

Letters

RESEARCH LETTER

Adverse Effects From Counterfeit Alprazolam Tablets

From October 15 to December 31, 2015, the California Poison Control System–San Francisco division identified 8 patients who experienced adverse effects associated with the ingestion of counterfeit alprazolam tablets found to contain fentanyl and, in some cases, etizolam. The identification of these patients resulted in a coordinated response that included state and local public health departments, a toxicology laboratory, and media outlets, and resulted in an investigation by local law enforcement agencies.

Report of Cases | A man in his late 20s and a woman in her late 30s (patients 1 and 2, respectively) (Table) were transported to the emergency department after ingesting illegally purchased tablets that were purportedly alprazolam. A third individual was found deceased at the same location as the first 2 patients. Both patients experienced unusually prolonged sedation and awoke with unilateral weakness and paresthesias. The neurologic manifestations in patient 1 were distal to his left elbow, while those in patient 2 were in her right lower extremity. Laboratory test results for patient 1 were significant for leukocytosis (white blood cell count, 30 000/ μ L [to convert to $\times 10^9$ /L, multiply by 0.001]), acute renal insufficiency (creatinine level, 1.68 mg/dL [to convert to micromoles per liter, multiply by 88.4]), and undetectable serum

ethanol. Results of the complete blood cell count and chemistry panel for patient 2 were normal, and her serum ethanol concentration was 68 mg/dL (to convert to millimoles per liter, multiply by 0.2171). Patients 1 and 2 had rhabdomyolysis (creatinine kinase level, 1012 and 354 U/L, respectively [to convert to microkats per liter, multiply by 0.0167]) and elevation of aspartate aminotransferase (528 and 120 U/L, respectively [to convert to microkats per liter, multiply by 0.0167]) and alanine aminotransferase levels (683 and 64 U/L, respectively [to convert to microkats per liter, multiply by 0.0167]), with normal hepatic function. Compression neuropathy was diagnosed in both patients after results of magnetic resonance imaging studies were unremarkable. Patients 1 and 2 were also diagnosed with demand cardiac ischemia with peak troponin levels of 4.62 and 1.43 ng/mL, respectively (to convert to micrograms per liter, multiply by 1.0). The patients' symptoms improved within 24 hours. During the following 2 months, 6 additional patients presented to the emergency department after exposure to counterfeit alprazolam tablets.

This study was exempt from approval by the University of California–San Francisco institutional review board. As no patient identifiers were included, informed consent was waived by the University of California–San Francisco institutional review board.

Results | The Table summarizes the demographic data, clinical characteristics, and laboratory test results of the patients exposed to counterfeit alprazolam. Their ages ranged from 8 months to 45 years, and central nervous system depression was the most common feature at presentation. Four patients

Table. Survivors Exposed to Counterfeit Alprazolam Products in the San Francisco Bay Area

Patient No./Sex/Age	Clinical Presentation	Serum Concentrations	Additional Drugs Identified in Serum ^a
1/M/Late 20s	Demand cardiac ischemia, rhabdomyolysis, compression neuropathy, and acute kidney injury after using alcohol and cocaine, and taking a tablet of alprazolam obtained illegally	Fentanyl 1.6 ng/mL, etizolam 0.60 ng/mL	Benzoylcegonine, cocaine, cocaethylene, norfentanyl
2/F/Late 30s	Demand cardiac ischemia, rhabdomyolysis, and compression neuropathy after using alcohol and cocaine, and taking a tablet of alprazolam obtained illegally	Fentanyl 0.61 ng/mL, etizolam <0.24 ng/mL ^b	Benzoylcegonine, cocaethylene, levamisole, norfentanyl
3/M/Early 20s	Obtundation requiring intubation, cardiogenic pulmonary edema, and biventricular heart failure after taking a tablet of alprazolam obtained illegally	Fentanyl 1.4 ng/mL, etizolam 0.26 ng/mL	Benzoylcegonine, norfentanyl
4/M/Mid 40s	Lethargy after ingesting chlordiazepoxide, alcohol, and 3 tablets of alprazolam purchased from a friend	Etizolam 22 ng/mL	Chlordiazepoxide, demoxepam
5/M/Late teens	Lethargy and ataxia after ingesting alprazolam obtained illegally	Fentanyl 0.15 ng/mL, etizolam 55 ng/mL, alprazolam 101 ng/mL	Norfentanyl
6/M/Late teens	CNS and respiratory depression requiring naloxone after taking alprazolam obtained illegally	Fentanyl 2.6 ng/mL	Diphenhydramine, naloxone, norfentanyl, sertraline
7/M/Infant	CNS depression requiring intubation after accidental exposure to alprazolam found on ground at home	Only urine available: fentanyl identified	Alpha-hydroxymidazolam, atropine, lorazepam, midazolam, norfentanyl
8/M/Mid 20s	Cardiac arrest after ingesting alprazolam obtained illegally	Fentanyl 1.4 ng/mL	Acetaminophen, diazepam, naloxone, nordiazepam, norfentanyl, oxazepam, temazepam

Abbreviation: CNS, central nervous system.

^a Drugs identified by laboratory analysis but not quantified. Benzoylcegonine = cocaine metabolite; cocaethylene = cocaine metabolite in the presence of ethanol; norfentanyl = fentanyl metabolite; alpha-hydroxymidazolam =

midazolam metabolite; demoxepam = chlordiazepoxide metabolite; oxazepam, temazepam, and nordiazepam = diazepam metabolites.

^b Below the limit of quantitation.

Figure. Counterfeit Alprazolam (Xanax) Tablet Compared With Brand-name Xanax Tablet



A, Counterfeit alprazolam tablet containing 3.4 mg of fentanyl and 10.6 µg of etizolam. B, Brand-name 2-mg Xanax tablet (Pfizer). Image reprinted with permission from <https://www.drugs.com>.

developed cardiovascular manifestations and most recovered within 24 hours. Patient 3, who developed biventricular heart failure, recovered after 5 days, while patient 8, who presented after cardiac arrest, recovered after 2 days.

Using a liquid chromatography high-resolution mass spectrometry (5600 QTOF MS; AB Sciex) method previously described,¹ fentanyl, norfentanyl, and etizolam were identified in the index cases. Serum fentanyl concentrations were 1.6 ng/mL in patient 1 and 0.61 ng/mL in patient 2. Analgesic serum concentrations of fentanyl range from 0.6 to 3.0 ng/mL.² Patient 1 also had a serum etizolam concentration of 0.60 ng/mL (peak serum concentration after therapeutic dosing, 9.3 ng/mL).³ The fatal case at the scene of the first incident was investigated by the San Francisco Office of the Chief Medical Examiner (N. P. Lemos, PhD, H. S. Narula, MD, X. van Wijk, PhD, K. Lynch, PhD, A. H. B. Wu, PhD, K. Vo, MD, A. Arens, MD; and C. Smollin, MD, unpublished data, March 2016). Postmortem urine and blood samples contained fentanyl. Analysis of a tablet (Figure) in the possession of patient 3 revealed 3.4 mg of fentanyl and 10.6 µg of etizolam.

Discussion | Fentanyl is a synthetic opioid with rapid onset of action and the potential to produce significant depression of the central nervous system and respiratory system.² Toxic cardiovascular effects have been previously described with the intravenous administration of fentanyl.⁴ Its incorporation into a counterfeit product may indicate the desire for a product with a faster, more potent high. Etizolam is a benzodiazepine analogue implicated in overdose deaths and is not approved for use in the United States.³ Etizolam can be purchased online, which may allow for easy incorporation into a counterfeit product.³ It is unclear how these alprazolam tablets were manufactured; however, pill press molds with the characteristics seen on the recovered tablets are available for purchase online.⁵

This case series represents a burgeoning public health threat. Clinicians should be aware of the potential for further outbreaks and serious toxic effects associated with counterfeit prescription medications.

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Invited Commentary

Counterfeit Medications and Fentanyl

The steep recent increase in overdose deaths and near-deaths nationwide involving fentanyl signals a new chapter in the epidemic of opioid use. Throughout the United States and Canada, seizures of pill presses, large quantities of active pharmaceutical ingredient in powder form, and counterfeit pills have been reported. Since fall 2013, the highly



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potent opioid fentanyl and its analogues have contributed to more than 5000 overdose deaths in the United States. In 2014, one-fifth of Ohio's overdoses were associated with fentanyl; in 2015, two-thirds of New Hampshire's fatal overdoses and half of Rhode Island's overdoses were associated with fentanyl. The research letter by Arens et al¹ in this issue of *JAMA Internal Medicine* reports a case series of counterfeit Xanax (alprazolam) tablets containing fentanyl and etizolam detected by poison control and emergency medical professionals in San Francisco, California. The authors should be commended for identifying and warning the public, to prevent further harm occurring as a result of the supply of this counterfeit medication.

The high potency of fentanyl means only tiny amounts are needed to cause rapid and profound respiratory depression and death. When fentanyl is injected intravenously, maximum respiratory depression is reached in 2 minutes, compared with 10 minutes for heroin. While fentanyl is approved by the US Food and Drug Administration for severe pain and is used by patients with cancer and other severe manifestation of diseases, clandestine manufacture and distribution of fentanyl and its analogues have emerged as a major public health threat.

From 2005 to 2007, at least 1013 people in Illinois, Maryland, Pennsylvania, Michigan, and New Jersey died as a result of heroin that was contaminated by fentanyl; supply decreased after the Drug Enforcement Administration closed a laboratory in Mexico that was manufacturing the drug. Small-scale production of acetylfentanyl in some localities led to outbreaks of overdoses in 2013, and by the end of that year, fentanyl had become established in many drug markets.

The current outbreak of illicitly synthesized fentanyl is notable for its wider geographic reach and more diverse groups of users, such as those documented by Arens et al.¹ The many sources of the illicitly synthesized fentanyl, including domestic clandestine laboratories, involve not just fentanyl hydrochloride or citrate but also more than 15 new fentanyl analogues identified by the Drug Enforcement Administration. These include furanylfentanyl (reported March 2016 in North Carolina and April 2016 in North Dakota); acetylfentanyl, which continues to be illegally available in domestic markets and prepared for consumption in new forms (eg, blotter paper); and butyrylfentanyl, which was added to Schedule I of the Controlled Substances Act in May 2016. Careful identification of specific forms of fentanyl is key to understanding the spread of new analogues into US markets and to mitigating risks associated with drugs of varying potency. Unfortunately, Arens et al¹ do not provide additional quantification and specification of the type of fentanyl involved in the overdoses they report, which diminishes the letter's utility for surveillance and preparing responses.

Arens et al¹ propose a hypothesis as to why someone would press fentanyl into the shape of a Xanax (alprazolam) tablet: desire for a faster, more potent high. However, most available evidence indicates that users are unaware of the fentanyl in their products, and many are not seeking it.² Several more plausible hypotheses exist.

Malice | These highly potent pills could have been created by a malicious actor to intentionally poison consumers or attract the attention of law enforcement to redistributors. This hypothesis

cannot be entirely ruled out by the evidence presented by Arens et al,¹ but it is less likely because the quantity of fentanyl identified in the counterfeit alprazolam tablets was significantly greater than would be required to harm unwitting consumers.

Accident | Counterfeit Xanax (alprazolam) tablets are often formulated with 3 to 4 mg of active ingredient; because forensic analysis showed that 3 to 4 mg of fentanyl was in the seized product, it suggests possible mislabeling or confusion of the active ingredient at some point in the supply chain or production process of the counterfeit drug. Forensic analysis of the counterfeit Xanax (alprazolam) tablets indicates amounts of etizolam that are insufficient to cause psychoactive effects, suggesting that cross-contamination with trace amounts of etizolam may have occurred via pill presses or other manufacturing equipment. The challenge of maintaining high levels of quality control in clandestine laboratories makes this a leading hypothesis.

Obfuscation | In California, trafficking and distribution of Schedule IV substances, such as alprazolam, carry less-severe criminal penalties than do trafficking and distribution of fentanyl. Using a Xanax imprint for a tablet primarily composed of fentanyl might be perceived as a way to obfuscate the tablet's true contents and avoid more-severe penalties. This hypothesis cannot be entirely rejected, but is unlikely, since testing seized drugs is a standard part of drug trafficking prosecutions.

Economic Considerations | Fentanyl is less expensive and easier to manufacture than heroin, and smaller, potent amounts reduce suppliers' transportation costs. In addition, local competition, especially after disruptions by law enforcement interventions affecting drug supply, may drive product innovation and differentiation.³ If inclusion of 3.4 mg of fentanyl per tablet was intentional, the use of a 4-segment pill shape may be an attempt to provide consumers a recognizable "brand" of fentanyl with a form factor that, compared with other pill shapes, is more easily partitioned to control dosage.

Geography is a determinant of risks associated with heroin, including exposure to fentanyl.⁴ Unlike in the Midwest and Northeast, where tainting of white- or brown-colored heroin and white cocaine with fentanyl is increasingly common, West Coast heroin is primarily black tar, which is not conducive to adding fentanyl. The appearance of fentanyl in various pill forms, first as counterfeit alprazolam and more recently in the West as counterfeits of the commonly misused hydrocodone hydrochloride tablets, is anticipated and will persist; vigilance is critical.

Fentanyl is likely a major impediment to the many efforts seeking to reduce overdose deaths. The leading medical interventions for reduction of overdose deaths are medication-assisted treatment with opioid agonists,⁵ naloxone distribution in high-risk populations,⁶ and facilities where illicit drug use can be medically supervised.⁷ The lethality of fentanyl challenges the effectiveness of these interventions. Fentanyl complicates the implementation of treatment, as drug users are more susceptible to death while on waiting lists for care or during relapses. Fentanyl narrows the time window for rescue with naloxone and may necessitate quantities of antidote that exceed the doses accessible to laypeople. A far more aggressive and stra-

tegic expansion of evidence-based interventions in geographic areas heavily affected by heroin and fentanyl is needed to reduce demand and stop deaths. The letter by Arens et al¹ demonstrates the importance of public health surveillance of emerging drugs but also conveys the inadequacy of our current approaches: detection requires exposure to drugs at levels that almost cause death. One surveillance strategy to spare lives, detect trends earlier, and influence product safety in illicit drug markets is provision of drug checking services, which conduct forensic analysis of publicly submitted drug samples, the individual results of which are shared anonymously and aggregated for surveillance. In many European countries, drug checking services facilitate clinical and consumer understanding of black-market products while providing low-threshold points of contact between supportive services and people who use drugs.⁸ New surveillance approaches and rapid expansion of evidence-based interventions are the missing parameters needed to shift the curve of the epidemic of opioid use. The Office of National Drug Control and Policy has provided leadership in supporting closer public health and public safety collaborations to address recent surges in heroin use. Similar oversight, direction, and coordination are needed to expedite implementation of responses and to navigate local, state, and federal opportunities and tensions around these new approaches.

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States Worse Than Death Among Hospitalized Patients With Serious Illnesses

Cohort studies and randomized trials among hospitalized patients with acute and serious illnesses commonly use mortality as the primary or key secondary outcome measure. Death is a patient-centered outcome because nearly everyone wishes to avoid it. Despite this general preference, however, studies among healthy outpatients and those with serious illnesses show that a significant minority, and sometimes a majority, rate states such as severe dementia as worse than death.¹⁻³

To our knowledge, there is no evidence as to whether patients with acute illnesses requiring hospitalization also consider certain states of debility as worse than death. This distinction is important because some evidence suggests that as death nears, people may choose more aggressive treatment options in an attempt to prevent it.⁴ We therefore sought to understand how hospitalized patients with serious illnesses would evaluate states of cognitive or functional debility relative to death.

Methods | We conducted a prospective cohort study nested within a randomized trial of different approaches to decision making among 180 patients with serious illnesses who were hospitalized between July 1, 2015, and March 7, 2016, at an academic medical center in Philadelphia, Pennsylvania. The cohort study consisted of structured interviews with inpatients 60 years or older with advanced solid malignant neoplasms, hematologic malignant conditions, class III or IV congestive heart failure, or severe obstructive or restrictive lung disease. None of these patients had limitations on any life-sustaining treatment documented in their electronic medical records.

All patients were asked to evaluate health states with specific physical and cognitive debilities, dependencies on forms of life support, and dependencies on others to perform various activities (**Figure**). Patients rated each state on a 5-point Likert scale indicating whether they considered the state to be worse than death, neither better nor worse than death, a little better than death, somewhat better than death, or much better than death. Combinations of states were not evaluated. The University of Pennsylvania institutional review board approved the protocol and patients provided written informed consent.

Results | Patients displayed considerable heterogeneity in their ratings of health states relative to death (**Figure**), but significant percentages of patients rated each evaluated state of serious functional debility as equal to or worse than death. For example, a majority of respondents considered bowel and bladder incontinence (124 [68.9%]), requiring a breathing tube to