BRITISH COLUMBIA CENTRE ON SUBSTANCE USE
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CLINICAL BULLETIN: BENZODIAZEPINES AND OPIOIDS

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IN THIS BULLETIN

- BC's drug checking services have seen a rapid increase in benzodiazepine-positive street opioids
- In January 2021, benzodiazepines were detected in more than 20% of street opioid samples tested in Vancouver
- Vancouver Island Drug Checking Project found benzodiazepines and etizolam in 59% of expected opioid samples collected in March 2021
- Benzodiazepines were detected in nearly 50% of suspected overdose deaths in January 2021, which is more than three times higher than the data reported only six months prior (16%)
- Opioid-benzodiazepine overdoses result in atypical and protracted overdose events that can be challenging to reverse

This bulletin highlights the risks associated with the emergence of benzodiazepine-adulterated drugs in the street opioid supply and provides guidance for the care of individuals who have been exposed to benzodiazepines through the use of adulterated opioids.

The scope of this bulletin is limited to individuals who have been exposed to benzodiazepines through the street opioid supply; care considerations for individuals who are prescribed benzodiazepines and those who meet the criteria for benzodiazepine use disorder is outside the scope of this document.[a]

[a] *Considerations for individuals prescribed benzodiazepines and those with benzodiazepine use disorder will be provided in a forthcoming document.*

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1.0 BENZODIAZEPINES DETECTED IN STREET DRUGS

While the vast majority of overdose deaths in BC remain linked to the presence of fentanyl and its analogues in the unregulated drug supply, the use of non-prescribed benzodiazepine receptor agonists is a growing concern, due to the emergence of highly potent "designer benzos" and the increasing adulteration of the street opioid supply with benzodiazepines and benzodiazepine analogues.[1-4] The concurrent use of benzodiazepines and opioids significantly increases the risk of respiratory depression, overdose, and death.[5-8]

Since the introduction of benzodiazepine testing to BC's drug checking services in October 2018, there has been an upward trend in the proportion of benzodiazepine-positive opioid samples, with a rapid increase documented since mid-2020.[4,9,10] In January 2021, over 20% of opioid samples tested in Vancouver drug checking facilities contained benzodiazepines, which is more than double the proportion (9%) of benzodiazepine-positive samples found in August 2020.[10] Vancouver Island Drug Checking Project, which uses a more advanced testing technology capable of reliably detecting benzodiazepine analogues such as etizolam, found benzodiazepines and etizolam in 59% of expected opioid samples collected in March 2021, which marked a nearly 20% increase over the previous month.[11] Several novel benzodiazepine analogues have been identified in drug samples that were sold as opioids, including etizolam, bromazolam, flualprazolam, and flubromazepam.[4,10] These benzodiazepine analogues can be significantly more potent than pharmaceutical-grade benzodiazepines such as diazepam (Valium) and alprazolam (Xanax).[10]

People who use illicit opioids are increasingly likely to unintentionally use mixtures of potent opioids and benzodiazepines or benzodiazepine analogues. An analysis of BC drug checking samples collected between October 2018 and January 2020 showed that the majority (70%) of the samples confirmed to contain benzodiazepines also contained high-potency opioids such as fentanyl or carfentanil.[4] According to BC Coroner's Service toxicology reports, benzodiazepines were detected in nearly 50% of suspected overdose deaths in January 2021, which is more than three times higher than the percentage reported only six months prior, in August 2020 (16%).[1]

According to available reports, opioid-benzodiazepine overdoses result in atypical and protracted overdose events that can be difficult to reverse.[4,12] The following sections provide brief guidance on responding to overdoses, managing withdrawal, and initiating treatment for individuals with opioid use disorder who have been exposed to benzodiazepines through the illicit supply and do not meet a benzodiazepine use disorder diagnosis.[b]

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[a] *The BCCSU acknowledges with gratitude the following resources, which helped inform the guidance provided in this document:*

- *BC Centre for Disease Control. Fact Sheet: Etizolam in British Columbia's Ilicit Drug Market. Updated January 6, 2021.*
- *BC Ministry of Mental Health and Addictions. Benzos and Overdose: Be Aware of the Risks and Signs. October 2, 2019.*
- *Ontario Harm Reduction Network. The Shifting Unregulated Drug Supply in Ontario. March 2020.*

2.0 SYMPTOMS OF BENZODIAZEPINE OVERDOSE

The symptoms of an acute benzodiazepine overdose are similar to an opioid overdose and may include[13,14]:

- Sedation and loss of consciousness
- Muscle relaxation and loss of movement control
- Slurred speech
- Blackouts and memory loss

Typically, benzodiazepine involvement is suspected when the person does not regain consciousness following the administration of naloxone. The sedation resulting from overdosing can last several hours or even longer due to the long half-life of benzodiazepines.

3.0 HOW TO RESPOND TO AN OPIOID OVERDOSE INVOLVING BENZODIAZEPINES

Naloxone should always be administered in the event of an overdose as it can reverse the effects of opioid overdose and restore breathing.

- Due to the similarities between the symptoms of benzodiazepine and opioid overdose, it is often difficult to know when benzodiazepines are involved in an overdose. Since opioids are implicated in the vast majority of overdoses, including those involving benzodiazepines, naloxone should always be used to reverse the respiratory depression caused by opioids and restore breathing. In the case of concurrent opioid and benzodiazepine overdose, the sedation and loss of consciousness related to benzodiazepines may last for several hours after naloxone is administered. However, sedation is not life-threatening once normal breathing is restored.
- If the first naloxone administration does not restore breathing, continue administering naloxone at 3- to 5-minute intervals until the person starts breathing normally. Naloxone administration must always be accompanied by standard resuscitation steps to prevent brain injury and death. For comprehensive instructions, refer to the BC Centre for Disease Control's Decision Support Tool: Administration of Naloxone. If normal breathing is restored but the person is still unconscious, they should be placed in recovery position and receive monitoring and supportive care.

The use of flumazenil to reverse the effects of benzodiazepines is not recommended.

- Flumazenil is a GABA[a] antagonist approved in Canada for reversing the sedative effects of benzodiazepines. However, due to the risk of serious adverse effects including seizures and ventricular dysrhythmias, flumazenil is not recommended in most circumstances.[15,16] Patients with overdoses involving mixed drugs, such as benzodiazepines mixed with opioids, may be at higher risk of experiencing seizures and other adverse effects from flumazenil administration.[16] These risks outweigh the potential benefits of flumazenil in most cases, considering the fact that sedation from a benzodiazepine overdose is rarely life threatening and can be managed with supportive care.[14,16]

4.0 MANAGEMENT OF BENZODIAZEPINE-OPIOID WITHDRAWAL

Since benzodiazepine dependence may have developed as a result of unintentional exposure to adulterants, health care providers should monitor patients who discontinue illicit opioid use (e.g., those who start opioid agonist treatment [OAT]) for symptoms of benzodiazepine withdrawal, even if they report only using opioids, and consider withdrawal management strategies as needed.

Common benzodiazepine withdrawal symptoms include[14,17]:

- Anxiety
- Headache
- Vomiting
- Nausea
- Tinnitus
- Anorexia
- Tremor
- Weakness
- Irritability
- Tachycardia

Severe withdrawal symptoms include[18,19]:

- Seizures
- Paranoia
- Hallucinations
- Withdrawal delirium

Mild benzodiazepine withdrawal symptoms are typically temporary (a few days to a week) and can be managed with supportive care. However, given the rapidly evolving landscape, with varying agents of varying concentrations adulterating the illicit opioid supply, it is impossible to provide generalized guidance for this population; addressing potential benzodiazepine withdrawal and ascertaining withdrawal severity requires individualized assessment. If benzodiazepine withdrawal is suspected in an individual who does not report using benzodiazepines, clinicians are encouraged to provide supportive care and consult the 24/7 Addiction Medicine Clinician Support Line or the RACE App for specialized case-based consultation.

Due to the overlapping symptoms of opioid and benzodiazepine withdrawal, it may be challenging to assess the severity of withdrawal from each substance; close monitoring is recommended to facilitate prompt identification of worsening withdrawal symptoms.

Clinicians are also encouraged to consult the 24/7 Addiction Medicine Clinician Support Line or the RACE App to discuss any concerns regarding potential benzodiazepine withdrawal symptoms and necessary monitoring measures when a patient is planning to abruptly discontinue illicit opioid use (e.g., for traditional buprenorphine/naloxone induction).

Note that the recommendations in this section are specific to individuals who have been exposed to benzodiazepines through adulterated unregulated opioids; this bulletin does not provide guidance for individuals who meet the criteria for benzodiazepine use disorder[c] or those who have been prescribed benzodiazepines.

[c] *Generally, benzodiazepine use disorder is managed through gradual tapering with a long-acting benzodiazepine formulation. For further information on benzodiazepine deprescribing strategies, refer to the College of Family Physicians of Canada's Deprescribing benzodiazepine receptor agonists: Evidence-based clinical practice guideline.*

5.0 IMPLICATIONS FOR OPIOID USE DISORDER TREATMENT

All patients who use opioids should be offered screening for benzodiazepine use and receive information on the risks of combining opioids and sedatives, whether prescribed or illicit.[19] Benzodiazepines should be included in urine drug tests for individuals who use illicit opioids and/or those who are on OAT. However, clinicians and patients should be aware that some benzodiazepines and benzodiazepine analogues (e.g., alprazolam, clonazepam, etizolam, temazepam, triazolam) may not be detected in standard urine drug tests despite the patient having been exposed.

Traditionally, prescribing OAT to patients also taking benzodiazepines has been contraindicated.[19] In light of the high risk of overdose death associated with illicit opioid use, it is not recommended to delay or withhold OAT if benzodiazepine exposure is suspected.[19] However, patients should not be started on OAT while sedated.[d]

Individuals starting OAT should be monitored for symptoms of benzodiazepine withdrawal. Benzodiazepine withdrawal management in such cases requires individual assessment and treatment planning. If benzodiazepine withdrawal is suspected, clinicians are encouraged to provide supportive care and contact the 24/7 Addiction Medicine Clinician Support Line or the RACE App for case-based consultation.

A recently published case-crossover study (n=23,036) found that buprenorphine/naloxone has a protective effect against drug-related poisonings in individuals prescribed benzodiazepines and z-drugs.[20] It is unknown whether this protection extends to the use of illicit benzodiazepines and benzodiazepine analogues. However, given buprenorphine's ceiling effect on respiratory depression, it should be considered first-line OAT for individuals with opioid use disorder who are using prescribed or illicit benzodiazepines and benzodiazepine analogues.

[d] *For guidance on OAT initiation, refer to Appendices 1, 2, and 3 of the BCCSU/MOH Guideline for the Clinical Management of Opioid Use Disorder.*

6.0 HARM REDUCTION AND EDUCATION

- Clinicians should inform individuals who use drugs of the increasing prevalence of benzodiazepine-adulterated street drugs, which increases their risk of unintentionally taking benzodiazepines.
- Clinicians should discuss the risks associated with use of multiple CNS depressants and encourage patients to decrease their use of other CNS depressants (e.g., alcohol) and offer treatment where appropriate, in order to help decrease risks associated with benzodiazepine analogues adulterating the illicit opioid supply.
- Individuals who use drugs should also be informed that overdoses involving a mix of opioids and benzodiazepines are different from other opioid overdoses in that they may last for several hours even after naloxone administration; however, naloxone should always be used in the event of an overdose.
- Clinicians should ensure that patients receive training for naloxone use and have access to take-home naloxone. A list of locations offering naloxone kits and training is available on Toward the Heart's Take-Home Naloxone Programs website.
- Individuals who use drugs should be encouraged to avoid using alone, and to use available harm reduction facilities including drug checking services and observed consumption services[21] (i.e., overdose prevention services and supervised consumption sites).
- People who use drugs should also be informed that benzodiazepine analogues may not be detected through drug-checking or urine drug testing; harm reduction precautions are recommended even in the case of negative drug checking results for benzodiazepine analogues.
- Education resources for people who use drugs and members of the community for responding to a suspected overdose involving benzodiazepines are available at the Toward the Heart website:

    - Do I Keep Giving Naloxone?
    - Opioids and Benzos or Etizolam

ADDITIONAL RESOURCES

- BCCDC Summary Sheet for Health Professionals: Benzodiazepines Found in Opioids in British Columbia
- BCCDC Fact Sheet: Etizolam in British Columbia's Illicit Drug Market
- BCCSU: Using Benzo Test Strips for Drug Checking Step-by-Step Guide
- First Nations Health Authority: Virtual Substance Use and Psychiatry Service

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