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Etizolam: a rapid review on pharmacology, nonmedical use and harms

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Key points

- Etizolam is thienodiazepine derivative, and is considered a short-acting benzodiazepine
- Etizolam is documented to have higher potency as an anxiolytic, but lower lethality compared with diazepam
- Few harms are documented with therapeutic use of etizolam
- Most harms are related to illicitly manufactured etizolam pills, and occur almost exclusively as mixed-drug toxicity
- Harm reduction measures are similar to other benzodiazepines, which include avoiding combining multiple substances, and using benzodiazepines of known strength.
- Strategies to shift use towards regulated products of known strength and ingredients may reduce harm

Abstract

Issues. Etizolam is a thienodiazepine derivative, with high affinity for the benzodiazepine site in GABAA receptors. It is often referred to as a new (or novel) psychoactive substance benzodiazepine, a ‘designer’ benzodiazepine or a ‘street benzodiazepine’. Increasing reports of nonmedical use, identification of etizolam as an ingredient in counterfeit medications, and the common identification of etizolam in drug-related deaths highlight the need for a greater understanding of etizolam.

Approach. A rapid narrative review was conducted using PubMed and Google Scholar to synthesise what is known about etizolam, with the aim of answering two research questions: (i) Does the pharmacological or toxicological profile of etizolam differ from other benzodiazepines?; and (ii) What is the nature and context of nonmedical use and harms related to etizolam?

Key Findings. Etizolam has a higher potency as an anxiolytic but lower lethality compared with diazepam. Few harms are documented with the therapeutic use of pharmaceutical products. Harms appear to be predominantly related the use of etizolam in illicitly manufactured pills, and occur almost exclusively in the context of mixed-drug toxicity.

Conclusion. At therapeutic doses, there is little to suggest that etizolam is more harmful than other benzodiazepines. Most harms with etizolam appear to be related to the wide availability of illicitly manufactured pills, which are taken in unknown doses and combined with other substances. Current harm reduction advice, including avoiding combining opioids and benzodiazepines, remains relevant and increasingly important within an emerging culture of nonmedical use.

Keywords: etizolam, designer benzodiazepine, street benzodiazepine, new psychoactive substance, review

Background

Etizolam is a thienodiazepine derivative, with high affinity for the benzodiazepine site in $GABA_A$ receptors [1]. It differs from classic benzodiazepines through having a benzene ring replaced with a thiophene ring.

Etizolam is an anxiolytic prescribed in Italy, India and Japan. Etizolam was originally developed in Japan, where it was introduced under the brand name of Depas in 1984 [2], though use of etizolam in Japan is relatively uncommon compared with other benzodiazepines [3,4]. Small early clinical trials suggest that etizolam has equivalent anxiolytic effects to alprazolam and bromazepam, with increasing anxiolytic effects seen over the 4 weeks of treatment [5]. Several small trials also suggest improvement in depressive symptoms in addition to anxiety symptoms [6-8].

Dependence potential, both physiological and behavioural, is documented in case reports [9,10]. Few signals of harm were identified until recent years where etizolam has been involved in rapidly increasing numbers of drug-related deaths in Scotland [11] and recent alerts in Australia and the US have identified that etizolam is appearing in counterfeit benzodiazepine tablets [12, 13].

In response to rising concern, this rapid review aims to answer two research questions:

1) Does the pharmacological or toxicological profile of etizolam differ from other benzodiazepines?
2) What is the nature and context of nonmedical use (i.e. use outside a medical context) and harms related to etizolam?

Method

An initial literature search was conducted in August 2019 to inform a World Health Organization Expert Committee critical review [14]. Updated searches were conducted in December 2019, and the literature synthesized to address the research questions for this review. Searches were conducted in PubMed and Google Scholar, supplemented by grey literature where available. Recent literature was used to describe use and harms, and older literature was examined to summarise pharmacological data. Preclinical data are used to address gaps in the human literature.

Results

Availability

Etizolam has been available as a prescription benzodiazepine for more than 35 years (See Appendix for trade names) [2]. It is often referred to as a 'designer benzodiazepine', 'street benzodiazepine' or 'research chemical', and can be purchased on surface websites as a research chemical at relatively low cost [15]. Etizolam is under national control in Denmark, Germany, Japan, Switzerland, Poland, the United Arab Emirates and the United Kingdom [16-18], and controlled in some US states [16]. Etizolam has been most recently reviewed in October 2019 by the World Health Organization Expert Committee on Drug Dependence for international control [14].

Pharmacology and toxicology

Etizolam has similar pharmacological profile to other benzodiazepines. It acts by allosterically potentiating chloride currents induced by GABA in $GABA_A$ receptors. Etizolam is taken orally, with a usual therapeutic doses between 0.5 to 2.0 mg/day, with a maximum of 3 mg/day.

Like most benzodiazepines, etizolam has good bioavailability [19, 20]. Etizolam, considered a short-acting benzodiazepine, has a half-life of 5-7 hours. This is shorter than alprazolam (8-15 h), temazepam (8-20 h) and diazepam (20-70 h) [19]. Liver enzymes (cytochrome P450 CYP3A4 and CYP2C19) are involved in the metabolism of etizolam. [21-23]. Carbamazepine (a CYP3A4 inducer) increases etizolam metabolism [24] and itraconazole (a CYP3A4 inhibitor) inhibits it [21], indicating interactions may occur with these drugs. CYP2C19 polymorphism can place poor metabolisers at higher risk of a drug-drug interaction [25]. CYP2C19 deficiency may lead to side-effects or toxicity with etizolam [22, 23]. The main metabolite of etizolam, α-hydroxyetizolam, formed via 1'-hydroxylation also has pharmacological activity comparable to that of etizolam, though a longer half-life which may contribute to the duration of etlizolam's effects [20].

In mice, etizolam has been shown to be *less* lethal than other benzodiazepines, requiring larger doses to lead to death [26, 27]. Similarly, in rats, the lethal dose values for etizolam were 2-5 times higher (i.e. diazepam was more lethal) [28].

As an anxiolytic, etizolam is considered 5-10 times more potent that diazepam; 1 mg of etizolam is considered approximately equivalent to 5 mg of diazepam. Preclinical studies suggests that etizolam may have a lower ability to induce tolerance compared to benzodiazepines such as lorazepam [29]. Etizolam is considered to possess mainly anxiolytic rather than sedative effects, thought to be due to a lower intrinsic activity at α1 subunit-containing $GABA_A$ receptors when compared to diazepam and alprazolam [1]. Etizolam has also been described to have some imipramine-like effects in preclinical studies [30].

At therapeutic doses (0.5 mg twice a day), etizolam has been shown to have no effect on cognitive function [31]. Consistent with this, an experimental study testing therapeutic doses (0.25 mg and 1 mg) of etizolam showed no effect on psychomotor performance [32]. No studies have examined effects on cognitive function outside therapeutic dose ranges.

Nonmedical use

Numerous reports describe nonmedical of use etizolam and related harms [10,11,33-35], though traditional abuse liability studies are not available. Common identification of etizolam in urine drug samples in an opioid dependence treatment cohort in Ireland [36], suggests that common nonmedical use now extends beyond Scotland.

In Scotland, in around 2010 the use of street benzodiazepines emerged following reduced benzodiazepine prescribing via primary care, prompted by concerns regarding dependence, diversion and harms (including their role in drug-related deaths) [37,38]. In illicit markets, these substances are often designed to look like the drugs they are being sold to substitute (for example, diazepam). The varying and unknown content of illicitly manufactured pills can lead to unpredictable consumption. This is risk is increased by use of unstudied supratherapeutic doses [38].

Nonmedical use of etizolam in pharmaceutical pills, other manufactured pills and, less commonly powders, was documented in 2014 [39]. Pills ranged from £1/pill for smaller quantities to 5p/ pill for larger quantities, indicating meaningful bulk-purchase discounts in the illicit drug market, and relatively low cost for suppliers and consumers. Widespread illicit manufacture and distribution of etizolam was reported in Scotland where pill-pressing machines manufacturing etizolam pills “on

an industrial scale" were seized [40,41]. The large seizure volumes and the common significant involvement of etizolam in drug-related deaths support that, in Scotland, etizolam is widely used nonmedically [11,40,41].

International programs that monitor emerging substances have reported on etizolam use and harms. These include the European Monitoring Centre for Drugs and Drug Addiction [42], the STRIDA project,[43], the Drug Enforcement Agency National Forensic Laboratory Information System [30] and analysis of US Poisons calls centres [44]. These all demonstrate that etizolam use is common, though the STRIDA project reported that between 2012 and 2016 other designer benzodiazepines had become more common than etizolam [43]. In contrast, the National Forensic Laboratory Information System database describes increasing reports relating to etizolam; from 3 in 2012 to 898 in 2017, with a total of 2445 drug reports of etizolam from 44 states from 2012 through June 2018.

Dependence

The potential for physical and behavioural dependence and nonmedical use of benzodiazepines is well-established [45-47]. To date, few case reports describe dependence or nonmedical use with patients prescribed etizolam. A case report of 23-year old man taking etizolam (up to 2.5 mg/ day) describes a patient who experienced characteristic benzodiazepine withdrawal symptoms (palpitations, insomnia, agitation and tremors) when attempting to reduce his dose [10]. A second report described a 22-year old woman taking 5 mg or more per day [48]. After unsuccessful self-managed cessation she was tapered off etizolam slowly (reducing 0.3 mg/week) and did not report withdrawal symptoms [48]. A more recent case from New York (USA, where etizolam is not available as an approved medicine) described a case where a 31-year old man presented at an emergency department with tonic-clonic seizures that were attributed to etizolam withdrawal following self-medication with etizolam [9]

Despite the suggested lower propensity to induce tolerance compared to other benzodiazepines, individual reports forums such as Bluelight.org and Erowid.org describe numerous user-reports describing tolerance, craving and withdrawal in addition to descriptions of pharmacology, drug effects and harm reduction advice relating to nonmedical use [34,35].

Harms

Illicit, non-prescribed use of etizolam was first notified to the European Monitoring Centre for Drugs and Drug Addiction in 2011 [42]. Concerns in the published literature regarding nonmedical use of etizolam were raised in 2015, with a case report from a US emergency department describing combined opioid and etizolam toxicity [33].

Recorded symptoms of high-dose etizolam consumption include central nervous system depression, slurred speech, severe sedation and unconsciousness [33,43]. The benzodiazepine antagonist flumazenil effectively reverses these symptoms [33,43]. The comparative toxicity of etizolam relative to other benzodiazepines, particularly when combined with other drugs, or whether mechanisms of toxicity for etizolam are similar to other benzodiazepines in overdose are unknown. One report on 'designer benzodiazepine' toxicity described symptoms that were consistent with a 'sedative-hypnotic toxidrome' [44] (reduced blood pressure, pulse and respiration depressed mental state, hyporeflexia and ataxia [49]).

For people who use opioids, benzodiazepines are commonly used to treat symptoms of psychiatric disorders, negative emotional states, opioid withdrawal symptoms, or to enhance the effects of opioids. This includes use at supratherapeutic or 'megadoses' many times the licensed dosage [42,50,51]. These higher doses increase the risk of interactions, adverse effects and severe respiratory depression within a culture of polypharmacy. Specific studies examining interactions with opioids, alcohol and etizolam were not identified, though in general, the risks of combining multiple central nervous system depressants such as opioids and alcohol with benzodiazepines are well-described [52].

Seizure-like activity was reported with co-ingestion of novel stimulant, 3-fluorophenmetrazine, with a high-dose etizolam [53]. Case reports also document blepharospasm [54] and prolonged myocardial toxicity when taken in combination with tizanidine [55].

A series of seven reports of deaths were identified from the international literature (Table 1). Consistent with benzodiazepines in general, death from etizolam taken as a sole substance is rare [44]. In most of these published cases it was concluded that death resulted from mixed-drug toxicity. Use of etizolam as a sole drug was uncommon. Alcohol was either not detected or not reported.

INSERT TABLE 1

Mortality related to etizolam is most marked in Scotland, with escalating mortality since 2012 (Figure 1). Etizolam is now among the most frequently detected substances in drug-related deaths [16] contributing to 46% (548/1187) of all drug-related deaths in Scotland in 2018 [11]. Consistent with other drug-related deaths, most decedents in etizolam-related deaths (74%) were male, and aged 35-44 years old. Fewer than ten of the 571 new psychoactive substance-related deaths (96% of which involved etizolam [n=548]) involved a single drug. Most benzodiazepine-related deaths in Scotland represent mixed-drug toxicity so the unique contribution of etizolam is hard to quantify. For example, data from Scotland's National Drug-related death database highlights that, in 2016, a combination of opioids and benzodiazepines was detected in almost 70% of cases (68.8%), benzodiazepines and alcohol in over two-thirds (36.1%), and heroin, benzodiazepines and alcohol combined in a quarter (24.7%) of all cases [61].

Discussion

There is little evidence to suggest that the pharmacological properties of etizolam contribute uniquely to harm. To date, the limited published literature suggest that at therapeutic doses etizolam is not more harmful than other benzodiazepines such as diazepam. The short half-life may contribute to more frequent dosing, though an active metabolite with a longer half-life may mean that the benzodiazepine effects last longer than half-life of etizolam may suggest. Clinical trials suggest that etizolam may have some advantages over other benzodiazepines, though the evidence base is limited to a few small, older trials. One explanation for increasing harms is the widespread availability at exceptionally low cost within a culture of mixed-drug toxicity (reported to be as little as 5p per tablet in Scotland), and illicit manufacturing practices leading to unknown or inconsistent dosing. One concern is that, as with opioids, as regulation has increased, more potent forms have emerged [62]. A similar concern may exist with benzodiazepines where other more potent and less regulated benzodiazepines may emerge following reduced access to pharmaceutical forms.

Future research

Future research may help to understand why people use etizolam, how they use etizolam, and what aspects of these practices may be modifiable to reduce harms. Extending our understanding in these areas may provide important consumer-led insights to address rising harm. Limited research informs the likely impact of supply-side interventions.

Conclusion

At therapeutic doses, low quality evidence suggests that etizolam is no more harmful than other benzodiazepines, though no research examines the higher doses typically used in nonmedical contexts, or how to reduce harms. Most harms with etizolam appear to be related to the wide availability of cheap, illicitly manufactured pills, which are taken in unknown doses in combination with other substances. Current harm reduction advice, including avoiding combining benzodiazepines with other sedatives (e.g. opioids or alcohol), remains relevant and increasingly important within an emerging culture of nonmedical use. For people who use drugs, regulated benzodiazepines with known content may be less harmful than illicitly manufactured etizolam.

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Table 1. Summary of published deaths where etizolam was identified

Country (Ref)	Year published	Number of cases	Substances involved/ other features reported	Etizolam deemed as causative
Japan [56]	2008	2	Focus of report was on analytical method for identifying etizolam and its main metabolites in two unnatural deaths. No alcohol detected in either case. Duration of use not reported.	Case 1. Etizolam use thought to contribute to drowning; Case 2. Not deemed a contributor
Norway [57]	2014	1	Multiple substances identified: etizolam (270 ng/ml), AH-7921 (330 ng/ml), methoxetamine (64 ng/ml), phenazepam (1330 ng/ml), 7-aminonitrazepam (43 ng/ml), diazepam (46 ng/ml), nordazepam (73 ng/ml), and oxazepam (18 ng/ml). No alcohol detected. Duration of use not reported.	Concluded likely that AH-7921 in combination with etizolam and phenazepam contributed to the death of the victim.
Japan [58] [Abstract in English]	2011	1	Etizolam (86 ng/ml), phenobarbital (5 mg/ml), promethazine (107 ng/ml), and chlorpromazine (144 ng/ml). No alcohol use or duration of etizolam use reported.	Multiple psychotropic medicines concluded as the cause of death.
Cyprus [59]	2016	1	Consumption of cathinones, designer benzodiazepines, and other drugs reported, screening was negative for alcohol. No duration of etizolam use reported.	The cause of death related to multidrug intoxication
USA [44,60]	2016	1	Etizolam and MT-45 (opioid, 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine) ingestion (unknown quantity). Diphenhydramine also detected, ethanol not detected. Decedent reported to have been purchasing monthly for ‘some time’.	Cause of death described as combined toxicity with etizolam and MT-45.
USA [44]	2019	1	One death associated with etizolam ingestion (unknown quantity).	No further information on whether etizolam was assessed to have a causal role in the death was documented.

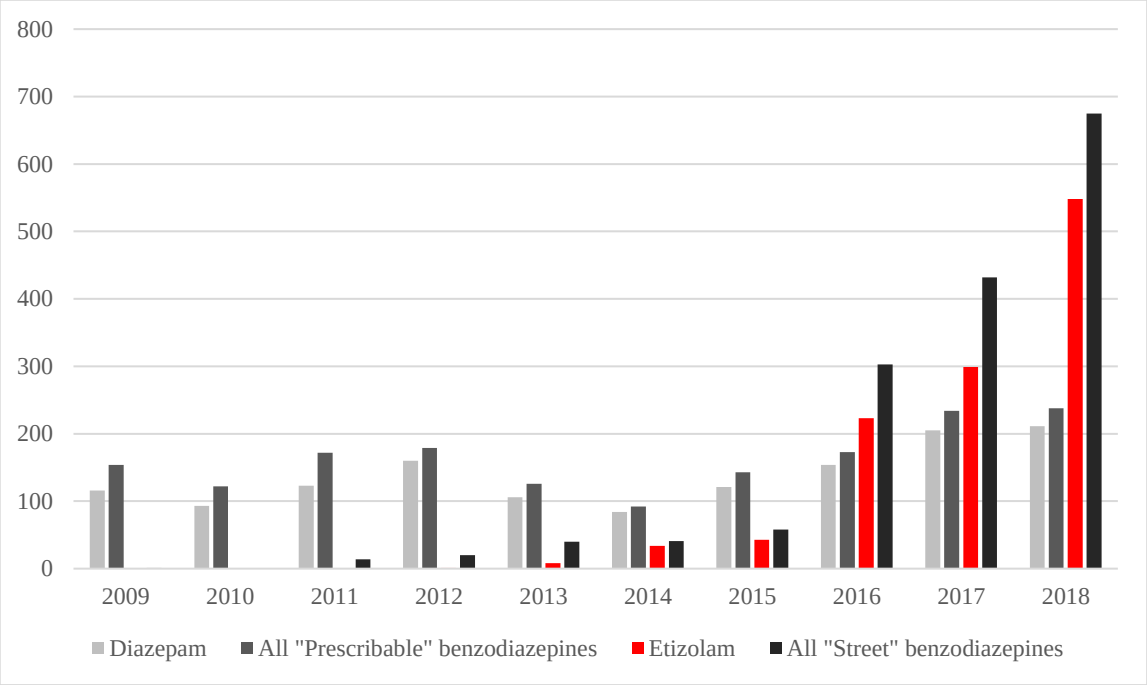

Figure 1- Benzodiazepine-related deaths in Scotland 2009-2018 (National Records of Scotland, 2019)

Appendix

Etizolam trade names

Arophalm (Nichi-Iko Pharmaceutical, Japan)
Capsafe (Ohara Yakuhin, Japan)
Depas (Abbott, Italy; Chong Kun Dang, South Korea; Tanabe Mitsubishi Pharma, Japan
Depas 1% (Tanabe Mitsubishi Pharma, Japan) Dezolam (Taisho Yakuhin, Japan)
Dezolam (Taisho Yakuhin, Japan)
E1 (Aarpik, India)
Eticalm (Towa Yakuhin, Japan)
Etilaam (Intas Pharmaceuticals, India)
Etisedan (Kyowa Yakuhin, Japan)
Etizola (Macleods, India)
Etizola Beta (Etizolam and Propranolol) (Macleods, India)
Etizolam Amel (Kyowa Yakuhin, Japan)
Etizolam EMEC (Sannova, Japan)
Etizolam KN (Kobayashi Kako, Japan)
Etizolam Nichi-iko (Nichi-Iko Pharmaceutical, Japan)
Etizolam Ohara (Ohara Yakuhin, Japan)
Etizolam SW (Medisa Shinyaku, Japan)
Etizolam TCK (Tatsumi Kagaku, Japan)
Etizolam Towa (Towa Yakuhin, Japan)
Etizolan (Kobayashi Kako, Japan)
Inxity (Archicare Limited, India)
Mozun (Tatsumi Kagaku, Japan)
New Zomnia (Molekule, India)
Nonnerv (Nisshin Pharmaceutical, Japan)
Palgin (Fujinaga Seiyaku, Japan)
Pasaden (Bayer, Italy)
Sedekopan (Choseido Pharmaceutical, Japan)
Sedekopan 1% (Choseido Pharmaceutical, Japan)
Sylkam (Dr. Reddy's, India)
Zoly (Grownbury Pharmaceuticals, India)
Etiz, Eitizzy, Etizest