



HSE update August 2020

The Changing Nature of the Benzodiazepine Market

Benzodiazepines

Benzodiazepines are a widely prescribed group of medicines with a range of clinical uses that include treating anxiety, insomnia, acute muscle spasms and managing alcohol withdrawal.

However, this group of medicines are often used outside of prescribing recommendations. They can be used by people, including those accessing addiction and homeless services as part of a poly drug use culture in Ireland. Like all medicines, benzodiazepines can produce side effects. They are also dangerous if mixed with other substances, particularly depressant type drugs such as opioids or alcohol.

There are many different types of benzodiazepines that range from short, medium and long lasting.

Some well-known types of benzodiazepines are Diazepam (Valium,D5/D10), Alprazolam (Xanax, Tranex), Lorazepam (Ativan), Triazolam (Halcion), Flurazepam (Dalmene), Chlordiazepoxide (Librium).

Benzodiazepines are commonly known as: 'Benzo', 'Xanax', 'Sticks', 'Street tablets', 'Xan', 'Up John', 'D5's', 'D 10's'.

In the past, much attention has been on the diversion of medicinal benzodiazepines. However, there has been an increase in the manufacturing and supply of illicitly produced benzodiazepines. We are aware that tablets sold by dealers or online may not be genuine prescription medication and are 'fake' copies of pharmaceutically made tablets. Some can contain what are considered new benzodiazepine-type substances or combinations of different substances.

What are new benzodiazepine-type substances?

New benzodiazepines are sometimes called 'novel', 'designer' or 'new psychoactive substances'.

New benzodiazepines can be:

- Newly developed substances that are closely related in chemical structure and pharmacology to traditional benzodiazepines but are often more potent at low doses.

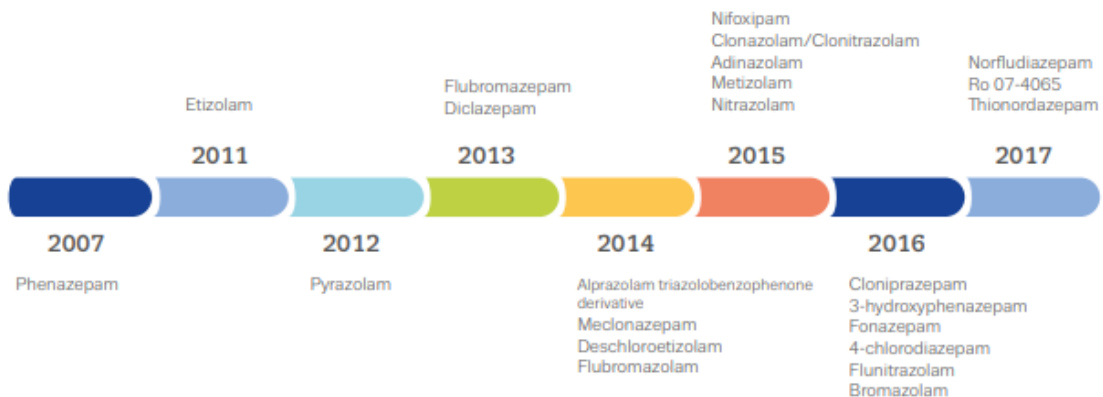


- Benzodiazepines that were developed many years ago but were never brought to the market. Some may be available in patient literature but have never undergone clinical trials.
- Some may be used in other countries but are not licenced for use in Ireland.

Limited information is available in relation to the health and social harms of newly emerging benzodiazepines.

Over the last decade, there has been an increase in the number, type and availability of these new drugs on the European drug market.

By the end of 2018, the EMCDDA was monitoring more than 730 new psychoactive substances, 55 of which were detected for the first time in Europe in 2018. These substances make up a broad range of drugs, such as synthetic cannabinoids, stimulants, opioids and at the end of 2018, 28 ‘new’ benzodiazepines. There are indications of increases in the quantities seized of opioids and benzodiazepine compounds. In most cases, new psychoactive substances are produced in bulk quantities by chemical and pharmaceutical companies in the Far East.



Concerns

NPS benzodiazepines appearing on the market are of concern due to high potency at low doses. This can produce strong sedation, respiratory depression and amnesia. Additional adverse effects include loss of coordination, drowsiness, dizziness, blurred vision, slurred speech, overdose and, in some cases, death. Risks are increased if one or more substances are used by the person, or if tablets are pressed to contain one or more substance

There is evidence in Scotland, where ‘street’ or unlicensed benzodiazepines were involved in 85% of the 792 deaths in 2018 where a benzodiazepine was implicated, while medicinal ‘prescribed’ benzodiazepines were reported in only 30%.

UK Alert 24th July 2020 ‘Evidence of harm from illicit or fake benzodiazepines’

A UK National Alert was issued on the 24th of July 2020 to drug treatment services and healthcare providers in relation to tablets being sold as benzodiazepines. Public Health England raised concern of the availability of, and harm from, illicit drugs sold as benzodiazepines, particularly when used in conjunction with alcohol and drugs with a respiratory depressant effect including gabapentinoids and opioids.

Significant concern was raised in relation to the nature of this market. This alert was based on evidence from toxicology results of illicit tablets being sold as diazepam, temazepam and alprazolam as well as evidence of recent hospitalisations, deaths and from police seizures. The alert highlighted tablets known as and/or marked

with 'DAN 5620' (on one side) and '10' (on the other), 'T-20', 'TEM 20', 'Bensedin' and 'MSJ' which may contain dangerously potent benzodiazepines or their analogues such as flubromazolam, flualprazolam and etizolam. Most of the tablets causing concern are blue (but they come in various colours) and these may stain people's mouths.

What new benzodiazepines have appeared in Ireland?

The potential for diverting licit prescription supplies to the illicit market has reduced due to tightening of prescribing practices, but of concern is the growing availability of these 'new' benzodiazepine type substances on the market in Ireland.

In Ireland, illicitly sources tablets are called 'street tablets' with newer varieties titled 'fake'. The most well know being 'benzo/Xanax sticks' or 'bars' that have been on sale for the past number of years.

Through analysis conducted by Forensic Science Ireland and the HSE National Drug Treatment Centre, we are aware of some of the novel substances that have been emerging in Ireland for the past number of years.

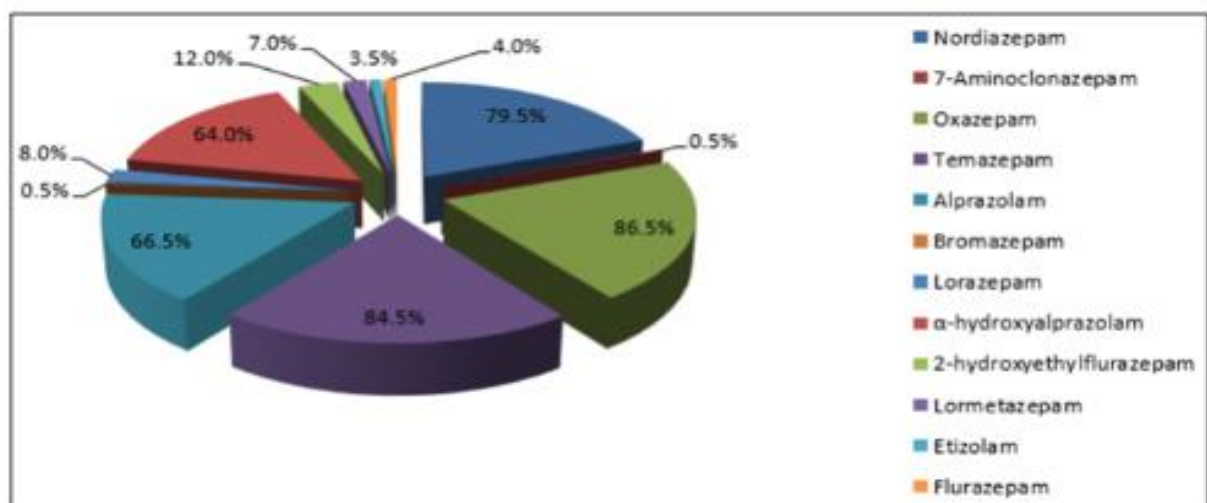
In 2016 the Forensic Science Ireland laboratory detected new benzodiazepines such as phenazepam, nitrazolam, etizolam and chlorodiazepam in drug seizures.

The HSE National Drug Treatment Centre conducted a specific study in 2019 to identify the emergence of newer benzodiazepine-type substances using a multi-residue method.

A total of 200 samples were analysed by LC-MS. The results were as follows:

(86.5%) oxazepam, (84.5%) temazepam, (79.5%) nordiazepam, (12.0%) 2- hydroxyethylflurazepam, (66.5%) alprazolam, (64.4%) α -hydroxyalprazolam, (8%) lorazepam, (7%) lormetazepam, (4%) flurazepam, (3.5%) etizolam, (0.5%) bromazepam, and (0.5%) 7-aminoclonazepam.

One patient was positive for six benzodiazepines or metabolites: nordiazepam, temazepam, oxazepam, alprazolam, and α -hydroxyalprazolam and etizolam, probably indicating diazepam, alprazolam and etizolam use.



Current concerns

This market has been changing for some time, it is difficult to identify if COVID-19 has impacted on this market. What is evident is that the tablets available nationally continue to change quickly with new varieties, brands and colours emerging. This market is constantly evolving, services should keep informed of trends and continue to link in with [drugs.ie](https://www.drugs.ie) for up to date development and links to reports.

As of the date of this publication, we are concerned regarding the below substances or combinations of substances appearing.

Etizolam

- From our knowledge, etizolam appears to be the most common benzodiazepine-type substance emerging in substances. It has appeared in falsified medication such as those labelled a Z type drugs and Xanax.
- It is readily absorbed after oral ingestion and it has a shorter half-life than many benzodiazepines. It was patented in the 1970s and has been marketed since the early 1980s. It is sold commercially as a medicine in a limited number of countries (Japan, Italy and India).
- It is potent at low doses. A 1mg tablet is equivalent to a 10mg diazepam (Valium) tablet.
- Could present as tablets marked as 'Etizolam' or 'EZ', but is commonly emerging in falsified products.
- It was first notified to the EMCDDA EU Early Warning system in 2011.
- In Ireland, it was first documented by Forensic Science Ireland in their 2016 Annual Report.
- Etizolam was first recorded in drug-related death data in Ireland in 2015 with 7 deaths recorded. Following this, 6 were recorded in 2016 and 5 in 2017.
- There were 575 deaths in Scotland in 2018 for which NPSs were implicated in, or potentially contributed to the cause of death. In 571 cases, the only NPSs present were benzodiazepines (usually etizolam, but sometimes – for example - diclazepam or phenazepam)

Flualprazolam

- Flualprazolam is a potent substance which has sedative effects similar to other benzodiazepines but much higher potency and a relatively short onset of action, similar to alprazolam (Xanax).
- It has strong depressant effects on the central nervous system, presenting a high risk of severe poisoning.
- Flualprazolam has recently emerged as a substance of concern in Ireland, contained in falsified Xanax sticks.
- Flualprazolam was patented in 1970 but was never marketed as a medicine.
- There is limited pharmaceutical information on flualprazolam, although said to be very similar in structure to alprazolam and flubromazolam, can cause sedation and impairment.
- First notified to the EMCDDA Early Warning System in November 2017 following a police seizure of powder in Sweden. Following this, more than 30,000 flualprazolam tablets were seized during 2018 in Europe.
- Seizures in Europe have been linked to falsified benzodiazepines.
- The Welsh Emerging Drug & Identification of Novel Substances (WEDINOS) found that, over the course of 2019, the presence of flualprazolam in samples increased significantly, with identifications almost doubling from 17 in the second quarter, to 30 in the third quarter of 2019. In many cases, these

samples were counterfeit diazepam tablets or white 'Xanax' bars. This is of concern because of the confirmed potency of this compound and its links to deaths across Europe.

- There have been 12 flualprazolam associated deaths in the UK.

Xanax sticks

- Xanax sticks have been used by people attending addiction services for some time. They are predominantly white but green and orange varieties have recently been in circulation. Other colours may also be available.
- Brands and varieties of sticks can be noted though online market places such as 'Red Devils'
- Samples analysed in Ireland have found that Xanax sticks can vary. Some samples have contained alprazolam as the only active ingredient, whereas others can contain multiple substances, including new benzodiazepine-type substances.
- The dosage of substances within Xanax sticks could range.



Nike brand tablets containing Tramadol and Alprazolam

- An Advisory Notice was issued by the HSE National Social Inclusion office in December 2019 regarding the risks associated with these tablets to highlight concerns regarding an increase in the risk of overdose or death.
- We are aware of adverse behavioural reactions linked with tablets branded 'Nike' in different locations in Dublin.



'Ksalol' brand tablets

- Known as 'Castles' by people who use drugs.
- Active ingredient believed to be Alprazolam, if not falsified.
- Appeared in drug seizures in Ireland in 2017, and documented in seizures reported in the media again during the COVID-19 period.
- Perceived as being a 'stronger' version of alprazolam.
- Concerns were recently raised by communities in relation to this brand of tablet during COVID-19.
- They are available online via the surface web and appear to be emerging in seizures from Eastern European Countries.



Harm reduction advice for people who use drugs

It's risky to take any benzodiazepine that has not been prescribed to you and it's safer not to use.

Always be extra careful when taking tablets, remember you can't be sure of the contents or strength. If you do make a decision to take an illicit or 'new' benzodiazepine then remember:

- **Tablets sourced without a prescription:** You can't trust the contents or dose 'strength'
- **There are new substances and combination of substances which increase your risk of overdose**
- **A tablet could contain a mixture of substances**
- **Start very low and go very slow** – take a test dose, slow down and leave at least two hours before taking more
- **Don't use alone** – have someone with you or let someone know
- **Don't use with other substances**, including with alcohol and prescription tablets. You increase the risk of overdose if you use with other substances like heroin, methadone, Lyrica, alcohol and other prescription medication
- **Benzodiazepines vary from short, medium and long lasting.** They could be active in your system for some time after use.
- **Place sleeping people in the recovery position.**
- **Avoid injecting tablets** - Injecting tablets increases the risks and could also seriously damage your veins and is associated with collapsed veins, clotted veins, infected skin and poor circulation.
- **Don't leave anyone alone who becomes unwell after using tablets.**
- **Don't be afraid to get help** – It's important to get medical help immediately if you or a friend becomes unwell after using by calling 999 or 112
- **Avoid using benzos to cope with difficult situations.** Talk to your GP or other professional.
- **Avoid using if you are feeling low, anxious, depressed or have a history of mental health concerns.**

Tolerance, dependency and withdrawal

Tolerance to benzodiazepines develops quickly which can lead to people using more, increasing the risk of dependency as well as overdose.

It is dangerous to suddenly stop using benzodiazepines if you have developed a dependency. Don't suddenly stop using as withdrawal can be unpredictable and could cause fits or seizures. Get medical support if you want to stop using.

Support for benzodiazepine use

- Talk to the persons GP about treatment – this could be community based or in a residential setting. The setting will be determined by individual need.
- Community Detoxification Guidelines ‘Benzodiazepines’ available on Drugs.ie.