

## Second Nationwide Tuberculosis Outbreak Caused by Bone Allografts Containing Live Cells — United States, 2023

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### Abstract

During July 7–11, 2023, CDC received reports of two patients in different states with a tuberculosis (TB) diagnosis following spinal surgical procedures that used bone allografts containing live cells from the same deceased donor. An outbreak associated with a similar product manufactured by the same tissue establishment (i.e., manufacturer) occurred in 2021. Because of concern that these cases represented a second outbreak, CDC and the Food and Drug Administration worked with the tissue establishment to determine that this product was obtained from a donor different from the one implicated in the 2021 outbreak and learned that the bone allograft product was distributed to 13 health care facilities in seven states. Notifications to all seven states occurred on July 12. As of December 20, 2023, five of 36 surgical bone allograft recipients received laboratory-confirmed TB disease diagnoses; two patients died of TB. Whole-genome sequencing demonstrated close genetic relatedness between positive *Mycobacterium tuberculosis* cultures from surgical recipients and unused product. Although the bone product had tested negative by nucleic acid amplification testing before distribution, *M. tuberculosis* culture of unused product was not performed until after the outbreak was recognized. The public health response prevented up to 53 additional surgical procedures using allografts from that donor; additional measures to protect patients from tissue-transmitted *M. tuberculosis* are urgently needed.

### Introduction

On July 7, 2023, a state health department notified CDC that an otherwise healthy adult experienced symptoms of meningitis 5 weeks after spinal fusion surgery that incorporated a bone allograft product containing live cells; *Mycobacterium tuberculosis* was identified in the cerebrospinal fluid. On July 11, a different state health department notified CDC of a patient with a persistent surgical site infection after a laminectomy that appeared to have used a similar product; drainage from the surgical site tested positive for acid-fast bacilli, and a nucleic acid amplification test confirmed the presence of *M. tuberculosis*. When reporting these cases to their respective public health authorities, the clinicians caring for these two patients independently noted similarities to the 2021 outbreak (1–4) and asked that CDC investigate.

#### INSIDE

- 1390 Notes from the Field: Supply Interruptions of First- and Second-Line Oral Drugs to Treat Tuberculosis During the Previous 12 Months — California, January–March, 2023
- 1392 Notes from the Field: Seizures, Hyperthermia, and Myocardial Injury in Three Young Adults Who Consumed Bromazepam Disguised as Alprazolam — Chicago, Illinois, February 2023
- 1394 QuickStats

Continuing Education examination available at [https://www.cdc.gov/mmwr/mmwr\\_continuingEducation.html](https://www.cdc.gov/mmwr/mmwr_continuingEducation.html)



## Investigation and Results

### Initial Identification

After receiving the first case report, CDC notified the Food and Drug Administration (FDA) and requested that the tissue establishment\* quarantine (i.e., store and prohibit use of) any remaining tissue from this donor (i.e., same product lot). On July 11, the tissue establishment quarantined the 53 units that had not yet been distributed and provided a list of all health care facilities that had purchased tissue units from that lot. Eight hospitals and five dental offices in seven states (California, Louisiana, Michigan, New York, Oregon, Texas, and Virginia) received a total of 50 bone allograft units from this product lot during February 27–June 20, 2023.

### Public Health Response

On July 12 (within hours of confirming that the two patients in both states had received units from the same product lot), CDC notified the seven affected state health departments, sharing with each a list of health care facilities in their states that had received units of the bone allograft. As during the previous outbreak, CDC recommended that any unused units be quarantined, recipients be evaluated and started on multidrug

treatment for TB disease regardless of signs and symptoms (1–4), and health care facilities implement TB-specific infection prevention and control measures during follow-up encounters with these patients (5). These outbreak response activities were reviewed by CDC, deemed not research, and conducted consistent with federal law and CDC policy.†

The deceased donor was a U.S.-born person whose donor risk assessment interview with next of kin documented no TB risk factors. A radiograph of the donor's chest before death demonstrated pulmonary infiltrates and a right upper lobe nodule; pneumonia and sepsis were documented as the causes of death.

By July 14 (1 week after receipt of the first case report by CDC), health departments had worked with affected hospitals and dental facilities to confirm that 36 patients had undergone procedures using at least one unit from the product lot under investigation. Unused units were sent to the National Veterinary Services Laboratories§ for nucleic acid amplification and culture-based testing for *M. tuberculosis*.

As of December 20, 2023, five of the 36 recipients had received a diagnosis of laboratory-confirmed TB disease, including four that were culture-confirmed. The two patients initially reported to CDC in July 2023 both subsequently died with TB as the cause of death. At least 10 other recipients had clinical signs or

\* A tissue establishment is defined as an entity that manufactures human cells, tissues, and cellular and tissue-based products and is regulated under 21 C.F.R. part 1271, 42 U.S.C. Sect. 216, 243, 263(a), 264, 265(c), 271. <https://www.fda.gov/vaccines-blood-biologics/biologics-establishment-registration/tissue-establishment-registration>

† 5 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

§ [https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/lab-info-services/sa\\_about\\_nvsl/ct\\_about\\_nvsl](https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/lab-info-services/sa_about_nvsl/ct_about_nvsl)

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symptoms compatible with TB disease. Among the 34 recipients with test results for *M. tuberculosis* infection reported, 27 (79%) had positive interferon-gamma release assay results. Whole-genome sequencing from culture-confirmed cases among recipients in four different states, along with positive *M. tuberculosis* cultures from the unused product, demonstrated an extremely close relationship with 0–1 single nucleotide polymorphism difference between *M. tuberculosis* genomes, confirming the bone allograft as the transmission source.

## Discussion

### Significance and Interpretation of Findings

This second nationwide TB outbreak in 2023 was detected when clinicians in two states recognized similarities to the 2021 outbreak and reported their concerns to their respective health departments, thereby initiating a rapid public health response that prevented as many as 53 additional surgical procedures with the implicated bone allograft material. Before the 2021 TB outbreak, which involved 113 recipients in 18 states, bone allograft-related *M. tuberculosis* transmission had last been reported in the United Kingdom in 1953 (1–6).

After the 2021 outbreak, tissue establishments considered whether to perform nucleic acid amplification testing for *M. tuberculosis* in tissues that retain live cells before distribution (7). The tissue establishment involved in both investigations voluntarily implemented such testing for bone allografts but did not detect the *M. tuberculosis* contamination of this second product lot.¶ Although extremely useful for diagnosing TB disease, nucleic acid amplification tests are less sensitive than are the slower culture-based tests for identifying *M. tuberculosis* (2). Therefore, more comprehensive laboratory evaluations for *M. tuberculosis* in donor tissues could include culture-based testing, which can take up to 8 weeks (56 days) for final confirmation. In this outbreak, *M. tuberculosis* was not identified from liquid cultures of the donor specimen until day 40 after inoculation.

Because false-negative culture results can occur, laboratory testing alone will not eliminate the risk of transmitting *M. tuberculosis* or other infectious agents through tissue products. Careful review of donor information with exclusion of those who do not meet current requirements (i.e., the donor is ineligible) is also critical. Both donors in the 2021 and 2023 outbreaks had evidence of sepsis during terminal hospitalization, but no TB testing was documented. Persons with evidence of sepsis should be determined to be ineligible for tissue donation (8). The second donor also had pneumonia and radiographic findings consistent with, but not specific for, TB disease.

¶ <https://investors.aziyo.com/news-releases/news-release-details/aziyo-biologics-announces-voluntary-recall-viable-bone-matrix>

Low *M. tuberculosis* concentrations in the bone allograft material might explain the negative nucleic acid amplification test results before distribution and why the positive culture from quarantined product did not occur within the 14–21-day period during which *M. tuberculosis* is typically isolated from culture (9). Low-level contamination could also help explain the apparently lower rate of symptomatic TB disease among recipients in this 2023 outbreak compared with the 2021 outbreak (2–5). In addition, prompt treatment might have interrupted the disease process and prevented morbidity. Identification of this outbreak likely facilitated initiation of multidrug treatment for some recipients before they might have otherwise become symptomatic. Nevertheless, five persons developed laboratory-confirmed TB disease, including two persons who died of TB after surgical implantation of this contaminated product.

### Implications for Public Health Practice

The tissue transplant industry is growing, with approximately 58,000 donors providing tissue allografts for 2.5 million transplants in the United States each year.\*\* Additional interventions are necessary to address gaps in transplant tissue safety in the United States. Informed consent, including discussion of infectious disease risks and alternative treatment options, is needed before patients receive tissue allografts, particularly those containing live cells, which carry a higher risk for disease transmission (2,10). Health care facilities should also implement tissue-tracking protocols similar to those required for solid organs and blood products (10). Routine postimplant monitoring should be conducted on all tissue allograft recipients, because prompt and systematic reporting of adverse events enables rapid implementation of mitigation measures among other recipients (10).

This outbreak serves as another reminder that TB has not been eliminated from the United States, where up to 13 million persons of all ages are living with untreated and often undiagnosed latent TB infection (LTBI).†† Diagnosing LTBI and TB disease is challenging because diagnostic tests have imperfect sensitivity. In addition, LTBI is asymptomatic, and nonspecific TB disease signs and symptoms overlap with many other disease processes. Because tissue allografts containing live cells are stored frozen and have expiration dates months or even years after manufacture, ample time exists for both culture-based testing and additional scrutiny of donor medical records. To reduce the risk for *M. tuberculosis* transmission through tissue allografts, culture-based testing of donor tissues before product distribution should be strongly considered, and current recommendations stipulating rejection of donors with sepsis§§ should be followed.

\*\* <https://donatelifelife.net/donation/organs/tissue-donation/>

†† <https://www.cdc.gov/tb/statistics/ltbi.htm>

§§ <https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/tissue-guidances>

**Summary****What is already known about this topic?**

Tuberculosis (TB) outbreaks associated with tissue transplantation are rare; one outbreak involving 113 patients occurred after surgical implantation of contaminated bone allografts in 2021.

**What is added by this report?**

Noting similarities to the 2021 outbreak, clinicians diagnosed and promptly reported two TB cases among bone allograft recipients. These case reports initiated an investigation that confirmed a bone allograft–related outbreak affecting 36 recipients. Removal of the product from further distribution prevented implantation of the implicated allografts in up to 53 additional persons.

**What are the implications for public health practice?**

This second outbreak of bone allograft–related TB in recent years underscores the urgent need to implement improved donor screening and culture-based testing to prevent tissue-derived *Mycobacterium tuberculosis* transmission.

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## Notes from the Field

### Supply Interruptions of First- and Second-Line Oral Drugs to Treat Tuberculosis During the Previous 12 Months — California, January–March, 2023

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Tuberculosis (TB) drug supply disruptions are a recurring concern in the United States (1). Contributors to these disruptions include loss of manufacturers to the U.S. market, inefficient supply chains, and lack of active ingredients available for import.\* The last severe U.S. TB drug shortage occurred in 2012, when isoniazid (INH) was temporarily unavailable for several months (2). INH and rifampin (RIF) are the cornerstones for treatment of drug-susceptible TB, and rifapentine (RPT), a long acting rifamycin, has been incorporated into shorter first-line regimens<sup>†</sup> to treat both latent TB infection (LTBI) (3) and TB disease<sup>§</sup> (4). In recent years, the U.S. supply of several TB drugs has again been disrupted. The Food and Drug Administration has declared shortages of RPT (on March 25, 2020), RIF (on December 22, 2021), and INH (on May 17, 2023).<sup>¶</sup> Approximately one fifth of all U.S. TB cases are reported from California (5). TB drug procurement is decentralized among the state's 61 local TB programs,\*\* mirroring the decentralization among U.S. states and territories. The California Department of Public Health and the California TB Controllers Association assessed the impact of the shortage on California's TB programs.

#### Investigation and Outcomes

A web-based Research Electronic Data Capture (REDCap) survey (version 13.1.30; Vanderbilt University) was distributed to TB controllers and program managers of all 61 California TB programs<sup>††</sup> to assess delays in

availability<sup>§§</sup> and unavailability of oral first- and second-line TB drugs during the preceding 12 months. On a priority scale of 1 (lowest) to 10 (highest), programs ranked the importance of addressing TB drug instability relative to other TB control priorities. Respondents were encouraged to confer with program, clinic, and pharmacy colleagues to obtain a single, comprehensive response for the TB program in each local health jurisdiction. Programs were categorized according to their average annual number of TB cases during 2016–2021 as high (15 or more cases) or low (fewer than 15 cases). This activity was reviewed by CDC and the California Department of Public Health, deemed not research, and conducted consistent with CDC policy.<sup>¶¶</sup>

Overall, 54 (89%) programs responded, including all categorized as high case-count programs. The mean priority level assigned to ensuring a stable supply of TB drugs was 8.6 (95% CI = 8.1–9.2) among all programs and 9.4 (95% CI = 8.8–9.9) among high case-count programs. Among the 50 programs in California reporting at least one TB case during 2016–2021, 32 (64%) experienced a delay in availability or unavailability of any oral first-line TB drug (Table). First-line oral TB drug supply interruptions led to delayed initiations or temporary pauses in treatment of TB disease or LTBI (37% for all programs and 55% for high case-count programs) and permanent changes in the choice of drugs to treat TB disease or LTBI and the duration of treatment (33% for all programs and 65% for high case-count programs). TB drug supply interruptions led to a negative patient outcome for 6% of all TB programs: two TB programs reported at least one case of prolonged treatment and a third program reported at least one adverse drug event.

#### Conclusions and Actions

Ensuring drug availability is a high priority for TB programs. This survey in California identified a high frequency of TB drug interruptions in 2022, which led to delayed treatment initiations and permanent regimen changes and restricted implementation of short-course regimens for both LTBI and TB disease. Programs also reported preventable negative patient outcomes

\* <https://www.hsgac.senate.gov/wp-content/uploads/2023-06-06-HSGAC-Majority-Draft-Drug-Shortages-Report.-FINAL-CORRECTED.pdf>

<sup>†</sup> Oral first-line TB drugs include RIF, RPT, INH, rifabutin, pyrazinamide, and ethambutol. Oral second-line TB drugs included cycloserine, ethionamide, levofloxacin, linezolid, moxifloxacin, para-aminosalicylate, and pretomanid. Bedaquiline and clofazimine were not included in this survey because they have unique procurement processes.

<sup>§</sup> These short course regimens include a 3-month regimen of weekly INH and RPT for LTBI treatment (3HP) and a 4-month regimen of INH, RPT, moxifloxacin, and pyrazinamide for drug-sensitive TB disease (4HPMZ).

<sup>¶</sup> <https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm> (Accessed August 30, 2023).

<sup>\*\*</sup> The 61 local TB programs in California have diverse infrastructures and TB incidences (average annual TB case counts during 2016–2021 ranged from zero to 508 cases).

<sup>††</sup> The survey was available for completion from January 29 to March 17, 2023.

<sup>§§</sup> TB drug delays were defined as short-lived interruptions in acquiring a drug, lasting a few weeks or less, and not broadly affecting programmatic or clinical practice. TB drug unavailability was defined as an interruption in the supply of a drug lasting more than a few weeks and potentially requiring a change in programmatic or clinical practice.

<sup>¶¶</sup> 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

**TABLE. Frequency and effects of the unavailability of oral first- and second-line tuberculosis drugs during the previous 12 months — California, January–March 2023**

Effects on program	no./No. (%)	
	High case-count programs*	All programs
<b>Delay<sup>†</sup></b>		
Rifampin	15/20 (75.0)	25/50 (50.0)
Rifapentine	16/20 (80.0)	25/50 (50.0)
Rifabutin	1/20 (5.0)	5/50 (10.0)
Isoniazid	5/20 (25.0)	8/50 (16.0)
Pyrazinamide	5/20 (25.0)	8/50 (16.0)
Ethambutol	3/20 (15.0)	3/50 (5.0)
Any second-line TB drug <sup>§</sup>	5/20 (25.0)	8/50 (16.0)
<b>Unavailability<sup>†</sup></b>		
Rifampin	6/20 (30.0)	11/50 (22.0)
Rifapentine	14/20 (70.0)	20/50 (40.0)
Rifabutin	0/20 (—)	2/50 (4.0)
Isoniazid	4/20 (20.0)	4/50 (8.0)
Pyrazinamide	0/20 (—)	2/50 (4.0)
Ethambutol	3/20 (14.0)	2/50 (4.0)
Any second-line TB drug <sup>§</sup>	1/20 (5.0)	2/50 (4.0)
<b>Delayed initiation or paused treatment</b>	11/20 (55.0)	20/54 (37.0)
TB disease only	2/11 (18.2)	5/20 (25.0)
LTBI only	8/11 (72.7)	11/20 (55.0)
Both TB disease and LTBI	1/11 (9.1)	4/20 (20.0)
<b>Permanently changed regimen</b>	13/20 (65.0)	18/54 (33.3)
TB disease only	2/13 (15.4)	2/18 (11.1)
LTBI only	11/13 (84.6)	15/18 (83.3)
Both TB disease and LTBI	0/13 (—)	1/18 (5.6)
<b>Recorded a negative patient outcome<sup>¶</sup></b>	2/20 (10.0)	3/54 (5.6)
<b>Not using 3HP due to rifapentine unavailability**</b>	11/12 (91.7)	13/24 (54.2)
<b>Not using 4HPMZ due to rifapentine unavailability**</b>	5/13 (38.5)	5/31 (16.1)

**Abbreviations:** LTBI = latent tuberculosis infection; TB = tuberculosis; 3HP = 3-month regimen of weekly isoniazid and rifapentine for LTBI treatment; 4HPMZ = 4-month regimen of isoniazid, rifapentine, moxifloxacin, and pyrazinamide for drug-sensitive TB disease.

\* High case-count programs are those reporting 15 or more TB cases during 2016–2021.

<sup>†</sup> Denominator includes only those programs reporting one or more TB case during 2016–2021.

<sup>§</sup> Oral second-line TB drugs included cycloserine, ethionamide, levofloxacin, linezolid, moxifloxacin, para-aminosalicylate, and pretomanid. Bedaquiline and clofazimine were not included in this survey because they have unique procurement processes.

<sup>¶</sup> One program recorded a negative patient outcome for LTBI only, and two reported negative patient outcomes for both TB disease and LTBI (two programs reported at least one case with prolonged treatment and one program reported at least one adverse drug event).

\*\* Denominator restricted to programs not using the stated regimen.

caused by drug delays or unavailability. Limitations of this analysis included a retrospective study design, possibility of recall bias, and variability in respondents' interpretation of the definitions of access delays and unavailability of TB drugs. To meet the standards of practice for TB disease and LTBI, and to continue progress toward TB elimination, California has established a centralized buffer supply of several TB drugs. Securing a more stable TB drug supply might avert some of the unfavorable clinical and programmatic effects of TB treatment interruptions.

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## Notes from the Field

### Seizures, Hyperthermia, and Myocardial Injury in Three Young Adults Who Consumed Bromazolam Disguised as Alprazolam — Chicago, Illinois, February 2023

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Bromazolam is a “designer” triazolobenzodiazepine synthesized in 1976 but never approved for therapeutic use (1). Since its first detection in Sweden in 2016, a significant increase has persisted in both the toxicologic identification of bromazolam in combination with fentanyl and its identification in counterfeit benzodiazepine preparations (2). The number of law enforcement seizures in the United States that involved bromazolam increased from no more than three per year during 2016–2018 to 2,142 in 2022, and 2,913 in 2023.\* In Illinois, bromazolam-involved† deaths increased from 10 in 2021 to 51 in 2022.§ Although human studies with clinical data are limited, animal models suggest bromazolam acts predominantly as a sedative, similar to other benzodiazepines, and to date, no signal for hyperthermia, myocardial injury, or seizures attributable to bromazolam intoxication exists (3). Although mostly detected alongside fentanyl or other opioids (88%–100% of tested samples),¶ consumption of bromazolam can be life-threatening even in the absence of other drugs. This report discusses a cluster of three young adult patients who were treated at local emergency departments for hyperthermia, seizures, and myocardial injury after consuming bromazolam disguised as alprazolam. This activity was reviewed by CDC, deemed not research, and was conducted consistent with applicable federal law and CDC policy.\*\*

\* The National Forensic Laboratory Information System (NFLIS) is an important resource in monitoring illicit drug trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS-Drug is a comprehensive information system that includes data from forensic laboratories that handle approximately 98% of an estimated 1.5 million distinct annual federal, state, and local drug analysis cases. NFLIS-Drug includes drug chemistry results from completed analyses only. Query date was December 14, 2023; data for 2023 are still being reported. <https://www.nflis.deadiversion.usdoj.gov/>

† A case was categorized as bromazolam-involved if bromazolam was listed as a contributing cause of death on the death certificate in the Illinois Vital Records system.

§ <https://dph.illinois.gov/data-statistics/vital-statistics.html>

¶ Per surveillance from the Center for Forensic Science and Education, and the DEA TOX 2022 Annual Report. [https://www.cfsre.org/images/content/reports/public\\_alerts/Public-Alert\\_Bromazolam\\_NPS-Discovery\\_061522.pdf](https://www.cfsre.org/images/content/reports/public_alerts/Public-Alert_Bromazolam_NPS-Discovery_061522.pdf)

\*\* 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

### Case Series

On February 1, 2023, in a southern suburb of Chicago, three previously healthy young adults, two men aged 25 years (patients A and B) and a woman aged 20 years (patient C), ingested pressed tablets of bromazolam that they reported they believed to be alprazolam, a drug prescribed for anxiety and panic disorders, but which is misused recreationally because its effects include disinhibition and euphoria. They were found unresponsive by patient A's mother approximately 8 hours later. All three received naloxone from emergency medical services without response and were unresponsive on arrival at local emergency departments.†† Patient A was hypertensive (blood pressure measurement = 152/100 mm Hg), tachycardic (heart rate 124/minute), and hyperthermic (temperature = 101.7°F [38.7°C]); pupils were dilated but reactive, and he experienced multiple generalized seizures. He was intubated to maintain airway control. Patient B was hyperthermic (temperature = 100.4°F [38.0°C]) and was intubated because of unresponsiveness and multiple generalized seizures. Patient C was obtunded with focal seizures and was intubated. All three had myocardial injury as demonstrated by elevated troponin levels. Urine drug screen for all three patients was positive for benzodiazepines. None of the patients received flumazenil, a benzodiazepine overdose antidote that can precipitate benzodiazepine withdrawal and cause seizures or tachyarrhythmias (4). All were admitted to an intensive care unit, and the Illinois Poison Center was contacted for assistance in evaluation and management (Table).

Patient A required intubation until hospital day 5 because of depressed mental status. After extubation, he had moderate aphasia and dysphagia, and was discharged on hospital day 11 with persistent neurologic deficits. Patient B was extubated on hospital day 1 and discharged on day 4 with mild hearing difficulty, but otherwise neurologically intact. Patient C progressed to status epilepticus despite administration of multiple antiepileptic medications (lorazepam, propofol, levetiracetam, and valproic acid), and persistent coma. She was transferred to a second hospital on day 11 and was subsequently lost to follow-up. Testing of serum (the preferred body fluid) or plasma samples from all three patients by the Drug Enforcement Administration's Toxicology Testing Program (DEA TOX)§§ confirmed the presence of bromazolam (range = 31.1–207 ng/mL), without the presence of fentanyl or any other opioid.

†† Patients A and B were transported to the same facility; patient C was transported to a separate facility.

§§ The Drug Enforcement Agency has contracted with the University of California San Francisco to analyze biologic samples from patients who overdose on suspected novel psychoactive substances as part of the DEA TOX program. [https://www.deadiversion.usdoj.gov/dea\\_tox/annual\\_reports/2022\\_Annual\\_Report.pdf](https://www.deadiversion.usdoj.gov/dea_tox/annual_reports/2022_Annual_Report.pdf)



**TABLE. Characteristics, circumstances, and co-occurring substances among bromazolam overdose patients — Chicago, Illinois, February 2023**

Characteristic	Patient A	Patient B	Patient C
Age, yrs; sex	25; Male	25; Male	20; Female
Blood pressure, mm Hg	152/100	Unknown	132/109
Bromazolam level, ng/mL (plasma or serum) by LCMS	207 (plasma)	70.5 (plasma)	31.1 (serum)
Heart rate per min	124	Unknown	118
In-hospital neurologic recovery (HD)	Yes (HD 5)	Yes (HD 1)	No
Myocardial injury (peak troponin, ng/L)	Yes (154)	Yes (239)	Yes (430)
Neurologic deficits at discharge	Moderate aphasia	Hearing loss	Unknown
Other LCMS findings using plasma (level, ng/mL)	8-aminoclonazepam (0.2)*	Aripiprazole (NQ), methamphetamine (0.5), <sup>†</sup> midazolam (NQ)	None
Rhabdomyolysis (finding)	Yes (CK 4067/Cr 1.41)	No	No
Seizures	Multiple	Multiple	Refractory status epilepticus
Temperature	101.7°F (38.7°C)	100.4°F (38.0°C)	98.8°F (37.1°C)
Urine drug screen result	BZD	AMP, BZD, THC	BZD

**Abbreviations:** AMP = amphetamine; BZD = benzodiazepine; CK = creatinine kinase; Cr = creatinine; HD = hospital day; LCMS = liquid chromatography–mass spectrometry; NQ = not quantified; THC = delta-9 tetrahydrocannabinol.

\* 8-aminoclonazepam is the primary metabolite of the designer BZD clonazepam, which is the 1,4-triazolo derivative of clonazepam. 0.2 ng/mL is under the lower limit of quantification (0.4 ng/mL) but above the lower limit of detection (0.1 ng/mL).

<sup>†</sup> Above the lower limit of detection (0.4 ng/mL) but below the lower limit of quantification (6.0 ng/mL).

## Preliminary Conclusions and Actions

Bromazolam has been misrepresented<sup>¶¶</sup> as a benzodiazepine approved by the Food and Drug Administration. The constellation of signs and symptoms in this case series is unexpected for a benzodiazepine overdose, which might 1) be a product of anoxic brain injury attributable to prolonged obtundation, 2) represent additional features of bromazolam in overdose or withdrawal, or 3) be due to an additional intoxicant not detected on liquid chromatography–mass spectrometry. Since 2021, 114 cases analyzed via DEA TOX had specimens that were positive for bromazolam, with mean blood levels reported as 44.8 ng/mL. Bromazolam has also been detected in drivers arrested for driving under the influence, in whom it produced a largely sedative toxidrome (5).

It is essential that physicians, medical examiners, toxicology laboratories, public health officials, and emergency responders be aware of the increased presence of bromazolam both in polydrug ingestions and in substance use disorder patients who report the use of benzodiazepines. Clinically, this knowledge can inform prognosis (two out of three patients in this cluster had confirmed recovery to near independence) and could indicate the need for aggressive seizure control. From a public health perspective, the constellation of findings reported should prompt close involvement with public health officials and regional poison centers, given the more severe findings in these reported cases compared with those expected from routine benzodiazepine overdoses. Clinicians, responders, and health officials should also consider bromazolam in cases of patients requiring treatment for seizures, myocardial injury, or hyperthermia after illicit drug use, as occurred in these case reports. Bromazolam intoxication should also be suspected in patients with a sedative toxidrome who do not respond adequately to naloxone reversal. In cases

of suspected bromazolam exposure, clinicians should call their poison center for additional guidance. Testing for bromazolam is not routinely available but can be arranged through a variety of send-out reference laboratories.<sup>\*\*\*</sup>

<sup>\*\*\*</sup> Send-out reference laboratories offer a wide variety of specialized testing that is typically not available at primary hospital laboratories. Examples include NMS Labs and Quest Diagnostics, among others, in addition to the DEATOX program.

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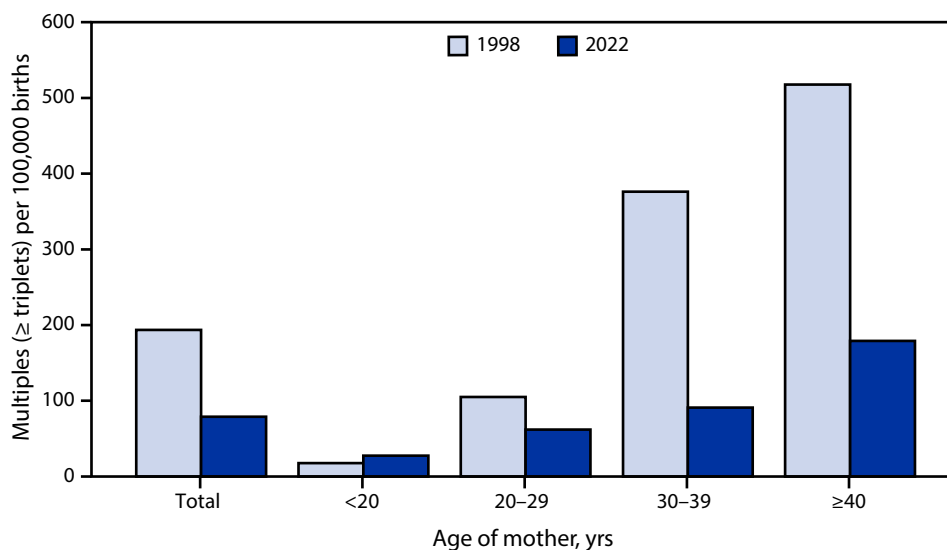
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<sup>¶¶</sup> Bromazolam, sold as alprazolam, submitted anonymously as sample ID 16949 analyzed by DrugsData, an independent laboratory testing. <https://drugsdata.org/view.php?id=16949>

## QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

## Rate of Triplet and Higher-Order Multiple Births<sup>\*,†</sup> by Age of Mother — National Vital Statistics System, United States, 1998 and 2022



\* Per 100,000 births.

† Triplet and higher-order multiple births are births in triplet, quadruplet, quintuplet, and higher-order deliveries.

The triplet and higher-order multiple birth rate declined from an all-time high of 193.5 per 100,000 total births in 1998 to 78.9 in 2022. From 1998 to 2022, triplet and higher-order birth rates increased among mothers aged <20 years (from 17.6 to 27.5) but declined among mothers aged ≥20 years. In both 1998 and 2022, triplet and higher-order multiple birth rates were lowest among mothers aged <20 years and highest among mothers aged ≥40 years (517.6 in 1998 and 179.0 in 2022) but differences across the age groups narrowed from 1998 to 2022.

**Source:** National Center for Health Statistics, National Vital Statistics System, Natality Data, 1998 and 2022. <https://www.cdc.gov/nchs/nvss/births.htm>

**Reported by:** Joyce A. Martin, MPH, [jcm9@cdc.gov](mailto:jcm9@cdc.gov).

For more information on this topic, CDC recommends the following link: <https://www.cdc.gov/art/key-findings/multiple-births.html>

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