less than 4 weeks are able to discontinue the medication without a taper, clinicians can consider a short taper *(Clinical Consensus, Conditional Recommendation)*.
        i. If the BZD is discontinued without a taper the patient should be counseled to report the emergence of withdrawal and/or rebound symptoms *(Clinical Consensus, Strong Recommendation)*.
            1. If significant symptoms emerge, the clinician can consider medications for symptom management or restarting the BZD and initiating a taper *(Clinical Consensus, Conditional Recommendation)*.

Level of Care Considerations

For patients without significant complicating factors, BZD tapering can usually be accomplished in an outpatient setting. This section details situations where additional support may be required to accomplish BZD tapering.

If the patient's presentation indicates an immediate risk of serious harm related to continued use of BZD, an inpatient setting should be considered. For example, patients who have experienced falls, vehicular crashes, or overdose related to BZD use, or are exhibiting suicidality or other self-harm are potential candidates for inpatient management and stabilization.

Inpatient care should be considered if the patient has a significant comorbidity – such as seizure disorder, or concomitant use of medications that lower the seizure threshold – that cannot be safely managed in an outpatient setting. Additionally, if the patient is experiencing or anticipated to experience severe or complicated withdrawal, or has a history of this, inpatient care should be considered. While withdrawal risk is difficult to predict, history of complicated withdrawal involving seizure or delirium is the most significant predictor of future complications. Patients who have a history of moderate to severe alcohol withdrawal may be more likely to also have more severe BZD withdrawal symptoms, due to the cross-tolerance of alcohol and BZD.

For patients with suspected or confirmed SUD or psychiatric disorders, additional support may be required, especially if the patient has had previous unsuccessful attempts to taper from BZD. Broader options for level of care are available for patients with SUD and psychiatric disorders, such as intensive outpatient and residential treatment programs. Specific considerations for these patients are discussed in the Population-Specific Considerations section.

In certain situations, patients may desire a more rapid taper. The committee noted that individual circumstances (e.g., work requirements or child custody issues) may motivate a patient to discontinue BZD use relatively rapidly. Assuming medical necessity can be established, these patients may be candidates for an inpatient taper.

It is important to note that the tapering process might take place in more than one setting. For example, patients who have significant risk factors as described above may be.g.in a BZD taper in an inpatient setting, and transition to an outpatient setting for continued management, once they are stable and able to tolerate the ongoing tapering process.

There are also situations in which an inpatient setting may not be an optimal option for a given patient. For example, hospital admission can trigger distress, confusion, and delirium and lead to worse outcomes in patients with dementia or other neurological issues.[51,52]

Recommendation for Level of Care Considerations

9. Inpatient care should be considered when:

a. Patient presentation indicates an imminent risk for significant harm related to continued use of BZD (e.g., overdose, accidents, falls, suicidality or other self-harm) *(Clinical consensus, Strong Recommendation)*;
b. Patient symptoms and/or co-occurring physical or mental health conditions [e.g., seizure disorder, concomitant use of medications that lower the seizure threshold] cannot be safely managed in the outpatient setting *(Clinical consensus, Strong Recommendation)*;
c. The patient is experiencing or imminently anticipated to experience severe or complicated withdrawal *(Clinical consensus, Strong Recommendation)*; and
d. The patient has a history of severe or complicated withdrawal *(Clinical consensus, Strong Recommendation)*.

BZD Tapering Strategies

Partnering with Patients

When BZD tapering is indicated, clinicians should initiate a conversation with patients with a goal of shared decision-making. Clinicians should invite patients to share their perceptions about the benefits and risks of continuing BZDs as well as share their own with the patient. While some patients will be understandably reluctant to consider tapering a medication they have been taking for a long time and consider helpful, others may welcome the opportunity to minimize potential adverse effects and explore more optimal ways of controlling their underlying condition.[30,31] Appendix G lists resources on the treatment of condition for which BZDs are commonly prescribed, including insomnia, anxiety, seizure disorders, and chronic pain.

Education is a vital component of conversations about tapering. Clinicians should inform patients about how the clinical benefits of BZD decrease over time while the risk of adverse effects increases. Clinicians should stress the benefits patients can expect from reducing or discontinuing their BZD medication, such as improved cognition and psychomotor functioning.[53] The reality of physiological dependence associated with prolonged BZD use should be acknowledged, as well as potential withdrawal and/or rebound symptoms that may arise during tapering. Patients should be reassured that they will be supported throughout the tapering process.

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Physiological dependence versus substance use disorder (SUD)

Physiological dependence on BZDs is a biological phenomenon that develops in response to repeated use of a medication. It results from downregulation of BZD receptors and/or adaptations in the response of the receptor. Physiological dependence is an expected result from ongoing use of BZD. Conversely, SUD is a chronic disease associated with functional changes to the brain circuits that mediate stress, decision making, and behavior reinforcement. In addition to physiological dependence, SUD is associated with specific criteria including impaired control over use of the substance and continued use despite adverse consequences. There are genetic, psychosocial, and environmental factors influencing the development and manifestations of SUD. A review of NSDUH data estimated that only 1.5% of people who use BZD met criteria for a BZD use disorder.[54] Patients who use BZD and are physiologically dependent on the medication are far more common than patients who have a BZD use disorder.

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The concept of shared decision making is built on engaging patients as active participants in their treatment rather than passive recipients.[55] Approaching tapering decisions as a partnership with the patient allows clinicians to gather valuable information to better tailor treatment plans, including BZD tapering protocols, to each individual patient's unique goals and preferences. It also highlights the value of the patient's own experiences, thereby promoting their autonomy and empowering them to actively contribute to their own care.[55]

Recommendation Statement for Partnering with Patients

10. The BZD tapering strategy should be developed in coordination with the patient and/or their care partner(s) in a shared decision-making process, whenever possible *(Clinical consensus, Strong Recommendation)*.

The Tapering Process

Prior to initiating a BZD taper, clinicians should attempt to coordinate care with any other prescribers of BZD and clinicians managing conditions that may be impacted by the taper. In

addition, clinicians should ideally assume management of all BZD prescriptions. If the patient has been taking multiple types of BZDs, the prescriber should convert and consolidate the medications to an equivalent dose of a single BZD prior to beginning the taper. Tapering at a mutually agreed upon rate between patient and clinician, while avoiding very prolonged taper can be an effective strategy for BZD discontinuation.[56]

Assessing the Potential for Withdrawal

Clinicians should consider the likelihood of a given patient developing withdrawal symptoms during the taper, as well as the anticipated severity of those symptoms. The development of more severe BZD withdrawal symptoms is associated with use of BZDs with a shorter half-life (e.g., alprazolam), higher total daily dose, daily use, longer duration of use, and history of severe withdrawal.[29,56,57] For patients with significant risk for withdrawal a slower initial pace of BZD tapering is likely to be safer and more effective. As discussed above, patients should be involved in determining the initial pace with clinicians, and the tapering pace should be agreed upon in a shared decision-making process.

Particular attention should be paid to ascertaining if patients have experienced seizures in the past, as such a history can increase the risk of BZD withdrawal seizures.[58] Clinicians should also conduct a thorough medication reconciliation as medications that lower the seizure threshold can increase the risk of withdrawal seizures.

The presence of certain psychiatric symptoms has been associated with an increased likelihood of experiencing more severe withdrawal symptoms, which can present challenges to successful completion of BZD tapering.[57,59] Patients who exhibit traits associated with cluster B personality disorders (i.e., antisocial, borderline, histrionic, and narcissistic) often experience considerable difficulty discontinuing BZD use.[57,59] See the Considerations for Patients with Co-occurring Psychiatric Disorders section for additional discussion.

Transitioning to a Longer-Acting BZD

Existing clinical guidelines disagree on whether patients who are currently taking a short-acting BZD should be transitioned to a longer-acting BZD (i.e., with a longer half-life) for the taper.[60] Some existing guidance suggests that switching to a longer-acting BZD allows the body “to adjust slowly to a decreasing concentration of the BZD” and to therefore reduce withdrawal

symptoms.[29,61] Conversely, switching to longer acting BZDs may be a concern for anyone with contraindications (e.g., significant liver dysfunction) and those taking multiple medications, due to risk of pharmacodynamic and pharmacokinetic interactions. The committee suggested that the decision to switch to a longer-acting BZD should be patient-specific, and that clinicians should consider liver function and concurrent medication use in patients before making a recommendation to switch to a longer acting formulation.

The issues related to switching to a longer-acting BZD are of particular concern in older adults due to differences in drug metabolism. Older adults may be at greater risk of medication-related harm because of age-related changes in pharmacokinetics and pharmacodynamics such as reduced clearance of certain sedative hypnotic medications.[62,63] Decreased metabolism in older adults changes how the body processes and responds to medications causing medications to stay in the body longer, increasing the risk of adverse effects.[62,63] Additionally, as people age, decreases in liver and kidney function may increase the risks of some medications. In a recent scoping review of several international guidelines for BZD tapering,[60] the two guidelines that did not recommend switching to a longer-acting BZD were both focused on older adults.[28,64] The committee agreed that switching to a longer-acting BZD for tapering would be less likely to be indicated in older adults.

Guidelines that recommend transitioning to a longer-acting BZD most commonly endorse switching to diazepam, though a few suggest clonazepam or chlordiazepoxide.[60,65] However, these medications are metabolized in the liver and have active metabolites, and neither should be used in patients with significant hepatic impairment.[60,66] Instead, shorter acting agents (e.g., lorazepam, oxazepam, and temazepam) are considered better agents to use in these patients.[60,66] The committee also noted that the conversion to diazepam equivalents is not straightforward. Clinicians should consider counseling patients currently taking alprazolam to transition to a longer-acting BZD for the taper, as alprazolam tends to be difficult to taper given that it is short-acting and has no active metabolites.[50] See Appendix H for estimated diazepam dose equivalents.

Tapering Schedules

BZDs should not be abruptly discontinued in patients taking the medication daily or near daily (e.g., more days than not) for longer than one month.[28,29,60] Most existing clinical guidelines

highlight the importance of gradual dose reductions to discontinue prolonged BZD use.[60] If patients are extremely reluctant or anxious about tapering, clinicians can suggest a "trial" dose reduction rather than asking patients to commit to a particular tapering plan. This approach may increase patients' motivation, self-efficacy, and willingness to continue with tapering.[67] However, it is important that the clinician clearly communicate any concerns for the patient's safety with ongoing BZD use.

Several BZD tapering schedules have been described in the literature.[60] Proposed tapering schedules vary from dose reductions in increments of 5% to 10% every 2-4 weeks with slower reduction at lower doses to reductions of 10% to 25% every 1-2 weeks.[60] Guidelines that outline specific dosing protocols generally recommend limiting dose reductions to no more than 25% every two weeks.[60,65] The committee highlighted the importance of the BZD dose and length of time the patient has been taking the BZD when determining an approach to tapering. Table 1 summarizes the committee's recommendations on initial approaches to tapering based on these factors.

Table 1. Example BZD tapering strategies based on dose and duration of use*

	Lower therapeutic dose (1-2x lowest therapeutic dose†))	***Higher therapeutic dose (3 or more x lowest therapeutic dose)***
Less than 12 months	*Clinicians can typically reduce the BZD dose by 25% every 2 weeks*	*Clinicians can typically reduce the BZD dose by 10-25% every 4 weeks* *Adjust based on the patient's response* *Taper should not exceed 25% every 4 weeks*
12 or more months	*Clinicians can typically reduce the BZD dose by 25% every 4 weeks* \	*Clinicians can typically reduce the BZD dose by 5-20% every 4 weeks* *Clinicians should consider the lower end of the range for the first reduction (e.g., 5-10%) to assess the patient's initial response.* *Adjust based on the patient's response*

		The taper should not exceed 20% every 4 weeks *Clinicians can consider a slower taper (e.g., every 6-8 weeks) as appropriate*

** These are examples of tapering approaches, but patient specific tapering strategies should be developed in collaboration with the patient with consideration of the duration and frequency of use, dose, metabolic concerns, and comorbidities.*

ǂ The lowest therapeutic dose is the lowest starting dose of the medication that is typically prescribed for a given indication and patient population (e.g., older adults). This is often the lowest dose per pill available.

Another consideration when developing tapering schedules may include the health condition or symptoms that BZDs are being used to manage. For example, if BZDs have been used for anxiety with insomnia, clinicians can recommend that the patient taper the morning dose first. See Appendix I for sample tapering schedules and case descriptions.

The CGC emphasized that clinicians should engage patients as active partners in a shared decision-making approach to develop an individualized tapering schedule that reflects a given patient's goals, needs, and preferences. The FDA also underscored the importance of developing individualized tapering strategies in a 2020 Drug Safety Communication[33]:

> To reduce the risk of acute withdrawal reactions, use a gradual taper to reduce the dosage or to discontinue benzodiazepines. No standard benzodiazepine tapering schedule is suitable for all patients; therefore, create a patient-specific plan to gradually reduce the dosage, and ensure ongoing monitoring and support as needed to avoid serious withdrawal symptoms or worsening the patient's medical condition (pg. 2).

Adjusting the taper schedule

Tapering does not have to proceed at the same pace over the entire process; rather, pacing should be adjusted based on the patient's response. While clinicians and patients can prepare for the BZD tapering process by setting realistic expectations around the potential withdrawal and/or rebound symptoms a given patient may be likely to experience, there is no way to accurately

predict the extent and severity of symptoms that will manifest once tapering is underway. For this reason, patients should be monitored for signs and symptoms of withdrawal with each dose reduction and counseled to report any concerning symptoms. Clinicians should discuss this inherent uncertainty with patients so that, together, they can adjust the planned tapering schedule as necessary. Adjustments could include pausing the taper, slowing the pace of the taper, and/or making smaller dose reductions. The committee noted that clinicians should generally avoid going back up to a previous dose as this can undermine the goal of re-setting BZD receptor levels in the brain.

This Guideline uses two terms to describe an interruption to the planned taper: pausing and maintaining. When a taper is paused, the intent is for the patient to remain at the current dose until their symptoms stabilize and then continue with dose reductions. When the patient is ready to resume tapering, the amount and pace of the subsequent dose reductions may need to be reassessed more frequently. Maintaining refers to circumstances in which there is no current plan to continue dose reductions, instead the patient is expected to continue taking BZDs at a lower dose (i.e., a partial taper). The dose should be maintained at the reduced level achieved by the partial taper; dose increases should be avoided unless absolutely necessary, such as in response to severe withdrawal symptoms.[29] The harms of BZDs are dose-dependent. Maintaining at a lower dose may be sufficient to reduce the risk of harm for a given patient.

Taper duration

Many existing guidance documents recommend a flexible approach to tapering, reducing the dose at a rate dictated by the patient's ability to tolerate withdrawal symptoms and allowing the process to take as long as the patient needs.[23,29,33,56,59,61,68,69] In contrast, one review recommended completing tapers within 6 months to prevent patients from becoming fixated on the process.[70] This Guideline recommends engaging patients as partners, individualizing tapering schedules to each patient's unique goals, needs, and preferences, and modifying as needed based on their response to the taper.

Tapering Process Recommendation Statements

13. Prior to beginning a taper, clinicians should conduct a thorough medication and health review, with particular attention to other psychoactive medications and conditions that may be impacted during the taper *(Clinical consensus, Strong Recommendation)*.
14. When determining the initial pace of the BZD taper, clinicians should generally consider dose reductions of 5-25%. The pace of the taper should not exceed 25% every 2 weeks (See Table 1)*(Clinical consensus, Strong Recommendation)*.
    a. Clinicians should consider current BZD dose and half-life, frequency and duration of BZD use, comorbidities, and patient response to any prior BZD tapering attempts *(Clinical consensus, Strong Recommendation)*.
    b. The overall tapering strategy should be designed to minimize harms, considering the risk for withdrawal symptoms and the risk of harm related to continued BZD use *(Clinical consensus, Strong Recommendation)*.
15. For patients without contraindications (e.g., liver dysfunction, interacting medications), clinicians can consider transitioning to a comparable dose of a longer-acting BZD for the taper *(Clinical consensus, Conditional Recommendation)*.
16. Tapering strategies should be tailored to the individual patient and adjusted based on the patient's response *(Clinical consensus, Strong Recommendation)*.
    a. Patients undergoing tapering should be evaluated for signs and symptoms related to the BZD taper with each dose reduction *(Clinical consensus, Strong Recommendation)*.
    b. For patients experiencing significant symptoms related to the BZD taper, clinicians should consider pausing or slowing the pace of the taper and/or making smaller dose reductions *(Clinical consensus, Strong Recommendation)*.
17. The BZD tapering process can be more difficult for patients as the total daily dose of BZD decreases. Clinicians should proactively consider smaller dose reductions and/or slowing the pace of dose reductions as the taper progresses *(Clinical consensus, Strong Recommendation)*.
18. If a patient is unable to tolerate further BZD dose reductions, the clinicians can consider – in partnership with the patient and other members of the care team – maintaining the patient on

the lower BZD dose with regular risk benefit assessment consistent with Recommendation #1 *(Clinical consensus, Conditional Recommendation)*.

Adjunctive Interventions During the Tapering Process

Adjunctive Psychosocial Interventions

Gradual tapering supported by adjunctive psychosocial interventions has been shown to be more effective than gradual tapering alone.[71] Psychosocial interventions encompass evidence-based behavioral interventions (e.g., cognitive behavioral therapy [CBT]), lifestyle factors (e.g., sleep hygiene), complementary health approaches (e.g., mindfulness), and peer specialist services if available. See Appendix J for adjunctive psychosocial interventions. The CGC recommends that adjunctive psychosocial interventions be offered to patients tapering BZDs.

A Cochrane review by Darker et al (2015) found moderate quality evidence that patients were more likely to successfully discontinue BZDs at four weeks and three months post-treatment when they received CBT during the tapering process.[72] While CBT has the most evidence, other behavioral interventions that have been studied include motivational interviewing (MI), direct-to-consumer educational interventions (e.g., letters and booklets mailed to patients), relaxation studies, and counseling via telemedicine.[48,72]

A recent meta-analysis showed that the rate of BZD discontinuation was significantly higher at 6 and 12 months among patients who received a brief intervention – such as short consultation with the prescriber or a letter from the prescriber recommending discontinuation - delivered in primary care compared to those receiving usual care.[73]

Sleep hygiene interventions may also help support a successful taper. Sleep hygiene refers to the sleep environment and behaviors around sleep—such as adopting a nightly routine, following a sleep schedule, avoiding caffeine and alcohol near bedtime, and avoiding napping during the day—that are conducive to optimizing restorative sleep.[74,75] Further, incorporating sleep hygiene education and psychosocial support during BZD tapering has been shown to lead to short-term reductions in BZD use as well as long-term discontinuation in older adults.[74]

Peer specialist services are another resource to support patients during a BZD taper. Peer specialists are individuals who have lived experience with BZD dependence and are trained to

provide services that promote recovery, foster resilience, and build on patients' strengths as they work through the BZD tapering process.[76] Peer specialist services can be delivered one-on-one or in a group setting, as well as either in-person or virtually.

The most important considerations when determining which strategies to incorporate are an individual patient's treatment preferences, their response to the BZD tapering process, and their access to adjunctive services.

Adjunctive Pharmacological Interventions

There is considerable disagreement in the literature on the utility of pharmacological interventions as an adjunct to tapering. Existing clinical guidelines that endorse adjunctive medications do not offer clear guidance on implementation (e.g., dosing, duration).[60] In a Cochrane review, Baandrup et al (2018) were unable to draw conclusions on the effectiveness and safety of various medications in facilitating BZD discontinuation because the quality of the evidence was low or very low and with high risk of bias.[77]

The CGC acknowledges that some patients might benefit from adjunctive medications. However, given the lack of evidence, the CGC recommends first pausing or slowing the tapering schedule per Recommendation #9, #10, and #13, and incorporating adjunctive psychosocial interventions per Recommendation #12 if a patient experiences challenging withdrawal symptoms. If pausing or slowing the taper has not been successful, a decision may be made—through a shared decision-making approach—to explore adjunctive pharmacological interventions. clinicians should first consider whether patients' symptoms are most likely primarily attributable to BZD withdrawal or an underlying condition. See Appendix K for adjunctive pharmacological interventions. In general, if the symptoms did not resolve after pausing the taper they are unlikely to be related to withdrawal. This distinction is key to the clinical approach: while evidence for medications to treat BZD withdrawal symptoms is lacking, treating symptoms of underlying conditions can be effective (e.g., SSRIs for general anxiety disorder). Appendix G provides a list of guidelines on the management of conditions for which BZD are commonly prescribed.

A few small studies suggested the anticonvulsant carbamazepine might have limited effectiveness as an adjunct during the BZD tapering process to reduce anxiety and withdrawal

symptoms.[77-80] However, there is no robust evidence that carbamazepine facilitates discontinuation and, thus, it is not recommended as an adjunct medication for withdrawal management. The committee noted that gabapentin and especially pregabalin have potential for non-medical use and therefore, while they may be useful in certain circumstances, should not be considered prior to other potential adjunctive medications.

Adjunctive Interventions Recommendation Statements

19. Adjunctive psychosocial interventions should be offered when tapering BZD *(Clinical consensus, Strong Recommendation)*.
    e. Patients undergoing BZD tapering should be offered, or referred for, behavioral interventions such as CBT *(Very Low Certainty, Strong Recommendation)*.
    f. Clinicians should educate patients on lifestyle factors that could support BZD tapering (e.g., sleep hygiene, physical activity as appropriate to ability) *(Clinical consensus, Strong Recommendation)*.
    g. Clinicians can consider recommending complementary health approaches such as mindfulness practices *(Clinical consensus, Conditional Recommendation)*.
    h. Clinicians can consider referring patients for peer specialist services to provide support during the taper *(Clinical consensus, Conditional Recommendation)*.
14. For patients experiencing symptoms that significantly interfere with the taper (e.g., sleep difficulty, anxiety symptoms), clinicians should first consider pausing or slowing the pace of the taper *(Clinical consensus, Strong Recommendation)*.
    a. Clinicians can also consider adjunctive medications to address symptoms interfering with the taper *(Clinical consensus, Conditional Recommendation)*.

BZD Withdrawal Management/Tapering with very long-acting medications

BZD Withdrawal Management

BZD withdrawal symptoms can range from anxiety and sleep problems to seizures and delirium (see Table 2).[23,56,61] It is often difficult to distinguish between withdrawal symptoms and recurrence or rebound of symptoms for which the BZD had been prescribed. The most commonly experienced symptoms of withdrawal – such as anxiety, insomnia and irritability – are often indistinguishable from the previously experienced symptoms associated with the underlying condition.[81] As discussed above, the pace of BZD taper should seek to minimize

withdrawal symptoms and clinicians should treat underlying conditions with evidence-based non-BZD therapies.

Table 2. *BZD Withdrawal Signs and Symptoms*[23,56,66]

Psychological Signs and Symptoms	**Physical Signs and Symptoms**
Cognitive impairment (e.g., poor memory, reduced concentration)	Chest pain
Confusion, delirium*	Palpitations
Depersonalization, derealization	Increased heart rate, tachycardia
Depression, dysphoria	Elevated blood pressure
Increased anxiety	Headaches
Irritability, agitation	Dysesthesia, kinesthetic disorders, Muscle twitching, jerks, fasciculations
Nervousness	Muscle pain (e.g., tension, weakness, spasms)
Panic attacks	Nausea/vomiting
Perceptual disturbance	Diarrhea
Psychosis symptoms, paranoia*	Seizures*
Restlessness	Tremors
Sleep disturbance (i.e., insomnia, nightmares, hypersomnia)	Sweating, night sweats
	Tingling, numbness, altered sensation
	Sensory hypersensitivity (light, sound, taste, smell)

* Typically associated with abrupt discontinuation of high doses of BZDs

While most patients can successfully taper from BZD in an outpatient setting, when a clinical scenario indicates the need for active medical management of acute BZD withdrawal, the following recommendations should be taken into consideration. As with any sedative-hypnotic withdrawal, seizure and delirium are two of the more serious adverse events that can occur. Clinicians should prioritize assessment and monitoring for seizure risk during BZD withdrawal management.

The CGC discussed strategies for managing seizure risk and noted that clinicians from different medical sub-specialties differ in how they manage seizure risk. For patients experiencing BZD withdrawal who have a history of withdrawal related seizures addiction medicine specialists commonly use pharmacotherapies (e.g., levetiracetam, carbamazepine) to prevent withdrawal

seizures. In these instances, clinicians are particularly concerned about the phenomenon of increasing severity of seizures with repeated episodes of withdrawal (i.e., kindling). Neurologists, however, generally do not prophylactically treat seizure risk. As such, the committee did not come to consensus on management of seizure risk in patients undergoing BZD withdrawal management. Seizures should be managed according to current standards of care.

With regard to the approach to tapering, symptom-triggered tapering – where medication is administered in response to withdrawal symptoms as opposed to on a specific schedule – has been demonstrated to be as effective as fixed tapering approaches, in terms of BZD withdrawal symptoms, duration of inpatient treatment, and BZD use one month following discharge.[82] While the authors of that study concluded that symptom-triggered approaches could not be favored over fixed approaches based on the data,[82] symptom-triggered approach are likely to be experienced as more patient-centered, and may yield a more positive experience for the patient.

Monitoring During Withdrawal Management

During withdrawal management, regular patient monitoring is critical. What constitutes regular monitoring will depend upon the treatment setting. Inpatient or other medically managed settings where withdrawal management occurs typically have protocols in place for monitoring withdrawal. The CGC noted that the two most important items to monitor are vital signs and patient reported withdrawal symptoms.

Scales designed for monitoring BZD withdrawal symptoms exist, including the Clinical Institute Withdrawal Assessment Scale – Benzodiazepines (CIWA-B) [83] and the BZD Withdrawal Symptom Questionnaire (BWSQ).[84] However, both these scales were developed using small numbers of patients, little to no evidence of validation was found for either, and they are not frequently used in clinical practice.[†]

[†] The committee noted that some facilities utilize the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) due to pragmatic reasons (e.g., it may already be incorporated in the electronic health record and staff may be more familiar with it). However, they noted that it is not indicated for BZD withdrawal management and is therefore not recommended for this purpose.

Inpatient Withdrawal Management

As discussed in the Level of Care Considerations section, inpatient BZD withdrawal management should be considered when the patient is at imminent risk for significant harm from continued BZD use, the patient has a comorbid physical or mental health condition that makes an outpatient BZD taper unsafe, or the patient is experiencing or imminently expected to experience severe withdrawal. As with any tapering plan, BZD tapering in an inpatient setting should focus on management and minimization of withdrawal symptoms, as well as supportive care and monitoring/management of comorbid conditions if appropriate.

Tapering with Very Long-Acting Agents

Some limited evidence exists for the use of very long-acting agents that modify responses to gamma-aminobutyric acid (GABA) (e.g., phenobarbital, chlordiazepoxide) to accomplish a BZD taper.[85] Phenobarbital and chlordiazepoxide both have very long half-lives (80-120 hours and 24-95 hours respectively), resulting in a gradual taper of effects after the medication is discontinued. The committee emphasized that this approach should be limited to situations where patient safety is a concern. This approach also may be effective for patients with SUD who have been unable to accomplish a gradual taper in an outpatient setting. Additionally, as described above, in some instances the patient may request this type of approach, due to the desire to quickly discontinue BZD use.[86]

Phenobarbital-based protocols for tapering have been found to be safe and effective based on two retrospective studies cumulatively evaluating outcomes of over 650 patients.[87] [85] In a retrospective case series of 310 patients treated with a 3-day phenobarbital protocol, while 27% of the patients experienced sedation, none experienced falls or seizures, and only 1% experienced delirium.[87] A more recent chart review study of patients undergoing a 6-day phenobarbital protocol found that no patients developed seizures, falls, or sedation.[85] While both studies had noted limitations (retrospective studies with no comparison group or long-term follow up data), they suggest phenobarbital-based protocols are a reasonable approach to BZD taper for selected patients.

Tapering with very long-acting medications should generally be conducted in a medically managed residential or inpatient setting but may sometimes be completed in outpatient settings by specialist physicians (e.g., addiction medicine) with appropriate experience.

Discharge planning

Discharge planning is critical following a BZD taper in an inpatient or medically managed residential setting. In cases where the taper is not completed during the inpatient or residential stay, clinicians should ensure that the patient has access to any medications, including BZD that are needed for continuing the tapering process. Discharge planning should include an outpatient follow-up appointment, ideally within a week.

During the follow up appointment, the clinician should assess the patient for ongoing signs and symptoms related to the reduction or discontinuation of BZD, including recurrence, rebound, and residual withdrawal symptoms.

Other pharmacological interventions

Flumazenil, a GABA-A receptor agonist, is effective in reversing central nervous system and respiratory depression due to BZD overdose. Recent RCTs have suggested that low-dose flumazenil may be effective for facilitating BZD discontinuation, especially among patients taking high doses of BZD.[88,89] Despite these findings, the committee had concerns about the high potential for refractory seizures, dysrhythmias, and other side effects when using flumazenil.[90] Therefore, the committee agreed that flumazenil should not be utilized for the purposes of BZD tapering. Similarly, very limited evidence was found for anesthetics such as ketamine for facilitating BZD withdrawal.[91] Both ketamine and propofol have significant risk of increased respiratory depression when combined with BZD, and there is no evidence supporting their use on a routine basis. Therefore, the committee agreed that the risks of ketamine as well as propofol in this population outweigh potential benefits and could not be recommended.

Recommendations for BZD Withdrawal Management

41. Patients undergoing BZD withdrawal management in an inpatient or other medically managed setting should be:
    a. Monitored for signs and symptoms of BZD withdrawal regularly using vital signs and a standardized assessment tool *(Clinical consensus, Strong Recommendation)*; and

b. Assessed for seizure risk and managed as appropriate *(Clinical consensus, Strong Recommendation)*.

42. Tapering with very long-acting agents (e.g., with phenobarbital, chlordiazepoxide) should typically be conducted in an inpatient or medically managed residential setting (e.g., ASAM Criteria Level 3.7). *(Clinical consensus, Conditional Recommendation)*.
    a. Tapering with very long-acting agents may also be conducted in outpatient settings with extended nurse monitoring (e.g., ASAM Criteria Level 2.7) by, or in consultation with, a clinician experienced in the use of these medications for BZD tapering. *(Clinical consensus, Conditional Recommendation)*.
43. Following a physiological taper, discharge planning should include an outpatient follow-up appointment, ideally, within 7 days *(Clinical consensus, Strong Recommendation)*.
44. The follow up clinician should:
    a. Assess the patient for ongoing signs or symptoms related to discontinuation of BZD, including re-emergence of symptoms for which the BZD was originally prescribed *(Clinical consensus, Strong Recommendation)*; and
    b. Consider medications and/or behavioral interventions to address ongoing signs or symptoms related to discontinuation of BZD *(Clinical consensus, Conditional Recommendation)*.
45. Due to risks for refractory seizure, dysrhythmias, and other side effects, for the purpose of BZD tapering, clinicians should avoid rapid BZD reversal agents such as flumazenil *(Clinical consensus, Strong Recommendation).*
46. For the purpose of BZD tapering, clinicians should generally avoid general anesthetics such as propofol or ketamine *(Clinical consensus, Conditional Recommendation)*.

Population-Specific Considerations

Patients Co-Prescribed BZD and Opioids

Although not recommended, patients with chronic pain are commonly prescribed BZDs and opioid medication for pain management concurrently.[92,93] Patients prescribed this combination of medications tend to be on relatively higher doses of opioids and they report higher levels of pain and lower self-efficacy for pain management.[94] They also have greater healthcare utilization, especially emergency department visits.[94] Finally, these patients are at greater risk for

nonmedical substance use and comorbid psychiatric conditions, compared to patients who never used BZD.[94]

For patients prescribed both opioids and BZD, these medications may be prescribed by different providers.[95] When the risks associated with the combined use of these medications outweigh the benefits for the patient the clinician should engage in shared decision making with the patient to determine which medication to taper. Prior to initiating a BZD taper, clinicians should attempt to coordinate care with any other prescribers. The committee noted that it may be challenging to reach other clinicians. Clinicians can consider coordinating with the payer or pharmacy as they may have alternative mechanisms for communicating with other clinicians involved in the patient's care.

Patients prescribed both opioids and BZD comprise a high-risk population. Clinicians should consider additional strategies for mitigating risk, including using lowest effective doses of BZD and opioid analgesic medications, and optimizing non-opioid interventions to manage pain. As emphasized in the *CDC Clinical Practice Guideline for Prescribing Opioids for Pain*[18]:

> When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest effective dosage. If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage, should carefully evaluate individual benefits and risks when considering increasing dosage, and should avoid increasing dosage above levels likely to yield diminishing returns in benefits relative to risks to patients.

The committee recommended that the risks and benefits of continued BZD prescribing should be reviewed frequently, at least every 3 months. In cases where the patient has other risk factors for adverse events, the risk benefit assessment should be conducted more frequently. As discussed in Recommendation #1a at a minimum risks and benefits should be assessed with each new prescription or prescription refill authorization. The Risk Index for Overdose or Serious Opioid-induced Respiratory Depression (RIOSOIRD) is a tool that can be utilized for this purpose (See Box).[96,97]

[START BOX]

The Risk Index for Overdose or Serious Opioid-induced Respiratory Depression (RIOSOIRD)

The RIOSOIRD is a screening instrument designed to provide clinically practical guidance for safer opioid prescribing. It was originally developed using administrative health care data from a large sample of patients served by the Veterans Health Administration and validated using a health plan claims dataset with data from over 115 million individuals.[96,97] The risk assessment looks at co-occurring SUD, mental health diagnoses, and biomedical conditions, as well as the type and formulation of opioids used, and co-prescribing of BZD and other medications. The RIOSOIRD showed strong predictive accuracy in both data sets.

[END BOX]

It is especially important to mitigate risk among patients who are co-prescribed BZD and opioids. As the combined use of these medications increases the risk for overdose,[15,16] opioid overdose reversal medication (e.g., naloxone) should be provided or prescribed. In addition, the committee recommends that clinicians use the lowest effective dose of BZD and follow the CDC guidelines for minimizing risks related to opioid prescribing.[18] This includes minimizing opioid doses where possible and optimizing non-opioid interventions for managing pain or other indications for which the opioid is being prescribed. This may include non-pharmacological treatments for pain management, including exercise, mindfulness-based interventions, and CBT.[18]

Recommendations for Patients Co-Prescribed BZD and Opioids

47. For patients who are co-prescribed BZD and opioids: Prior to initiating a BZD taper, the clinician should seek to coordinate care with any other clinician(s) who may also be prescribing BZD or opioids *(Clinical consensus, Strong Recommendation)*.
48. Because of the increased risk for respiratory depression with concurrent use of BZD and opioids, the prescribing clinician should assess the risks and benefits of continued BZD prescribing at least every 3 months *(Clinical consensus, Strong Recommendation)*.
    a. Risk benefit assessments should be conducted more often when the patient has other risk factors for adverse events *(Clinical consensus, Strong Recommendation).*
49. Clinicians should provide or prescribe naloxone for all patients co-prescribed BZD and opioids *(Clinical consensus, Strong Recommendation)*.

50. Clinicians should consider additional strategies for mitigating risk, including using lowest effective doses of BZD and opioid medications, and optimizing non-opioid interventions *(Clinical consensus, Strong Recommendation)*.

Patients with BZD Use Disorder or Other SUD

Some patients with BZD use disorder may be able to successfully taper BZD in an outpatient setting. However, some patients, such as those taking very high doses of BZD, and/or who are using other substances may require a more intensive level of care. For example, patients with SUDs at high risk for medical instability or severe withdrawal, or with a history of withdrawal-related seizure, should be managed in a medically managed residential or inpatient setting because of the available 24-hour nurse monitoring and medical care to support stabilization and withdrawal management.[98] The ASAM Criteria provides guidance on determining an appropriate level of care for patients with SUD (see Box).[98]

[START BOX]

***The ASAM Criteria* – Levels of Care**

First published in 1991, The ASAM Criteria offers an evidence-based and standardized way of determining the appropriate level of SUD services based on an individual's needs and circumstances. A multidimensional assessment is used to determine the most appropriate level of care based on intoxication and withdrawal-related risks; need for addiction medications; co-morbid biomedical, psychiatric and cognitive conditions; substance-use related risks; and recovery environment considerations.

The ASAM Criteria describes SUD treatment as a continuum marked by four broad levels of care – outpatient, intensive outpatient, residential, and inpatient. Decimal number express gradations of intensity and types of care provided. Level x.7 programs are Medically managed programs (bolded below) provide withdrawal management, including management of BZD withdrawal, and biomedical services along with integrated psychosocial services.

- Level 1: Outpatient Treatment
    - Level 1.5: Outpatient Therapy
    - **Level 1.7: Medically Managed Outpatient**

- Level 2: Intensive Outpatient/Hi-Intensity Outpatient Treatment
  - Level 2.1: Intensive Outpatient
  - Level 2.5: High-Intensity Outpatient
  - **Level 2.7: Medically Managed Intensive Outpatient**
- Level 3: Residential Treatment
  - Level 3.1: Clinically Managed Low-Intensity Residential
  - Level 3.5: Clinically Managed High-Intensity Residential
  - **Level 3.7: Medically Managed Residential**
  - **Level 3.7 BIO: Biomedically Enhanced Medically Managed Residential**
- **Level 4: Medically Managed Inpatient Treatment**

For more information, see https://www.asam.org/asam-criteria.

[END BOX]

Assessing Risks and Benefits of Continued BZD Prescribing

Patients who use BZD and have concurrent alcohol use disorder (AUD) or opioid use disorder (OUD) are at particularly high risk of morbidity and mortality because of the cross-tolerance and combined respiratory depressant effects of these substances.[17,40] The committee agreed that the risk/benefit assessment of continued BZD prescribing should be reviewed at least monthly for patients with co-occurring AUD or OUD. In patients with a history of other SUDs, BZD use should be reviewed frequently as individuals with a SUD related to one substance have an increased prevalence of other SUD**s** compared to those without a history of SUD.[99]

Considerations for the BZD Taper in Patients with SUD

As with all patients, abrupt cessation of BZD is dangerous and gradual dose reduction individualized based on the patient's response is recommended.[22,23] If more rapid tapering is indicated, the taper approach using very long-acting agents described in the Withdrawal Management section can be considered. Clinicians should consider a patient's psychosocial situation and co-occurring disorders when determining the appropriate timing of a BZD taper.

If BZD tapering is indicated, the underlying SUD should be managed concurrently with the taper. For patients with OUD, medications for OUD should typically be initiated and stabilized prior to initiating a BZD taper and the dose of OUD medication should be kept stable throughout

the BZD tapering process.[100,101] Psychosocial interventions (e.g., cognitive behavioral therapy) to treat the underlying SUD(s) should be provided in parallel with pharmacotherapy.[101] As emphasized in ASAM's National Practice Guideline for the Treatment of OUD, "The use of benzodiazepines and other sedative-hypnotics should not be a reason to withhold or suspend treatment with methadone or buprenorphine. While the combined use of these medications increases the risk of serious adverse effects, the harm caused by untreated opioid use disorder can outweigh these risks."[101]

81. Monitoring patients during and after BZD tapering is a key aspect of clinical management of successful BZD discontinuation. Approaches to reduce return to BZD use include ongoing treatment of underlying SUD and co-occurring physical and mental health conditions, recovery support services (e.g., peer support), and addressing environmental risk factors (e.g., housing instability, lack of a recovery supportive network). Patients should be referred to an appropriate level of care for ongoing SUD treatment following BZD dose reduction or discontinuation.[101]

Drug testing

While drug testing can be helpful to detect the use of substances, there are limitations to urine immunoassays for BZDs due to limitations in specificity. They are generally not sensitive to therapeutic doses of BZDs and the performance of the tests vary depending on the manufacturer.[102] For this reason, there is an increased risk of false negatives, and confirmatory testing is often indicated. The interpretation of test results can be complicated by the presence of BZD metabolites as some metabolites are themselves parent compounds.[103] The application and frequency of drug testing should be determined by the patient's clinical needs and the treatment setting. Multiple existing guidance emphasizes that drug test results should not be used punitively, they should be used to engage the patient therapeutically and to inform the treatment plan.[56,68,101]

Harm Reduction

In most areas of the country, it is common for heroin, cocaine, methamphetamine, and counterfeit prescription drugs to be contaminated with fentanyl, presenting significant risks of overdose. This risk is exacerbated by BZD use. All patients who may intentionally or unintentionally use opioids should be educated about this risk and given or prescribed opioid overdose reversal medication (e.g., naloxone). Patients should also be connected to local harm

reduction organizations for provision of drug checking or other safe use supplies (e.g., fentanyl test strips, sterile syringes) as appropriate given their patterns of substance use.

Recommendations for Patients with BZD Use Disorder and/or Co-Occurring SUD

51. For patients with SUD, clinicians should consider using existing standards for level of care recommendations such as *The ASAM Criteria (Clinical consensus, Strong Recommendation)*.
    a. For patients unlikely to effectively participate in an outpatient taper, clinicians should consider a residential or inpatient setting *(Clinical consensus, Strong Recommendation)*.
52. For patients with BZD use disorder, alcohol use disorder, or opioid use disorder: Clinicians should assess the risks and benefits of continued BZD prescribing at least monthly *(Clinical consensus, Strong Recommendation)*.
53. For patients with other comorbid addictions (e.g., stimulant use disorder, cannabis use disorder, behavioral addictions): Clinicians should consider more frequent assessments of the risks and benefits of continued BZD prescribing compared to the general guidance (Recommendation #1). *(Clinical consensus, Strong Recommendation)*.
54. When tapering BZD in a patient with SUD, the underlying SUD should be managed concurrently with the BZD taper *(Clinical consensus, Strong Recommendation)*.
55. Any medications for SUD treatment, including buprenorphine and methadone, should be continued during the BZD taper *(Clinical consensus, Strong Recommendation)*.
56. Following the taper, clinicians should continue to monitor and treat underlying SUD or refer the patient to an appropriate level of care for continuing care *(Clinical consensus, Strong Recommendation)*.
57. Clinicians can consider using toxicology testing to support the risk/benefit assessment *(Clinical consensus, Strong Recommendation)*.
58. Clinicians should provide or refer for harm reduction services, which may include but are not limited to:
    a. Provision of naloxone and related training *(Clinical consensus, Strong Recommendation)*; and
    b. Provision of drug checking or other safe use supplies (e.g., fentanyl test strips, xylazine test strips, sterile syringes) *(Clinical consensus, Conditional Recommendation)*.

Patients with Psychiatric Disorders

Many patients with psychiatric conditions are able to taper from BZDs in outpatient settings, but some may require a more intensive level of care. BZD tapering may exacerbate or cause recurrence of psychiatric symptoms, which may warrant more intensive medical oversight.[23,104] Consideration should be given to any underlying psychiatric conditions, including treatment history, prior to beginning a taper. Clinicians can consider using the Level of Care Utilization Services Tool (LOCUS) for guidance determining the appropriate treatment setting for patients with psychiatric conditions (see BOX).

[START BOX]

Level of Care Utilization System – Level of Care

Developed in the 1990's by the American Association for Community Psychiatry (AACP), The Level of Care Utilization System (LOCUS) offers an evidence-based, standardized, and organized way for connecting adults with mental health services based on their individual needs and circumstances. A multidimensional assessment is used to determine the most appropriate level of care for an individual based on their risk of harm; functional status; medical, addictive, and psychiatric co-morbidity; recovery environment; treatment and recovery history; and engagement and recovery status. The LOCUS describes seven levels of care of different service intensities, including:

- Level Zero: Basic Services: Universal Prevention and Health Maintenance
- Level One: Recovery Maintenance and Health Management
- Level Two: Low Intensity Community-based Services
- Level Three: High Intensity Community-based Services
- Level Four: Medically Monitored Non-residential Services
- Level Five: Medically Monitored Residential Services
- Level Six: Medically Managed Residential Services

For more information, see the LOCUS and Toward a National Standard for Service Intensity Assessment and Planning for Mental Health Care white paper .[105,106]

[END BOX]

Patients who have used BZDs for a long time may be reluctant to taper this medication due to fear of adverse effects of discontinuation.[30,107,108] As BZD tapering can lead to rebound mental health symptoms (e.g., anxiety, insomnia), clinicians should consider optimizing evidence-based treatments for any co-occurring mental health conditions prior to initiating a BZD taper.[109,110] Non-BZD therapies such as SSRIs, cognitive behavioral therapy (CBT), or other evidence based interventions may be appropriate alternatives to BZD for many patients (see Appendix J).[111-113]

Clinicians should educate patients regarding potential rebound psychiatric symptoms and how they will be managed and offer or refer for appropriate mental health services. As discussed earlier, providing behavioral interventions during the BZD taper is associated with successful tapering of BZD.[111-113]

Patients with PTSD

The Department of Veterans Affairs (VA) recommends that BZDs be avoided if a patient has symptoms of PTSD and provides guidance on alternative treatments for management of anxiety and insomnia in these patients.[114] BZDs are ineffective for the treatment of PTSD; they do not reduce the core symptoms of PTSD or improve PTSD-related sleep dysfunction[115,116]. BZD use is associated with increased risk of substance use, depression, aggression, increased PTSD severity, and decreased efficacy of trauma-focused psychotherapy.[117] When tapering BZD in a patient with PTSD it is important to consider that withdrawal of BZDs can worsen existing PTSD symptoms (e.g., increased anxiety, rage, increased nightmares, intrusive thoughts, hyper-alertness). The committee noted that clinicians can consider consultation with a psychiatric specialist to develop a tapering strategy that minimizes these risks.

Management of sleep disturbance in patients with psychiatric conditions

Sleep disturbance is a common symptom during a BZD taper,[23] which may contribute to symptom exacerbation of underlying mood or psychotic disorders.[118,119] The committee recommends that sleep be monitored closely in these individuals. If sleep disturbance occurs, the clinician should pause the taper until symptoms resolve. In addition to pausing the taper, clinicians can provide sleep hygiene information and provide or refer the patient for alternative treatment options such as CBT.[113,120] Additionally, clinicians can consider consulting with a psychiatrist or sleep medicine specialist to help guide treatment plans.

Recommendations for patients with co-occurring psychiatric disorders

59. For patients with psychiatric conditions, clinicians should consider using existing standards for level of care recommendations such as The Level of Care Utilization System (LOCUS) *(Clinical consensus, Strong Recommendation)*.
60. Clinicians should consider optimizing evidence-based treatment for any psychiatric disorder prior to the taper *(Clinical consensus, Strong Recommendation)*.
61. For patients with PTSD, clinicians should strongly consider tapering BZD medications *(Clinical consensus, Strong Recommendation)*.
62. Clinicians should monitor sleep closely in patients with mood or psychotic disorders undergoing a BZD taper, particularly for patients with bipolar disorder, as sleep disturbance can trigger episodes of mania *(Clinical consensus, Strong Recommendation)*.
    a. Due to the risk for destabilization, if a patient experiences significant sleep disturbance, clinicians should pause the taper until the symptoms resolve *(Clinical consensus, Strong Recommendation)*.
        i. Clinicians can also consider providing or referring for behavioral interventions (e.g., CBT, sleep hygiene education) *(Clinical consensus, Conditional Recommendation)*.
        ii. Clinicians can also consider consulting with a clinician with psychiatric expertise. *(Clinical consensus, Conditional Recommendation)*.

Considerations for Older Adults

While BZDs may offer short-term benefits, the adverse effects associated with their use—including risk of falls and cognitive impairment—have generally been shown to outweigh the marginal benefits in adults 65 years or older.[36] Chronic BZD use is also a significant concern for older adults given that they are likely to be prescribed multiple medications, increasing their risk of morbidity and mortality from polypharmacy.[121,122] For these reasons, the American Geriatrics Society Beers Criteria recommends avoiding the use of both long- and short-acting BZDs in adults over 65 years of age.[123] The CGC recommends that clinicians make every effort to taper BZD use in older adults—developing individualized tapering plans through shared decision-making—unless there are compelling reasons for continuation. Clinicians should consider alternative treatment options with more favorable safety profiles.

Fragmented care can be a barrier to effective BZD tapering because attitudes, knowledge, and conflicting advice from a patient's medical teams—including primary care, psychiatry, neurology, and other specialty providers—and care partners can influence the BZD deprescribing process.[62,124,125] Further complicating the matter is that metabolic changes associated with aging make older adults more sensitive to BZDs, increasing their risk of adverse events such as cognitive impairment—particularly in the domains of memory, learning, attention, and visuospatial ability.[62,126,127] Tapering older adults—particularly those with cognitive impairment—from long-term BZD use can be challenging. Direct educational interventions (e.g., brochures) can help engage older adults, including those with mild cognitive impairment, and their care partners in shared decision-making around BZD tapering and discontinuation.[128] A patient's medical teams and care partners may be essential in shared decision-making between the patient and provider regarding BZD tapering methods that consider the patient's individual needs.

Transitioning to a Longer-Acting BZD for Tapering

Recommendation #8 states that clinicians can consider transitioning patients without contraindications (e.g., liver dysfunction) to a comparable dose of a longer-acting BZD for the taper. However, metabolic changes associated with aging—namely, reduced hepatic clearance—may increase risk of adverse events and toxicity.[126] As a result, the CGC cautions against transitioning older adults to longer-acting BZDs prior to tapering.

Level of Care Considerations for Older Adults

Older adults, especially those with any degree of cognitive impairment, are at increased risk for poor outcomes in inpatient settings due to hospital-induced delirium and decompensation.[129] The CGC emphasizes that clinicians should attempt to taper BZDs in older adult patients in an outpatient setting unless there is a specific indication for an inpatient setting. Tapering may need to occur in a residential or inpatient setting if it would be unsafe to taper in an outpatient setting—for example, because family members or the care team cannot manage the older adult in their home environment. In these cases, a specialized inpatient unit for older adults is preferred if available.

Recommendation Statement for Older Adults

63. Clinicians should taper BZD in most older adults unless there are compelling reasons for continuation *(Clinical consensus, Strong Recommendation)*.

Considerations for Pregnant Patients

BZD use in pregnancy has been found to be associated with an increased risk for miscarriage, preterm birth, and low birth weight, as well as an increased risk of the newborn requiring admission to the neonatal intensive care unit.[130-132] However, antenatal exposure to BZDs is not associated with major congenital malformations.[130,133] Approximately 20% to 40% of neonates who have been exposed to BZDs in utero during late pregnancy develop neonatal withdrawal,[134,135] with symptoms including irritability, increased sedation, abnormal muscle tone, poor feeding, sleep problems, and mild respiratory distress.[136-138] Floppy infant syndrome (FIS)—which presents with hypotonia, lethargy, sucking difficulties, low Apgar score, hypothermia, apnea, cyanosis, hyperbilirubinemia, and CNS depression—has also been observed in newborns who have been exposed to BZDs in utero during the third trimester and may be a result of BZD toxicity.[139,140] Both neonatal BZD withdrawal and FIS typically present within the first hours of life and continue for up to 14 days.[139]

While BZD use carries some risk to the fetus, similar risks—including an increase in miscarriage, preterm birth, and low birth weight—are also present if maternal anxiety, mood, and sleep disorders are left untreated.[130,141] In general, existing clinical guidelines recommend optimizing alternative therapeutic approaches but allow for the use of BZDs during pregnancy to manage anxiety and poor sleep but advise caution with dosing, recommending that BZDs be prescribed sparingly and at the lowest effective dose and with consideration of pharmacokinetic changes that occur during pregnancy (see Appendix L).[142,143] BZD tapering can be done safely in pregnancy[142,143]; however, the American College of Obstetricians and Gynecologists notes that[141]:

> [I]t is also critical to consider the risks of a taper for the pregnant individual and the fetus. For example, if attempts to taper the benzodiazepine precipitate re-emergence of anxiety, the benefits of continuation may outweigh the risks.

As such, the CGC advises clinicians to discuss the risks and benefits of BZD use and discontinuation for the maternal–fetal dyad with pregnant patients, considering each patient's unique needs and engaging in shared decision-making to determine whether to taper. Lorazepam is generally preferred in pregnancy and lactation due to lack of active metabolites and low relative infant dose (RID). Referral to or consultation with specialists in reproductive psychiatry, if available, may also be considered.

Breastfeeding

In general, breastfeeding is not contraindicated in the presence of maternal BZD use.[144] The long term-effects of BZD exposure are unknown, but evidence suggests that the amount of BZD transferred into breast milk is low.[145,146] Evidence has suggested that breastfeeding—while unlikely to prevent NAS—can substantially delay the onset and reduce the severity of NAS, decrease the need for pharmacologic treatment, and lead to shorter hospitalization stays compared to formula-fed infants.[147] Further, breastfeeding has been shown to enhance parental bonding, promote attachment, and is associated with a reduced rate of child removal.[148] Thus, the CGC recommends that clinicians encourage breastfeeding to help reduce potential symptoms of NAS in the infant.

Recommendations for Pregnant Patients

64. When considering a BZD taper for pregnant patients, clinicians should weigh risks and benefits for the maternal-fetal dyad *(Clinical consensus, Strong Recommendation)*.
65. Clinicians should monitor closely for psychiatric symptoms during the taper as these symptoms may evolve rapidly during the pregnancy and postpartum period and may require treatment *(Clinical consensus, Strong Recommendation)*.
66. Clinicians can consider a referral to or consultation with a healthcare professional with expertise in reproductive psychiatry *(Clinical consensus, Conditional Recommendation)*.
67. For infants with long-term BZD exposure *in utero*, clinicians should:
    a. Encourage breastfeeding, which can reduce neonatal withdrawal symptoms *(Clinical consensus, Strong Recommendation);* and
    b. Communicate with the infant's healthcare provider (with parental consent) regarding exposure to BZD *(Clinical consensus, Strong Recommendation)*.

When a shared decision cannot be reached with the patient

As discussed above, prescribers should work with patients in a shared decision-making process when considering BZD tapering. However, there are some instances when a prescriber may initiate a taper when the patient is ambivalent about or against tapering, including:

- When a patient poses a threat to the safety of the clinician, staff, or other patients
- When a patient is diverting their medication
- When a patient engages in criminal behaviors within the treatment setting

In these instances, the prescriber should explain the reasons for their decision with the patient and carefully document the rationale and related discussions. Best practices include providing a written summary to the patient. They should also offer a referral to an appropriate alternative treatment individualized to the patient's needs that can manage the tapering process, providing a warm handoff if appropriate and if the patient is amenable. If the patient declines referral, the prescriber may consider a plan to taper BZD that considers the safety of all parties.

In the situations detailed above, the prescriber may need to initiate a more rapid taper than would typically be indicated. The prescriber may need to balance conflicting obligations. For example, the prescriber has a duty to report suspected medication diversion and to discontinue prescribing medications if they are being diverted. [Note that if a patient is known to be diverting their BZD medication and has not been taking the medication regularly, ongoing prescriptions to support a taper are not necessary.] At the same time, the prescriber has a duty to the patient who may be at risk for life threatening withdrawal if medications are abruptly discontinued. Clinicians should consider seeking the advice of le.g.al counsel, risk management, and or health systems administrators in these complex situations. State licensing boards and professional organizations may also have guidance available. The prescriber may consider a discharge taper to prevent severe or complicated withdrawal. For example, providing a 14-to-30-day prescription with detailed instructions on how to taper the medication over that time period. When determining the dose and number of pills the clinician should carefully consider the individual patient's risks including suicidality and overdose. Given uncertainties regarding patient follow up after discharge, a prescription for adjunctive medications may also be considered to help alleviate potential withdrawal symptoms(See Adjunctive Medications Table). The prescriber should

clearly communicate that this will be the last BZD prescription provided, the risks of abrupt discontinuation of BZD, and what symptoms should trigger them to seek emergency medical care. This encounter should be well documented.

Some patients may be upset at the prospect of medication tapering. Clinicians should be aware of this risk and consider how to mitigate risks to themselves, their staff, and other patients. De-escalation strategies may be helpful to reduce anger and frustration. Other strategies can include being close to the door, having another person in the room, conducting the appointment via telemedicine, and alerting clinic security in advance if available. Clinics that experience these types of challenges more often can also consider implementing help buttons that allow clinicians to silently alert other staff of the need for assistance.

These situations are challenging for prescribers, staff, and patients. Providers should consider consultation with their organization's le.g.al or risk management team and/or their malpractice carrier if they have concerns. Furthermore, it is recommended that organizations have policies and procedures in place to support providers and staff in situations where a patient's preferences are not congruent with safe medical prescribing. Prescribers and staff should also be cognizant of their own mental wellness when dealing with difficult patient encounters and be able to pursue support without fear of repercussions.

<u>When the risks of continued prescribing outweigh the benefits for the patient</u>

When the prescriber is concerned that continued BZD use is not in the patient's best interest, they should discuss this with the patient. It is important to listen to the patient's concerns and any reasons for disagreement. Clinicians should be mindful of unconscious bias when initiating a taper against a patient's wishes. If after this discussion, the clinician and the patient (or care partner) do not agree on the need for a taper consider referral for a second opinion.

When initiating a taper when the patient does not agree, the prescriber should follow the guidance provided in the Tapering Strategies section. They should clearly communicate their rationale for initiating a taper to the patient. As discussed above, it is important to closely monitor the patient's response to the taper and adjust the strategy as appropriate.

<u>Inherited patients</u>

In some instances, a prescriber may inherit a patient who has been prescribed high dose and/or long-term BZD. Clinicians have an obligation to promote patient safety, including not continuing to prescribe a medication (or dosages of the medication) that poses a significant risk to the patient. They can attempt to consult with the prior prescriber and other relevant mental health or physical healthcare providers. If the prescriber is not comfortable assuming responsibility for the prescription, they can consider referral to another provider or to a more intensive level of care if appropriate with a bridging prescription to prevent abrupt discontinuation of the medication.

Emergency departments (ED) have unique considerations as they are subject to the Emergency Medical Treatment and Active Labor Act (EMTALA) which requires them to provide necessary stabilizing treatment for emergency medical conditions for any individual who comes to the hospital. Patients should not be routinely referred to the ED unless they are experiencing or imminently expected to experience severe acute withdrawal. ED providers may initiate a short taper or provide a bridging BZD prescription if appropriate. However, a clear plan for a safe taper and follow-up should be in place at the time of discharge. Due to the lack of capacity for direct follow up, ED providers may initiate, or admit the patient for inpatient care to initiate, a taper using very long-acting agents (e.g., phenobarbital protocol) and referral to an appropriate provider for any ongoing care needs.

Strategies for preventing diversion

If a prescriber is aware that a patient is diverting controlled medication and continues to prescribe that medication, it can create le.g.al risk for them. In addition, their Drug Enforcement Agency (DEA) and license to practice could be in jeopardy. As discussed above, this can lead to complex situations in which the prescriber is balancing this risk against the risks to the patient associated with rapid discontinuation of BZD. Prescribers should educate patients on the consequences of medication diversion in a patient-centered manner, including required reporting and medication discontinuation. If the prescriber is concerned about the potential for diversion they can consider:

- Screening for and addressing substance misuse and use disorders
- Pill checks
- Medication agreements
- Shorter duration between prescriptions

- Limiting refills
- Partnering with collateral contacts (e.g., family member, friend, or care partner)
- Coordinating with the pharmacy
- Checking the PDMP when initiating or refilling a prescription

Prescribers can include a note to the pharmacist in the e-prescription asking the pharmacist to only fill BZD prescriptions from their office. Integrated care systems may consider including a pharmacist on treatment teams. Some payers, including Medicaid, can restrict who is allowed to prescribe controlled substances for a given patient. If a controlled substance agreement is used, it can include that the patient can only get controlled substance prescriptions filled by a specific pharmacy. Prescribers can also work with payers to request a case manager who can conduct drug utilization reviews which allows them to see all medications, not just those in the PDMP.

Final Thoughts

The CGC was surprised by the lack of controlled studies related to many of the topics discussed in this Guideline. Our systematic review found no trials comparing BZD tapering strategies, or other important aspects of management of this patient population. Further research into best practices for BZD tapering strategies that support patient safety and optimal outcomes is needed.

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Appendix A. Glossary of Terms

addiction: A treatable chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences. Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic diseases.

addiction medication: Medications that are specifically indicated for and prescribed to treat substance use disorders (SUDs) as an initial lifesaving measure, motivational engagement strategy (i.e., withdrawal management), and as part of a long-term treatment plan similar to medications used to treat other chronic diseases such as bipolar disorder or diabetes.

addiction medicine: A medical subspecialty concerned with the prevention, evaluation, diagnosis, treatment, and recovery of people with the disease of addiction and substance-related health conditions, as well as people who use substances—including nicotine, alcohol, prescription medications, and other licit and illicit drugs—in an unhealthy manner. Addiction medicine is recognized as a distinct medical sub- specialty within preventive medicine by the American Board of Medical Specialties (ABMS).

care partner: A person who provides support to a person with a chronic condition to help manage their healthcare needs. The term "care partner" is preferred over caregiver because it emphasizes the person's role in shared decision making with the patient and their providers.

clinician: A health professional with the scope of practice to provide medical or clinical services (see **clinical staff, medical staff**).

drug testing: The process of analyzing a biological specimen to check for the presence of chemicals that indicate exposure to selected substances.

inpatient treatment: Intensive 24-hour-a-day services delivered in a hospital setting.

level of care: A discrete intensity of clinical services available in a given program or setting (see setting).

medically managed program: a program with a primary focus of treating withdrawal and/or stabilizing biomedical and psychiatric concerns while also providing the full spectrum of psychosocial services for patients who are able to participate effectively.

patient: An individual receiving substance use disorder treatment. Interchangeable with client, which is used more commonly in nonmedical settings.

setting: A general environment in which treatment is delivered.

substance use disorder (SUD): A medical illness consisting of a cluster of cognitive, behavioral, and physiological symptoms caused by repeated misuse of a substance or substances. Characterized by clinically significant impairments in health, social function, and impaired control over substance use (see **addiction**).

symptom-triggered taper: Withdrawal management strategy where medication is administered in response to withdrawal symptoms versus on a specific schedule

warm handoff: A care transition in which the referring clinician facilitates a direct (i.e., face-to-face) introduction of the patient to the receiving clinician at their next level of care.

Appendix B. Abbreviations and Acronyms

AAFP	American Academy of Family Physicians
AAN	American Academy of Neurology
AANP	American Academy of Nurse Practitioners
AAPA	American Academy of Physician Associates
AAPP	American Association of Psychiatric Pharmacists
ACOG	American College of Obstetricians and Gynecologists
AGS	American Geriatrics Society
AHRQ	Agency for Healthcare Research and Quality
APA	American Psychiatric Association
ASAM	American Society of Addiction Medicine
BWSQ	Benzodiazepine Withdrawal Symptom Questionnaire
BZD	Benzodiazepine
CBT	Cognitive Behavioral Therapy
CDC	Centers for Disease Control and Prevention
CGC	Clinical Guideline Committee
CNS	Central nervous system
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CIWA-Ar	Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised
CIWA-B	Clinical Institute Withdrawal Assessment Scale - Benzodiazepines
CPG	Clinical Practice Guideline
CPG-MOS	CPG Methodology Oversight Committee
CYP	cytochrome P450
DEA	Drug Enforcement Agency
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-5-TR	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision
EBI	Evidence-based Intervention
ED	Emergency department
EMTALA	Emergency Medical Treatment and Active Labor Act

ETD	evidence-to-decision
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
LOC	Level of Care
LOCUS	The Level of Care Utilization System
MH	Mental Health
MI	Motivational Interviewing
MOUD	Medications for Opioid use disorder
NIH	National Institutes of Health
NSDUH	National Survey on Drug Use and Health
OTC	Over the counter
OTP	Opioid treatment program
OUD	Opioid use disorder
PDMP	prescription drug monitoring program
PICO	Population, Intervention, Comparators, Outcomes
PTSD	post-traumatic stress disorder
QIC	Quality Improvement Council
RCT	randomized controlled trial
RIOSOIRD	Risk Index for Overdose or Serious Opioid-induced Respiratory Depression
SSRI	selective serotonin reuptake inhibitor
SUD	Substance use disorder
UDT/UDS	Urine drug testing/screening
VA	Department of Veterans Affairs

Appendix C. Methodology

A systematic literature review was conducted to establish a foundation of evidence for guideline recommendations. Methods followed current best practices from the Agency for Healthcare Research and Quality (AHRQ) for systematic reviews,[149] including screening and data extraction in duplicate, risk of bias assessment using standardized instruments, and a synthesized narrative summary of findings. In accordance with PRISMA standards,[150] the systematic review was registered prospectively in the PROSPERO international prospective register of systematic reviews database (Identification Number: CRD42023408418).

The literature review informed the deliberations of a committee of experts, which developed recommendation statements that consider an intervention's clinical benefits and harms, as well as patient values and preferences. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) method was used to develop recommendations in areas with sufficient evidence.[25] Where evidence was lacking, a modified Delphi process was used to develop clinical consensus statements.[26] As there is relatively little research on BZD discontinuation of long-term BZD prescriptions this strategy allowed for the inclusion of guidance in areas for which the evidence is highly limited.

Clinical Practice Guideline Team

Clinical Guideline Committee Formation and Oversight

ASAM's Quality Improvement Council (QIC) and Clinical Practice Guideline Methodology and Oversight Committee (CPG-MOS) oversaw the development of this guideline. The FDA provided guidance on the content and development of the CPG but did not dictate the content. The QIC, working with partner medical societies and the FDA, oversaw the appointment of a Clinical Guideline Committee (CGC) comprised of clinicians with broad subject matter expertise across medicine, psychiatry, and pharmacology representing regional and demographic diversity. Partner medical and professional societies included:

- The American Academy of Family Physicians (AAFP),
- The American Academy of Neurology (AAN),
- The American Academy of Physician Associates (AAPA),
- The American College of Medical Toxicology (ACMT),

- The American Association of Nurse Practitioners (AANP),
- The American Association of Psychiatric Pharmacists (AAPP)
- The American College of Obstetricians and Gynecologists (ACOG),
- The American Geriatrics Society (AGS), and
- The American Psychiatric Association (APA).

A list of members, their areas of expertise, and conflict of interest disclosures are available in Appendix D. Members of the CPG-MOS and the Ethics Committee reviewed disclosures of interest. No members of the CGC had high level conflicts of interest in relation to the guideline topic. One member [BBS] was determined to have a moderate conflict of interest due to the potential for industry profit from education on the Guideline delivered through their LLC. As a mitigation strategy this member was asked to not accept financial or any other compensation from a for-profit or industry group for speaking engagements related to the topic of this Guideline for a period of 24 months following the completion of the Guideline.

Patient Panel

ASAM reached out to leading patient advocacy organizations to nominate representatives to serve on a panel of individuals with lived experience with BZD discontinuation (the Patient Panel). The panel was engaged throughout the development process, providing input on:

(1) the key clinical questions
(2) critical and important outcomes
(3) the recommendation statements

Key Questions and Outcome Development

The CGC, with input from the FDA and Patient Panel, identified the following key clinical questions to be addressed by the systematic review and guideline:

4. What is the efficacy and/or safety of tapering strategies for BZDs?
5. What factors influence the outcomes of BZD tapering and should be monitored?
6. How can shared decision-making and patient-centered health care be utilized to support the effectiveness and safety of BZD tapering?

The questions were used to develop a Population, Intervention, Comparators, Outcomes (PICO) framework for identifying relevant research literature to answer each of the key clinical questions.

2) Population: Adults who have been using one or more BZD for at least 2-4 weeks.
3) Interventions: Two types of interventions were considered:
    a. Interventions to promote the successful discontinuation of BZD use
    b. Interventions to manage withdrawal symptoms when discontinuing BZDs
4) Comparators: Alternative interventions, treatment as usual, placebo, or active control condition
5) Outcomes: BZD cessation or dose reduction, BZD withdrawal severity, recurrence/rebound of BZD-indicated condition (e.g., insomnia, anxiety), sleep problems, cognition, mood, quality of life/patient satisfaction, global functioning, study attrition, other substance use, and adverse events.

Literature Review

The following databases were searched during March and April 2023: EMBASE, PsycINFO, PubMed, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). The search was limited to controlled trials, cohort studies with a comparison condition, and systematic reviews of randomized controlled trials (RCTs) published in English on January 1, 2000 or later. To be included, studies needed to have at least 20 adult participants using one or more BZDs at baseline for at least two weeks and include a BZD discontinuation strategy aimed at patients (i.e., not targeting healthcare systems or provider prescribing behavior). Articles were reviewed in duplicate for inclusion at the title, abstract, and full-text levels. Discussion and consensus between two research associates resolved uncertainty about article inclusion. Hand-searching for included publications was also completed.

Three supplemental searches were conducted on predictors for developing BZD withdrawal, patient preferences and values, and validated BZD withdrawal scales. A grey literature search was conducted to search websites for BZD-related literature. The CGC and patient panel also provided grey literature.

Evidence Review

A risk of bias assessment was completed for each included study. Quality was rated using the AMSTAR-2 tool for systematic reviews,[151] the revised Cochrane Risk of Bias (RoB 2) tool for randomized trials,[152] and the National Institutes of Health (NIH) tool for observational cohort studies.[153]

Characteristics of Individual Studies tables of the included studies including key information about study methods and risk of bias ratings, as well as a narrative synthesis of the results for each intervention found by the literature review was provided to the CGC to review. Where the CGC determined that the evidence for an intervention was sufficient to potentially lead to a recommendation, the relevant study results were extracted into Cochrane Review Manager (RevMan) software.[154] Following best practices as outlined in the Cochrane Handbook,[155] outcome data were pooled and uploaded into GRADE profiler (GRADEpro) software[156] to construct 'Summary of Findings' tables and assist in the assessment of the quality of the body of evidence for an intervention.

The quality of the body of evidence was rated as high, moderate, or low based on the quality (risk of bias) of the included studies, the consistency and precision of the included studies' results, the direct relevance of the studies to the key questions, and the potential for publication bias. The level of quality reflects a level of confidence—or certainty—in how closely effect estimates reflect the true effect and, therefore, the extent to which the evidence can be relied upon when making recommendation decisions.

Recommendation Development

In deliberations about recommendations, decisions on whether a recommendation could be made were based on the available evidence and judgments regarding the recommendation's expected benefits and harms and its acceptability and feasibility for potential stakeholders. The CGC completed an evidence-to-decision (ETD) table to document the evidence and their judgments for these recommendations, included in Appendix E. When clinical evidence was of low quality, unclear, or nonexistent, the CGC decided whether a recommendation could still be made on the basis of the committee's clinical expertise or should be delayed until further evidence is produced and whether failing to make a recommendation could lead to potential harm.

Consensus-based recommendations also considered their expected clinical impact, acceptability, and feasibility. Consensus-based recommendations are labeled using "Clinical consensus", whereas evidence-based statements include a certainty of evidence rating.

A 70% agreement among CGC members was required to approve a recommendation. The CGC graded the strength of each accepted recommendation as strong or conditional based on the overall balance of benefits and harms, the certainty of the evidence of treatment effects, and patient preferences and values. Recommendations were worded to reflect their strength. For example, "clinicians should" indicates a strong recommendation while "clinicians can" indicates a weaker recommendation. The strength of the recommendation was determined via committee vote, with a 70% threshold required for consensus.

External Review

ASAM is inviting major stakeholder organizations, partner organizations, relevant committees, and its Board of Directors to provide comments on this Guideline draft. The CGC and Patient Panel will be asked for final comments. In addition, ASAM will work with the FDA and partner organizations to broadly disseminate a call for public comment. The CGC will review all comments and identify issues to be addressed before publication. Major edits will be subject to a vote by the CGC.

Appendix D. Disclosures of Interest

Disclosures and Conflicts of Interest

A. 2024 Guideline Committee Member Relationships with Industry and Other Entities

Guideline Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/Principal	Institutional, Organizational or other financial benefit	Research
Maryann Amirshahi, MD, PharmD, MPH, BCPS, FASAM	MedStar Washington Hospital Center; National Capital Poison Center; George University	Expert Witness*; FDA Advisory Panels*	None	None	None	None
Emily Brunner, MD, DFASAM (Chair)	Gateway	None	None	None	None	None
Chwen-Yuen Chen, MD, FACP, FASAM	Standford University; Private Practice	Anonymous Health*; Expert Witness*	None	Private Practice**	None	None
Tracy Klein, PhD, FAANP, FAAN	Washington State University	Expert Witness*	None	None	Oregon Prescription Drug Monitoring Program Advisory Committee	None
Donovan Maust, MD, MS	University of Michigan	Expert Witness**	None	None	None	None
Marcia Mecca, MD	VA Connecticut	None	None	None	None	None
Deanna Najera, MPAS, MS,	Medstar Emergency	None	PA Foundation*; American Academy	None	None	None

PA-C, DFAAPA	Physicians; Carroll County Health Department; TrueNorth Wellness Services		of Physician Associates*; Maryland Academy of Physician Assistants*; Pennsylvania Society of Physician Associates*			
Chinyere Ogbonna, MD, MPH	Kaiser Permanente San Jose	None	None	None	None	None
Kiran Rajneesh, MD, MS	The Ohio State University	Merck Pharmaceuticals*	None	None	None	None
Elizabeth Roll, MD	Yukon Kuskokwim Health Corporation	None	None	None	None	None
Amy Sanders, MD, MS, MPHIL, FAAN	StealthCo	Ionis Pharmaceuticals*	None	None	None	None
Brett Snodgrass, FNP-C, CPE, ACHPN, FAANP	Baptist Memorial Health Care	None	Salix Pharmaceuticals**	None	None	None
Amy Vandenberg, PharmD, BCPP	University of Michigan College of Pharmacy	Expert Witness*	None	None	None	None
Tricia Wright, MD, MS, FACOG, DFASAM	University of California San Francisco	None	None	None	None	None

B. 2024 ASAM Quality Improvement Council Relationships with Industry and Other Entities

Quality Improvement Council Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/Principal	Institutional, Organizational or other financial benefit	Research
Itai Danovitch, MD, MBA, FAPA, DFASAM	Cedars-Sinai Medical Center	Expert Witness**	None	None	Bexon Biomedical Board of Directors*; Workit Health*; California Mental Health Services Commissioner	None
Kenneth I. Freedman, MD, MS, MBA, FACP, AGAF, DFASAM	Aetna/CVS Health; The Recovery Research Network	None	None	None	National Quality Forum	None
Michael P. Frost, MD, DFASAM, FACP	Wayspring; Pocket Naloxone Corp; Frost Medical Group, LLC	Accord Healthcare UK*	Braeburn Pharmaceuticals*	Frost Medical Group, LLC**	None	None
R. Jeffrey Goldsmith, MD, DLFAPA, DFASAM	None	None	None	Bristol-Myers Sqiubb**; Gilead Sciences Inc.**; Merck and Company Inc.**; Pfizer Inc.**; Sanofi ADR**	Windhorse Zen Community Board Member*	None
Margaret A. Jarvis, MD, DFASAM	Geisinger	American Society of Addiction Medicine**; Expert Witness**	None	None	PA Governor's Behavioral Health Council; American Board of Preventive Medicine Exam Subcommittee**	None

Navdeep Kang, Psy.D.	Acadia Healthcare	Bonfire Analytics*	None	Brightview Health**	Talbert House Board of Trustees	None
Tiffany Y. Lu, MD, MS	Albert Einstein College of Medicine	None	None	None	None	None
Tami Mark, PhD, MBA	RTI International	None	None	None	None	None
Stephen Martin, MD, FASAM	Boulder Care; Greylock Recovery	None	None	Boulder Care	None	None
Melissa B. Weimer, DO, MCR, FASAM	Yale School of Medicine; Medical Le.g.al Consulting; St. Peters Health Partners, Yale New Haven Hospital; PCSS-MAUS (Spouse)	CVS Health (Spouse)**	None	None	American Society of Addiction Medicine (Spouse)**	None

C. 2024 ASAM Board of Directors Relationships with Industry and Other Entities

Board Member	**Employment**	**Consultant**	**Speakers Bureau**	**Ownership/ Partnership/Principal**	**Institutional, Organizational or other financial benefit**	**Research**
Anika Alvanzo, MD, MS, FACP, DFASAM	Health Management Associates; Absolute Care	Uzima Consulting Group, LLC**	None	None	None	None
Keyghobad Farid Araki, MD,	Centre for Addiction and Mental Health	None	None	None	None	None

FRCPC, ABAM, FASAM						
Nicholas Athanasiou, MD, MBA, DFASAM	University of California Los Angeles	None	None	None	None	None
Emily Brunner, MD, DFASAM	Gateway	None	None	None	None	None
Me.g.an Buresh, MD, DFASAM	Johns Hopkins University School of Medicine	None	None	None	American Journal of Medicine*	None
Itai Danovitch, MD, MBA, FAPA, DFASAM	Cedars-Sinai Medical Center	Expert Witness**	None	None	Bexon Biomedical Board of Directors*; Workit Health*; California Mental Health Services Commissioner	None
Alta DeRoo, MD, MBA, FACOG, DFASAM	Hazelden Betty Ford Foundation	None	None	None	None	None
Michael Fingerhood, MD, FACP, DFASAM	Johns Hopkins University	None	None	None	American Academy of HIV Medicine	None
Kenneth I. Freedman, MD, MS, MBA, FACP,	Aetna/CVS Health; The Recovery Research Network	None	None	None	National Quality Forum	None

AGAF, DFASAM						
William F. Haning, III, MD, DLFAPA, DFASAM	University of Hawai'i John A. Burns School of Medicine	Hawai'i State Department of Education (Spouse)	None	None	Honolulu Police Commission (Spouse)	None
Brian Hurley, MD, MBA, FAPA, DFASAM	Los Angeles County Department of Public Health; Private Practice; Centers for Care Innovation, PsyBAR; Camden Center	None	None	None	Frank Foundation Board of Directors	None
Teresa Jackson, MD, DFASAM	Lakeside-Milam Recovery Center	None	None	None	None	None
Margaret A. E. Jarvis, MD, DFASAM	Geisinger	American Society of Addiction Medicine**; Expert Witness**	None	None	PA Governor's Behavioral Health Council; American Board of Preventive Medicine Exam Subcommittee**	None
Christina E. Jones, MD, FASAM	Teleleaf, LLC	None	None	None	None	None
Lori D. Karan, MD, FACP, DFASAM	VA Loma Linda Healthcare Center; Loma Linda University Health Education Consortium	None	None	None	None	None
Audrey M. Kern, MD, DFASAM	DynamiCare Health	None	None	None	New Hampshire Healthy Families Board of Directors*	None

Marla D. Kushner, DO, FACOFP, FAOAAM, FSAHM, DFASAM	Marla D. Kushner, DO, S.C.; Bicycle Health	None	None	Marla D. Kushner, DO, S.C	None	None
Nicole Labor, DO, FASAM	Optimus Transformative Medicine, LLC; Laborhood Change Project, Inc.; OneEighty, Inc.; Interval Brotherhood Homes, Inc.; Esper Treatment Center	None	None	None	None	None
James P. Murphy, MD, DFASAM	Murphy Pain Center	None	None	Murphy Pain Center**	Kentucky Harm Reduction Coalition Board of Directors; University of Louisville School of Medicine	None
Cara A. Poland, MD, MEd, FACP, DFASAM	Michigan State University College of Human Medicine	None	None	None	None	None
Shawn Ryan, MD, MBA, FASAM	Brightview Health	Dynamicare*	None	Brightview Health*	None	None
Kelly S. Ramsey, MD, MPH, MA, FACP, DFASAM	Kelly S. Ramsey Consulting, LLC.; Case Western Reserve University	None	None	None	None	None

Surita Rao, MD, FASAM	University of Connecticut School of Medicine	None	None	None	None	None
Stephen M. Taylor, MD, MPH, DFAPA, DFASAM	Stephen M. Taylor, MD, PC; Pathway Healthcare Services, LLC	None	None	Stephen M. Taylor, MD, PC**	Medical Review Officer Certification Council Board of Directors; Addiction Prevention Coalition Board of Directors	None
Michael F. Weaver, MD, DFASAM	University of Texas Health Science Center at Houston and Center for Neurobehavioral Research on Addiction	None	None	None	American Board of Preventive Medicine	None
Timothy Wiegand, MD, FACMT, FAACT, DFASAM	University of Rochester Medical Center; Huther Doyle; Helio Health/Syracuse Behavioral Health; UpToDate; Aids Institute Department of Health	Medicole.g.al Consulting**	None	None	American College of Medical Toxicology; Medical Toxicology Foundation	None
Aleksandra E. Zgierska, MD, PhD, DFASAM	Pennsylvania State University	Pennsylvania Medicaid*	None	None	American Academy of Pain Medicine*	National Institutes of Health; National Institute on Drug Abuse

Appendix E. Evidence to Decision Tables

ETD Table 1 - Question: Taper (+/- Placebo) compared to Abrupt Cessation (+/- Placebo) for BZD discontinuation

Brief Evidence Summary

The systematic review identified two RCTs with 70 participants with an unclear risk of bias that compared a gradual BZD taper to abrupt cessation. The "gradual" taper schedules used were relatively rapid, lasting only 7 to 8 days. The meta-analysis results found no difference in the rate of complete BZD discontinuation, return to BZD use after a period of discontinuation, delirium, or study completion between groups. However, patients undergoing a gradual taper reported significantly less severe BZD withdrawal and insomnia symptoms after 4 days (mid-taper) and up to 4 weeks compared to patients who suddenly stopped their BZD use. Patients undergoing a gradual taper also reported significantly less intense BZD cravings after 4 days (mid-taper), but this effect was no longer detected after 7 days (taper end).

Summary of Findings Table

Certainty assessment							№ of patients		Effect			
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Taper**	**Abrupt Cessation**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
BZD discontinuation @ taper end (assessed with: self-report)												
1[1]	randomized trials	not serious	not serious	not serious	very serious[a]	none	19/20 (95.0 %)	20/20 (100.0%)	**RR 0.95** (0.83 to 1.09)	**5 fewer per 100** (from 17 fewer to 9 more)	⨁⨁◯◯ Low	CRITICAL
BZD discontinuation @ 1-week follow-up (assessed with: self-report)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Taper	Abrupt Cessation	Relative (95% CI)	Absolute (95% CI)		
1[1]	randomized trials	not serious	not serious	not serious	very serious[a]	none	18/20 (90.0%)	17/20 (85.0%)	**RR 1.06** (0.84 to 1.34)	**5 more per 100** (from 14 fewer to 29 more)	⨁⨁◯◯ Low	CRITICAL
BZD discontinuation @ 3-week follow-up (assessed with: self-report)												
1[1]	randomized trials	not serious	not serious	not serious	very serious[a]	none	16/20 (80.0%)	10/20 (50.0%)	**RR 1.60** (0.98 to 2.61)	**30 more per 100** (from 1 fewer to 81 more)	⨁⨁◯◯ Low	CRITICAL
Return to BZD use after discontinuation @ 12-month follow-up (assessed with: General Practitioner-report)												
1[1]	randomized trials	not serious	not serious	not serious	very serious[a]	none	8/16 (50.0%)	6/10 (60.0%)	**RR 0.83** (0.41 to 1.69)	**10 fewer per 100** (from 35 fewer to 41 more)	⨁⨁◯◯ Low	CRITICAL
Experienced delirium during taper												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Taper	Abrupt Cessation	Relative (95% CI)	Absolute (95% CI)		
1[1]	randomized trials	not serious	not serious	not serious	very serious[a]	none	0/20 (0.0%)	2/20 (10.0%)	**Peto OR 0.13** (0.01 to 2.13)	**10 fewer per 100** (from 25 fewer to 5 more)[b]	⨁⨁◯◯ Low	CRITICAL
Withdrawal severity score @ mid-taper (assessed with: BWSQ; Self-report study scale, score range 0-40, higher = more severe)												
2[1,2]	randomized trials	not serious	not serious	not serious	serious[c]	none	39	30	-	SMD **0.72 SD lower** (1.22 lower to 0.22 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Withdrawal severity score @ mid-taper (assessed with: Observer-rated study scale, score range 0-4, higher = more severe)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Taper	Abrupt Cessation	Relative (95% CI)	Absolute (95% CI)		
1[2]	randomized trials	serious[d]	not serious	not serious	very serious[a]	none	20	10	-	MD **0.44 lower** (1.32 lower to 0.45 higher)	⨁◯◯◯ Very low	CRITICAL
Withdrawal severity score @ taper end (assessed with: BWSQ; Self-report study scale, score range 0-40, higher = more severe)												
2[1,2]	randomized trials	not serious	serious[f]	not serious	serious[c]	none	39	30	-	SMD **0.54 SD lower** (1.05 lower to 0.04 lower)	⨁⨁◯◯ Low	CRITICAL
Withdrawal severity score @ taper end (assessed with: Observer-rated study scale, score range 0-4, higher = more severe)												
1[2]	randomized trials	serious[d]	not serious	not serious	very serious[a]	none	20	10	-	MD **0.22 higher** (0.27 lower to 0.7 higher)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Taper**	**Abrupt Cessation**	**Relative (95% CI)**	**Absolute (95% CI)**		
Withdrawal severity score @ 1-week follow-up (assessed with: BWSQ)												
1[1]	randomized trials	serious[f]	not serious	not serious	serious[c]	none	18	17	-	MD **1.3 lower** (1.69 lower to 0.91 lower)	⨁⨁◯◯ Low	CRITICAL
Withdrawal severity score @ 3-week follow-up (assessed with: BWSQ)												
1[1]	randomized trials	serious[f]	not serious	not serious	serious[c]	none	16	10	-	MD **1.88 lower** (2.37 lower to 1.39 lower)	⨁⨁◯◯ Low	CRITICAL
Dropout												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Taper	Abrupt Cessation	Relative (95% CI)	Absolute (95% CI)		
2	randomized trials	not serious	not serious	not serious	very serious[a]	none	1/20 (5.0%)	0/20 (0.0%)	**RD -0.03** (-0.07 to 0.13)	**30 more per 1,000** (from 70 fewer to 130 more)[b]	⨁⨁◯◯ Low	IMPORTANT

BWSQ: Benzodiazepine Withdrawal Symptom Questionnaire, score range 0-40, higher = more severe withdrawal symptoms, self-report; **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardized mean difference

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Explanations

a. Small sample size (n<100) and 95% CI crosses the line of null effect.

b. Absolute effect calculated from the risk difference due to zero events in one or both arms.

c. Small number of participants (<100 participants)

d. High risk of performance and detection bias from lack of personnel and assessor blinding for a majority of participants.

e. Significant heterogeneity (I^2 = 77%, p=0.04).

f. High risk of attrition bias. No follow-up data collected from dropouts. Dropout higher in the abrupt cessation group.

Question

Should Taper vs. Abrupt Cessation be used for BZD discontinuation?	
POPULATION:	Patients discontinuing long-term BZD use
INTERVENTION:	BZD taper (with or without placebo)
COMPARISON:	Abrupt cessation of BZD (with or without placebo)
MAIN OUTCOMES:	BZD discontinuation (self-report); Return to BZD use after discontinuation (reported by patient's General Practitioner-); Experienced delirium during taper; Withdrawal symptom severity score; Dropout.
SETTING:	Any clinical setting where
PERSPECTIVE:	Individual-level
CONFLICT OF INTERESTS:	None identified

Assessment

Problem Is the problem a priority?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

Desirable Effects How substantial are the desirable anticipated effects?		
Judgement	Research evidence	Additional considerations
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	See Summary of Findings Table above	Based on their experience, the Committee agreed that in general a gradual taper is beneficial compared to abrupt BZD cessation. However, a taper over only 1 week may be too rapid to see a significant benefit over abrupt cessation. Also, a taper without other supportive adjuncts may not be sufficient.
Undesirable Effects How substantial are the undesirable anticipated effects?		
Judgement	Research evidence	Additional considerations
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	One participant dropped out of the study early (from the taper group). Two out of 70 participants experienced delirium, both following abrupt cessation of BZDs. Although the incidence of delirium was low (2.9%), the harm is severe enough to warrant consideration.	Neither study reported the incidence of seizures. The committee pointed out that no IRB of the recent era would allow randomized abrupt discontinuation in patients at risk for seizures. Gerra et al. 2002 did not

<table>
<tr><td></td><td></td><td>include any post-taper follow-up.</td></tr>
<tr><td colspan="3">Certainty of evidence

What is the overall certainty of the evidence of effects?</td></tr>
<tr><td>Judgement</td><td>Research evidence</td><td>Additional considerations</td></tr>
<tr><td>○ Very low
● Low
○ Moderate
○ High
○ No included studies</td><td>
<table>
<tr><th>Outcomes</th><th>Importance</th><th>Certainty of the evidence (GRADE)</th></tr>
<tr><td>BZD discontinuation @ taper end
assessed with: self-report</td><td>CRITICAL</td><td>⨁⨁◯◯
Low[a]</td></tr>
<tr><td>BZD discontinuation @ 1-week follow-up
assessed with: self-report</td><td>CRITICAL</td><td>⨁⨁◯◯
Low[a]</td></tr>
<tr><td>BZD discontinuation @ 3-week follow-up
assessed with: self-report</td><td>CRITICAL</td><td>⨁⨁◯◯
Low[a]</td></tr>
<tr><td>Return to BZD use after discontinuation @ 12-month follow-up
assessed with: GP-report</td><td>CRITICAL</td><td>⨁⨁◯◯
Low[a]</td></tr>
<tr><td>Experienced delirium during taper</td><td>CRITICAL</td><td>⨁⨁◯◯
Low[a]</td></tr>
</table>
</td><td></td></tr>
</table>

Withdrawal severity score @ mid-taper assessed with: BWSQ; Self-report study scale	CRITICAL	⊕⊕⊕◯ Moderate[b]	
Withdrawal severity score @ mid-taper assessed with: Observer-rated study scale	CRITICAL	⊕◯◯◯ Very low[a,c]	
Withdrawal severity score @ taper end assessed with: BWSQ; Self-report study scale	CRITICAL	⊕⊕◯◯ Low[b,d]	
Withdrawal severity score @ taper end assessed with: Observer-rated study scale	CRITICAL	⊕◯◯◯ Very low[a,c]	
Withdrawal severity score @ 1-week follow-up assessed with: BWSQ	CRITICAL	⊕⊕◯◯ Low[b,e]	
Withdrawal severity score @ 3-week follow-up assessed with: BWSQ	CRITICAL	⊕⊕◯◯ Low[b,e]	
Dropout	IMPORTANT	⊕⊕◯◯ Low[a]	

a. Small sample size (n<100) and 95% CI crosses the line of null effect.
b. Small number of participants (<100 participants)
c. High risk of performance and detection bias from a lack of personnel and assessor blinding for most participants.
d. Significant heterogeneity (I^2 = 77%, p=0.04).
e. There is a high risk of attrition bias. No follow-up data were collected from dropouts, and dropouts were higher in the abrupt cessation group.

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the		

intervention ○ Varies ○ Don't know		
Resources required How large are the resource requirements (costs)?"		
Judgement	Research evidence	Additional considerations
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know		
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
Judgement	Research evidence	Additional considerations

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies		
Acceptability Is the intervention acceptable to key stakeholders?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Providers and key stakeholders are against abrupt cessation. The Committee also agreed that the interventions included in the research evidence do not reflect a patient-centered process or clinical practice due to the lack of patient input and sense of control.	
Feasibility Is the intervention feasible to implement?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no		

○ Probably yes ● Yes ○ Varies ○ Don't know		

1

Summary of judgements

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	JUDGEMENT						
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

Conclusions

Recommendation

[3a] Clinicians should avoid abruptly discontinuing BZD medication in patients who have been taking BZD daily or near daily (e.g., more days than not) for 1 month or longer.

[3ai] While many patients who have been taking BZD for less than 4 weeks are able to discontinue the medication without a taper, clinicians can consider a short taper.

[3b] If the BZD is discontinued without a taper the patient should be counseled to report the emergence of withdrawal and/or rebound symptoms.

[3bi] If significant symptoms emerge, the clinician can consider medications for symptom management or restarting the BZD and initiating a taper.

Justification

The small size and risk of bias in the studies evaluated mean the evidence of treatment effect is uncertain. Tapering showed a small benefit over abrupt cessation by moderately reducing withdrawal symptoms. Tapering also showed a small benefit over abrupt cessation in the incidence of delirium. Two out of 70 participants experienced delirium, both following abrupt cessation. Although the incidence was low and the difference between interventions was non-significant, the Committee decided that the harm was sufficiently severe to warrant consideration. They determined that the balance of effects probably favors a taper over abrupt cessation. It was decided that the recommendation should be strong despite the low quality of evidence of effect, as the CPG Committee agreed that the 1-week tapers included in the research evidence might be too rapid to see a significant benefit over abrupt cessation. Also, they agreed that patients highly value reducing the severity of withdrawal symptoms.

References Summary

1. Gerra G, Zaimovic A, Giusti F, Moi G, Brewer C. Intravenous flumazenil versus oxazepam tapering in the treatment of benzodiazepine withdrawal: a randomized, placebo-controlled study. Addiction Biology. 2002;7(4):385-395. doi:10.1080/1355621021000005973
2. Petrovic M, Pevernagie D, Mariman A, Van Maele G, Afschrift M. Fast withdrawal from benzodiazepines in geriatric inpatients: a randomised double-blind, placebo-controlled trial. Eur J Clin Pharmacol. 2002;57(11):759-764. doi:10.1007/s00228-001-0387-4

ETD Table 2 - Question: CBT for Indicated Condition + Taper compared to Taper alone for BZD Discontinuation

In patients who are initiating a gradual taper to discontinue their long-term BZD use, does CBT that targets a specific underlying psychological condition (e.g. CBT for Insomnia, CBT for General Anxiety Disorder) result in better benzodiazepine reduction and clinical outcomes than tapering alone?

Brief Evidence Summary

The systematic review identified six RCTs with 279 participants, four with a high risk of bias from lack of blinding (Baillargeon 2003; Morin 2004; Otto 1993; Otto 2010) and two with an unclear risk of bias from partial blinding (Gosselin 2006; Spiegel 1994), that compared CBT interventions for specific conditions plus a gradual BZD taper to a gradual BZD taper alone. Three of the CBT interventions targeted panic disorder (Otto 1993; Otto 2010; Spiegel 1994), two targeted insomnia (Baillargeon 2003; Morin 2004), and one General Anxiety Disorder (Gosselin 2006). The meta-analysis results for critical outcomes found a higher rate of complete BZD discontinuation immediately after and up to 12 months following taper in the CBT + Taper groups compared to Taper alone (Baillargeon 2003; Gosselin 2006; Morin 2004; Otto 1993; Otto 2010; Spiegel 1994). Although the results were mixed for the rate of return to BZD use after a period of cessation, likely because of the significant heterogeneity at different time points, the overall pattern favors CBT + Taper.

Summary of Findings Table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT for Indicated Condition + Taper	Taper	Relative (95% CI)	Absolute (95% CI)		
BZD discontinuation @ 0-4 weeks post-taper												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT for Indicated Condition + Taper	Taper	Relative (95% CI)	Absolute (95% CI)		
6[1,2,3,4,5,6]	randomized trials	serious[a]	not serious	not serious	not serious	none	103/136 (75.7%)	57/142 (40.1%)	**RR 1.86** (1.48 to 2.32)	**345 more per 1,000** (from 193 more to 530 more)	⊕⊕⊕◯ Moderate	CRITICAL
BZD discontinuation @ 2-4-month follow-up												
6[1,2,3,4,5,6]	randomized trials	serious[a]	not serious	not serious	not serious	none	89/136 (65.4%)	47/142 (33.1%)	**RR 1.88** (1.48 to 2.43)	**291 more per 1,000** (from 159 more to 473 more)	⊕⊕⊕◯ Moderate	CRITICAL
BZD discontinuation @ 12-14-month follow-up												
3[1,3,6]	randomized trials	serious[a]	serious[b]	not serious	not serious	none	59/92 (64.1%)	29/85 (34.1%)	**RR 1.88** (1.35 to 2.64)	**300 more per 1,000** (from 119 more to 560 more)	⊕⊕◯◯ Low	CRITICAL
Return to BZD use @ 3-month follow-up												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT for Indicated Condition + Taper	Taper	Relative (95% CI)	Absolute (95% CI)		
4[1,3,4,5]	randomized trials	not serious	serious[c]	not serious	serious[d]	none	10/67 (14.9%)	8/36 (22.2%)	**Peto OR 0.60** (0.21 to 1.74)	**70 fewer per 1,000** (from 230 fewer to 80 more)[e]	⊕⊕◯◯ Low	CRITICAL
Return to BZD use @ 6-month follow-up												
2[3,4]	randomized trials	not serious	not serious	not serious	serious[f]	none	3/33 (9.1%)	8/19 (42.1%)	**Peto OR 0.15** (0.04 to 0.58)	**330 fewer per 1,000** (from 580 fewer to 90 fewer)[e]	⊕⊕⊕◯ Moderate	CRITICAL
Return to BZD use @ 12-month follow-up												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT for Indicated Condition + Taper	Taper	Relative (95% CI)	Absolute (95% CI)		
2[1,3]	randomized trials	not serious	serious[g]	not serious	very serious[h]	none	10/44 (22.7%)	7/24 (29.2%)	**RR 0.78** (0.34 to 1.77)	**64 fewer per 1,000** (from 192 fewer to 225 more)	⊕◯◯◯ Very low	CRITICAL
BZD dose reduced 50% or more from baseline @ 0-4 weeks post-taper												
1[6]	randomized trials	serious[i]	not serious	not serious	serious[f]	none	33/34 (97.1%)	20/29 (69.0%)	**RR 1.41** (1.09 to 1.81)	**283 more per 1,000** (from 62 more to 559 more)	⊕⊕◯◯ Low	IMPORTANT
BZD dose reduced 50% or more from baseline @ 3-month follow-up												
1[6]	randomized trials	serious[i]	not serious	not serious	very serious[h]	none	25/34 (73.5%)	19/29 (65.5%)	**RR 1.12** (0.91 to 1.56)	**79 more per 1,000** (from 59 fewer to 367 more)	⊕◯◯◯ Very low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CBT for Indicated Condition + Taper**	**Taper**	**Relative (95% CI)**	**Absolute (95% CI)**		
BZD dose @ 0-4 weeks post-taper (assessed in: mg/week diazepam equivalents)												
2[1,3]	randomized trials	serious[i]	not serious	not serious	serious[d]	none	58	55	-	MD **4.49 mg/week fewer** (17.83 fewer to 8.85 more)	⊕⊕◯◯ Low	IMPORTANT
BZD use frequency @ end of taper												
1[1]	randomized trials	serious[i]	not serious	not serious	serious[f]	none	23	25	-	MD **2.09 nights/week fewer** (3.35 fewer to 0.83 fewer)	⊕⊕◯◯ Low	IMPORTANT
BZD use frequency @ 3-month follow-up												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT for Indicated Condition + Taper	Taper	Relative (95% CI)	Absolute (95% CI)		
1[1]	randomized trials	serious[i]	not serious	not serious	very serious[h]	none	27	25	-	MD **0.7 nights/week fewer** (2 fewer to 0.6 more)	⨁◯◯◯ Very low	IMPORTANT
Withdrawal severity score @ 0-2 weeks post-taper (assessed with: PhWC, CIWA-B)												
2[2,3]	randomized trials	not serious	not serious	not serious	very serious[h]	none	40	43	-	SMD **0.28 SD higher** (0.15 lower to 0.71 higher)	⨁⨁◯◯ Low	IMPORTANT
Anxiety score @ 2-week follow-up (assessed with: PSWQ)												
1[3]	randomized trials	not serious	not serious	not serious	serious[f]	none	27	26	-	MD **5.63 lower** (9.72 lower to 1.54 lower)	⨁⨁⨁◯ Moderate	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT for Indicated Condition + Taper	Taper	Relative (95% CI)	Absolute (95% CI)		
Anxiety score @ 3-month follow-up (assessed with: PSWQ)												
1[3]	randomized trials	not serious	not serious	not serious	serious[f]	none	27	27	-	MD **6.11 lower** (10.77 lower to 1.45 lower)	⨁⨁⨁◯ Moderate	IMPORTANT
Persistence of GAD symptoms @ 2-week follow-up (assessed with: ADIS-IV)												
1[3]	randomized trials	not serious	not serious	not serious	serious[f]	none	11/31 (35.5%)	24/30 (80.0 %)	**RR 0.44** (0.27 to 0.74)	**448 fewer per 1,000** (from 584 fewer to 208 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Persistence of GAD symptoms @ 3-month follow-up (assessed with: ADIS-IV)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT for Indicated Condition + Taper	Taper	Relative (95% CI)	Absolute (95% CI)		
1[3]	randomized trials	not serious	not serious	not serious	serious[f]	none	10/31 (32.3%)	18/30 (60.0 %)	**RR 0.54** (0.30 to 0.97)	**276 fewer per 1,000** (from 420 fewer to 18 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Persistence of GAD symptoms @ 6-month follow-up (assessed with: ADIS-IV)												
1[3]	randomized trials	not serious	not serious	not serious	very serious[h]	none	12/31 (38.7%)	16/30 (53.3 %)	**RR 0.73** (0.42 to 1.26)	**144 fewer per 1,000** (from 309 fewer to 139 more)	⨁⨁◯◯ Low	CRITICAL
Sleep problem score @ end of taper (assessed with: Insomnia Severity Index)												
2[1,3]	randomized trials	not serious	not serious	not serious	not serious	none	55	53	-	MD **2.04 lower** (4 lower to 0.08 lower)	⨁⨁⨁⨁ High	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT for Indicated Condition + Taper	Taper	Relative (95% CI)	Absolute (95% CI)		
Sleep problem score @ 3-month follow-up (assessed with: Insomnia Severity Index)												
2[1,3]	randomized trials	serious[i]	not serious	not serious	serious[d]	none	55	53	-	MD **0.17 higher** (2.04 lower to 2.38 higher)	⨁⨁◯◯ Low	IMPORTANT
Serious adverse events												
1[6]	randomized trials	serious[a]	not serious	not serious	very serious[h]	none	0/35 (0.0%)	0/30 (0.0%)	**RD 0.00** (-0.06 to 0.06)	**0 fewer per 1,000** (from 60 fewer to 60 more)[e]	⨁◯◯◯ Very low	CRITICAL
Dropout												
5[1,2,3,4,6]	randomized trials	serious[a]	not serious	not serious	serious[d]	none	7/120 (5.8%)	11/126 (8.7%)	**Peto OR 0.51** (0.24 to 1.08)	**80 fewer per 1,000** (from 160 fewer to 10 more)[e]	⨁⨁◯◯ Low	CRITICAL

ADIS-IV: Anxiety Disorders Interview Schedule for DSM–IV; **CI:** confidence interval; **CIWA-B**: Clinical Institute Withdrawal Assessment – Benzodiazepines, score range unclear, higher = more severe, physician and patient rated; **Insomnia Severity Index**: score range 0-28, higher = more sleep difficulty**; MD:** mean difference; **PhWC:** Physician Withdrawal Checklist, score range unclear, higher = more severe; **PSWQ:** Penn State Worry Questionnaire, score range unclear, scale direction unclear**; RR:** risk ratio; **SMD:** standardized mean difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Note: significant heterogeneity p<0.10. Note: significant heterogeneity p<0.10.

Explanations
a. High risk of performance bias from lack of blinding for a majority of participants.
b. Significant heterogeneity (I^2=65%, p=0.06). Two studies favor CBT + Taper (Baillargeon 2003; Gosselin 2006) and one study found no difference (Morin 2004).
c. Significant heterogeneity (I^2=74%, p=0.01). Point estimates favor CBT+Taper in two studies (Gosselin 2006; Spiegel 1994) and Taper alone in two studies (Morin 2004; Otto 1993).
d. 95% CI crosses the line of null effect.
e. Absolute effect calculated from the risk difference due to zero events in one or both arms.
f. Small sample size (n<100).
g. Significant heterogeneity (I^2=67%, p=0.08). Point estimates favor CBT+Taper in one study (Gosselin 2006) and Taper alone in one study (Morin 2004).
h. Small sample size (n<100) and 95% CI crosses the line of null effect.
i. High risk of performance and detection bias for unblinded subjective measures for a majority of participants.

Question

Should CBT for Indicated Condition + Taper vs. Taper be used for patients discontinuing long-term BZD use?

QUESTION	
POPULATION:	Patients discontinuing long-term BZD use
INTERVENTION:	CBT for Indicated Condition (e.g. CBT for Insomnia, CBT for General Anxiety Disorder) + Taper
COMPARISON:	Taper
MAIN OUTCOMES:	BZD discontinuation; Return to BZD use after a period of cessation; BZD dose; BZD frequency; Withdrawal severity score; Anxiety score; Persistence of GAD symptoms; Sleep problem score; Serious adverse events; Dropout
SETTING:	Any clinical setting where
PERSPECTIVE:	Patient-level
CONFLICT OF INTERESTS:	None identified.

Assessment

Problem Is the problem a priority?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		
Desirable Effects		

How substantial are the desirable anticipated effects?		
Judgement	Research evidence	Additional considerations
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	CBT + Taper shows a benefit compared to Taper alone in a majority of critical and important outcomes. CBT + Taper increased BZD discontinuation rates and significant dose reductions, decreased the persistence/ of GAD, and may decrease return to BZD use after discontinuing. It also decreased the severity of anxiety symptoms and may decrease sleep problems. Taper alone may be slightly favored in decreasing withdrawal severity, but this is a very uncertain effect.	There are multiple timepoints for the same outcome (BZD discontinuation, Return to BZD use). However, all the timepoints favor CBT + taper over taper.
Undesirable Effects How substantial are the undesirable anticipated effects?		
Judgement	Research evidence	Additional considerations
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Neither intervention is favored in critical undesirable effects; no serious adverse events were reported. CBT + Taper is favored in one important negative effect; dropout was lower in the CBT + Taper group.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
Judgement	Research evidence	Additional considerations

● Very low
○ Low
○ Moderate
○ High
○ No included studies

Outcomes	Importance	Certainty of the evidence (GRADE)
BZD discontinuation @ 0-4 weeks post-taper	CRITICAL	⊕⊕⊕◯ Moderate[a]
BZD discontinuation @ 2-4 month follow-up	CRITICAL	⊕⊕⊕◯ Moderate[a]
BZD discontinuation @ 12-14 month follow-up	CRITICAL	⊕⊕◯◯ Low[a,b]
Return to BZD use @ 3-month follow-up	CRITICAL	⊕⊕◯◯ Low[c,d]
Return to BZD use @ 6-month follow-up	CRITICAL	⊕⊕⊕◯ Moderate[e]
Return to BZD use @ 12-month follow-up	CRITICAL	⊕◯◯◯ Very low[f,g]
BZD dose reduced 50% or more @ 0-4 weeks post-taper	IMPORTANT	⊕⊕◯◯ Low[e,h]
BZD dose reduced 50% or more @ 3-month follow-up	IMPORTANT	⊕◯◯◯ Very low[g,h]
BZD dose @ 0-4 weeks post-taper assessed with: mg diazepam equivalents	IMPORTANT	⊕⊕◯◯ Low[d,h]
BZD frequency @ end of taper	IMPORTANT	⊕⊕◯◯ Low[e,h]
BZD frequency @ 3 month follow-up	IMPORTANT	⊕◯◯◯ Very low[g,h]

Withdrawal severity score @ 0-2 weeks post-taper assessed with: PhWC, CIWA-B	IMPORTANT	⊕⊕◯◯ Low[g]	
Anxiety score @ 2-week follow-up assessed with: PSWQ	IMPORTANT	⊕⊕⊕◯ Moderate[e]	
Anxiety score @ 3-month follow-up assessed with: PSWQ	IMPORTANT	⊕⊕⊕◯ Moderate[e]	
Persistence of GAD symptoms @ 2 week follow-up assessed with: ADIS-IV	CRITICAL	⊕⊕⊕◯ Moderate[e]	
Persistence of GAD symptoms @ 3-month follow-up assessed with: ADIS-IV	CRITICAL	⊕⊕⊕◯ Moderate[e]	
Persistence of GAD symptoms @ 6-month follow-up assessed with: ADIS-IV	CRITICAL	⊕⊕◯◯ Low[g]	
Sleep problem score @ end of taper assessed with: Insomnia Severity Index	IMPORTANT	⊕⊕⊕⊕ High	
Sleep problem score @ 3-month follow-up assessed with: Insomnia Severity Index	IMPORTANT	⊕⊕◯◯ Low[d,h]	
Serious adverse events	CRITICAL	⊕◯◯◯ Very low[a,g]	
Attrition/Dropout	CRITICAL	⊕⊕◯◯ Low[a,d]	
Note: significant heterogeneity p<0.10.			

	a. High risk of performance bias from lack of blinding for most participants. b. Significant heterogeneity (I^2=65%, p=0.06). Two studies favor CBT + Taper (Baillargeon 2003; Gosselin 2006) and one study found no difference (Morin 2004). c. Significant heterogeneity (I^2=74%, p=0.01). Point estimates favor CBT+Taper in two studies (Gosselin 2006; Spiegel 1994) and Taper alone in two studies (Morin 2004; Otto 1993). d. 95% CI crosses the line of null effect. e. Small sample size (n<100). f. Significant heterogeneity (I^2=67%, p=0.08). Point estimates favor CBT+Taper in one study (Gosselin 2006) and Taper alone in one study (Morin 2004). g. Small sample size (n<100) and 95% CI crosses the line of null effect. h. High risk of performance and detection bias for unblinded subjective measures for most participants.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important	There was no evidence in the literature review about values and preferences of outcomes. Outcomes include BZD discontinuation, return to BZD use, BZD dose reduction, weekly BZD frequency, withdrawal severity score, recurrence/persistence of indicated condition (GAD), sleep problem score, and serious adverse events.	Likely variability across patient population but lack direct research evidence.

uncertainty or variability		
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Both the desirable and undesirable effects favor CBT + Taper	
Resources required How large are the resource requirements (costs)?"		
Judgement	Research evidence	Additional considerations

○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know		
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies		
Acceptability Is the intervention acceptable to key stakeholders?		
Judgement	Research evidence	Additional considerations

○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Other evidence: An Australian survey done at pharmacies (Sake 2019) reported that 48 of 75 participants did not prefer behavioral therapies for various reasons which included: lack of confidence in behavioral therapies, lack of time, dependency on sleeping pill, participants' perception that behavioral therapies take longer to produce effect, perception that seeing a psychologist is costly, or other undefined reasons (participants were allowed to select multiple answers).	
Feasibility Is the intervention feasible to implement?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	There have been multiple mentions that CBT is not accessible in all geographic locations. The availability of in-person high-quality CBT is likely low. Adequate training and experience of therapists is necessary. Online CBT resources are more easily available, but quality may be difficult to assess. Feasibility may vary on geographic location.	

Summary of judgements

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies

	JUDGEMENT						
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Conclusions

Recommendation
[13a] Patients undergoing BZD tapering should be offered, or referred for, behavioral interventions such as cognitive behavioral therapy (CBT).

Justification
The small size and high risk of bias in most studies evaluated mean the evidence of treatment effect is very uncertain. The evidence consistently showed a benefit of CBT + Taper compared to Taper alone in a majority of the critical outcomes and that the balance of desirable and undesirable effects probably favors CBT + Taper. The Committee acknowledges that there are potential limitations in patient acceptability and provider feasibility. Therefore, the recommendation is conditional.

References Summary

1. Baillargeon L, Landreville P, Verreault R, Beauchemin JP, Grégoire JP, Morin CM. Discontinuation of benzodiazepines among older insomniac adults treated with cognitive-behavioural therapy combined with gradual tapering: a randomized trial. *CMAJ*. 2003;169(10):1015-1020.
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3. Morin CM, Bastien C, Guay B, Radouco-Thomas M, Leblanc J, Vallières A. Randomized Clinical Trial of Supervised Tapering and Cognitive Behavior Therapy to Facilitate Benzodiazepine Discontinuation in Older Adults with Chronic Insomnia. *AJP*. 2004;161(2):332-342. doi:10.1176/appi.ajp.161.2.332

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5. Otto MW, Pollack MH, Sachs GS, Reiter SR, Meltzer-Brody S, Rosenbaum JF. Discontinuation of Benzodiazepine Treatment: Efficacy of cognitive-behavioral therapy. *Am J Psychiatry*. 1993;150(10):1485-1490.
6. Spiegel DA, Bruce TJ, Gregg SF, Nuzzarello A. Does cognitive behavior therapy assist slow-taper alprazolam discontinuation in panic disorder? *Am J Psychiatry*. 1994;151:176-881.

Appendix F. Pharmacokinetic Properties of BZD

Benzodiazepine	Time to Peak Plasma Level (oral)	Relative Lipid Solubility	Onset of Action (min)*	Elimination Half-Life (h) (active metabolite)**	Metabolism***
Alprazolam	1-2 h (tablet or ODT) 5-11 h XR	Moderate	15-30	6-12	3A4
Chlordiazepoxide	0.5-4 h	Moderate	15-30	5-10 (36-200)	3A4
Clonazepam	1-2 h	Low	15-30	18-50	3A4
Clorazepate (hydrolized to nordiazepam in stomach)	0.5-2 h	High	15		Metabolite 2C19,3A4
Diazepam	0.5-2 h	High	≤ 15	20-100 (36-200)	1A2, 2C9, 2C19, 3A4
Estazolam	2 h	Low	30-60	10-24	3A4
Flurazepam	0.5-2 h	High	≤ 15	(40-250)	2C19, 3A4
Lorazepam	2-4 h	Moderate	15-30	10-20	Glucuronide conjugation
Oxazepam	2-4 h	Low	30-60	4-15	Glucuronide conjugation
Quazepam[2]	2 h	High	15	39 (73)	2C9, 2C19, 3A4
Temazepam	2-3 h	Moderate	30-60	10-20	Glucuronide conjugation
Triazolam	1-2 h	Moderate	15-30	1.5-5	3A4

*Rapid onset of action associated with high lipid solubility as well as potential increased potential for reinforcing properties and misuse

**Agents with moderate to high lipid solubility will have shorter duration of action with single or intermittent doses than suggested by the elimination half-life as these medications distribute rapidly into adipose tissue. With initial dosing, multiple daily doses may be needed to maintain effect. With chronic use and repeated dosing, accumulation is more likely to occur with these agents, especially those with long elimination half-lives (e.g., diazepam). [3]

***Agents with glucuronide conjugation do not have pharmacokinetic interactions and are considered to be safer in older adults and patients with hepatic impairment.

Sources:

1. Procyshyn R, Bezchlibnyk-Butler KZ, Jeffries JJ. *Clinical Handbook of Psychotropic Drugs*. Hogrefe Verlag GmbH & Co. KG; 2021. https://elibrary.hogrefe.com/book/10.1027/00593-000
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Appendix G. Guidelines for the Treatment of Underlying Conditions

BZD are prescribed for a variety of conditions. In most cases, other pharmacological and psychosocial interventions are more effective and associated with lower risk. This Appendix includes references for clinical practice guidelines for these conditions that may be considered before, during or after BZD tapering.

Insomnia

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Appendix H. Diazepam Dose Equivalents

Milligram oral dose equivalent to 10 mg diazepam

	ATC Therapeutic Class	WHO CCDSM*	VA/DoD CPG SUD 2021	Ashton Manual 2002
Diazepam	Anxiolytic	10	10	10
Alprazolam	Anxiolytic	1	1	0.5
Chlordiazepoxide	Anxiolytic	30	25	25
Clonazepam	Antiepileptic	8	1	0.5
Clorazepate	Anxiolytic	20	15	15
Lorazepam	Anxiolytic	2.5	2	1
Oxazepam	Anxiolytic	50	30	20
Estazolam	Hypnotic/ Sedative	3	1	1-2
Flurazepam	Hypnotic/ Sedative	30	15	15-30
Quazepam	Hypnotic/ Sedative	15	10	20
Temazepam	Hypnotic/ Sedative	20	15	20
Triazolam	Hypnotic/ Sedative	0.25	0.25	0.5

*The defined daily doses (DDDs) for the anxiolytics are based on the treatment of anxiety. DDDs for the antiepileptics are based on combination therapy. DDDs for the Hypnotic/Sedatives are based on use of the drugs as hypnotics.

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Appendix I. Sample Tapering Schedules and Case Descriptions

Tapering Case Descriptions

This Appendix contains five case descriptions highlighting a variety of aspects of BZD tapering, including patient engagement, considerations for tapering, tapering strategies, withdrawal management, and population considerations. These cases are not meant to endorse specific tapering schedules or protocols but are meant to illustrate how the recommendations in this Guideline may be applied to a variety of clinical scenarios.

Mr. Z

Mr. Z is a 59-year-old male who has been taking 4 mg clonazepam per day for an unknown number of years. He stated he was started on the medication "years ago" during a period of high stress when he had lost his job and gotten divorced. You have an established relationship with Mr. Z as his PCP treating him for hypertension and diabetes. Mr. Z's psychiatrist recently retired, leaving you to manage his psychiatric medication.

You engage Mr. Z in a discussion of his BZD medication. You express concern that his dose is fairly high, especially considering his other medical conditions. He objects at first, stating that his psychiatrist never saw a problem with the amount of medication he was taking. You educate Mr. Z on the common risks of continued use, and you share that he may feel better taking less medication. He states that he is afraid to stop taking the medication, because when he once missed a dose, he experienced intolerable anxiety. You educate Mr. Z on withdrawal symptoms, and that the symptoms he experienced when skipping a dose may have been withdrawal symptoms. You assure Mr. Z that he will likely experience some withdrawal symptoms, but that you will work with him to minimize these and make them tolerable. Mr. Z agrees to try tapering.

Prior to beginning the taper, you help Mr. Z locate a therapist to help with stress management. You and Mr. Z agree that a small reduction from 4 mg to 3.5 mg per day would be the best place to start, given the symptoms he experienced with missing an entire dose previously. Mr. Z remains on this dose for a month with what he describes as "mild" sleep difficulty and anxiety. After another few weeks, Mr. Z states he is ready to do another small reduction. Although it takes about six months, Mr. Z is able to completely stop his BZD.

Ms. D

Ms. D is a 36-year-old female who has been taking 0.5mg alprazolam 3x/day for 3 years. She was initially prescribed alprazolam for anxiety with panic attacks, but reports it is also helpful for her irritable bowel syndrome, migraines, and menstrual cramps. She had not tried other medication classes or therapy before starting alprazolam. Ms. D has previously received medication from her gynecologist and gastroenterologist at separate times, and she is now transitioning care to you as PCP. Ms. D is requesting an increase in her dose because she is experiencing an increase in anxiety.

Given the potential harms associated with BZD, current guidelines are that they should be reserved for treatment-resistant cases of anxiety disorders where other treatment options have failed. For Ms. D, it would be best to try some other strategies with fewer associated risks to see if they might be effective. You engage Ms. D in a discussion of the evidence-based treatment options for her medical conditions, and share that BZD are not first-line treatments for these conditions. You educate Ms. D about the risks associated with ongoing use of BZD, and you assure her there are other pharmacological and non-pharmacological treatments that can be helpful. You reassure Ms. D that you are committed to finding an approach that will treat her symptoms, but that this process may take time. Ms. D is amenable to trying an SSRI and CBT and to tapering from her alprazolam once the SSRI has been titrated to an effective dose for her.

Due to the potential difficulty in tapering from alprazolam (given its short half-life and lack of active metabolites), you be.g.in by switching Ms. D to an equivalent dose of diazepam and explain that a longer-acting medication will be easier to taper. While she is acclimating to the new medication (7.5 mg [one and a half 5 mg tablets] 2x/day), you locate a CBT treatment provider, and facilitate the referral. You also start Ms. D on sertraline to address symptoms of anxiety as well as IBS and migraines. When the sertraline begins to show clinical effect, Ms. D begins the tapering process and reduces her dose of diazepam to 7.5 mg morning and 5 mg at night. You encourage Ms. D to share any withdrawal symptoms she is experiencing. Ms. D successfully decreases her dose by 2.5 mg every two weeks for a month, but then begins to experience increased withdrawal symptoms. You pause the After pausing the taper for another

two weeks, she is ready to continue, and however when she has tapered to 2.5 mg daily dose, she states her withdrawal symptoms are intolerable. In reviewing the risk benefit ratio, you decide to maintain Ms. D on this dose until she is ready to consider tapering again.

Mr. M

Mr. M is a 75-year-old male who was prescribed lorazepam 2 mg at bedtime PRN for insomnia. He does not recall when he was first prescribed the medication, but he remembers that his dose was increased a few years ago when he was having more trouble sleeping after the loss of his brother. He lives at home with his wife. Electronic records indicate that the patient is filling the PRN prescription regularly, and Mr. M confirmed he is taking the medication daily.

Mr. M denies excessive daytime sedation. However, Mr. M's wife is concerned that his memory is declining, and at times he seems confused and disorganized. You engage Mr. M in a conversation about the relationship of BZD with cognitive impairment. Mr. M admits that he feels "foggy" sometimes, but that he did not realize his medication could be the cause. He confirms that he is willing to try tapering the BZD but worries that he will not be able to sleep. You share with Mr. M that BZD are not intended to be used long-term for sleep . You reassure Mr. M that there are other strategies that might even help him sleep better. Unfortunately, you are unable to locate any providers who specialize in CBT-I, however you recommend a mobile app CBT-I Coach that is recommended by the Veterans Administration and you provide education on sleep hygiene strategies. You also provide education on withdrawal symptoms that he might experience, and you encourage Mr. M to let you know right away if these symptoms are intolerable.

Mr. M agrees to reduce his dose by 0.5 mg for one week by quartering tablets and taking ¾ of a tablet. The goal is to reduce the overall dose down to a safer level and hopefully improve cognition. After one week, Mr. M reports a few bothersome withdrawal symptoms, and says he does not feel ready to reduce the dose any further. The following week, he reports fewer symptoms, and agrees to try another reduction, this time reducing to ½ tablet (dose = 1 mg). After one month, Mr. M's wife reports that his memory seems to be improving. When he is due for a prescription refill, 0.5 mg tablets are prescribed to allow for more dose flexibility. After a

few more months, Mr. M's dose is down to 0.5 mg at bedtime. Toward the end of the taper, you slow the pace until Mr. M is ready to start skipping doses, and after a year is able to discontinue the medication.

Ms. L

Ms. L is a 32-year-old female who is 8 weeks pregnant. She has been taking 10mg diazepam 2x/day for anxiety. She expresses a desire to taper from her BZD for the health of her baby, although she is also concerned about how she will manage her anxiety during pregnancy.

You engage Ms. L in a discussion about the risks and benefits of continuing her BZD, as well as alternative treatment options. You reassure her of treatment options to address anxiety that are safe for her baby, including SSRI/SNRI. While educating Ms. L on SSRI/SNRI, you explain that while these medications can cause neonatal withdrawal symptoms, these are generally less severe and shorter duration compared to BZD-related neonatal withdrawal. You also provide education on withdrawal symptoms and encourage her to let you know if they become intolerable. Ms. L expresses high motivation to try SSRI medication and virtual therapy sessions with a mental health provider, and taper from her BZD. You locate a referral for a therapist skilled in CBT, and prescribe a course of escitalopram.

At 10 weeks, Ms. L initially reduces her midday dose to 7.5mg [one and a half 5mg tablets] and continues to reduce by her dose every three weeks through the second trimester. At 24 weeks, she has tapered down to 3 mg and reports increased withdrawal symptoms. You adjust the tapering process to smaller and less frequent dose reductions, and by 34 weeks she has tapered from the BZD medication completely. Ms. L delivers a healthy baby. You continue to follow Ms. L closely to monitor for postpartum anxiety.

Mr. B

Mr. B is a 22-year-old male, who started using alprazolam he obtained from friends to "deal with stress". Mr. B then be.g.an purchasing BZD pills from websites. He has been taking BZD for about 3 years and also drinking alcohol in combination with the BZD. He has a history of a seizure in the context of prior withdrawal. Mr. B presents to a withdrawal management service in

an ASAM Criteria Level 3.7 residential addiction treatment facility, requesting help with tapering because he has tried stopping and is unable to do so on his own. He reports that he does not have a PCP.

Mr. B meets criteria for a severe BZD use disorder. Because of his current estimated dose of alprazolam (5-7.5 mg) and history of seizure, Mr. B is at risk for severe withdrawal. You would not consider outpatient treatment for this patient due to safety concerns. You admit this patient to the residential withdrawal management unit to be.g.in phenobarbital taper (See sample residential (ASAM Criteria Level 3.7) protocol).

However, once admitted you conducted a drug screen that is positive for opioids. You suspect Mr. B has been taking counterfeit alprazolam that are contaminated with opioids (including fentanyl), and it is apparent he is also experiencing opioid withdrawal. The patient is transferred to the hospital for management as management of BZD and opioid withdrawal concurrently is likely to be more complex. Buprenorphine is initiated in the hospital along with a phenobarbital taper. (See sample hospital (ASAM Criteria Level 4.0) protocol).

During discharge planning, Mr. B is offered ongoing care for SUD, and treatment options are discussed. Mr. B states he prefers to be.g.in a residential treatment program, as his partner is continuing to use substances, and is referred to a local program for SUD treatment and management.

Sample Residential (3.7) Protocol for Phenobarbital Taper*

- Do not start phenobarbital until it has been at least 8 hours after last BZD use
  - Patients with primarily alprazolam use may have significant withdrawal symptoms before 8 hours. If the patient has significant objective signs and symptoms of withdrawal, phenobarbital protocol can be started
- Consider the patient's risk for seizure and manage as appropriate
- If patient shows signs of oversedation, delay the following phenobarbital dose
- Although the phenobarbital protocol is only 6 days, the long half-life ensures the medication will continue to be active for several days afterward, resulting in an auto-taper

During first day, patient must be assessed at least every 4 hours for safety, even if this involves waking them up

DAY 1

- 64.8mg initial dose and then 32.4mg every 4 hours
- Depending on withdrawal symptoms, may add 32.4mg dose
- 226.8mg total scheduled; max dose 330mg

DAY 2

- 32.4mg every 4 hours
- Depending on withdrawal symptoms, may add 32.4mg dose
- 194.4mg total scheduled; max dose of 300mg

DAY 3

- 32.4mg every 6 hours
- Depending on withdrawal symptoms, may add 32.4mg dose
- 129.6mg total scheduled; max dose of 240mg

DAY 4

- 32.4mg every 8 hours
- Depending on withdrawal symptoms, may add 32.4mg dose
- 97.2mg total scheduled; max dose of 180mg

DAY 5

- 32.4mg q 12 hours
- Depending on withdrawal symptoms, may add 32.4mg dose
- 64.8mg total scheduled; max dose of 150mg

DAY 6+

- The patient may be discharged (or, for patients with SUD, transitioned to a less intensive level of care) when dose <60mg within 24 hours

***Disclaimer:** This is a **sample** protocol, and should not be interpreted as an exact recommended protocol

Sample Hospital (4.0) Protocol for Phenobarbital Taper*

- Administer a test dose of 64.8 mg PO phenobarbital
- Assess the patient 1 hour after dose to ensure no evidence of oversedation or intoxication

If test dose is tolerated, continue with the following phenobarbital taper schedule:

- 129.6 mg PO every 4 hours x 6 doses
- 129.6 mg PO every 6 hours x 4 doses
- 129.6 mg PO every 8 hours x 3 doses

Hold dose for oversedation or evidence of intoxication

After 72 hours, patient is safe to be discharged (and, for patients with SUD, transitioned to a less intensive level of care) without additional phenobarbital or BZD.

Following BZD taper, may add valproate 500 mg PO BID 2-4 weeks for post-acute symptoms of withdrawal and mood stabilization

***Disclaimer:** This is a **sample** protocol, and should not be interpreted as an exact recommended protocol.

Appendix J. Adjunctive Psychosocial Interventions

This Appendix was created to support Recommendation #12. Adjunctive psychosocial interventions should be offered when tapering BZD. This list is not meant to be exhaustive and partnering with community mental health providers is recommended to support to enhance patient success.

	Brief Description	Papers/Resources
Behavioral Interventions		
CBT[157-162]	Cognitive Behavioral Therapy is a structured psychological treatment that helps to change thoughts, feelings, and behaviors, to treat a variety of problems.	CBT for Panic (Otto 2010; Otto 1993; Spiegel 1994) CBT for BZD Withdraw (O'Connor 2008; Oude Voshaar 2003) CBT for GAD (Gosselin 2006)
CBT-I[163-165]	Cognitive Behavioral Therapy for Insomnia is a structured psychological treatment that helps to change thoughts, feelings, and behaviors that are contributing to insomnia.	Coteur 2022; Moring 2004; Baillargeon 2003.
Behavior Modification[28]	Behavior modification is a psychotherapeutic intervention used to eliminate or reduce unwanted behavior.	Pottie et al 2018
Mental Health Counseling	There are a variety of psychotherapy approaches used in practice. While the ones listed above have the most evidence for BZD withdrawal, other methods may be as or even more effective for specific patients. In general, any mental health provider that is comfortable addressing the reason for the initial BZD prescription as well as managing symptoms that may develop during the withdrawal process (e.g. anxiety, insomnia) will likely be helpful for the patient.	American Counseling Association National Association of Social Workers
Lifestyle Factors		

Sleep Hygiene[74,163]	Sleep hygiene refers to environment and behaviors that are conducive to optimizing restorative sleep. These may include avoiding caffeine, stimulants, alcohol near bedtime. Along with setting up a night routine and sleep schedule that is conducive to good sleep.	Lahteenmaki 2013; Coteur 2022.
Exercise/Physical Activity[61,166]	Gentle exercise (e.g., walking or swimming) may be helpful. The Ashton Manual recommends regular moderate enjoyable exercise during a benzodiazepine taper.	Reconnexion. The Benzodiazepine Toolkit, 2018;p54. The Ashton Manual. 2002.
Diet[61,166]	Staying well-hydrated, eating a well-balanced diet, and eliminating caffeine and alcohol may be helpful.	Reconnexion. The Benzodiazepine Toolkit. 2018;p53. The Ashton Manual. 2002.
Complementary Health Approaches		
Mindfulness[167]	Mindfulness is a cognitive skill, usually developed through meditation, involving "two primary elements: focused attention and open monitoring" as described by Garland & Howard.	Garland EL, Howard MO. Mindfulness-based treatment of addiction: current state of the field and envisioning the next wave of research. Addiction science & clinical practice. 2018;13:1-4.
Acupuncture[168]	Yeung described acupuncture as "Acupuncturists insert fine needles at special acupoints on the body according to the traditional Chinese meridian theory. The inserted acupuncture needles can be connected by an electric-stimulator to deliver electric-stimulation and is termed as electroacupuncture."	Yeung 2019 (Electroacupuncture).

Progressive Muscle Relaxation[157]	Progressive muscle relaxation involves alternatively tensing then relaxing muscles, one by one.	Otto 2010
Anxiety Management Training[169]	Elesser described AMT as "Patients were asked to imagine unpleasant events which they had experience, concentrate on early signs of distress and counteract them with relaxation."	Elsesser 1996
Peer Specialist Services		
Peer Support[29,170]	Primarily individuals with lived experience in mental health and/or substance use that provide support one-on-one or in a group setting, either in-person or through a virtual format to support the person going through the BZD taper.	National Institutes for Health and Care Excellence, 2022 Lynch et al., 2022

Appendix K. Adjunctive Pharmacological Interventions

This Appendix was created to support Recommendation #14. For patients experiencing symptoms that significantly interfere with the taper (e.g., sleep difficulty, anxiety symptoms), clinicians should first consider pausing or slowing the pace of the taper. [a] Clinicians can also consider adjunctive medications to address symptoms interfering with the taper.

Table 1. *Medications for Anxiety-related Conditions*

Medication	Class/ Mechanism	Considerations for Use	Other Population Considerations
Acute Anxiety			
Clonidine****	Central alpha-2 agonist	Avoid in hypotensive patients If used as scheduled medication, taper to discontinue	Monitor blood pressure, avoid in hypotensive patients
Gabapentin****	GABA analogue	Indicated for tremors Risk of being reinforcing	Avoid in patients with history of sedative use disorder Risk of combining with other medications, particularly opioids
Hydroxyzine*	Antihistamine	Avoid in first trimester of pregnancy or patients with history of QTc prolongation	Avoid in older adults, and pre-existing QTc prolongation
Propranolol****	Beta-blocker	Contraindicated in bradycardia, greater than first-degree block; avoid in uncontrolled bronchial asthma May be scheduled or dosed as needed for situational anxiety	Contraindicated in bradycardia, greater than first-degree block; avoid in uncontrolled bronchial asthma
Chronic Anxiety (GAD, Panic, PTSD, Social Anxiety)			
Buspirone**	5HT1A receptor agonist	Not effective as PRN agent	Only effective for GAD
SSRIs***	Antidepressant	May be anxiogenic upon initiation and dose increase. Start low and titrate slowly. Variable interactions with other medications	Consider potential interactions with other medications

SNRIs***	Antidepressant	May be anxiogenic upon initiation and dose increase. Start low and titrate slowly. May increase blood pressure	May help neuropathic pain; caution in uncontrolled hypertension
Mirtazapine*	Serotonin and norepinephrine modulator	Not FDA approved for treatment of anxiety disorders May be anxiolytic upon initiation.	More sedating than SSRIs/SNRIs, upon initiation
Prazosin****	Central alpha-1 antagonist	Approved for hypertension, but may be used off-label for PTSD related nightmares, not other symptoms of anxiety	Monitor blood pressure, avoid in hypotensive patients

*FDA approved
**FDA approved for GAD only
***Variably approved for GAD, Panic, PTSD and social anxiety disorder
****Not FDA approved for anxiety disorders
FOOTNOTE: Use in individual patients should always include review of medical and medication history and individual prescribing information to assess for any relative/absolute contraindications.
FOOTNOTE: Antidepressants (SSRI and SNRI) have black box warnings regarding suicidality, especially in adolescents and emerging adults.

Table 2. *Medications for Insomnia-related Conditions*

Medication	Class/ Mechanism	Considerations for Use	Other Population Considerations
Doxepin *	Antihistaminic tricyclic antidepressant	AASM approved for sleep maintenance insomnia[1,2] Caution in patients >65 or with coronary artery disease, arrhythmia	Avoid in patients with suicidal ideation/behavior
Diphenhydramine **			Avoid in older adults, may have paradoxical effects in children
Doxylamine **			Avoid in older adults, may have paradoxical effects in children
Hydroxyzine ****	Antihistamine		Avoid in older adults Avoid in first trimester of pregnancy or patients with history of QTc prolongation
Melatonin **	Sedative/Hypnotic		Avoid during pregnancy and breastfeeding; insufficient evidence of safety.
Ramelteon *	Agonist of melatonin receptors 1 and 2	AASM approved for sleep onset insomnia[1,2] Prone to significant interactions with CYP inhibitors and inducers	
Trazodone ****	Antidepressant	Use with caution in older adults and start with lower doses to avoid orthostasis	Use with caution in older adults and start with lower doses to avoid orthostasis

* FDA approved
**FDA approved (OTC)
****Not FDA approved for insomnia

FOOTNOTE: Use in individual patients should always include review of medical and medication history and individual prescribing information to assess for any relative/absolute contraindications
FOOTNOTE: Non-BZD hypnotics. e.g. Zolpidem, are not recommended for patients with sleep issues who are undergoing BZD taper due to similar receptor action

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Appendix L. Pregnancy Related Considerations

Table 1. *BZD Medication Considerations During Pregnancy and Lactation*

Medication	Does medication cross placenta?	Relative Infant Dose (RID)	Comments
Alprazolam	All benzodiazepines are expected to cross the placenta	2-9%[146]	Lorazepam is generally preferred in pregnancy and lactation due to lack of active metabolites and low RID
Chlordiazepoxide		Unknown	
Clonazepam		2.5-4.6%[146]	
Clorazepate		Unknown, shares metabolite with diazepam	
Diazepam		Up to 11%[171]	
Estazolam		Unknown	
Flurazepam		Unknown	
Lorazepam		0.7% to 4.4%[146]	
Oxazepam		10-33%[172]	
Quazepam		0.2-2.5% Hilbert 1994	
Temazepam		Dose dependent 0-10%[173]	
Triazolam		Unknown	

*For optimal safety, target relative infant dose is <10%

Table 2. *BZD Tapering Considerations by Pregnancy Trimester*

	1st Trimester	2nd Trimester	3rd Trimester	Post-partum
Potential Fetal Effects of Benzodiazepines	Minimal evidence of fetal malformations[174,175] Increased risk preterm birth (OR 1.38 to 1.48)		Increase risk preterm birth (OR 2.57), low birth weight (OR 1.89-3.41), cesarean delivery (OR 2.45), ventilatory support (OR 2.85)	Concern for withdrawal and potential fetal effects if high doses used during lactation
Potential Effects of Pregnancy on Benzodiazepines	Increased volume of distribution and CYP 2C19, 3A4, 2C9 metabolism (decreased effect) Decreased 1A2, 2C19 activity	Increased volume of distribution and CYP 2C19, 3A4, 2C9 metabolism (decreased effect); Decreased 1A2, 2C19 activity	Increased volume of distribution and CYP 2C19, 3A4, 2C9 metabolism (decreased effect); Decreased 1A2, 2C19 activity	Reversal of pregnancy changes – may increase effect[176]
Causes of insomnia	Nausea, urinary frequency, back pain	Fetal movements, heartburn, leg cramps, shortness of breath	Fetal movements, heartburn, leg cramps, shortness of breath	Infant care, pain
Considerations for tapering benzodiazepines	If alternative planned (e.g., SSRI) start alternative early to allow 6-8 weeks for effect before tapering BZD. Per above, BZD effect may decrease even before taper		Lowest dose possible to avoid neonatal withdrawal	Monitor sleep closely
Alternative medication for insomnia	Diphenhydramine	Antihistamines, trazodone	Antihistamines, trazodone	
Alternative medication for acute anxiety	Hydroxyzine*	Hydroxyzine	Hydroxyzine	Hydroxyzine
Alternative for severe	SSRI	SSRI	SSRI**	Sertraline has lowest relative infant dose

chronic anxiety				
Medications for anxiety or insomnia that are contraindicated	Propranolol	Propranolol	Propranolol	

*Limited data suggests possible low risk with first trimester use

** Possible increase in PPHN with number needed to harm of 1000