Neurol Ther
https://doi.org/10.1007/s40120-024-00628-3

REVIEW

Fake Xanax: Designer Emerging Benzodiazepine Epidemic Linked to Morbidity and Mortality a Narrative Review

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Received: March 26, 2024 / Accepted: April 30, 2024

ABSTRACT

Etizolam is a thienodiazepine derivative which produces an anxiolytic effect similar to benzodiazepines such as alprazolam (Xanax). Like classic benzodiazepines, etizolam has a high affinity towards the $GABA_A$ receptor, and allosterically potentiates the effects of GABA resulting in neuronal hyperpolarization related to chloride influx. When taken in therapeutic doses, etizolam produces a similar effect to Xanax. Counterfeit Xanax tablets contain variable amounts of etizolam. Tablets with high amounts of etizolam can cause toxicity if ingested, especially when combined with other substances. When toxic symptoms occur in patients, they may include severe sedation, unconsciousness, and depression of the medullary respiratory center. In this

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Published online: 10 May 2024

regard, there is the potential for death. Additionally, the rise in fake Xanax tablets containing etizolam and other counterfeit medications has been exacerbated by the difference in regulations regarding these substances in different countries as well as the illegal drug trade. Healthcare providers may also play a role through the over- or underprescribing of certain medications. Thus, in order to combat the rise in counterfeit medications such as fake Xanax, international cooperation, regulation, and enforcement of laws pertaining to the manufacture, prescription, and distribution of these substances are needed.

Keywords: Etizolam; Benzodiazepines; Designer benzodiazepines; Counterfeit Xanax; Multidrug intoxication

Key Summary Points

Etizolam is a thienodiazepine derivative which produces an anxiolytic effect similar to benzodiazepines such as alprazolam (Xanax).

The substantial number of etizolam reports in 2022 from the US National Forensic Laboratory Information System, totaling 1473 and comprising 3.21% of all tranquilizer and depressant reports, underscores the significant prevalence and impact of this substance in the context of substance misuse and illicit drug trade.

In the USA, etizolam is not authorized by the FDA (US Food and Drug Administration) for medical use.

In order to combat the rise in counterfeit medications such as fake Xanax, international cooperation, regulation, and enforcement of laws pertaining to the manufacture, prescription, and distribution of these substances are needed.

INTRODUCTION

Xanax, which has the generic name alprazolam, is a member of the benzodiazepine class of medications [1]. Currently, alprazolam is approved by the FDA (US Food and Drug Administration) for treatment of panic and anxiety disorders. In addition, it is utilized to treat insomnia, premenstrual syndrome, and depression though it is not FDA approved for these conditions [1]. Those who use alprazolam have commonly reported side effects such as drowsiness, dizziness, memory issues, poor coordination, and difficulty concentrating [2]. Additionally, alprazolam may be misused in order to achieve a euphoric state by causing disinhibition of dopaminergic neurons which project to the nucleus accumbens [3]. The misuse of alprazolam and other prescription drugs has also been promoted by artists such as Lil Durk, King Von, and Juice Wrld. This cultural and societal normalization of prescription drug misuse is believed to have contributed, in part, to the rise of prescription drug misuse as well as the proliferation of counterfeit tablets [4].

An additional issue regarding benzodiazepines such as Xanax is the potential for counterfeits which lack alprazolam and instead contain other, possibly dangerous ingredients. One potentially lethal drug often substituted for alprazolam in pills advertised as Xanax is etizolam. Etizolam, is a thienodiazepine which, like alprazolam, is able to bind to the $GABA_A$ receptor, where it acts as a positive allosteric modulator to potentiate the effects of GABA [5]. It has approved medical uses in certain countries such as in Japan and Italy though it remains a Schedule I drug in the USA, where it is unable to be prescribed by physicians [6]. Etizolam is typically ingested as a pill though it may also be taken as a powder, sublingually, or as a liquid [7]. In preclinical studies involving mice, etizolam has been shown to be less lethal than other commonly used benzodiazepines [8]. It may also have reduced sedative effects in comparison to alprazolam and other benzodiazepine; however, etizolam use may still be dangerous, especially when taken for nonmedical reasons, as it is extremely potent compared to benzodiazepines like diazepam [6, 9].

Use of etizolam recreationally has increased in recent years in certain parts of the world, in part, due to current practices in the healthcare industry. Under- and overprescription of benzodiazepines by healthcare workers is partly to blame. When providers overprescribe certain medications like benzodiazepines there is a risk of developing dependence to these drugs. On the other hand, underprescription can drive those who may truly need these medications to be forced to seek counterfeit pills, which may contain unknown substances like etizolam [10]. The prevalence of substances like etizolam in the USA is mostly due to illegal importation from other countries. Strengthening regulatory frameworks to prevent the production and distribution of counterfeit medications, enhancing surveillance mechanisms, imposing stricter penalties for offenders, and fostering international cooperation to combat illicit drug trade networks can all be possible solutions to slowing the influx of drugs like etizolam into countries like the USA [11]. Thus, the purpose of this review, therefore, is to raise awareness and appreciate pharmacological considerations regarding fake Xanax pills containing etizolam along with other harmful compounds and highlight the dangers these drugs pose.

This article is based on previous studies and contains no new studies with human participants or animals performed by any authors.

OVERVIEW OF BENZODIAZEPINE PHARMACOLOGY

Benzodiazepines are a widely used class of drug that bind to a component of the $GABA_A$ receptor complex, ultimately leading to depression of the central nervous system [1, 12]. In addition to having antiseizure properties, benzodiazepines also have sedative-hypnotic, anxiolytic, muscle relaxant, and amnesic effects [1]. These properties are a result of the activation of the benzodiazepine and $GABA_A$ receptors on the GABA receptor complex. Activation of the benzodiazepine receptor leads to increased frequency in the opening of the $GABA_A$ Cl^- channel when GABA is present. This causes an influx of chloride anions leading to membrane hyperpolarization, and ultimately neuronal inhibition and CNS depression [1, 12]. There are dozens of benzodiazepines currently in use for indications such as acute seizures, anxiety disorders (e.g., alprazolam, lorazepam, and oxazepam), insomnia (e.g., estazolam, flurazepam, and temazepam), induction of amnesia (midazolam), seizure disorders (e.g., clobazam), spastic disorders, and agitation [1]. Some of the most important benzodiazepines are midazolam and lorazepam which are used for the treatment of convulsive status epilepticus with the latter being a first-line drug for the treatment of convulsive status epilepticus [13]. Some common adverse effects of benzodiazepines include respiratory depression, respiratory arrest, confusion, headaches, syncope, nausea, vomiting, diarrhea, tremors, and most commonly, drowsiness [1]. Older individuals, particularly over the age of 65, tend to be more susceptible to these adverse effects while those with a history of alcohol or barbiturate misuse tend to be resistant to the CNS depressant properties of benzodiazepines [12]. Benzodiazepines also have severe drug–drug interactions when combined with substances like ethanol, other benzodiazepines, and sedatives. Taken with any of these other substances may result in a synergistic effect on respiratory depression. Lorazepam and oxazepam should also not be concurrently administered with uridine diphosphate glucuronosyltransferases (UGTs), as it may increase metabolism and decrease efficacy due to lorazepam and oxazepam being metabolized by UGTs [1].

While the development of physical dependence is less common, tolerance and psychological dependence are quite frequent with individuals taking benzodiazepines. Additionally, a pronounced withdrawal syndrome can occur upon discontinuation of benzodiazepines after long-term use [12]. Rebound insomnia can also occur, where the duration and quality of the individuals sleep are reduced [14].

While benzodiazepines have a relatively high margin of safety, overdoses do occur. However, this is usually due to combining alcohol or other drugs with benzodiazepines. Overdose from benzodiazepines alone mostly involves elderly patients, young children, iatrogenic

overdosing, or suicides [12]. In the case of an overdose, patients may be administered flumazenil, a benzodiazepine antagonist, in an effort to prevent benzodiazepine from binding to the $GABA_A$ receptor thus reducing their toxic effects [15].

ETIZOLAM: PHARMACOKINETICS AND PHARMACODYNAMICS CONSIDERATIONS

Etizolam is a thienodiazepine derivative, differing from traditional benzodiazepines in that it has a thiophene ring in place of a benzene ring. Etizolam is a full agonist at $GABA_A$ receptors, and when bound increases GABAergic signaling leading to the opening of GABA-induced chloride channels. The influx of chloride ions then leads to neuronal hyperpolarization, and ultimately CNS depression [5, 16]. According to a study of 10 designer benzodiazepines, etizolam was shown to be the most euphoric and among the most potent of the drugs studied [17]. This is likely due to etizolam's high affinity towards $GABA_A$ α1 subunit-containing receptors. Binding of α1 subunit-containing receptors produces an anxiolytic effect while α2 and α3 subunit-containing receptors produce a sedative effect when bound [16].

Etizolam has a half-life of 5–7 h, which is shorter than many benzodiazepines such as alprazolam (8–15 h), lorazepam (9–19 h), and diazepam (20–70 h), but longer than midazolam (1.5–3 h) [5, 18, 19] (Table 1). Etizolam's oral bioavailability of 93% is typical when compared to classic benzodiazepines [16]. Diazepam and lorazepam both have a slightly lower oral availability of 90%, while alprazolam has an oral bioavailability of 80–100% [18, 20, 21]. Midazolam, however, is an outlier, with an oral bioavailability of only 40–50% due to extensive first pass metabolism [19]. Etizolam's plasma protein bound distribution is average compared to other benzodiazepines at 92.8% [22]. Somewhat similar to diazepam (98%), lorazepam (90%), and midazolam (94–98%), while alprazolam has a lower plasma protein bound distribution of 80% [18, 20, 21, 23]. Liver enzyme CYP3A4 is a main player in the metabolism of etizolam as well as many other benzodiazepines. Therefore, when administered with a CYP3A4 inhibitor such as itraconazole, its metabolism is inhibited, while a CYP3A4 inducer such as carbamazepine increases metabolism [5, 24]. CYP3A4 is also the metabolizer for alprazolam, diazepam, and midazolam [19–21]. Lorazepam, on the other hand, undergoes enterohepatic recirculation and direct glucuronidation without prior cytochrome p450 metabolism, and therefore it has no CYP metabolizer [18].

Adverse effects associated with using etizolam are similar to those reported with benzodiazepines and include slurred speech, severe sedation, unconsciousness, and depression of the respiratory center in the medulla [25]. A comparison of observed adverse effects of etizolam compared to other designer benzodiazepines can be found in Table 2. Additionally, etizolam is believed to be significantly more dangerous when combined with other medications, as most

Table 1 Pharmacodynamics of etizolam compared to classic benzodiazepines

	Half-life (oral)	Bioavailability (oral)	Distribution (protein bound)	CYP metabolizer
Etizolam [5, 16, 22]	5–7	93%	92.8%	CYP3A4
Alprazolam [5, 20]	8–15	80–100%	80%	CYP3A4
Diazepam [5, 21]	20–70	90%	98%	CYP2C19/ CYP3A4
Lorazepam [18]	9–19	90%	90%	N/A
Midazolam [19, 23]	1.5–3	40–50%	94–98%	CYP3A4/CYP3A5

Table 2 Observed adverse effects of etizolam compared to designer benzodiazepines

	Adverse effects	Dose (ng/ml)
Etizolam [28]	Accidental death, multiple drugs	Blood 12
Adinazolam [29]	Death	Blood 18 Urine 82.1
Flualprazolam [30]	CNS depression, mild respiratory depression	Blood 14.6 Urine 19.4
Flubromazepam [25]	Apnea, coma, rattling breath, hypothermia, myosis, tachycardia, unconsciousness	Blood 830
Pyrazolam [31]	Death	Blood 28 Central blood 28 Urine 500

CNS Central Nervous System

reported overdoses involving etizolam typically involve polypharmacy—including coadministration with several other drugs such as prescription opioids, heroin, and alcohol [26]. These dangerous effects are especially concerning related to the fact that etizolam may be used as a substitute for other drugs such as alprazolam. Counterfeit drugs, which are marketed as Xanax, may also contain other drugs such as fentanyl. This further increases the risk of toxicity from drug–drug interactions [27].

CASE STUDIES

Etizolam has been associated with various adverse effects and dangers. It poses a significant global health risk related to its association with counterfeit pharmaceuticals and concerning prevalence within the illicit drug market. Demonstrating the prevalence and potential dangers of etizolam in counterfeit tablets, Blakey et al. conducted a dosage survey of designer benzodiazepines in counterfeit pharmaceuticals and found etizolam was the most frequently detected compound in the illicit tablets. Researchers also found etizolam to have the most significant variation in dosage in visually similar counterfeit tablets, ranging from 0.7 to 8.3 mg per tablet [32]. The potency of etizolam is reported to be similar to that of alprazolam, but with some counterfeit tablets containing a significantly higher dose than the recommended therapeutic dose of alprazolam, this poses significant risks to individuals who unknowingly consume these products. Several case reports have highlighted the potential risks and toxic effects of etizolam, including severe adverse effects, overdose, multidrug intoxication, withdrawal, death, and even drug intoxication of children.

Arens et al. identified a series of patients presenting to a California emergency department after ingesting counterfeit alprazolam tablets containing etizolam. Two of the patients, a man in his late twenties and a women in her late thirties, developed rhabdomyolysis, demand cardiac ischemia, and compression neuropathy [27].

Shapiro et al. detailed a case of a 30-year-old man presenting for assistance with detoxification from etizolam. The patient described taking an average dosage of 50 mg per day for several months but had recently increased his dosage to 100 mg or more daily. He was also concurrently taking diclazepam the week of admission [33]. Typical recreational dosages of etizolam and diclazepam are 0.25–3 mg and 1 mg, respectively [34]. The patient obtained the prohibited benzodiazepines via the Internet. Patient described a history of withdrawal seizures and withdrawal symptoms of anxiety, temperature sensitivity, and sensitivity to light and sound. Lorazepam,

a metabolite of diclazepam, was found on the urine toxicology screen, and etizolam and lorazepam were both found on a benzodiazepine confirmation panel [33].

O'Connell et al. detailed an overdose of etizolam in a 31-year-old man found unresponsive beside an empty syringe believed to contain heroin. It was also known that the patient had been ingesting multiple etizolam tablets throughout the day. Upon arrival at the hospital, he intravenously administered 0.2 mg of flumazenil, which resulted in immediate and complete reversal of his overdose symptoms. His serum concentration of etizolam was 103 ng/mL [35]. Typical plasma concentrations after consumption of a single therapeutic dose of etizolam (1–3 mg) range from 2 to 30 ng/mL [28].

Drevin et al. describe a case of a 42-year-old French man presenting to the hospital with acute etizolam and cocaine intoxication. As a result of his state of agitation, the patient was placed in restraints and midazolam and loxapine succinate were administered. His plasma concentration of etizolam was 64 ng/mL [36].

Kolbe et al. described a lethal etizolam and caffeine overdose of a 49-year-old German man. The deceased had purchased counterfeit alprazolam. Toxicologic testing revealed etizolam concentrations in femoral blood and cardiac blood to be 770 ng/mL and 2820 ng/mL, respectively. Hair samples taken from the deceased also revealed the presence of alprazolam, indicating repeated use of the drug. Researchers concluded that the cause of death was a result of "acute toxic effects of etizolam and caffeine" [37]. The impact of designer benzodiazepines on vulnerable populations, such as children, is a subject of concern. Love et al. described a unique case of etizolam exposure to three boys aged 6, 9, and 10. Each of the boys presented to the Oregon emergency department with lethargy, impaired coordination, dilated pupils, and drooling after ingesting etizolam disguised as Pez candy [38]. Thus, counterfeit benzodiazepines present a notable threat to public health, leading to potential dangers such as multidrug intoxication, challenges with withdrawal, and, in some cases, fatal overdoses.

CONCLUSION

The substantial number of etizolam reports in 2022 from the US National Forensic Laboratory Information System, totaling 1473 and comprising 3.21% of all tranquilizer and depressant reports, underscores the significant prevalence and impact of this substance in the context of substance misuse and the illicit drug trade. The description of case studies outlined in the paper additionally highlights the real-world consequences of etizolam misuse and counterfeit medication distribution. These cases serve as poignant reminders of the potential dangers associated with etizolam misuse and counterfeit medication consumption. Thus, as the problem regarding etizolam misuse has become increasingly problematic in recent years, it is crucial that policies are created that seek to limit its harmful effects so that less people are harmed from its consumption.

Author Contributions. Alan D Kaye, Joseph P Tassin, William C Upshaw, Camille M Robichaux, Mark V Frolov, Mark M Dupaquier, Julia E Fox, Jeffrey Sterritt, Jibin Mathew, Sahar Shekoohi, Adam M Kaye and Amber N Edinoff have made a direct and intellectual contribution to the work and have been approved for publication.

Funding. No funding or sponsorship was received for this study or publication of this article.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Alan D Kaye, Joseph P Tassin, William C Upshaw, Camille M Robichaux, Mark V Frolov, Mark M Dupaquier, Julia E Fox, Jeffrey Sterritt, Jibin Mathew, Sahar Shekoohi, Adam M Kaye and Amber N Edinoff have no conflict of interest. Alan D Kaye is an Editorial Board member of *Pain and Therapy*. Alan D Kaye was not involved in the selection

of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethical Approval. This article is based on previous studies and contains no new studies with human participants or animals performed by any authors.

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