

# CCENDU Bulletin

## Risks and Harms Associated with the Nonmedical Use of Benzodiazepines in the Unregulated Drug Supply in Canada

### Summary

Substance use risks are significantly higher for people who obtain drugs on the unregulated market as there is no quality control and drug contents are unpredictable. This lack of predictability has increased during the COVID-19 pandemic as supply chains have been disrupted by border closures and safety measures. This leaves people who use drugs (PWUD) increasingly susceptible to consuming adulterated or unfamiliar substances. In some regions, COVID safety measures have also reduced capacity and access to services for PWUD, making it more difficult to prevent and address the health harms of adulterated substances.

Although benzodiazepines are among the most frequently prescribed drugs in the world, they and benzodiazepine-like substances that are not used in a medical context are increasingly being identified in drugs on the unregulated market, particularly in drugs sold as opioids. This bulletin refers to these drugs as nonmedical benzodiazepines or NMBs.

This situation warrants attention for three reasons:

1. **The combination of NMBs and opioids increases the risk of drug poisoning.** These substances compound each other's effects as both slow vital functions such as breathing. This is thought to be contributing to record-high drug poisoning fatalities.
2. **Drug poisonings involving opioid-NMB combinations can be complicated to reverse.** Naloxone can reverse the opioid effects by restoring breathing but not the sedation caused by the NMB. This means a person could start breathing again but not regain consciousness, complicating first response protocols and care.
3. **Regular use of benzodiazepines can produce tolerance.** This includes unintentional or unknown use of NMBs that are added to other substances. Stopping use of the intended drug can lead to an abrupt end of unknowingly using NMBs, which can produce benzodiazepine withdrawal symptoms that need medical management.

This bulletin is intended for harm reduction service providers, first responders, medical and public health professionals, policymakers and PWUD. It provides an overview of the most common NMBs detected in Canada and points to locally developed resources. It aims to inform local responses for preventing and reducing associated health harms.

This bulletin concludes with considerations and possible response options at the individual, program and policy level, as well as a call for more demographic information, including sex- and gender-specific data.



## Background

In 2020, the Canadian Community Epidemiology Network on Drug Use (CCENDU), coordinated by the Canadian Centre on Substance Use and Addiction (CCSA), provided an overview of adulterants and contaminants frequently found in drugs on the unregulated market in Canada.<sup>1</sup> The report showed that the addition of unexpected or undesired substances to unregulated drugs was common and widespread. A follow-up bulletin showed that this trend had increased during the COVID-19 pandemic.<sup>2</sup> This has been associated with an increase in harms, including record-high drug poisoning rates, particularly among males and individuals aged 20 to 49 years.<sup>3</sup>

Benzodiazepines and benzodiazepine-like substances that have been either illegally produced or diverted from legal sources for use in nonmedical settings have been identified with increasing frequency in drugs purchased on the unregulated market in Europe<sup>4</sup> and North America,<sup>5,6</sup> including Canada. (This bulletin refers to these as nonmedical benzodiazepines or NMBs.) This pattern has raised concerns as it is associated with harms to people who use drugs (PWUD) and creates unique considerations for harm reduction and treatment services.

This bulletin is intended for harm reduction service providers, first responders, medical and public health professionals, policymakers, and PWUD. It:

- Highlights and profiles the NMBs that have been most frequently detected in the unregulated drug supply in Canada (see Box 1);
- Provides a brief description of each;
- Lists relevant references for further information; and
- Concludes with a summary of implications and potential next steps.

### Box 1: Nonmedical benzodiazepines discussed in this bulletin

- Etizolam
- Flubromazolam
- Flualprazolam
- Clonazolam
- Meclonazepam
- Bromazolam
- Flubromazepam
- Deschloroetizolam

Although efforts were made to apply sex- and gender-based analysis (SGBA+) to the data presented in this bulletin, data were often not available for such an analysis. (For more information and resources, see <https://www.ccsa.ca/sex-and-gender-based-analysis>.) Knowledge gaps around sex, gender, race, ethnicity, income and other demographic information highlight the need to consider more detailed data collection and communication.

## What Are Benzodiazepines

Benzodiazepines are classified as central nervous system depressants or sedative-hypnotics. They slow down the nervous system, giving them calming, sleep-inducing properties. Some are used medically to treat anxiety, sleep and seizure disorders.<sup>7</sup> Common benzodiazepines available by prescription are clonazepam (Klonopin®), lorazepam (Ativan®), alprazolam (Xanax®) and diazepam (Valium®). By some estimates, these are among the most frequently prescribed drugs in the world,<sup>8</sup> and are significantly more likely to be prescribed to women than to men.<sup>9</sup>



## Nonmedical Benzodiazepines

In addition to benzodiazepines used for medical purposes, there are numerous substances that we collectively refer to in this bulletin as NMBs (see Box 2). These include benzodiazepines and benzodiazepine-like substances that:

- Are medically available but have been diverted for nonmedical purposes or appear in jurisdictions where they are prohibited;
- Were developed but not brought to market in Canada; or
- Are newly synthesized “designer” drugs.

### Box 2: Common terms for drugs included here as NMBs

- Novel psychoactive substance (NPS) benzodiazepines
- Legal benzodiazepines
- Designer benzodiazepines (DBZD)
- Benzodiazepine analogs

Many NMBs are classified as novel psychoactive substances (NPS), have never been tested in humans or animals, and are of unclear legal status. As of October 2020, at least 29 NMBs had been identified in 49 countries and territories around the world.<sup>10</sup>

## Why Are Nonmedical Benzodiazepines a Concern?

NMBs are often used, intentionally or unintentionally, in combination with other substances. This mix of substances is colloquially known in some regions of Canada as “benzodope.” Some people use NMBs purposefully along with opioids, stimulants or other substances to modify the high or cope with withdrawal.<sup>11</sup> However, there is also evidence that NMBs are added to substances and consumed unintentionally or unknowingly. Either way, the combination of NMBs with other substances raises three key concerns:

1. **The combination of NMBs and opioids increases the risk of drug poisoning.** These substances compound each other’s effects as both slow vital functions such as breathing. This is thought to be contributing to record-high drug poisoning rates.
2. **Drug poisonings involving opioid-NMB combinations can be complicated to reverse.** Naloxone can reverse the opioid effects by restoring breathing but not the sedation caused by the NMB. This means a person could start breathing again but not regain consciousness, complicating first response protocols and care.
3. **Regular use of benzodiazepines can produce tolerance.** This includes unintentional or unknown use of NMBs that are added to other substances. Stopping use of the intended drug (e.g., through opioid agonist or abstinence-based treatment, hospitalization or incarceration) can lead to an abrupt end of unknowingly using NMBs, which can produce benzodiazepine withdrawal symptoms that need medical management.

These concerns are particularly relevant for women who use drugs. The higher rates of benzodiazepine prescriptions among women can increase the risk of experiencing benzodiazepine toxicity when combined with NMBs on the unregulated market. It can also increase the severity of benzodiazepine tolerance and withdrawal.

## Evidence of NMBs and Associated Harms in Canada

The increasing presence of NMBs in the unregulated drug supply was confirmed by all reporting CCENDU sites (B.C., Manitoba, Ontario, Quebec, and Nova Scotia). (For full list of sites, see [www.ccsa.ca/partners-and-collaboration-ccendu](http://www.ccsa.ca/partners-and-collaboration-ccendu).) For example, urine toxicology data from a commercial laboratory in B.C. showed that among samples that screened positive for



benzodiazepines, the presence of etizolam rose from about 40% at the beginning of the COVID-19 pandemic in April 2020 to about 70% in July 2021. Flubromazepam presence rose from less than 10% to more than 20% in July 2021. (Data provided to the B.C. CCENDU site by LifeLabs, a commercial laboratory performing urine toxicology to indicate recent exposure to specific substances.) As these data were not broken down by sex, gender or other demographic factors, differences in exposure to NMBs according to these factors are unknown.

Most CCENDU sites also confirmed that the rise of NMBs was associated with increased health harms, reflected in increasing numbers of community health advisories and corroborated by data from coroners and medical examiners. For example, an Ontario report on opioid-related deaths during the COVID-19 pandemic<sup>12</sup> showed that benzodiazepines were detected in nearly half (46%) of opioid-related deaths recorded during the pandemic (March to December 2020). That was a significant increase from 30% pre-pandemic (March to December 2019). This increase was driven by a significant increase in etizolam, from a 5% detection rate pre-pandemic to 25% during the pandemic. The report further showed a significant rise in opioid-related deaths among males, although it is unclear whether this was driven by benzodiazepines. In B.C., the presence of benzodiazepines in illicit drug toxicity deaths increased from 15% in July 2020 to 47% in June 2021, with etizolam appearing in 40% of cases over this period.<sup>13</sup> That number peaked at 60% in May 2021. Sex- or gender-specific and other demographic data could help further detail who is at risk for exposure to NMBs and associated harms.

### ***Samples Seized by Law Enforcement***

Health Canada's Drug Analysis Service (DAS) analyzes the contents of drugs seized by law enforcement officers and submitted to the DAS laboratory. (DAS lists all substances detected in each sample but not their quantities or what the substance was intended to be bought or sold as.) Analysis of DAS data indicates that 7.5% of samples submitted in the first half of 2021 (3,878 of 51,741 total samples) contained at least one benzodiazepine (prescribed and NMB) – an increase from 2.5% (1,386 of 55,967 samples) in the first half of 2019.

Appendix A presents information on the presence of benzodiazepines in samples analyzed from January to June 2021. The table shows that the top three detected benzodiazepines were NMBs (etizolam, flubromazepam and flualprazolam). They accounted for nearly 80% of all detected benzodiazepines.

In addition to total counts, the table also shows co-occurrence with other psychoactive substances (i.e., how often a benzodiazepine was detected as the sole ingredient of a sample or alongside opioids, stimulants or both). Benzodiazepines approved for medical use tended to appear alone, suggesting they may be diverted pharmaceuticals. In contrast, most of the NMBs co-occurred with other substances, suggesting they may be adulterants. For example, lorazepam (Ativan®) occurred alone 98% of all times it was detected, while etizolam occurred alone only 7% of all times it was detected. Eighty-six percent (86%) of the time etizolam was detected, it co-occurred with an opioid. Co-occurrence with stimulants was also observed but was less frequent.

Detection of benzodiazepines and co-occurrence with other substances was not the same across the country (see Appendix A Table 2 for details). For example, of the 501 benzodiazepines detected in samples submitted by law enforcement agencies in B.C., 63 (12.6%) occurred alone, 18 (3.6%) co-occurred with a stimulant and 404 (80.6%) co-occurred with an opioid. By contrast, of the 789 benzodiazepines detected in samples submitted by law enforcement agencies in Quebec, 500 (63.4%) occurred alone, 26 (3.3%) co-occurred with a stimulant and 90 (11.4%) co-occurred with an opioid. Summary reports of drugs analyzed by DAS are updated periodically and are available at [Drug Analysis Service, Analyzed Drug Report](#).



Correspondence with the Canada Border Services Agency (CBSA) provided further information about the presence of NMBs in the unregulated drug supply in Canada. Data from samples analyzed by CBSA laboratories since January 2019 indicate that NMBs are imported in significant quantities from other countries, primarily China and Hong Kong for bulk powder and commonly the Netherlands for dosage form products (tablets, capsules, etc.). Further, with few exceptions, NMBs that are seized entering Canada tend to be pure (i.e., the only substance, whether psychoactive or not, in analyzed samples). This information stands in contrast with the DAS data, which indicate that NMBs tend to co-occur with other substances, suggesting their use as an adulterant may occur domestically.

### **Information Provided by Drug Checking Programs**

There are currently only a few drug checking programs across Canada that have the capacity to detect or identify NMBs in the unregulated drug supply. Most services do not have access to sophisticated drug checking technology, and those that do are not always able to detect NMBs at sufficiently low concentrations.

Although benzodiazepine test strips are readily available, they have limitations. They have a high false negative rate (sensitivity to etizolam is 50% to 70%) as benzodiazepines do not dissolve well in water, which is necessary for testing. For this reason people need training to use the strips correctly (see the B.C. Centre on Substance Use's [Step-By-Step Guide](#)). Further, the strips can only determine the presence or absence of an NMB, but not the specific substances or concentration.

Despite these limitations, three drug checking programs with access to the necessary technology provided information for this bulletin, corroborating the increase in NMBs described above:

1. In November 2020, the B.C. Centre on Substance Use (BCCSU), which coordinates drug checking data from multiple services and health authorities in B.C., reported NMBs in 14.6% of substances expected to be opioids. In July 2021, this had increased to 24.3%.
2. During the same timeframe, Vancouver Island Drug Checking, which uses distinct technologies that are more sensitive than BCCSU, reported a rise in the same measure from 20% to 36%, peaking at 69% in April 2021. Etizolam accounted for 30% of NMB-positive samples, peaking at 56% in April 2021. This group also noted that submitted samples included large amounts of counterfeit Xanax® pills containing etizolam, and that NMBs were increasing not just in the frequency with which they were detected but also in concentration.
3. Similarly, Toronto's Drug Checking Service reported that in July 2021, 70% of expected fentanyl samples contained one or more NMB, as compared to 34% when the service launched in fall 2019. (The Drug Checking Project is coordinated by the Centre for Drug Policy Evaluation and uses hospital laboratory equipment for sample analysis.) To date, the service has identified 13 benzodiazepine-related drugs in Toronto's unregulated opioid supply (see Appendix B for details).

Corroborating the increase in health harms, Toronto's drug checking service reports that 76% of expected fentanyl samples known to be associated with a drug poisoning between October 2019 and Aug. 31, 2021, contained at least one benzodiazepine-related drug.

Up-to-date drug checking results, including detection of NMBs, are available at:

- [Toronto's Drug Checking Service](#)
- [BCCSU Drug Checking](#)
- [Vancouver Island Drug Checking Project](#)





## Profiles of Select Nonmedical Benzodiazepines

Profiles of select NMDs are provided in Appendix C. These NMBs have been detected in the drug supply in Canada and have been associated with health harms. The list of compounds is not meant to be exhaustive, and the descriptions are not meant to be comprehensive, but rather highlight relevant sources of information. Where possible, readers are referred to more comprehensive information.

## Conclusions and Implications

The unregulated drug supply in Canada is highly unpredictable, and PWUD often do not know what substances they are consuming or in what quantities. This issue has become more urgent during the COVID-19 pandemic when the drug supply has become more unpredictable and access to services for PWUD has decreased in some parts of the country because of safety measures. The presence of NMBs in the drug supply is thought to contribute significantly to the recently observed increase in drug poisonings, specifically through the frequent combination of NMBs and opioids in many regions of Canada. This presumption is primarily supported by coroners' data and community alerts.

There are three major implications of combining NMBs with other drugs in the unregulated supply:

1. Increased risk of drug poisoning;
2. More complex care required for people experiencing drug poisoning; and
3. Inadvertent dependence on benzodiazepines and withdrawal if stopped abruptly.

The following sections discuss these implications. Policy and program considerations and sex, gender and equity considerations are also discussed.

### *Increased Risk of Drug Poisoning*

Benzodiazepines and opioids compound each other's effects as both slow vital functions, such as breathing. This increases the risk of drug poisoning among people who use NMBs alongside opioids, both knowingly and unknowingly. Further, different populations have different risk profiles. For example, women are prescribed benzodiazepines more often than men and tend to experience the effects at lower doses.<sup>14</sup> This potentially increases women's risk of drug poisoning when exposed to NMBs.

The following response options could help prevent or reduce drug poisoning cases.

### Response Options

**Facilitate informed decision making.** To mitigate the risks of unintentional NMB use, PWUD need access to services and tools that provide information about the contents of their drugs. This includes access to reliable drug checking information, such as better-quality information than test strips alone can provide. It also includes the provision of substances whose contents are known and regulated (see the Policy and Program Considerations section below) and the removal of gendered barriers to accessing harm reduction services.<sup>15</sup>

**Raise awareness on risks and harm reduction strategies.** Information campaigns about the presence and risks of NMBs in the drug supply, as well as different risk profiles among different subpopulations, could help PWUD prepare and respond appropriately. Campaigns should be developed by or with PWUD to ensure the campaigns are relevant and credible.<sup>16</sup> Campaigns should include information about the limitations of harm reduction services and tools (e.g., limited sensitivity of drug checking instruments) to emphasize that caution is always warranted. Awareness and understanding of the



[Good Samaritan Drug Overdose Act \(GSDOA\)](#) remains limited among law enforcement and some groups of PWUD.<sup>17</sup> Campaigns should aim to increase awareness and encourage PWUD to call 911 in case of an emergency. However, despite the GSDOA, law enforcement officers may be mistrusted by or traumatizing for PWUD.

## More Complex Protocols for Reversing Drug Poisoning

In the case of a drug poisoning involving a combination of NMBs and opioids, response protocols such as administration of naloxone are appropriate but require more knowledge and time. Naloxone can reverse the effects of opioids (e.g., depressed breathing) but not the effects of benzodiazepines (e.g., loss of consciousness). This means that a person receiving naloxone could start breathing again but not wake up. Moreover, due to the long duration of some NMBs (about 7–15 hours for etizolam; see Box 3), drug poisoning events can last longer. Further, because NMBs can take longer to take effect than opioids, people may appear fine shortly after consuming them but lose consciousness later. Together, these factors create complex needs for both the person experiencing the drug poisoning and the person responding. For example, if not properly trained or informed, responders may try to administer multiple doses of naloxone if a person does not regain consciousness. This could result in opioid withdrawal symptoms such as vomiting, which can be dangerous for a person who is unconscious and unattended. In addition, being unconscious and not easily roused for long periods of time can leave people at risk of assault or theft, or exposed to the elements if outside.

### Response Options

**Adjust first response protocols.** People experiencing a drug poisoning should be monitored for an extended period. In particular, breathing should be monitored. Tools such as pulse oximeters (a device that measures oxygen in the blood and can help determine whether a person requires rescue breathing) have been shown to be acceptable and helpful.<sup>18</sup> The resources in Boxes 3 and 4 include specific suggestions for how to modify first response protocols for NMBs. These adjustments can place additional demands on harm reduction staff, which should be accounted for and equitably compensated.

### Raise awareness among PWUD and first responders.

PWUD and first responders should be aware of the symptoms of a drug poisoning involving a combination of NMBs and opioids, as well as the additional knowledge, time and tools needed to properly respond. PWUD and first responders should also be aware that it is safe and recommended to administer naloxone to someone who is unconscious and not breathing, as the person may also have opioids in their system. However, there is no need to keep administering naloxone as long as the person is breathing.

#### Box 3: Key resources for healthcare professionals

- [Clinical Bulletin: Benzodiazepines and Opioids](#)
- [Summary Sheet for Health Professionals: Benzodiazepines found in Opioids in BC](#)
- [ALERT! Benzos on the Rise in Illicit Opioid Overdoses in B.C.](#)
- [Potent sedatives in opioids in BC: Implications for resuscitation, and benzodiazepine and etizolam withdrawal](#)

#### Box 4: Key resources for PWUD

- [Information Sheet for the General Public: Withdrawal from Benzodiazepines Mixed in BC's Illicit Drug Supply](#)
- [Do I Keep Giving Naloxone?](#)
- [Overdose Resources: Opioids and Benzos or Etizolam](#)
- [Mixed Opioid and Benzodiazepine Overdose](#)



## **Withdrawal If Stopped Abruptly**

Some PWUD enjoy the combined effects of NMBs and opioids, but many may not know they are consuming NMBs for extended periods of time, given their frequent use as an adulterant. Tolerance to benzodiazepines can develop in as few as four weeks. If a person starts opioid-assisted therapy, enters abstinence-based treatment or is hospitalized or incarcerated, sudden discontinuation of NMBs can cause benzodiazepine withdrawal symptoms ranging from anxiety, irritability, headache, dizziness, nausea and vomiting to potentially life-threatening symptoms such as palpitations, rapid heartbeat and seizures (see Box 3). Since NMB use can be inadvertent, these symptoms may be unexpected or unfamiliar. Further, since benzodiazepines are prescribed at higher rates to women than men, the risk of tolerance and withdrawal could be especially high among women. It can also be difficult for healthcare providers to distinguish benzodiazepine withdrawal from opioid withdrawal or stimulant toxicity. Urine toxicology may not detect specific NMBs.

### **Response Options**

**Raise awareness among PWUD and healthcare providers.** Healthcare professionals, service providers and PWUD should be aware of the possibility of inadvertent exposure to NMBs. Healthcare and service providers should be prepared to support benzodiazepine withdrawal even if a person reports only opioid use, especially among women. PWUD, particularly women who use drugs, need to know what the withdrawal symptoms are, including the potential for seizures, and that they may require medical attention or tapering off.

**Provide supportive care.** Healthcare providers should be aware of the possibility of benzodiazepine withdrawal and provide appropriate care. For specific guidelines, see the resources in Box 3.

**Consider appropriate pharmacotherapies.** Although flumazenil can reverse the effects of benzodiazepines, it is not recommended for use in drug poisoning reversal as the risks outweigh the benefits. Healthcare providers should consider treatment of opioid use disorders with buprenorphine, as it has recently been shown to prevent drug poisoning in people who also use benzodiazepines.<sup>19</sup>

## **Policy and Program Considerations**

Increasing the predictability of the contents of drugs in the unregulated drug supply could decrease substance-related harms, including those associated with NMBs. Response options to reduce the harms associated with the unregulated drug supply are meant to be part of a comprehensive approach, with options building on each other. For programs and policies to be effective, they need the meaningful engagement, support and guidance of PWUD.<sup>20-22</sup>

### **Response Options**

**Support for drug checking services.** Drug checking services require an exemption under Section 56 of the *Controlled Drugs and Substance Act*. Streamlining and clarifying the regulatory process for receiving such an exemption will encourage the spread of drug checking services. Further, permanent exemptions and sustainable funding would make these services more widely available across the country.<sup>23</sup>

**Expand access to a safer supply.** Safer supply programs are being piloted to increase access to substances of known composition, mitigating the risks of an adulterated and toxic unregulated drug supply.<sup>24</sup> Expanding existing programs that enable access to a more predictable and reliable supply (e.g., heroin assisted treatment)<sup>25</sup> and supporting new pilot programs can create effective, sustainable and scalable approaches that mitigate drug toxicity. Provincial and territorial governments and regulatory colleges could expand low-barrier tablet or injectable opioid distribution programs





through existing locations, such as pharmacies and public health clinics, which could increase access to a safer drug supply without major infrastructure hurdles or investment.

**Improve emergency response protocols.** Policy makers and police could support efforts to encourage PWUD to call 911 in case of distress through the GSDOA, including by removing potential barriers within the Act, such as the “outstanding warrants” exclusion. Police officers’ and PWUD’s awareness and understanding of the GSDOA should be improved.<sup>17,26</sup> In addition, first responders should take anti-stigma and trauma-informed training to improve care when helping PWUD.<sup>27,28</sup> Contact with first responders can be traumatizing, particularly for those who have experienced stigma or racism in previous encounters. Police should not attend drug-harm related calls unless asked to or if no other respondents are available. These protocols can reduce barriers to care for individuals who use drugs.

**Continue and expand harm reduction.** Provinces and territories can continue to help reduce harms by providing continued support and expansion of existing harm reduction tools such as naloxone availability and drug poisoning response training including updated protocols to respond to inadvertent polysubstance use. Ensuring free availability of naloxone will increase accessibility to those who need it. Increasing access to more novel tools such as pulse oximeters can further help address the harms associated with NMBs and other adulterants in the drug supply.

**Explore decriminalization and other legislative and regulatory changes.** There is an opportunity to further advance evidence-based and health-focused drug policies to reduce the harms of drug toxicity associated with the unregulated drug market. This includes exploring further exemptions under Section 56 of *the Controlled Drugs and Substances Act*, as well as considering other models for the decriminalization of personal possession of drugs.<sup>29</sup> Evidence to support a regulated supply could also be explored beyond the decriminalization of personal possession of drugs.

**Increase investment in substance use-related interventions, services and supports.** Increased and stable investment in evidence-informed harm reduction interventions and treatment options by all levels of government will ensure the sustainability of and timely access to care options when and where they are needed. An accessible continuum of services is needed with decriminalization to shift from an enforcement approach to a more comprehensive health and wellness approach.

**Create a national drug observatory.** A Canadian drug observatory could support national monitoring of drug contents and tracking of adverse health effects to identify concerning trends, improve harmonization of data collection to allow comparison across regions in Canada, and rapidly disseminate drug-related health alerts and response options.

### **Sex, Gender and Equity Considerations**

The data presented in this bulletin are limited by the lack of specific findings and considerations for certain subpopulations. This includes drug poisoning risk profiles and barriers to accessing harm reduction services that are specific for sex, gender, race, age, ability, income and other socioeconomic dimensions. For example, women are more likely to be prescribed benzodiazepines, and physiological factors affect dose, tolerance and withdrawal patterns in females. The risks of drug poisoning and benzodiazepine withdrawal may be higher for women and warrant particular attention. In addition, more trauma-informed services are needed as domestic and sexual violence can create barriers to services for women who use drugs, including harm reduction services.

### **Response Options**

**Data collection.** The collection and communication of data about the epidemiology of substance use risks should be broken down by sex, gender and other demographic characteristics, so specific considerations can better guide service provision and policy development.



**Sex- and gender-based analysis.** A complete sex- and gender-based analysis (SGBA+) of the issues raised in this bulletin could help pinpoint questions and issues that need consideration and targeted responses. (For resources on SGBA+, see <http://bccwh.bc.ca/category/post/research-methods-sgba>.)

## General Resources

Highlighted here are key resources that address the issue of NMBs as a whole:

- [Collated BC resource: Benzodiazepine/etizolam in illicit opioids](#) – Developed by the BCCDC, contains links to resources developed for people who use drugs, peer responders and health professionals
- [Clinical Bulletin: Benzodiazepines and Opioids](#) – Developed by the B.C. Centre on Substance Use, highlights the risks of benzodiazepines and provides guidance for care
- [Drug Checking: A Supplemental Report on British Columbia’s Unregulated Drug Supply Amidst Dual Public Health Emergencies](#) – Developed by the B.C. Centre on Substance Use, presents a snapshot of point-of-care drug checking results including benzodiazepine contamination in expected opioid and nonopioid drug samples
- [Potent sedatives in opioids in BC: Implications for resuscitation, and benzodiazepine and etizolam withdrawal](#) – B.C. Centre for Disease Control opinion published in the *B.C. Medical Journal* summarizes recent data and suggested next steps
- [An outbreak of novel psychoactive substance benzodiazepines in the unregulated drug supply: Preliminary results from a community drug checking program using point-of-care and confirmatory methods](#) – Research article documents detection of etizolam, flualprazolam, flubromazolam and flubromazepam in B.C. and the accuracy of different drug checking technologies

CCENDU will continue to monitor benzodiazepines in the unregulated drug supply in Canada. If you have any questions, comments, information to contribute or corrections to the information contained in this bulletin, or you wish to subscribe and receive updates as new information becomes available, please email [CCENDU@ccsa.ca](mailto:CCENDU@ccsa.ca).

For more information on CCENDU and to review previous CCENDU alerts and bulletins, please visit [www.CCENDU.ca](http://www.CCENDU.ca).

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## Appendix A

### *Benzodiazepines (Including Nonmedical Benzodiazepines) Detected in Samples Analyzed by Health Canada's Drug Analysis Service*

**Table 1:** Benzodiazepines and benzodiazepine-like substances, including prescribed and nonmedical benzodiazepines (NMBs), detected in 3,878 samples submitted by law enforcement agencies across Canada between January and June 2021. Note that among the 3,878 benzodiazepine-containing samples, the total number of benzodiazepines detected was 4,000, as one sample can contain more than one benzodiazepine.

Detected Benzodiazepine	Times the benzodiazepine was detected, <i>n</i> (% of 4,000 total*)	Times detected alone, <i>n</i> (% of first column)	Times detected with any stimulant, <i>n</i> (% of first column)*	Times detected with any opioid, <i>n</i> (% of first column)†
Etizolam (NMB)	2,490 (62.25)	169 (6.79)	147 (5.90)	2,137 (85.82)
Flubromazolam (NMB)	346 (8.65)	100 (28.90)	8 (2.31)	100 (28.90)
Flualprazolam (NMB)	328 (8.20)	169 (51.52)	17 (5.18)	135 (41.16)
Clonazepam (Klonopin®)	215 (5.38)	211 (98.14)	4 (1.86)	0 (0.00)
Lorazepam (Ativan®)	162 (4.05)	160 (98.77)	1 (0.62)	1 (0.62)
Alprazolam (Xanax®)	142 (3.55)	105 (73.94)	21 (14.79)	5 (3.52)
Diazepam (Valium®)	85 (2.13)	74 (87.06)	0 (0.00)	1 (1.18)
Adinazolam (Deracyn®)	53 (1.33)	5 (9.43)	10 (18.87)	2 (3.77)
Clonazolam (NMB)	47 (1.18)	44 (93.62)	1 (2.13)	0 (0.00)
Meclonazepam (NMB)	37 (0.93)	9 (24.32)	4 (10.81)	27 (72.97)
Oxazepam (Serax® and others)	26 (0.65)	25 (96.15)	1 (3.85)	0 (0.00)
Temazepam (Restoril®)	20 (0.50)	19 (95.00)	0 (0.00)	0 (0.00)
Bromazolam (NMB)	12 (0.30)	1 (8.33)	0 (0.00)	10 (83.33)
Flubromazepam (NMB)	8 (0.20)	0 (0.00)	0 (0.00)	7 (87.50)
Deschloroetizolam (NMB)	7 (0.18)	2 (28.57)	2 (28.57)	1 (14.29)



Nitrazepam (Mogadon®, Nitrazadon®)	7 (0.18)	7 (100.00)	0 (0.00)	0 (0.00)
Bromazepam (Lectopam®)	6 (0.15)	5 (83.33)	0 (0.00)	0 (0.00)
Chlordiazepoxide (Librium®)	4 (0.10)	4 (100.00)	0 (0.00)	0 (0.00)
Flurazepam (Dalmane®, Som- Pam®)	2 (0.05)	2 (100.00)	0 (0.00)	0 (0.00)
Other	3 (0.09)	2 (66.67)	0 (0.00)	0 (0.00)
<b>Total</b>	<b>4,000 (100.00)‡</b>	<b>1,113 (27.83)</b>	<b>216 (5.40)</b>	<b>2,426 (60.65)</b>

**Note.** Counts of times benzodiazepines were detected in combination with other substances are not mutually exclusive because a single sample may contribute to the count for stimulants and opioids. Not shown are counts of times in which two or more benzodiazepines were detected together without any other type of substance (stimulant or opioid).

\* Stimulants include methamphetamine, cocaine, MDMA and others, including analogs of methamphetamine and amphetamine, and piperazines. Caffeine was not included.

† Opioids include heroin, fentanyl, carfentanil, synthetic opioids and “u-drugs.”

‡ There were 3,878 samples containing benzodiazepines in this period. Samples may contain more than one benzodiazepine, bringing the total number of times a benzodiazepine was detected to 4,000.

**Table 2:** Benzodiazepines detected in each province and territory, and how often the benzodiazepines detected in that province or territory occurred alone and with other substances

Province or territory	Times a benzodiazepine was detected, <i>n</i> (% of 4,000 total)*	Times detected alone, <i>n</i> (% of first column)	Times any stimulant, <i>n</i> (% of first column)*	Times detected with any opioid, <i>n</i> (% of first column)†
British Columbia	501 (12.53)	63 (12.57)	18 (3.59)	404 (80.64)
Alberta	407 (10.18)	67 (16.46)	25 (6.41)	307 (75.43)
Saskatchewan	29 (0.73)	8 (27.59)	6 (20.69)	17 (58.62)
Manitoba	70 (1.75)	12 (17.14)	4 (5.71)	39 (55.71)
Ontario	2,109 (52.73)	386 (18.30)	133 (6.31)	1,561 (74.02)
Quebec	789 (19.73)	500 (63.37)	26 (3.30)	90 (11.41)
New Brunswick	57 (1.43)	49 (85.96)	3 (5.26)	2 (3.51)
Nova Scotia	32 (0.80)	25 (78.13)	1 (3.13)	5 (15.63)
Newfoundland and Labrador	3 (0.08)	3 (100.00)	0 (0.00)	0 (0.00)
Prince Edward Island	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Yukon	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Northwest Territories	3 (0.08)	0 (0.00)	0 (0.00)	1 (33.33)
Nunavut	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
<b>Total</b>	<b>4,000 (100.00)‡</b>	<b>1,113 (27.83)</b>	<b>216 (5.40)</b>	<b>2,426 (60.65)</b>

**Note.** Counts of times benzodiazepines were detected in combination with other substances are not mutually exclusive because a single sample may contribute to the count for stimulants and opioids. Not shown are counts of times in which two or more benzodiazepines were detected together without any other type of substance (stimulant or opioid).

\* Stimulants include methamphetamine, cocaine, MDMA and other, including analogs of methamphetamine and amphetamine, and piperazines. Caffeine was not included.

† Opioids include heroin, fentanyl, carfentanil, synthetic opioids and “u-drugs.”

‡ There were 3,878 samples containing benzodiazepines in this period. Samples may contain more than one benzodiazepine, bringing the total number of times a benzodiazepine was detected to 4,000.



## Appendix B

### *Benzodiazepine-Related Drugs Identified in Toronto's Unregulated Opioid Supply, Oct. 10, 2019, to Aug. 31, 2021*

	Drug name	First identified	Found in expected opioid samples checked, <i>n</i> *
1	Etizolam	Oct. 15, 2019	1,067
2	Deschloroetizolam	Nov. 10, 2020	317
3	Flualprazolam	Nov. 12, 2019	172
4	Flubromazolam	Nov. 7, 2019	53
5	Meclonazepam	Jan. 23, 2020	49
6	Bromazolam	April 19, 2021	41
7	Alprazolam (Xanax®)	Dec. 20, 2019	16
8	Diazepam (Valium®)	Jan. 19, 2021	9
9	Flubromazepam	May 13, 2021	8
10	Desalkylflurazepam	March 12, 2021	5
11	Flurazepam (Dalmane®)	April 13, 2021	3
12	Temazepam	March 19, 2021	1
13	Clonazepam	July 13, 2020	1
	<b>Total</b>		<b>1,721</b>

\* 2,071 opioid samples checked were expected to be carfentanil, codeine, “down,” fentanyl, heroin, hydromorphone or methadone.



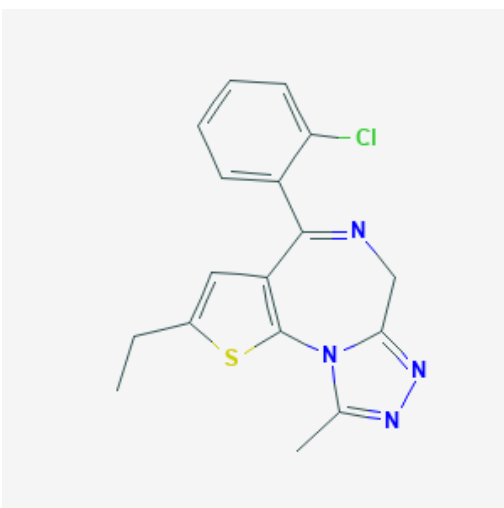
## Appendix C

### Nonmedical Benzodiazepines in the Drug Supply in Canada

The substances listed here are nonmedical benzodiazepines (NMBs) that have been detected in the unregulated drug supply in Canada and have been associated with harm. The list of compounds included is not meant to be exhaustive, and the descriptions are not meant to be comprehensive, but rather highlight relevant sources of information. Where possible, readers are referred to more comprehensive information. A general overview of new benzodiazepines appearing in the unregulated market was published by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in 2021.<sup>4</sup>

All chemical structures included in this appendix come from the National Center for Biotechnology Information, PubChem Compound Database: <https://pubchem.ncbi.nlm.nih.gov/>. All PubChem resources were last accessed in September 2021.

#### Etizolam



Chemical structure of etizolam (PubChem CID 3307; C<sub>17</sub>H<sub>15</sub>ClN<sub>4</sub>S  
<https://pubchem.ncbi.nlm.nih.gov/compound/Etizolam>.)

#### What Is It?

Etizolam is chemically related to benzodiazepines (it is a thienodiazepine) and has effects that are clinically very similar. It was patented in 1974 and was introduced in Japan in 1983 to treat anxiety and sleep disorders. It is marketed as a prescribed medication in Japan, Italy and India, but it is not licensed for use in Canada or the United States.

#### Why Is It Important?

In Canada, etizolam was first detected in seized samples in April 2018 and has become the most frequently appearing NMB in the unregulated drug supply. In the first six months of 2021, it was detected in 62% ( $n = 2,490$ ) of all benzodiazepine-containing samples analyzed by Health Canada's Drug Analysis Service (DAS). It has been detected in opioids and stimulants in British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Nova Scotia, and Newfoundland and Labrador. It frequently appears with powerful opioids such as fentanyl and carfentanil. It was present in 39% of drug toxicity deaths in British Columbia between July 2020 and May 2021 and 25% of opioid-related deaths in Ontario between March and December 2020.

#### For More Information

##### Data, Reports and Resources

- [Collated BC resource: Benzodiazepine/etizolam in illicit opioids](#) – Developed by the B.C. Centre for Disease Control (BCCDC), contains links to resources for people who use drugs, peer responders and health professionals





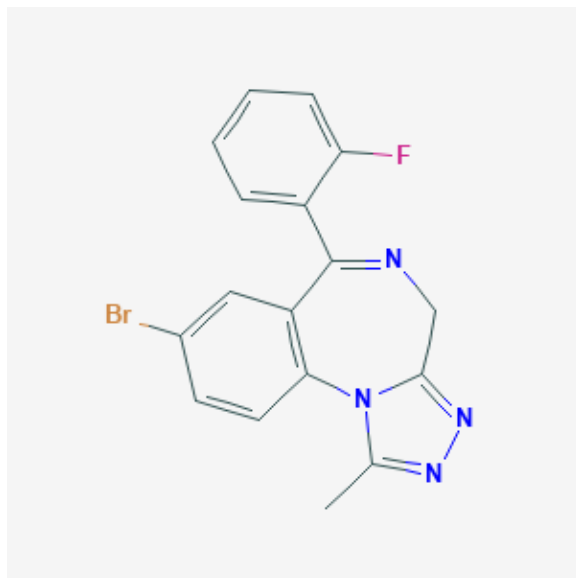
- [Fact Sheet: Etizolam in British Columbia's Illicit Drug Market](#) —Developed by the BCCDC, summarizes the legal status, pharmacology and prevalence in B.C., with clinical and harm reduction guidelines
- [Etizolam: Public Notice](#) — Developed by Alberta Health Services
- [Etizolam](#) — Developed by KFL&A Public Health (Ontario)
- [Benzodiazepines in the unregulated drug supply in Ontario](#) — Developed by the Ontario Harm Reduction Network, contains Ontario coroner data on etizolam up to September 2019
- [Etizolam: Critical Review Report](#) — Developed by the World Health Organization's Expert Committee on Drug Dependence, contains information on chemistry, pharmacology, toxicology and potential for dependence, among other factors

### Advisories and Alerts

- [Drug Advisory: Etizolam detected in overdose case in Regina](#) — Developed by the College of Physicians and Surgeons of Saskatchewan
- Nova Scotia Health — June 11, 2021: [A grey rock-like substance that may appear like MDMA tested positive for cocaine, opioids, etizolam, and an amphetamine analogue](#)
- Nova Scotia Health — July 27, 2021: [A substance seized in the Halifax area \(blotter paper\) was confirmed to be Etizolam](#)
- [Appel à la vigilance – Agrégat de surdoses liées à la consommation de contrefaçons d'alprazolam \(Xanax\) dans un milieu scolaire](#) — Developed by the Centre intégré de santé et de services sociaux de la Montérégie



## Flubromazolam



Chemical structure of flubromazolam (PubChem CID 21930924;  $C_{17}H_{12}BrFN_4$  <https://pubchem.ncbi.nlm.nih.gov/compound/Flubromazolam>)

### What Is It?

Flubromazolam is an extremely potent and long-acting benzodiazepine derivative (specifically, a triazolobenzodiazepine or TBDZ). There is no literature on its synthesis, suggesting it was designed as a more potent version of flubromazepam (see below), one of the first designer benzodiazepines to appear on the unregulated market.

### Why Is It Important?

Flubromazolam is the second most frequently appearing NMB in samples seized by law enforcement officers in Canada. In the first half of 2021, it was detected in 9% ( $n = 346$ ) of all benzodiazepine-containing samples. It has been detected in samples expected to be fentanyl by drug checking services in Toronto as recently as September 2021. Toronto's drug checking service has flagged it as an "unexpected noteworthy drug," which they define as "a substance that is linked to overdose or other adverse effects, highly potent or related to highly potent drugs, and/or not desired by some clients." Given its high potency, it can pose higher risks of adverse reactions than other NMBs. Its detection in counterfeit Xanax tablets has triggered drug alerts in Winnipeg and southern Quebec (see below).

## For More Information

### Data, Reports, and Resources

- [Characterization of the four designer benzodiazepines clonazolam, deschloroetizolam, flubromazolam, and meclonazepam, and identification of their in vitro metabolites](#)
- [Flubromazolam: Critical Review Report](#) — Developed by the World Health Organization's Expert Committee on Drug Dependence, contains information on chemistry, pharmacology, toxicology and potential for dependence, among other factors
- [Flubromazolam](#) — Developed by PsychonautWiki, a community-driven platform, contains experiential data and other information

### Advisories and Alerts

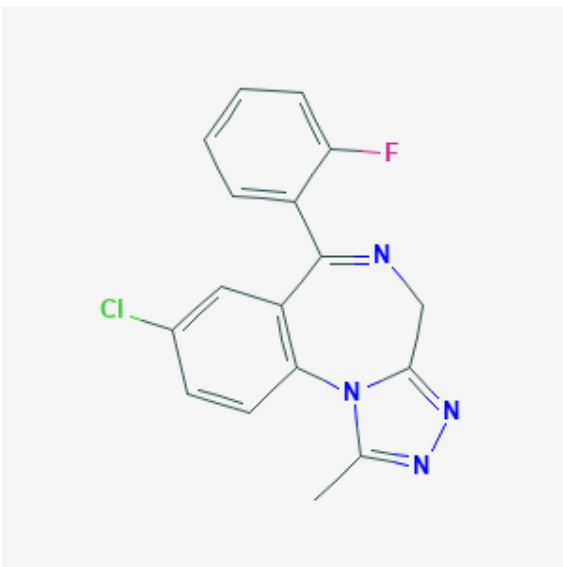
- [Appel à la vigilance — Surdoses sévères en lien avec l'ingestion de flubromazolam vendu comme du Xanax](#) — Developed by the Centre intégré de santé et de services sociaux de la Montérégie



- [Appel à la vigilance: Cas de surdoses sévères liés à l'ingestion de flubromazolam vendu comme du Xanax](#) — Developed by the Centre intégré de santé et de services sociaux de l'Estrie
- [Appel à la vigilance — Agrégat de surdoses liées à la consommation de contrefaçons d'alprazolam \(Xanax\) dans un milieu scolaire](#) —Developed by the Centre intégré de santé et de services sociaux de la Montérégie
- [Drug and Overdose Alerts Winnipeg: June 20, 2019, Fake Xanax TS Tablets \(Xani Bars\) containing carfentanil, fentanyl, and strong benzodiazepines](#)



## Flualprazolam



Chemical structure of flualprazolam (PubChem CID 10359044;  $C_{17}H_{12}ClFN_4$  <https://pubchem.ncbi.nlm.nih.gov/compound/Flualprazolam#section=2D-Structure>)

### What Is It?

Flualprazolam is a benzodiazepine derivative (a TBDZ) that is very similar in structure to alprazolam (Xanax®) but has a longer duration and higher potency. It was first patented in the 1970s, but it was never brought to market.

### Why Is It Important?

Flualprazolam is the third most frequently appearing NMB among samples seized by Canadian law enforcement officers. It was first detected in seized samples in April 2019. In the first half of 2021, it was detected in 8% ( $n = 328$ ) of benzodiazepine-containing samples. In Toronto, it has been detected by drug checking services in samples expected to be fentanyl, cocaine and crack cocaine. Toronto drug checking flagged it as an “unexpected noteworthy drug.” It has also been sold as counterfeit Xanax. Because of its potency, it can increase the risk of adverse reactions. It has been detected in an increasing number of forensic and clinical cases internationally.

## For More Information

### Data, Reports, and Resources

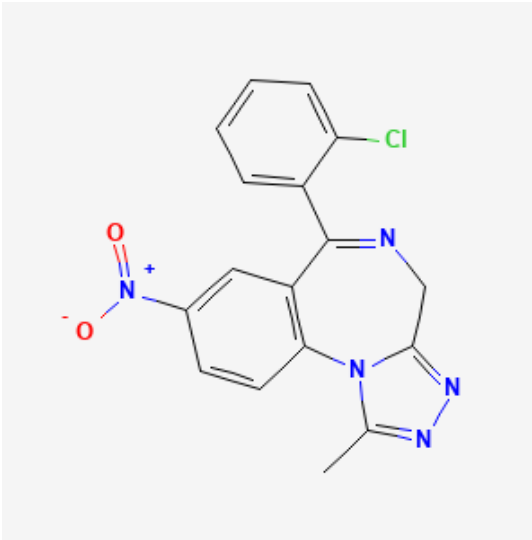
- [Critical Review Report: Flualprazolam](#) – Developed by the World Health Organization’s Expert Committee on Drug Dependence, contains information on chemistry, pharmacology, toxicology and potential for dependence, among other factors
- [A fluorine turns a medicinal benzodiazepine into NPS: the case of flualprazolam](#) – Literature review on chemistry, pharmacology, toxicology, prevalence and legal status

### Advisories and Alerts

- [Benzodiazepines in the unregulated drug supply in Ontario](#) – Developed by the Ontario Harm Reduction Network (OHRN)
- Nova Scotia Health, Jan. 8, 2021 – [A recent sample from Windsor, Nova Scotia, tested positive for Flualprazolam](#)



## Clonazepam



Chemical structure of Clonazepam  
(PubChem CID 12317881; C<sub>17</sub>H<sub>12</sub>ClN<sub>5</sub>O<sub>2</sub>  
<https://pubchem.ncbi.nlm.nih.gov/compound/Clonazepam>)

### What Is It?

Clonazepam was first synthesized in the 1970s, but it was never approved for medical use. It is structurally related to clonazepam (Klonopin®) and alprazolam (Xanax®) but is more potent than alprazolam.

### Why Is It Important?

Even though clonazepam was first detected in samples seized by law enforcement officers in April 2018, it appears in far fewer samples than the previous three NMBs discussed (1% or 47 samples in the first six months of 2021). While there are no reports of clonazepam co-occurring with opioids in samples analyzed by DAS or drug checking, it is a highly potent benzodiazepine and therefore may pose higher risks of adverse reactions than other NMBs (e.g., sedative effects when combined with opioids, or withdrawal symptoms).

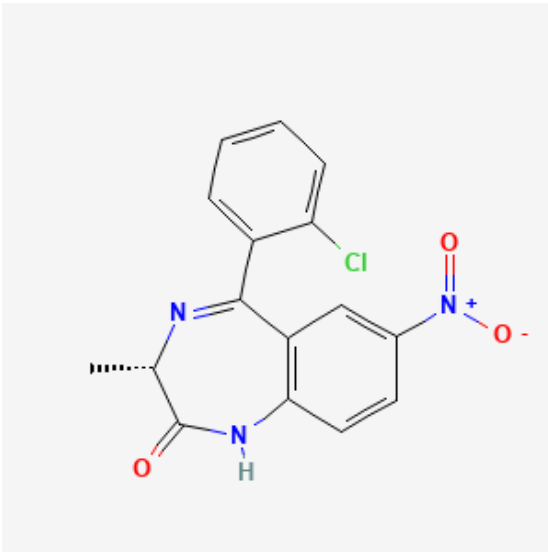
### For More Information

- [Characterization of the four designer benzodiazepines clonazepam, deschloroetizolam, flubromazolam, and meclonazepam, and identification of their in vitro metabolites](#)
- [Critical Review Report: Clonazepam](#) – Developed by the World Health Organization’s Expert Committee on Drug Dependence, contains information on chemistry, pharmacology, toxicology and potential for dependence, among other factors
- [Updated Trend Reporting for the NPS Benzodiazepine Clonazepam Based on Data-Mining for 8-Aminoclonazepam](#)
- [Clonazepam](#) – Developed by PsychonautWiki, a community-driven platform, contains experiential data among other information





## Meclonazepam



Chemical structure of meclonazepam  
(PubChem CID 3033985; C<sub>16</sub>H<sub>12</sub>ClN<sub>3</sub>O<sub>3</sub>  
<https://pubchem.ncbi.nlm.nih.gov/compound/Meclonazepam#section=Structures>)

### What Is It?

Meclonazepam is an analog of clonazepam (Klonopin®). It was patented in 1988 as an anti-parasitic drug but it was never brought to market.

### Why Is It Important?

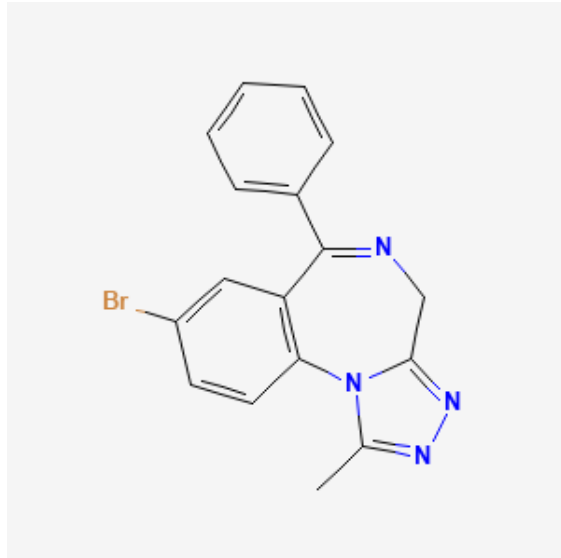
Meclonazepam was detected in 1% or 37 of the benzodiazepine-containing samples seized by law enforcement officers in the first six months of 2021. It was first detected in the unregulated drug supply in February 2021, suggesting this substance has only just emerged as an adulterant and should be monitored carefully. Research for this bulletin found only one case in which it was detected by drug checking programs. Toronto's drug checking service identified it in 49 samples as of Aug. 31, 2021.

### For More Information

- [Characterization of the four designer benzodiazepines clonazolam, deschloroetizolam, flubromazolam, and meclonazepam, and identification of their in vitro metabolites](#)



## Bromazolam



Chemical structure of bromazolam  
(PubChem CID 12562546;  $C_{17}H_{13}BrN_4$   
<https://pubchem.ncbi.nlm.nih.gov/compound/12562546#section=Structures>)

### What Is It?

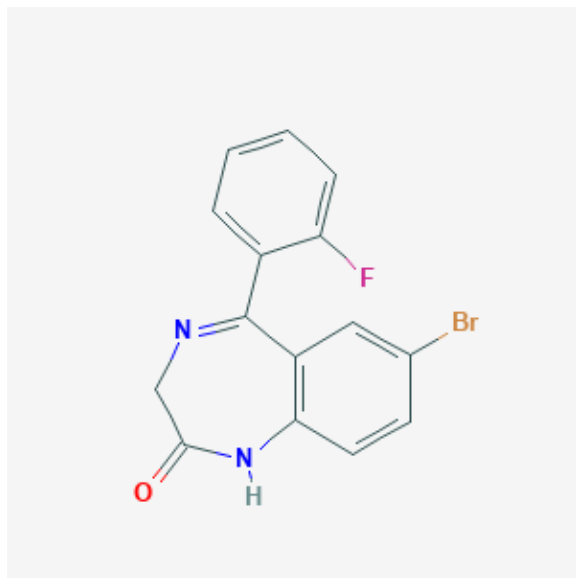
Bromazolam is a TBDZ and an analog of alprazolam (Xanax®). It was first synthesized in the 1970s. It was patented for antihypertensive use in 1982, later as an anxiolytic with reduced sedative effects, and for pain suppression. However, it was never brought to market.

### Why Is It Important?

Bromazolam was detected in only 12 samples (<1% of benzodiazepine-containing samples) seized by law enforcement officers in the first six months of 2021. In all instances but one it co-occurred with an opioid.



## Flubromazepam



Chemical structure of flubromazepam (PubChem CID 12947024;  $C_{15}H_{10}BrFN_2O$  <https://pubchem.ncbi.nlm.nih.gov/compound/Flubromazepam#section=2D-Structure>)

### What Is It?

Flubromazepam was one of the first designer benzodiazepines to appear on the unregulated market. It has a very long duration and is closely related to flubromazolam, which is its triazolo-analog.

### Why Is It Important?

Flubromazepam was first detected in seized samples in Canada in September 2018. In the first half of 2021, it was detected in less than 1% ( $n = 6$ ) of all benzodiazepine-containing samples. Although rarely detected in DAS data, three-quarters of the time that it was detected in 2021, it appeared with fentanyl. It has been flagged by Toronto drug checking as an “unexpected noteworthy drug.” It was also detected in a drug poisoning death in Saskatchewan. Its detection in a fentanyl sample in B.C. triggered a drug alert (see For More Information, below).

### For More Information

#### Data, Reports, and Resources

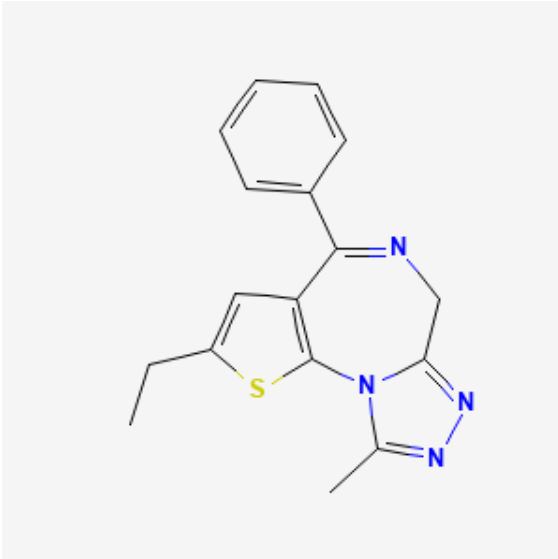
- [Detection and identification of the designer benzodiazepine flubromazepam and preliminary data on its metabolism and pharmacokinetics](#)
- [Flubromazepam](#) – Developed by Wikipedia
- [Characterization of the four designer benzodiazepines clonazolam, deschloroetizolam, flubromazolam, and meclonazepam, and identification of their in vitro metabolites](#)

#### Advisories and Alerts

- [Drug Alert Poster Kamloops June 29 2021.pdf \(interiorhealth.ca\)](#) – Issued by Interior Health



## Deschloroetizolam



Chemical structure of deschloroetizolam  
(PubChem CID 827322; C<sub>17</sub>H<sub>16</sub>N<sub>4</sub>S  
<https://pubchem.ncbi.nlm.nih.gov/compound/Deschloroetizolam>)

### What Is It?

Deschloroetizolam is closely related to etizolam, but less potent and longer lasting. It was patented in 1988 but never developed for medical use.

### Why Is It Important?

Deschloroetizolam was first detected in seized samples in Canada in February 2019. In the first half of 2021 it was detected in only one benzodiazepine-containing sample. However, it has also been detected by Toronto's drug checking service.

### For More Information

- [Characterization of the four designer benzodiazepines clonazepam, deschloroetizolam, flubromazolam, and meclonazepam, and identification of their in vitro metabolites](#)
- [Deschloroetizolam](#) – Developed by PsychonautWiki, a community-driven platform, contains experiential data among other information

Prepared by the CCSA in partnership with the  
Canadian Community Epidemiology Network on Drug Use (CCENDU)

The Canadian Community Epidemiology Network on Drug Use (CCENDU) is a nationwide network of community level partners who share information about local trends and emerging issues in substance use and exchange knowledge and tools to support more effective data collection.

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