

Drug Facts: Benzodiazepines & related compounds

AKA: *Benzos, tranx, sleepers, downers.* Specific drugs are referred to by their chemical name, brand name, and some have got slang names. Brand names vary around the world adding to confusion so for example the drug Diazepam is known by the brand name Valium in the UK, but is also known internationally by many other trade names including Mano, Anxol, Placidox and many other.

Related Compounds: Benzodiazepines are linked by a common chemical structure. Closely related compounds include the ***thienodiazepines***, and other similar drugs which aren't strictly benzos as they have a different chemical structure. The reasons for use and risks are however likely to be the same. Likewise, closely related compounds such as the "Z-drugs" (e.g. Zopiclone and Zimovane) are not benzos but for treatment and harm-reduction purposes are interchangeable.

More common benzodiazepines include:

Name	Brand	Slang	Notes
ALPRAZOLAM	Xanax	Xs, Xans	Not an NHS stock drug; Available in UK on private prescription
CHLORDIAZEPOXIDE	Librium		Primarily used in in alcohol detox
DIAZEPAM	Valium	<i>Vallies, blues</i>	Widely prescribed for daytime anxiety
FLUNITRAZEPAM	Rohypnol	<i>Rohies, rufies</i>	Strong associations with drink spiking
NITRAZEPAM	Mogadon	<i>Moggies</i>	
TEMAZEPAM	Normison	<i>temazies, jellies, eggs</i>	Used to be widely injected
ETIZOLAM			Widely available as an illicit benzo; not prescribed in UK

Source: Benzodiazepines are widely prescribed as sedatives, to combat anxiety, as skeletal muscle relaxants, anti-epileptics and anti-convulsants. Benzodiazepines have always leaked on to the streets and are widely used outside of prescription settings.

For a number of years an additional route for sourcing benzodiazepines was the overseas prescription market. A number of websites, located outside the UK, would offer an online "consultation" with a "doctor" and then a "prescription" would be issued and "benzos" supplied. In practice the variability of the supplied pills was massive and many of these websites have been shut down.

From 2009, abandoned experimental benzodiazepines and novel ones appeared on the UK drugs market including etizolam, pyrazolam and flubromazepam. These were initially not covered by the MoDA and were legally sold on-line and via 'head-shops.' These novel benzos were almost all brought under the MoDA in May 2017. Any not covered or emerging since then are automatically covered by the Psychoactive Substances Act 2016.

At present the key sources of benzodiazepines in the UK are:

- NHS GP prescriptions

- Private Prescriptions
- Leaked Pharmaceutical products
- Imported internet and darkweb sources
- Street supply of home-pressed and imported pills

Trends: GPs are regularly reminded not to over-prescribe benzodiazepines and those on long term prescriptions are meant to have these reviewed and where possible be tapered off their medication.

This approach has been nominally successful with a significant and sustained drop in benzodiazepine prescribing.

However as the charts below show in the first instance the drop in Benzo prescribing represented in part simply a shift from one sedating drug to another. Initially the Z drugs started to get used in place of Benzos. They were initially not controlled drugs and not perceived to be addictive.

Subsequently further drops in benzo prescribing were balanced by increased use of the gabapentinoids.

Figure 1: Prescriptions dispensed in the community in England from 1980 to 2009 (from Reed et al, 2011)

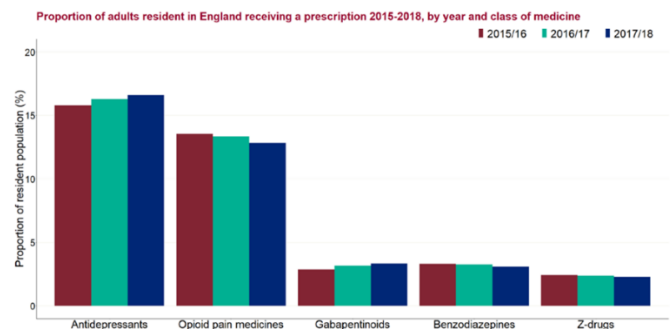
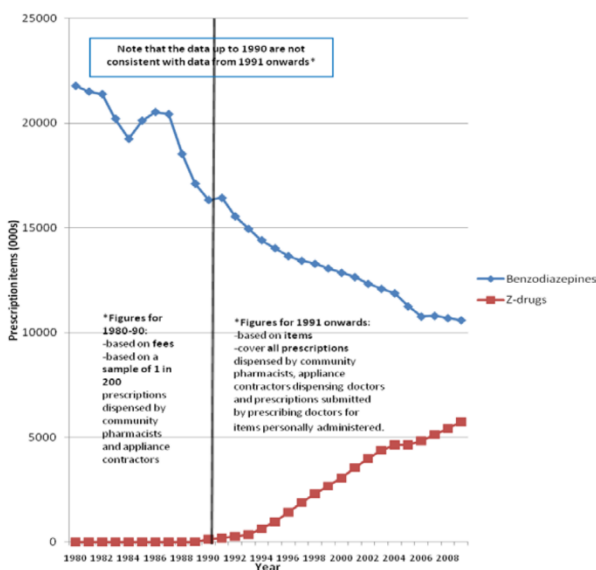


Figure 1: Proportion of adults resident in England receiving a prescription 2015 to 2018, by year and class of medicine

Subsequently even though benzos and related drugs became harder to get through legitimate routes, the massive growth of legal benzos as part of the NPS scene and their subsequent consolidation as an illicit street drug has meant that in some areas illicit benzos are more of an issue now than leaked prescribed benzos.

The CSEW Survey of UK drug trends says that 0.8% of 16-25 year olds disclosed use of benzos (2019/20). This figure is down from 2017/28. This figure probably under-represents the true picture. It may be that the nature of the questions posed and exclusion of key benzo-using populations (prisoners, homeless, hostels, bail hostels) means figure is less than accurate.

Appearance: Raw benzodiazepines are generally white powders, which are then pressed into pills, put in capsules or put into ampoules with appropriate colour, coating, printing etc.

Most are distributed as tablets or capsules. A small number of unregulated compounds are sold as powders. Benzos may also turn up as a cut in other drugs, especially heroin. Overdoses linked to “strong heroin” or “fentanyl” in heroin often turn out to be benzos cuts.

A few also come in preparations for injection, such as Valium ampoules, which command a higher street value.

Different brands of drug will vary from company to company. Tablets will vary in colour, shape and markings. The appearance of each drug varies widely so visual pill identification is difficult.

While it's no guarantee that pills that are sold in intact foil strips with UK specific labelling are less likely to be counterfeit.

Drugs supplied loose, or in overseas packaging are more likely to be counterfeit.

The mainstay of the street benzodiazepine market has, since the 80s, been **diazepam**. The most widespread and popular strength, a 10mg tablet, is often a scored blue tablet. As a result, people manufacturing tablets to sell as diazepam invariably produce a blue tablet. These can vary massively in consistency and strength. Some are merely white powders, dyed blue and compressed into tablets.



Alprazolam (Xanax) has become increasingly popular in the UK. As it is not widely prescribed on the NHS, Alprazolam sold in the UK may be from private prescriptions, overseas pharmacies, or grey-market tablets batched from raw alprazolam powder. These can vary greatly in strength and consistency. Alprazolam is typically sold as white, scored bars with XANAX printed on them.

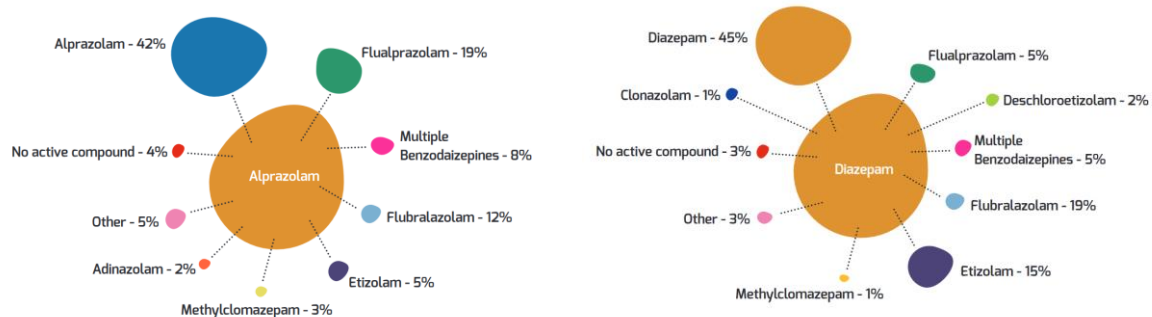
Cost: At a street level, benzodiazepines have a very low value, typically around 50p per tablet. Ampoules can cost £5 and are rarely available now. Depending on dose and quantity stronger pills like Xanax can sell for between £1-5 depending on claimed dose.

Quality: If pills are genuine pharmacy product, quality is assured. However, it is impossible to correctly identify loose drugs in this family by eye, let alone assay the strength, so mistakes in strength and name are frequent amongst those purchasing non-medical products.

With so many imported, fake, unlicensed and novel products entering the market, the risks with non-pharmacy products will increase. Products could contain something stronger, weaker or different.

It is possible to send pills to a service like WEDINOS <https://www.wedinos.org/> to find out which drug(s) are present in a batch. Whilst useful to identify compounds, WEDINOS doesn't share information about dose or level of different compounds so is of limited benefit from a harm reduction or dependency/taper point of view. While the service may indicate a blue pill contains diazepam and etizolam it won't say how many milligrams of each drug are present.

WEDINOS analysis shows high level of variability of street benzos. Less than half of tested pills contained the intended drug in the case of Alprazolam or Diazepam submitted for testing.



[Source WEDINOS Annual Report 2021-22]

Methods of Use: Tablets are designed for oral use, though some users crush and inject tablets. As diazepam has very poor solubility in water this is damaging and not very effective. Diazepam itself is relatively short acting; on ingestion it is metabolised in to a long-acting metabolite nor-diazepam so the risk is that people need to redose more frequently if taking via routes other than swallowing. There are some reports of snorting, especially of novel, unregulated benzodiazepines.

Detection: Immuno-assay (urine test) kits can detect a range of benzodiazepine metabolites and related compounds. They are not sensitive for all benzos. This varies according to:

- the test kit used
- the drug used
- quantity of the drug used
- time since the drug was used.

High dose, lower potency, longer acting benzos structurally closer to diazepam will show up on most tests.

Shorter acting drugs, highly potent drugs and drugs that produce other metabolites may not show up.

In situations where a person is adamant that they are using a benzo-type drug but the urine tests negative, it could be that this specific drug at this specific dose

doesn't show up on this specific urine test. Double checking via a different brand of test or, ideally, via GC/MS would be a better option.

Mechanism of Action: Benzodiazepines interact with the GABA system in the brain. The regulatory neurotransmitter gamma-amino butyric acid (GABA) plays a role in moderating electrical activity in the brain. As GABA levels increase, so electrical activity in relevant neurons goes down.

Some drugs, like GHB and Barbiturates, are GABA agonists (mimics).

Benzodiazepines are not thought to be full GABA mimics. Instead, benzodiazepines bind to Benzodiazepine Receptors (BZ receptors) and appear to increase the regulatory effect of GABA. They need GABA, or a GABA-mimic present to work.

Specific benzodiazepines are believed to be more active at different BZ receptors. This may result in different benzos having greater or lesser sleep-inducing, muscle relaxing or anxiolytic effects.

The system to an extent self-regulates. As electrical levels drop in the brain it reduces levels of GABA release. As GABA drops the benzos can't work.

Importantly, if a GABA-mimic (such as alcohol) was present this self-regulation system can't work. The co-presence of a GABA mimic AND benzos means that brain activity can be reduced to dangerous or fatal levels.

There are thought to be at least three different types of Benzodiazepine (BZ) receptor. These are thought to impact differently on sleep, muscle relaxation and anxiety. Specific benzos may bind to these receptors differently, making some drugs more useful for sleep, others for muscle spasm and for anxiety.

Benzodiazepines are thought to mimic naturally-occurring brain chemicals, which have been described as *endozepines*. However how these chemicals may occur is poorly understood.

Reasons for Use: Benzodiazepines are still used medically for a range of conditions including:

Anti-convulsants
muscle relaxant

anti-anxiety (anxiolytic)
amnesiac

sleep-inducing (hypnotic)
alcohol detoxification

Non-medical use follows similar patterns, self-medicating for a range of conditions including anxiety and insomnia. They are also popular as "come-down" drugs following use of stimulants. The sense of intoxication when used with opiates or alcohol is greater, so these combinations are widely used. This brings a bigger risk of overdose.

Benzodiazepines are moderately euphoric, especially in users who have little tolerance.

Benzos can help people not remember or remember without emotion making them

popular choices for managing traumatic memories. They can create a sense of detachment, depersonalisation or “derealization,” making the real world feel less present or intrusive.

The sense of calm, detachment, well-being and relaxation from benzos makes them highly sought after amongst people experiencing negative mental health symptoms.

Strength: Important: this information assumes that we know which benzo is being used. As street benzos are of unknown strength and purity this information cannot be used to work out dose equivalence for street benzos.

Benzodiazepines vary significantly in strength. They are generally compared in potency using diazepam (Valium) as a benchmark. Potencies are expressed in relation to 10mg of diazepam. 5mg of Alprazolam (for example) is equivalent to 10mg of diazepam. Alprazolam is around twenty times the strength of diazepam. Very strong benzos such as Flubromazolam are believed to be 40x the strength of Diazepam. If a pill contained 1mg of flubromazolam, this would be the equivalent of 40mg of diazepam (i.e. 4 x 10mg diazepam.)

Relative Potency

KFX
Learning of Substance

Benzodiazepines usually compared against a benchmark - typically 10mg of diazepam

POM/CD in UK	CD non POM (as at 31.5.17)	Discontinued in UK
<p>10mg diazepam Valium → 1-1.5hrs ↔ 20-100 hrs</p> <p>7mg midazolam Dormicum → 15 mins ↔ 1-6hrs</p> <p>0.5mg alprazolam "Xanax" → 1-2hrs ↔ 9-20hrs</p> <p>1mg flunitrazepam Rohypnol → .5-3hrs ↔ 36-200hrs</p> <p>10mg nitrazepam Mogadon → .5-7hrs ↔ 15-38hrs</p> <p>20mg temazepam Normison → .5-3hrs ↔ 8-22hrs</p> <p>0.5mg clonazepam Rivotril → 1-4hrs ↔ 18-50hrs</p> <p>1mg Lorazepam → 2-4hrs ↔ 10-20hrs</p> <p>15-30mg flurazepam Dalmane → 1-1.5hrs ↔ 40-250hrs</p> <p>20mg oxazepam → 3-4hrs ↔ 4-15hrs</p> <p>25mg chlordiozepoxide Librium → 1.5-4 ↔ 36-200 hours</p>	<p>0.25mg Flubromazolam → 30-60 mins ↔ 12-18 hrs</p> <p>0.5mg Clonazolam → 10-30mins ↔ 6-10hrs</p> <p>1mg Nifoxipam → 45-120min ↔ 10-75 hrs</p> <p>1mg Etizolam → .5-1hr ↔ 8hrs</p> <p>1mg Pyrazolam → 1-1.5hrs ↔ 9-12hrs +</p> <p>1mg Diclazepam → 1.5-4 hrs ↔ 42hrs+</p> <p>2-4mg Metizolam → 30-90 mins ↔ 5-8 hrs</p> <p>2-4mg Deschloroetizolam → 1-5 mins ↔ 8-10hrs</p> <p>5mg Flubromazepam → 4-8hrs ↔ 100hrs</p> <p>1-2mg Cloniprazepam → 15-45mins ↔ 6-9hrs</p> <p>0.5mg Phenazepam → 2-3 hrs ↔ 60hrs</p> <p>0.25mg/0.5mg Flualprazolam → 30mins ↔ 6-14hrs</p>	<p>0.5mg triazolam Halcyon</p> <p>1-2mg (estazolam)</p> <p>5-6mg bromazepam</p> <p>15mg Clorazepate</p> <p>20mg Quazepam</p> <p>Adinazolam Bromazolam 4' Chlorodiazepam Fonazepam Meclonazepam Nitrazolam</p> <div style="border: 1px solid black; padding: 2px; font-size: 0.7em; margin-top: 5px;"> PSA: cinzepam, cloxazolam, gidazepam </div>

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Dose ranges: Medical guidance specifies upper dose ranges for medical use. In the UK, for adults with anxiety, the upper dose range is 30mg, with 60mg being the BNF daily maximum for muscle spasm.

In street settings upper dose range will vary massively according to tolerance. Some people will build up dose tolerance far above therapeutic dose range.

Onset and Duration: As with strength and dose, benzodiazepines vary significantly in terms of how fast they start working, and how long their effects last.

In the diagram above the first arrow is an indication of onset and the second is the duration of effect. Slow-onset benzodiazepines increase the risk that a person will re-dose before drugs have started working properly.

Some benzodiazepines produce active metabolites, with very long half-lives. Some can last 100-200 hours or longer. These long-acting drugs increase the risk of building up tolerance, and that any later drug use will be taking place on top of residual benzodiazepines. For example, diazepam used on Sunday will probably still be in the system on Tuesday or Wednesday. This means that alcohol use on these days is effectively taking place on top of benzodiazepines.

Indicators of Use: Aside from physical evidence such as packaging, there are few markers for benzo use. Illicit fake diazepam can cause blue staining to lips and tongue. Otherwise indicators are simply drowsiness, relaxation and possibly appearing drunk, but without the smell of alcohol.

Whilst older benzos will show up on urine tests, some of the newer products such as Etizolam are sufficiently structurally different so won't show up on some urine tests.

Effects: Benzos can cause physical relaxation, reduce stress and anxiety. Users may become drowsy or fall asleep. They can have a big impact on memory, causing amnesia. They can also cause slurred speech, clumsiness, and confusion. People report euphoria and some people find benzos disinhibiting, in the same way that alcohol is. Some users gain a feeling of invulnerability or invisibility when using benzodiazepines. They may find this useful when, for example, shoplifting. Some users experience depression and, paradoxically, a few users become over-excited or violent.

Dependency: When used within a supervised medical regime, benzodiazepines should not be used for extensive periods as tolerance develops rapidly and withdrawal can be an unpleasant and, in some cases, dangerous process. After a few weeks, and certainly within a few months, their therapeutic value decreases. The person using them will still experience effects, some of which are placebo and some of which are relief from withdrawal symptoms.

For physically dependent users, abrupt withdrawal can cause a range of symptoms. These can range from the mild to the life threatening. Several factors including underlying physical and mental health conditions, duration of use, dose and expectations can influence the experience of withdrawal.

Symptoms can range from mild anxiety and sleep disruption to severe panic, phobic conditions, hallucinations, and psychosis. Physical symptoms can range from mild shakes and tremors through to severe convulsions.

Withdrawal from Benzodiazepines should always be tapered rather than done suddenly.

Where there is evidence of high doses, long-term use, or where the person has a history of illness such as epilepsy, withdrawal should be done under medical supervision. **IT IS POSSIBLE TO DIE DUE TO SEVERE BENZODIAZEPINE WITHDRAWAL.**

In order to reduce physical and psychological discomfort from benzo withdrawal a common approach, popularised in the so-called "Ashton Manual" was for conversion from whichever benzo was being used on to an equivalent dose of Diazepam and then conduct a slow taper in steps of 1-2mg or less over weekly intervals.

The approach had great utility where people were on NHS dose ranges of up to 30mg of diazepam and could see reductions completed within 30-60 weeks.

The situation is now far more complex and at present there is a lack of effective treatment for people dependent on non-prescribed benzos.

The problem has a number of dimensions:

- with street benzos we don't know the strength or type of pill making dose-equivalence harder to calculate;
- The BNF prescribing limits are 30mg for anxiety and 60mg for spasms;
- Benzos aren't currently licensed as a detox treatment;
- with high strength newer benzos, a person can have developed a habit equivalent to 100-200mg easily; a daily 4 x 2mg Alprazolam habit is the same as a 160mg diazepam habit;
- there is a reluctance on the part of GPs and drug treatment providers to prescribe at all for benzo dependency unless it's a taper from an existing prescription;
- those that do typically only prescribe up to 30-40mg, and rarely offer the slow tapers proposed in the Ashton Manual. <https://www.benzo.org.uk/manual/>

Detoxes with a starting dose of 30mg and reduced over 1-3 months is the norm where treatment is available;

- there is always going to be a need for psychosocial support during and after benzo treatment. However mental health teams will typically not see people while they are still receiving drug treatment or perceived to be "still using" meaning that it will fall to drug services to address underlying issues such as anxiety or traumatic memories until other services are prepared to engage.

This lack of provision and strategy for people who are dependent on benzos outside of medical settings has created a huge obstacle for people who want to address benzo dependency.

A gold standard service would be able to:

- have street tablets assessed for strength and composition
- calculate a dose equivalent and prescribe to that
- do a taper at a pace comfortable for and in agreement with the person using
- engage from the start with psychosocial services

- where customers are using opiates, alcohol and benzos problematically, undertake stabilisation prescribing on the benzos and address alcohol and opiate use sequentially before addressing the benzos.

In lieu of such a service which doesn't exist in the UK, the minimum service offering should be:

- assessment of likelihood and severity of withdrawal symptoms
- assessment of assets and resources (housing, support)
- assessment of aggravating factors (mental health, epilepsy, trauma)

- for high risk individuals, inpatient detox would be required;
- for individuals with a high risk of convulsions substitute prescribing up to 60mg to manage symptoms, faster withdrawal down to 30mg and then slow taper from 30mg.
- for individuals with lower risk of fitting taper from 30mg.

The KFx screening pack for Benzodiazepines and related compounds can be found here: <http://www.kfx.org.uk/resources/XanaxSAT9.19.pdf>

Overdose: There is a low risk of fatal overdose when benzodiazepines are used on their own. They have a very high therapeutic index, and while there's a risk of unconsciousness or possible coma, the risk of death is relatively low. This risk is raised through ignorance as to the strength of various tablets.

However, in combination with other drugs, especially alcohol and opiates, the risk of fatal overdose is far higher. A large number of dependent drinkers and people on opiate substitution therapy are also prescribed diazepam, increasing risk of dangerous polydrug use.

Death rates featuring benzodiazepines have dramatically increased over the past two decades. In 2000 220 deaths featured benzos, increasing to 436 in 2019 and 507 in 2020. This has in large part been driven by polydrug use and an increase in stronger non-prescribed benzodiazepines.

Opiate antagonists are not useful in benzo only or benzo/alcohol overdoses. Where benzos are used with heroin, use of naloxone is useful as it can restore respiration suppressed by opiates.

It is therefore important to stress the importance of calling an ambulance to all overdoses in case it is a benzo-primary overdose, not an opiate-primary.

There is a blocker for benzo which can be used in OD but as it can cause convulsions, is less suitable for peer distribution like naloxone.

Other risks: When tablets are crushed for injection, this brings with it a range of associated health risks. Of specific concern were Temazepam Capsules. These capsules were originally introduced as a response to liquid from temazepam capsules being drawn up for injection. The reformulated capsules contained Gelthix, a jelly that was intended to discourage injecting. However, users found that heating the jelly made it become liquid, and so injected it. However, as the liquid cooled to

body temperature, the gel solidifies, and a large number of gruesome injecting injuries were reported. Gel capsules have not been legitimately available in the UK for over ten years.

Legal Status: Most Benzodiazepines are class C drugs and nearly all are Schedule 4i drugs, meaning that they can only be supplied, produced and possessed by those authorised to do so. The law on Schedule 4 drugs changed in 2002; prior to that it was not an offence to possess benzodiazepines without prescription.

The penalty for supply of a Class C drug was increased from 5 years to 14 years but significant sentences are not common.

Temazepam and Flunitrazepam (Rohypnol) were rescheduled Schedule 3 drugs.

Formerly unregulated benzodiazepines (such as etizolam) were brought under the MoDA in May 2017. The benzos were added as a list rather than via an “analogue” clause which means that there is scope for developing new benzos that will not be covered by the MoDA. Any such emergent benzos will automatically be covered by the Psychoactive Substances Act 2016.

Other Information: Benzodiazepines were introduced and have largely supplanted the BARBITURATE group of drugs, which were widely prescribed and widely misused in the seventies. Benzos were seen as preferential to barbiturates as the risks of overdose, dependence and side-effects were thought to be less. They were massively overprescribed. As awareness grew of the risks of tolerance and dependency this overprescribing has been reduced but there are still a huge number of people inappropriately prescribed. Unfortunately, in a knee-jerk reaction to this over-prescribing some doctors are removing people from prescribed medication with fast tapers and a lack of additional support. Some of these benzo patients get referred to drug services. Increasing numbers end up getting stronger benzos through other routes so the well-intentioned restriction in prescribing is creating a bigger problem by pushing people on to the unregulated street market.

Prescribers are very aware of benzodiazepine over prescribing, and in many areas greater care is now taken to reduce and monitor prescribing. However, a number of other drugs have been less closely monitored and have increased in popularity.

Initially, the “Z-Drugs” (Zopiclone, Zimovane, Zaleplon) increased and of course started to be misused. The law in relation to some of these has now been tightened and they are now Controlled Drugs.

More recently, Gabapentin and Pregabalin have emerged as the latest of the sedating drugs to shift from medical to non-medical settings. Although not benzodiazepines, they work in the same parts of the brain, with similar risks in terms of tolerance, dependency and overdose.

As misuse and deaths featuring these drugs went up they too were added to the Misuse of Drugs legislation.

Whilst the use of prescribed diazepam is undoubtedly lower, levels of benzo-type drugs (including illicit market, novel psychoactives, and similar prescribed drugs) means overall use is probably increasing. Workers have reported people entering treatment with staggeringly high levels of benzodiazepine dependency, built up exclusively using street benzos.

Benzos are used recreationally in a number of settings. Alcohol and benzos are used together to enhance and increase intoxication. Some stimulant users take benzodiazepines to alleviate the "come-down" from speed, Ecstasy or cocaine, and to promote sleep.

It is not uncommon for dependent heroin users to use benzodiazepines when heroin is unavailable, or low quality. It is also used to help offset some of the symptoms of withdrawal. The use of benzos on top of prescribed opiates - such as with methadone or Subutex - is also common as it can make the effects of the opiates feel stronger. Such use increases risk of overdose.

Many people self-medicate with benzodiazepines to alleviate mental discomfort caused by mental health problems, painful memories, or to escape unpleasant circumstances. For such users, where unsupervised use may be long-term and extensive, careful assessment of needs, of underlying reason for the drug use, and comprehensive care plans are likely to be needed to achieve reduction and cessation of drug use.

Alongside opiates, alcohol and strong stimulants, benzos remain a core feature of the UK drug scene. Despite being such significant drugs, the level of training and range of services for people using benzos is very limited.



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