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 Commentary

# Yet Another Public Health Threat: A Commentary and Examination of the Extensive Use of Bromazolam

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## ABSTRACT

In this commentary, we examine the current state of the science as it pertains to the public health dangers of Bromazolam and its various illicit distribution networks, not only in North America but across the world. We also examine possible directions the substance use disorder (SUD) field may undertake to address the proliferation and abuse of this substance along with overdose prevention efforts that include the public health dangers of Bromazolam use.

## Keywords

Bromazolam; Fake Xanax; Opioid misuse; Addiction; Overdose.

## INTRODUCTION

In June of 2022, a report written for the National Institute of Justice warned the scientific community about the dangers associated with Bromazolam, an emerging novel benzodiazepine.<sup>1</sup> The title of their report, “*Bromazolam Prevalence Surging Across the United States, Driven in Part by Increasing Detections Alongside Fentanyl*”, provided a significant indicator of the true prevalence of this deadly drug combination. They defined novel benzodiazepines as “*synthetically manufactured drugs with unknown biological effects and health risks*”.<sup>1,2</sup> As such, these novel benzodiazepines, which when consumed are often paired with opioids, create public health and safety concerns because of their potential for devastating user effects including drowsiness, dizziness, blurred vision, muscle relaxation, respiratory depression, and, in some cases, death. Despite these dangers, Bromazolam is not technically a controlled substance on the federal level in the United States. However, it may be considered a Schedule 1 controlled substance on the state level. The fact that Bromazolam is short-acting potentially makes it more addictive, as well as resulting in withdrawal symptoms being more likely than other longer-acting benzodiazepines.

## COMMENTARY

Bromazolam, a non-opioid synthetic drug, was first developed and synthesized during medicinal drug development in the 1970s

but was never approved for therapeutic use in the United States. Bromazolam is the brominated counterpart to the chlorinated drug alprazolam.<sup>1</sup> It is increasingly being found in the illicit drug supply, mixed with other drugs like fentanyl and heroin, among others. Because it is not currently listed as a controlled substance on the federal level, it is easily obtainable online, and prior research suggests it is inexpensive, relatively easy to manufacture, and available on a wider scale than previous years.<sup>2</sup> Its emergence came around the time that similar drugs, Clonazolam, Etizolam, Flualprazolam, Diclazepam, and Flubromazolam, were temporarily placed on Schedule 1 of the Controlled Substance Act in December 2022.<sup>3</sup> It is sold as powder, tablets, and gummies. In their toxicological report, Mérette et al<sup>4</sup> reported that Bromazolam has been found to be used by drug dealers to enhance other street drugs. They further reported that when mixed with opioids, it often proves fatal because it both depresses the respiratory system and counters the effects of antidotes like naloxone.<sup>4</sup> It's in the same drug class as Xanax and Valium and is known by its street names, including “fake Xanax.”<sup>5,6</sup>

Within its Executive Summary Draft in Geneva in 2022, the World Health Organization (WHO) stated the following: “Bromazolam (Chemical Abstracts Service [CAS] registry number: 71368-80-4; CAS name: 8-bromo-1-methyl-6-phenyl-4H-S-triazolo[4,3-a][1,4] benzodiazepine) is a triazolobenzodiazepine that was originally manufactured as a medication but was never approved for use. The first documented detection of illicit Bromazolam by

government authorities was in Sweden in 2016. The WHO further reported that since that time, “the compound has been detected in products or in biological samples in nine countries: Australia, Austria, China, Finland, Germany, India, Sweden, the United Kingdom (Wales), and the USA”. It is also noteworthy that Bromazolam is not under international control. As indicated by the WHO, “it is classified in Schedule IV under Canadian law and is controlled under psychoactive drug regulations in Germany and the United Kingdom.”<sup>7</sup>

Bromazolam was never approved for medical use anywhere in the world. Yet the powerful sedative is being sold and shipped openly in Canada.<sup>5,8</sup> In December 2022, the acting chief medical officer of health in New Brunswick, Canada, issued a public health warning in regard to Bromazolam, stating that “it is especially concerning that people do not know it is contained in their street drugs. There are no warning signs of Bromazolam’s presence, as it cannot be detected by sight, smell, or taste. There are no telltale signs.”<sup>8</sup> In British Columbia, for example, an extensive study conducted by Mérette et al<sup>4</sup> reported that in 2021, Bromazolam was detected in 41 post-mortem cases and quantitatively confirmed by standard addition using liquid chromatography-tandem mass spectrometry. The mean Bromazolam concentration observed was  $11.4 \pm 53.7$  ng/mL (median concentration: 1.6 ng/mL), with a range from 0.5 to 319.3 ng/mL.<sup>4</sup> Significantly, most of the cases they found co-occurred with fentanyl. These low concentrations may be indicative of a presumed enhancement of opioid effects rather than being used as a stand-alone drug, as also found by other researchers.<sup>9</sup> Yet another frightening study finding was that the researchers discovered that Bromazolam was always detected with opioids (fentanyl and carfentanyl), stimulants (methamphetamine), and/or other benzodiazepines (etizolam and flualprazolam), indicating a clear proliferation within the illicit drug market. Although first emerging in the recreational drug supply in 2016 (Europe) and 2019 (the United States), presently, Bromazolam has been linked to adverse events resulting in hospitalization and death and is commonly reported in combination with other drugs, including the opioid fentanyl.<sup>1</sup> In the United States, the detection of Bromazolam with fentanyl has increased dramatically, and 75% of Bromazolam-positive samples also contained fentanyl in 2022.<sup>1</sup> In Canada, fentanyl was detected in 88% of 41 post-mortem Bromazolam-positive samples between July 2020 and December 2021, and in these cases, Bromazolam was the only benzodiazepine detected in 41% (n=17) of the cases.<sup>4</sup>

Previous research demonstrated conclusively that this was indeed the case for another deadly drug, Xylazine.<sup>10</sup> Even more concerning are recent reports identifying the ever-increasing presence of carfentanil (which can be as much as 100 times more potent than fentanyl) in at least 35 urine samples collected from 12 states within the United States in 2023.<sup>11</sup> This increase is an indication that carfentanil use is again on the rise, increasing the possibility that illicit Bromazolam synthetics may also be adulterated with fentanyl analogs. As reported elsewhere, in July 2023, the US White House unveiled an unprecedented national response strategy to address the escalating concern surrounding the combination of fentanyl and Bromazolam.<sup>9</sup> This strategy centers around six fundamental principles for action that the federal government intends to pursue: 1) Testing; 2) Data Collection; 3) Implementation of Evidence-Based

Prevention, Harm Reduction, and Treatment Measures; 4) Supply reduction; 5) Scheduling; and 6) Research.<sup>10</sup> While they will be pursuing these steps, they also acknowledge that it will require a whole-of-society effort to save lives, and their plan includes practical steps states and individuals can take to help address this issue.<sup>10</sup>

The Welsh Emerging Drugs and Identification of Novel Substances (WEDINOS) Annual Report 2022-2023 reported that Bromazolam was the illicit drug most commonly identified in Wales last year.<sup>12</sup> Bromazolam is the substance most likely to be sold under the belief that the buyer was purchasing a different product, usually diazepam, unknowingly putting the user at a greater risk of overdose given Bromazolam’s greater potency.<sup>12</sup>

The European Drug Emergencies Network (Euro-DEN) plus project in Europe reported 2,767 benzodiazepine-related emergency department presentations between 2014 and 2016 (17.3% of all Euro-DEN Plus presentations), with Bromazolam use being the reported highest in France.<sup>13</sup>

## RISK OF BROMAZOLAM USE

Because it is relatively novel, epidemiologic research regarding the full extent of the effects of this drug on individual and public health is scarce and mostly from user reports and case studies; clinical data is minimal. Prolonged use may lead to physical and psychological dependence, while abrupt drug discontinuation may result in unpleasant withdrawal symptoms. Tolerance may develop with subsequent drug use, ultimately requiring continuous dose increments; consequently, drug-seeking behavior is more likely.<sup>14</sup> Bromazolam overdose is rarely lethal when taken alone; however, severe respiratory and central nervous system depression may occur if it is abused with other major central nervous system-depressing drugs, which is being reported with much more frequency.<sup>15</sup> Combining Bromazolam with other drugs (e.g., ethanol, marijuana, stimulants, opioids, and other psychoactive substances) is not only risky; the lack of reliable data about any possible synergistic and antagonistic effects further complicates these drug combinations and their potential interactions.<sup>14</sup> Despite all these severe consequences and dire outcomes, sadly, bromazolam is easily obtainable online, openly shipped, and used by dealers to enhance other street drugs. As mentioned above, these combinations often prove fatal when mixed with opioids, as has become the norm in recent years. This is especially true given Bromazolam’s physical effects, including respiratory system depression, and its ability to counter the effects of antidotes like naloxone.<sup>5</sup>

In February 2023, three young adults were found unresponsive and later died at a hospital in the suburbs of Chicago, Illinois, USA, after they had ingested counterfeit pills containing Bromazolam that they believed to be alprazolam. No other illicit drugs were found to be in the counterfeit pills. This incident, along with the increasing fatalities involving Bromazolam, prompted the centers for disease control and prevention (CDC) to issue a public health warning about Bromazolam.<sup>16</sup>

## FIRST-PERSON ACCOUNT OF BROMAZOLAM USE

To gain greater insight into Bromazolam use on the streets of a large city in the Midwestern US, we interviewed a Bromazolam user.

### Method

We spoke to the individual at a local community corrections ankle monitoring facility (electronic tagging) who volunteered to participate in an interview. The facility administrator granted us access during a weekly check-in. We made the individual aware that we were not conducting an actual scientific study but an informal discussion about new drugs hitting the streets. We collected the interview information anonymously and voluntarily; no names were used, and we adhered to the highest standards of respecting the anonymity and confidentiality of the individual. We paid the individual \$10 for their time and informed them that they did not have to answer any questions they did not want to or felt uncomfortable answering. Further, they were informed that they would still be compensated despite not answering any questions that caused them discomfort.

### Interview

We began by asking what the main areas are where they are seeing Bromazolam being sold and how they know it isn't simply Xanax. The response was: *"It is all over, especially near any of the old 'stomping grounds' (indicating areas where illicit drug use is often witnessed). And a lot of dudes don't want to be caught up in any illegal madness, especially if they are 'on paper' (probation or parole). I mean, what's the sense of getting popped (arrested) for something stupid like fake Xanax? You might as well have the real deal or some 'tranq dope' (Xanax or opioids mixed with Xylazine)".*<sup>9</sup>

We then asked how they knew it wasn't just simply Xanax, and they were calling it fake Xanax or "Brom." The response was: *"See, the thing is that when you get regular Xanax, like from somebody who has a 'scrip' (legal prescription), you know what to expect and you will get what you expect (indicating the usual high experienced when 'regular Xanax' is consumed). Now these dudes out here are mixing all kinds of shit into Brom, so you can almost bet for sure that if you are taking a bit of street Brom, there is probably some fentanyl or even some regular dope in it".*

## PUBLIC HEALTH PREVENTION IMPLICATIONS

Governmental and public health entities' prevention efforts tailored to individuals at high-risk might prove successful. Still, they should also include outreach to individuals who do not have access to harm reduction services. These efforts should also include substance abuse and mental health professionals so they can better identify the populations at the highest-risk. This may be the most successful effort to prevent or reduce overdose deaths.

Since education plays a critical role in preventing substance abuse, the Drug Enforcement Agency (DEA) in the United States offers a free resource guide, Drugs of Abuse, which contains information on the most abused and misused drugs.<sup>17</sup> The comprehensive guide provides information about the harms and

consequences of drug use, overdose potential, and other essential facts, as well as a list of additional drug education and prevention resources. Utilizing guides of this sort, in combination with adequate screening and assessment efforts, may help address the onslaught of illicit substance use and abuse of legal substances.

In Canada, in the province of New Brunswick, the Office of Public Health is currently contacting frontline organizations that work with people using street drugs about how they can lower their risk of overdose and death and recommends that people who are using street drugs:

1. Be aware that Bromazolam is in the province and could be in street drugs without their knowledge, and to avoid benzo-dope.
2. Do not use drugs alone. Leave your door unlocked and tell someone to check on you.
3. Take advantage of an overdose prevention site if one is available in your community.
4. Do test to check drug strength. Begin with a small amount, use less, and pace yourself.
5. Have naloxone on hand; it will not help with Bromazolam but could help with opioids such as fentanyl.
6. Talk with a health-care provider about reducing risk.<sup>8</sup>

In the province of Ontario, the Peterborough Public Health issued a toxic drug alert in March 2023 in response to Bromazolam pills being sold as 'Xanax' and reminded people that they should not assume drugs purchased over the internet are safe.<sup>18</sup>

It would also be beneficial to screen for opioid use or abuse *via* a method other than, or in addition to, toxicology, specifically to identify overdose risk potential when other drugs might be used in conjunction with opioids. A frequently used instrument for this purpose is the Substance Abuse Subtle Screening Inventory (SASSI-4), which provides a screening outcome score for prescription drug use (Rx Scale) that indicates likely abuse and produces an overall screening outcome for high or low probability of any type of substance use disorder (SUD).<sup>19</sup> The Rx scale was validated against the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnoses of opioid and sedative SUD and has an accuracy rate of 94%.<sup>20</sup> The questions on the Rx scale specifically address the non-medical use of prescription medication. Thus, this score could be used as a predictor of potential opioid overdose, as well as for such use when in combination with fentanyl analogs, in addition to novel benzodiazepines such as Bromazolam.

Because people seeking out "fake Xanax" may not be aware of the presence of illicit drugs, the distribution of fentanyl test strips (home tests that can identify the presence of fentanyl in other drugs) as a harm reduction technique throughout communities may reduce the number of accidental overdoses from laced Bromazolam. However, a lesson we can learn from individuals on the street, like the one whom we spoke with, who seek out "fake Xanax," is that many individuals like the "X factor" of not knowing

what may be mixed with the Bromazolam. They are aware that they are probably getting some fentanyl or even some regular “dope” in the Bromazolam, and that prospect is exciting; therefore, they have no desire to test it. If the supply did test positive, it would be viewed as a perk and not a pitfall and would not hinder usage. This is a monumental public health challenge. There is no denying that Bromazolam is a public health crisis for many countries. Still, every crisis provides an opportunity to do things differently than what may have been done in the past with other crises’, and we should reflect and learn from those with “an entire world view.” The voice of the actual user should be listened to and learned from in the development of treatment and intervention to be effective. Substance abuse causes devastation in so many lives, and we must never lose sight of the impact education and intervention can have on future use and distribution patterns.

Providing early intervention and access to prevention resources and educational messaging in all communities and populations on the various Bromazolam risks and the general dangers associated with the use of counterfeit pills will prove key to successfully reducing accidental overdoses. Although the challenges to public health in this regard are monumental, the proper tools and information chains will inevitably assist the field in meeting these numerous challenges effectively.

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