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Evidence review: Current trends in benzodiazepine use in Scotland

HEALTH AND SOCIAL CARE

social research

Evidence review: Current trends in benzodiazepine use in Scotland

Key Findings

- Motivations for benzodiazepine use among people who use drugs are wide-ranging and have been evidenced to include a range of psychological, social, economic, and supply-driven factors. Motivations often include the self-management of psychiatric disorders and adverse experiences; their pleasurable effects, and affordability/ease of access.
- In 2020, benzodiazepines were implicated in 73% of drug-related deaths (DRDs), or 974 out of 1,339, continuing the steep rise in benzodiazepine deaths since 2016. Deaths from 'street' benzodiazepines accounted for 66% of drug-related deaths in 2020, the majority of which were related to etizolam.
- There is evidence of high benzodiazepine use and harms among people who use opioids, in addition to high frequency of use and consumption of high doses. In 2020, opioids were implicated in 94% of benzodiazepine-implicated deaths, while heroin/morphine were implicated in 49%.
- Numbers of benzodiazepine-implicated deaths in 2020 were highest for those in the 35-44 year age bracket, closely followed by the 45-54 year age bracket; and higher among men, who accounted for 74% of benzodiazepine-related deaths.
- Hospital stays for sedative/hypnotics (including benzodiazepines) have increased sharply since the mid-2010s to 54 stays per 100,000 in 2020/21, the highest recorded rate across the time series.
- Etizolam was the second most commonly seized drug after cannabis in Scotland in 2019/20, with approximately 5.3 million benzodiazepine tablets seized by Police Scotland, compared with 2.1 million tablets seized in 2018/19. Etizolam accounted for 94% of benzodiazepine seizures in 2019/20.
- Diazepam prescriptions for specialist drug treatment have decreased by 67% since 2006/07.
- In 2019/20, 2,495 people out of 10,900 individuals recorded on the Scottish Drug Misuse Database (SDMD) (29%) used diazepam in the month before entering treatment.
- In 2019/20, 882 of 8,573 individuals assessed for a new specialist drug treatment episode (10%) recorded diazepam as the main drug for which they were seeking treatment.
- Current UK guidelines for the treatment of substance dependency recommend minimising long-term prescription of benzodiazepines, while recent guidelines published by the Drug Deaths Taskforce advocate for some benzodiazepine prescribing in a harm reduction framework.

1. Introduction

Benzodiazepines and similar drugs such as z-drugs[1] are widely prescribed in the treatment of a variety of conditions, ranging from anxiety, insomnia, and seizures to musculoskeletal pain and palliative care. The use of both prescribed and non-prescribed or 'street' benzodiazepines has been well-documented among people who use drugs in Scotland since at least the 1980s, however recent years have witnessed a sharp increase in benzodiazepine-related and benzodiazepine-implicated harms and deaths, largely due to street benzodiazepines.[2] There has been a similar rise in benzodiazepine-related hospital admissions.[3]

The purpose of this paper is to present an overview of current knowledge of trends around benzodiazepine-related deaths, hospital admissions, police seizures and prescribing practices, and to draw together key considerations for further discussion. The paper also presents an annotated bibliography of studies relating to benzodiazepines in Scotland (Annex A), which informs some of the considerations presented.

2. Key trends

2.1 Motivations for use

There is a general lack of evidence relating to the reasons for increased prevalence of benzodiazepines in Scotland, although a number of recent studies indicate a complex range of factors. These include changes in prescribing practices (specifically a significant decrease in benzodiazepine prescribing throughout the 2000s); widespread availability due to illicit overseas imports; and vastly increased domestic production of illicit benzodiazepine tablets. There are similarly a range of other issues associated with drug dependency and problematic drug use in Scotland, such as high rates of deprivation, high social inequality and historical social policy.[4]

Motivations for use have been varyingly explored in literature, broadly encompassing a range of psychological, social, economic and supply-driven factors. For example, benzodiazepines are often used to self-manage psychiatric disorders, anxiety, insomnia, substance withdrawal symptoms, and as a means of coping with traumatic experiences, grief and loss, boredom, and isolation. They are also used for their pleasurable effects and their ability to both alter perceptions of time and enhance the effects of opioids and other substances. Their affordability and ease of access likewise comprise motivations for use.[5] [6]

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[1] Z-drugs have different chemical structures to benzodiazepines but exhibit broadly similar effects.
[2] National Records of Scotland (2021). Available at: Drug-related deaths in Scotland in 2020, Report (nrscotland.gov.uk).
[3] Information Services Division (ISD) (2021). Available at: Drug-Related Hospital Statistics (ISDscotland.org).
[4] McAuley et al. (2021). Available at: From the clinic to the street: the changing role of benzodiazepines in the Scottish overdose epidemic (sciencedirect.com).
[5] Neilson and McAuley (2020). Available at: Etizolam: A rapid review on pharmacology, non-medical use and harms - PubMed (nih.gov).
[6] Roe (2020). Available at: Echoes of endlessness : time, memory, and experience for heroin users in Scotland (ethos.bl.uk).

A recent long-term ethnography of polydrug use in Scotland Roe, 2020 explored in part the experiences of people who use benzodiazepines, including motivations for use and contextual factors underpinning substance dependency.[7] Participants in the research, most of whom considered heroin as the main drug on which they were dependent, often used benzodiazepines on an everyday basis, frequently in combination with other substances.[8] Roe states that, at times, benzodiazepines were purposefully combined and taken with other drugs, and at others different drugs were taken opportunistically over the course of the day. Several participants noted the ability of benzodiazepines to ease feelings of stress, anxiety and loneliness, and to distance painful or traumatic memories, effects that were strengthened when used in combination with heroin, alcohol and other substances. Participants also described a distinct bodily pleasure and even at times sense of 'fulfilment' afforded by benzodiazepines, alongside their ability to provide moments of relaxed calm amidst often strenuous and volatile circumstances.

Roe also notes that benzodiazepines, particularly when combined with other substances, often produced particular effects on the passage of time, such as slowing or halting time, or removing one from time altogether. Altering time perception constituted a particular motivation for use, as intoxication acted to counter time was that felt as overwhelming fast-paced or chaotic, or else time that was experienced as empty, dragging or overly repetitive. For instance, the author quotes a female participant describing the effects of Valium on time, who stated, "Downers like Vallies just slow everything right down, in a nice way though. Relax you. [. . .] Things just fall away, ken, nothing matters."[9]

The physiological effects of combining benzodiazepines with heroin, alcohol and/or cocaine were pleasurable, but could equally be severe and unintentional, such as "physical and emotional distress; extreme nausea; hallucinations; extreme memory and time loss/fragmentation" as well as non-fatal and fatal overdose.[10] Research participants equally spoke of effects of benzodiazepines lessening over time and the need to continually increase doses. There were a limited number of instances in which participants, who were not involved in treatment services remarked that they had purchased diazepam and methadone in order to detox themselves from heroin and alcohol.

Other works have explored the exceptional availability and affordability as significant motivations for benzodiazepine use.[11] McAuley and colleagues note that benzodiazepine prescriptions increased throughout the 1990s until the mid-2000s, at which point there was a shift in clinical guidance in response to escalating drug-related deaths. The diversion of benzodiazepine prescriptions to the illicit market increased its use among populations who used drugs, with decreases in prescribing

[7] Ibid.
[8] The author notes that Valium (diazepam) tablets, or tablets thought by participants to be diazepam, were the tablets most commonly available during the research.
[9] Roe (2021). Available at: Isolation, Solitude and Social Distancing for People Who Use Drugs: An Ethnographic Perspective - PubMed (nih.gov).
[10] Roe (2020). Available at: Echoes of endlessness: time, memory, and experience for heroin users in Scotland (ethos.bl.uk).
[11] McAuley et al. (2021). Available at: From the clinic to the street: the changing role of benzodiazepines in the Scottish overdose epidemic (sciencedirect.com).

coinciding with the emergence of novel psychoactive substances (NPS), including new benzodiazepines.[12] Vast quantities of new benzodiazepines, such as phenazepam, began to be imported into the UK. A shift has occurred, however, in recent years towards the domestic production of benzodiazepines, particularly etizolam, in Scotland, with "domestic industrial laboratories capable of producing millions of pills per day," at extremely low cost to consumers.[13]

Qualitative and ethnographic studies have likewise noted high frequency of benzodiazepine use among substance-using populations, and that benzodiazepines are commonly used in combination with other drugs, using a variety of consumption methods; including oral, snorting, intramuscular and intravenous.[14]

2.2 Role of benzodiazepines in drug-related deaths (DRDs) in Scotland

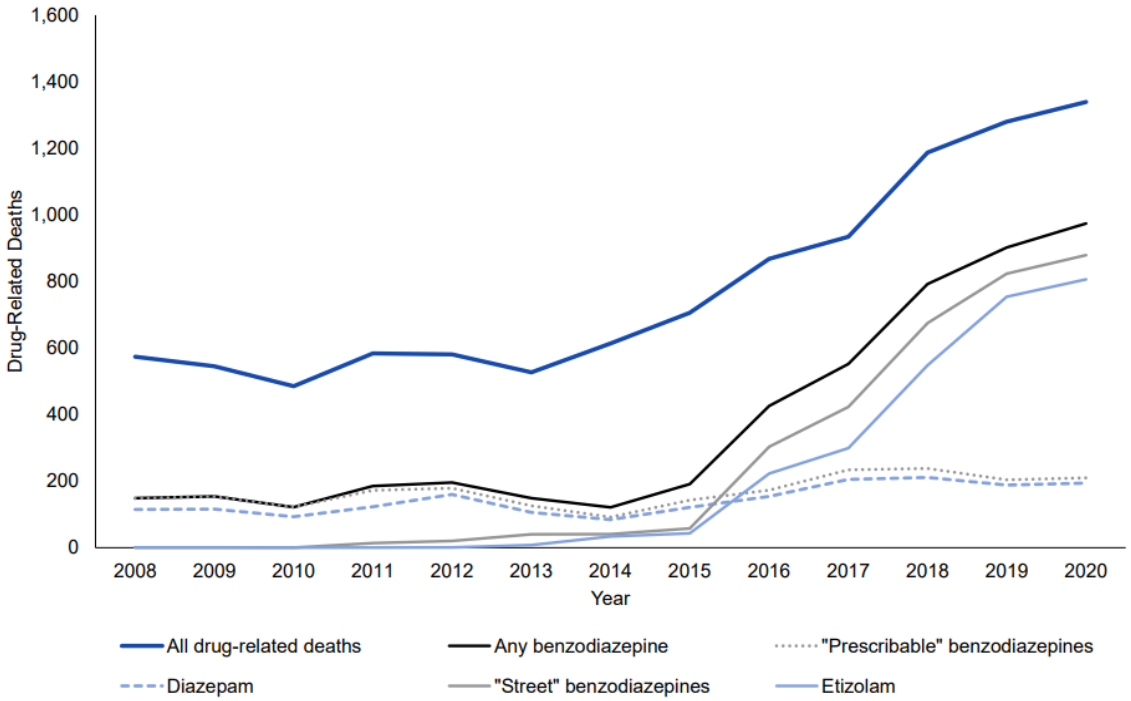
There were 1,339 drug-related deaths in Scotland in 2020, the highest number ever recorded and a continuation of upward trends since 2014. Benzodiazepines were implicated in 974 deaths (73% of all drug-related deaths), continuing the steep rise in benzodiazepine deaths since 2016.[15] Between 2008 and 2015, for instance, benzodiazepines were implicated in fewer than 200 deaths per year, before rising to 426 in 2016; 552 in 2017; 792 in 2018 and 902 in 2019 (Figure 1).

The increase of benzodiazepine-related/implicated deaths over the past five years appears largely attributable to street benzodiazepines.[16] For instance, deaths where street benzodiazepines were implicated have risen from 58 in 2015 (8.2% of total DRDs) to 879 in 2020 (66% of total DRDs). These were largely related to etizolam, a substance which only emerged on the market in the mid-2010s and has risen sharply in its implication in deaths to 806 in 2020 (Figure 1).[17]

Deaths for which 'prescribable' benzodiazepines were implicated have remained relatively stable, with the figure for 2020 (210 deaths) being lower than in 2017 and 2018 (234 and 238 respectively). Diazepam was formerly the most commonly implicated in benzodiazepine-related deaths until the mid-2010s when illicit street benzodiazepine-implicated deaths sharply increased.

[12] 'New benzodiazepines' are defined by the EMCDDA as NPS that contain a benzodiazepine core and that are not controlled under the international drug control system, although some 'new' benzodiazepines, such as phenazepam, etizolam and flualprazolam, have since been controlled.
[13] Ibid.
[14] Ibid.
[15] National Records of Scotland (2021). Available at: Drug-related deaths in Scotland in 2020, Report (nrscotland.gov.uk).
[16] The Information Services Division (ISD) of NHS National Services Scotland, which is now part of Public Health Scotland (PHS) defines 'prescribable' benzodiazepines as those licensed for prescription in the UK and widely prescribed in Scotland (but which may not actually have been prescribed to the person who died after taking them), such as diazepam, and 'street' benzodiazepines as those not licensed for prescription in the UK or thought to have originated from an illicit source.
[17] National Records of Scotland (2021). Available at: Drug-related deaths in Scotland 2020 (nrscotland.gov.uk).

Figure 1. Number of drug-related deaths in Scotland: in total, and for which certain benzodiazepines were implicated in the cause of death, 2008 to 2020.



Source: NRS 2021

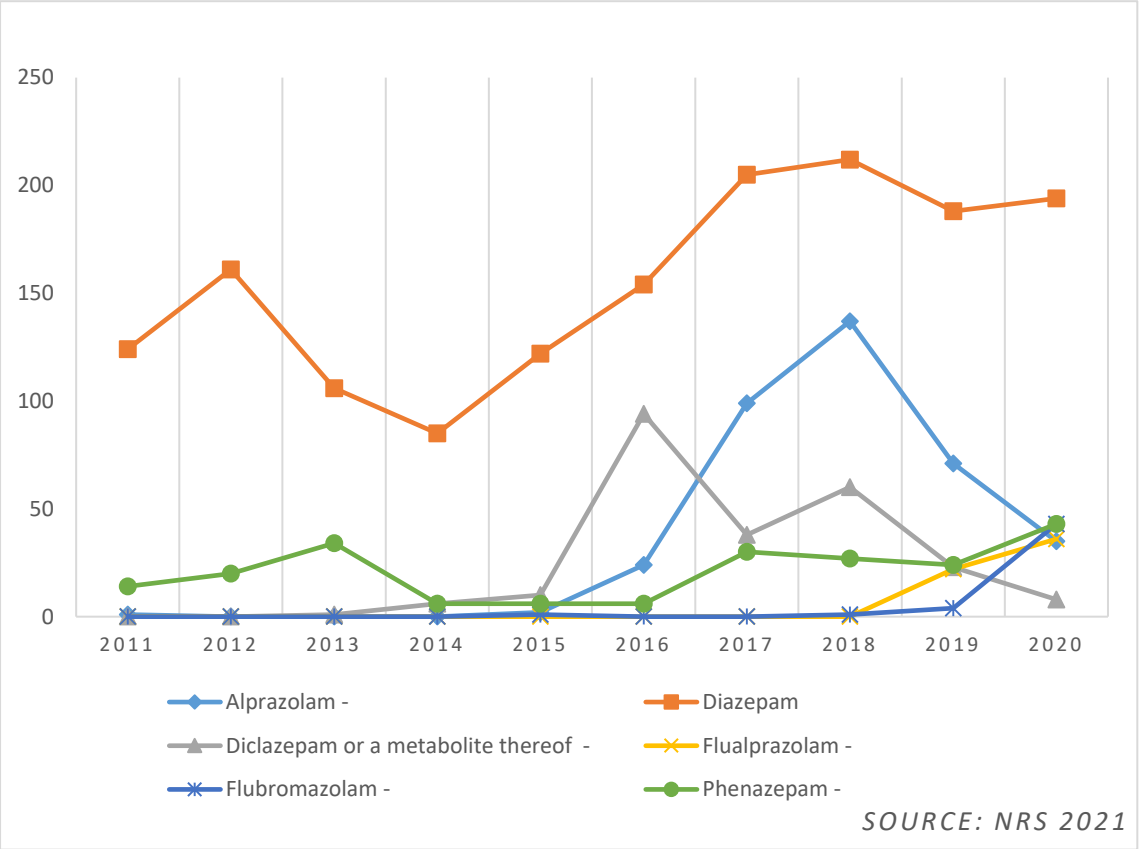
While etizolam remained the most prevalent street benzodiazepine in 2020, more detailed toxicology data within the NRS drug-related deaths report also evidence broadly increasing prevalence of different variations, such as alprazolam (Xanax), diclazepam, flualprazolam, flubromazolam and phenazepam (Figure 2). As of 28 February 2021, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) was monitoring 30 new benzodiazepines through the EU Early Warning System.[18] Of these, more than 80% were detected for the first time between 2014 and 2020. Etizolam and many other street benzodiazepines, such as flualprazolam and diclazepam, were not controlled substances in the UK until the Psychoactive Substances Act of May 2016, before being included under the Misuse of Drugs Act in May 2017.

As unregulated imitations of prescription drugs, street benzodiazepines are often widely variable in potency, much more potent than their prescribed counterparts, and may contain a number of unmarked harmful substances. For example, etizolam is roughly 6-10 times more potent than diazepam. Etizolam is, however, a licensed prescription medication in Italy, India and Japan, and shows relatively comparable signs of harm to diazepam when used therapeutically.[19] The harms of street benzodiazepines largely stem from their illicit manufacture and to their often being disguised and sold as genuine medications, with exceptionally high availability and

[18] EMCDDA (2021). Available at: New benzodiazepines in Europe – a review (europa.eu).
[19] Neilson and McAuley (2020). Available at: Etizolam: A rapid review on pharmacology, non-medical use and harms - PubMed (nih.gov).

affordability leading to consumption of huge quantities.[20] The use of higher doses – often supratherapeutic or 'megadoses' – greatly increase the risk of overdose, dangerous drug interactions and adverse effects. Additionally, both their generally shorter half-lives and common side-effect of memory loss likely lead to more frequent dosing.[21]

Figure 2. Emerging and lesser known benzodiazepines implicated in Drug poisoning deaths* (excluding etizolam), 2013 to 2020.**



*These data are reported on the bases of the Office for National Statistics (ONS) 'wide' definition of Drug poisoning deaths rather than the NRS drug-related death definition.
**Etizolam, by far the most common benzodiazepine, has been excluded from this chart for scale.

As Figure 2 demonstrates, a distinct shift is apparent in 2016 with a severe rise in drug-related deaths attributable to street benzodiazepines.[22] Implicated deaths for alprazolam and phenazepam have continued to fluctuate, while flualprazolam and flubromazolam have emerged to show potential indications of following the trajectories of etizolam, although there is currently insufficient data to predict trends.

[20] Medicines and Healthcare products Regulatory Agency (2020). *Evidence of Harm from Illicit or Fake Benzodiazepines*. Medicines and Healthcare products Regulatory Agency.
[21] Neilson and McAuley (2020). Available at: Etizolam: A rapid review on pharmacology, non-medical use and harms - PubMed (nih.gov).
[22] Street benzodiazepines here include alprazolam, diclazepam, etizolam, flualprazolam, flubromazolam and phenazepam.

Drug-related death data also highlight that benzodiazepines are likely to be used in combination with other drugs. In 2020, 98.7% of benzodiazepine-implicated deaths had more than one drug present, with a total of 13 deaths in which only one benzodiazepine was implicated. Eight of these deaths were implicated solely by etizolam, meaning only 1% of etizolam-related deaths involved etizolam alone. Opioids were implicated in 94% of benzodiazepine-implicated deaths, with heroin/morphine being implicated in 49% of all benzodiazepine-implicated deaths (Figure 3). [23] This trend is widely mirrored in all DRDs, of which 184 (14%) involved only one drug.

Figure 3. Substances implicated in benzodiazepine-implicated deaths, 2008 to 2020.

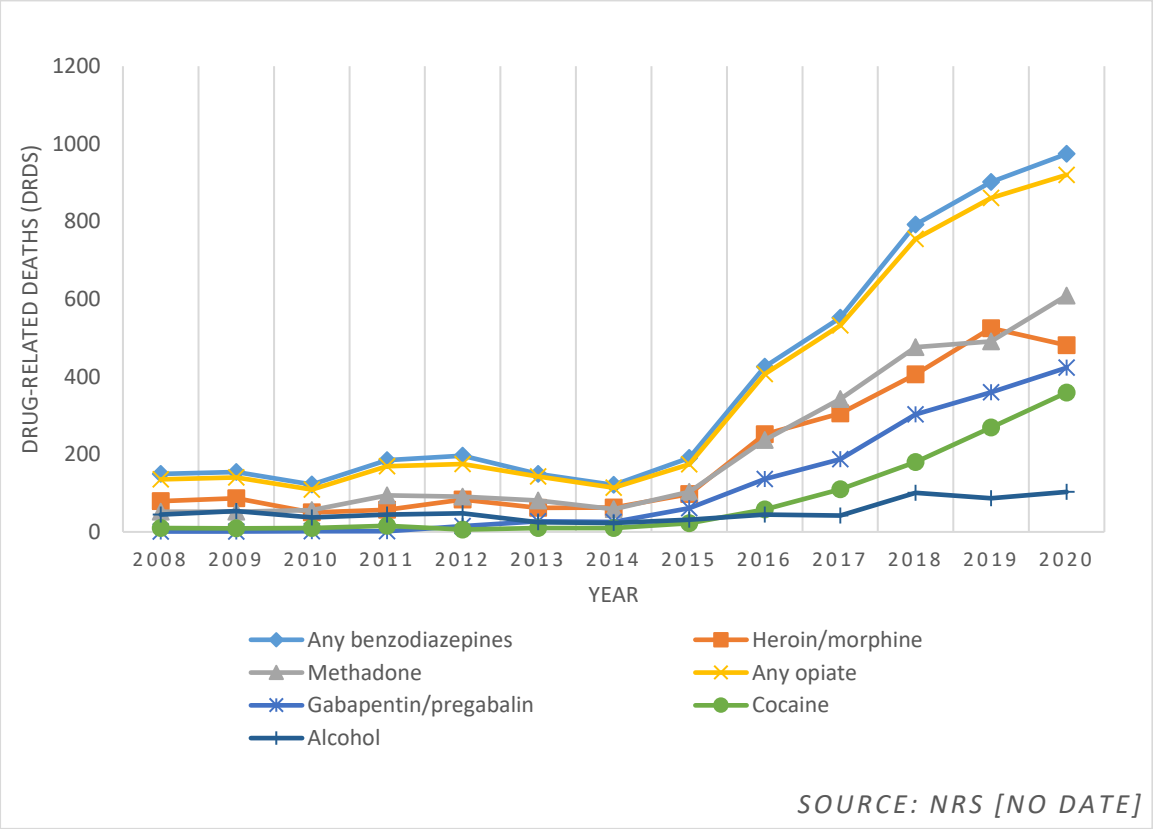


Figure 3 demonstrates that in 2020 the most common combinations of substances in benzodiazepine-implicated deaths were:

- Any opiates/opioids: implicated in 94% (920) of benzodiazepine-implicated deaths.
- Methadone: implicated in 63% (609) of benzodiazepine-implicated deaths.
- Heroin/morphine: implicated in 49% (481) of benzodiazepine-implicated deaths.
- Gabapentin/pregabalin: implicated in 43% (423) of benzodiazepine-implicated deaths.

[23] This specific data was sourced from the National Records of Scotland at the request of the Scottish Government and is currently unpublished.

- Cocaine: implicated in 37% (359) of benzodiazepine-implicated deaths.
- Alcohol: implicated in 11% (103) of benzodiazepine-implicated deaths.

2.2.1 Benzodiazepine-implicated deaths by age, gender, deprivation profile and NHS board

Overarching trends in all drug-related deaths in 2020 suggest an ageing cohort of users and higher overall deaths among men, although with a sharper increase in DRDs among women.[24] DRDs across all substances are strongly associated with poverty and deprivation, with people in the most deprived quintiles[25] being 18 times more likely to have a drug-related death than those in the least deprived quintiles. These trends are largely consistent with benzodiazepine-related deaths. In 2020, as with all DRDs, the rates of benzodiazepine-implicated deaths were highest for those in the 35-44 year age bracket, closely followed by those aged 45-54 years.

Men accounted for 717 (74%) of benzodiazepine-implicated deaths in 2020, relatively consistent with recent years, while 257 (26%) benzodiazepine-implicated deaths were in women. These figures are also closely mirrored in deaths implicated by street benzodiazepines, and etizolam specific deaths, when broken down by sex.

Most NHS boards had similar percentages of benzodiazepine-implicated deaths to that of the overall figure for Scotland, in the range of 72-79%. The lowest rates belonged to Grampian with only 57% of DRDs implicating benzodiazepines, while the highest rates were in Forth Valley (81%).

There were notable differences between areas in which prescribable benzodiazepines and street benzodiazepines were implicated in deaths. Compared against the overall figure for Scotland of 16% (of all DRDs having prescribable benzodiazepines implicated), the highest rates of deaths implicated by prescribable benzodiazepines were Lothian (42%, or 66 out of 159); Grampian (40%, or 40 out of 99) and Fife (26%, or 17 out of 65), while the lowest rates belonged to Greater Glasgow & Clyde (2%, or 11 out of 444), Ayrshire & Arran (3%, or 3 out of 106), and Lanarkshire (4%, or 7 out of 185).[26]

The highest percentage of deaths implicated by street benzodiazepines were in Tayside (76%, or 80 out of 105) and Forth Valley (74%, or 57 out of 77), while the lowest were in Grampian (33%, 33 out of 99) and Lothian (52%, or 83 out of 159). Table 1 presents data for deaths in which benzodiazepines were implicated by NHS Board. [27]

[24] NRS (2021). Available at: Drug-related deaths in Scotland in 2020, Report (nrscotland.gov.uk).
[25] Based on the quintiles outlined by the Scottish Index of Multiple Deprivation (SIMD).
[26] This comparison may be affected by differences in reporting practices between areas.
[27] It should be noted that deaths presented in Table 1 may be implicated by or involve both prescribable and street benzodiazepines, hence the individual numbers for each may equate to more than the total number of benzodiazepine-related deaths when combined.

Table 1. Drug-related deaths by selected drugs reported in 2020 and NHS Board area.

NHS Board	*All drug-related deaths*	*Percentage implicated by any benzodiazepine*	*Percentage implicated by any prescribable benzodiazepine*	*Percentage implicated by any street benzodiazepine*
Scotland	**1,339**	**73**	**16**	**66**
Ayrshire & Arran	106	73	3	71
Borders	18	72	11	67
Dumfries & Galloway	22	73	5	73
Fife	65	78	26	71
Forth Valley	77	81	21	74
Grampian	99	57	40	33
Greater Glasgow & Clyde	444	73	2	72
Highland	49	78	53	51
Lanarkshire	185	72	4	70
Lothian	159	72	42	52
Orkney	3	67	33	33
Shetland	4	25	0	25
Tayside	105	79	19	76
Western Isles	0	0	0	0

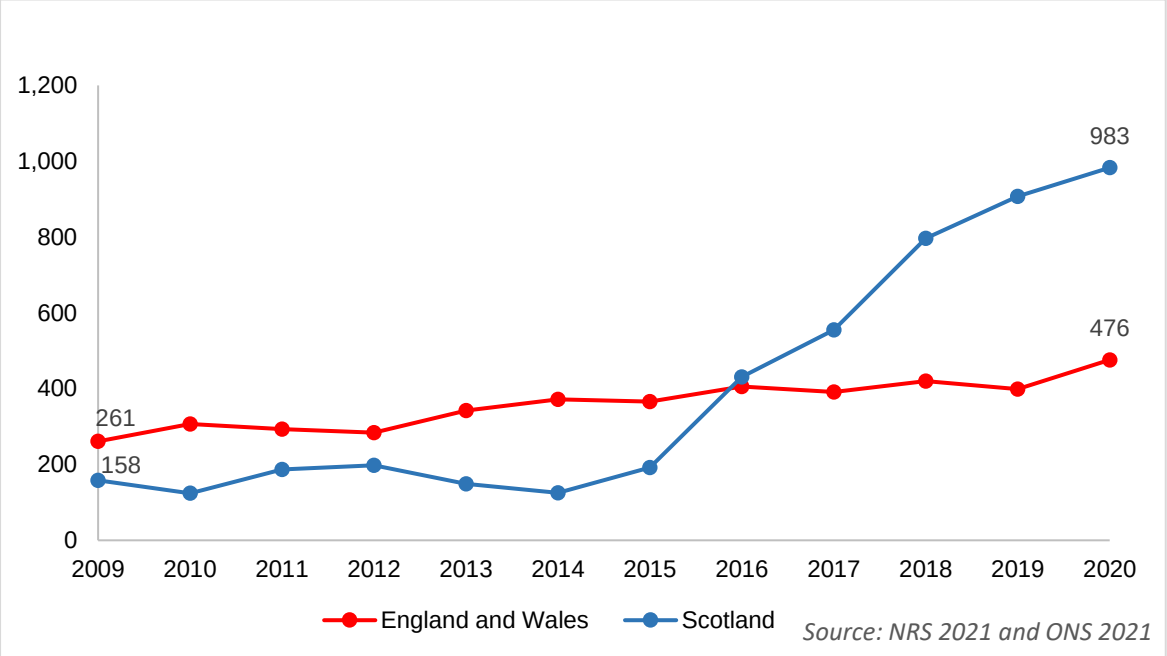
Source: NRS 2021

2.2.2 Scotland's benzodiazepine-related deaths in comparison with England and Wales and wider Europe

Benzodiazepine-related deaths in Scotland are substantially higher than in England & Wales, although rates have been increasing in both areas. Figure 4 displays the absolute numbers of benzodiazepine poisoning deaths in Scotland and England & Wales between 2009 and 2020.[28] Given Scotland's smaller population, the rates of benzodiazepine poisoning deaths are markedly higher.

[28] Some difference may be accounted for by different toxicology practices among Scotland and England & Wales.

Figure 4. Comparison of the trend in benzodiazepine poisoning deaths in Scotland and England & Wales, 2009-2020.



The EMCDDA notes that benzodiazepines are related to an increasing proportion of drug-related deaths in several countries, and highlights Scotland as a primary country of concern.[29] [30] The EMCDDA also note growing concerns across Europe around increasing availability of benzodiazepines through prescription diversion or the proliferation of unlicensed benzodiazepines on the illicit market.[31]

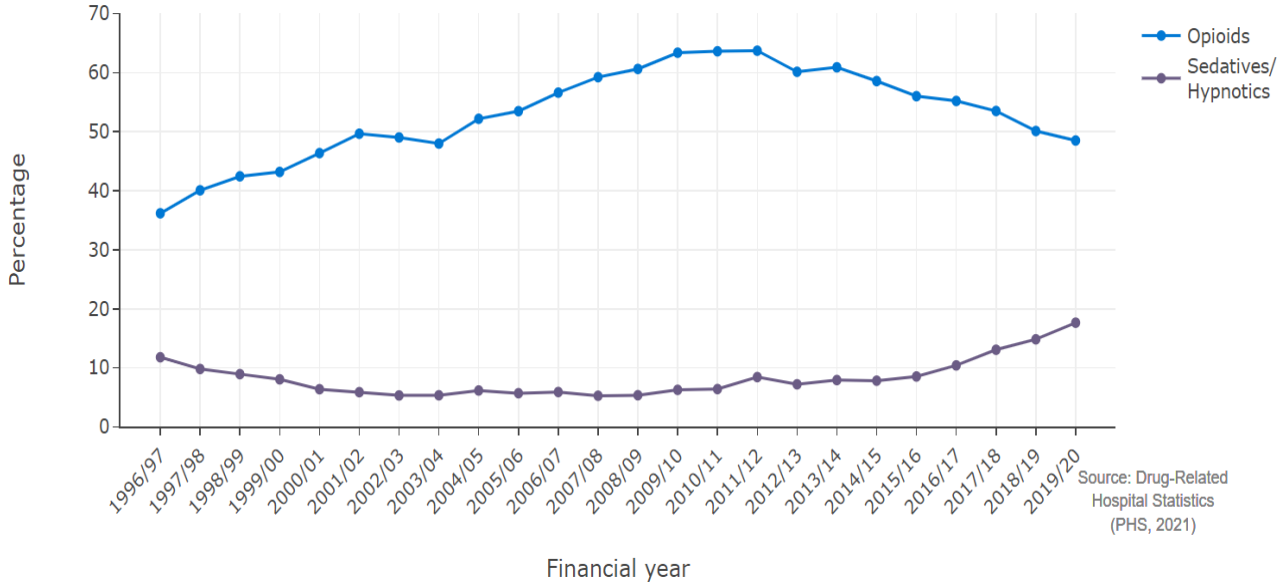
2.3 Benzodiazepine-related hospital stays

The overall number of drug-related hospital stays decreased in 2020/21 (from 284 stays per 100,000 population in 2019/20 to 270 per 100,000 in 2020/21), likely as a result of the COVID-19 pandemic. However sedative/hypnotic-related hospital stays (including benzodiazepines) increased to their highest rate on record.[32]

Out of 14,310 stays in 2020/21, the highest stay rate was associated with opioids at 127 per 100,000, which constituted a decrease from 140 per 100,000 in 2019/20. Sedative/hypnotic-related hospital stays (including benzodiazepines), increased from 50 stays per 100,000 in 2019/20 to 54 stays per 100,000 (2,643 stays) in 2020/21, the highest recorded rate since 1996/97, reflecting the continuation of a stark upward trend since the mid-2010s. For further comparison, the percentage of stays related to opioids dropped from 50.11% to 48.5% between 2018/19 and 2019/20, while sedative/hypnotic stays increased from 14.84% to 17.65%.

[29] EMCDDA (2021). Available at: Drug-related deaths and mortality in Europe: update from the EMCDDA expert network (europa.eu)
[30] Many countries do not register deaths involving only benzodiazepines as an overdose death, which may affect data reporting.
[31] EMCDDA (2021). Available at: European drug report 2021: trends and developments (europa.eu)
[32] ISD (2021). Available at: Drug-Related Hospital Statistics (ISDscotland.org)

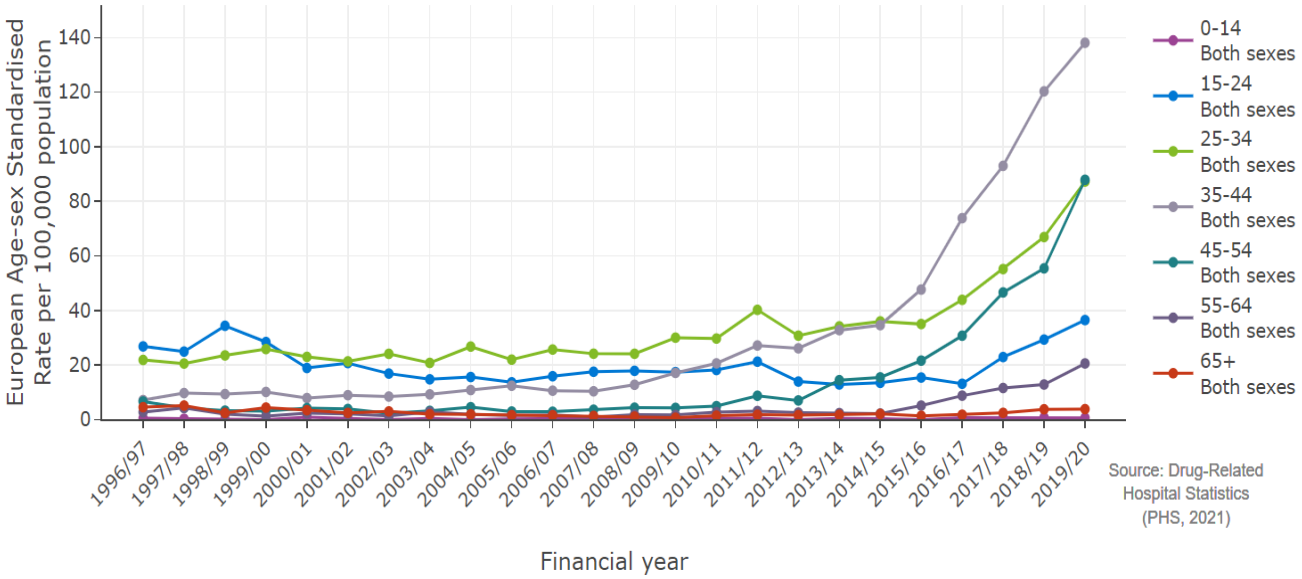
Figure 5. Drug Related Hospital Stay percentages for selected drug types 1996/97 to 2019/20 (Scotland; Any hospital type; Any diagnosis).



2.3.1 Benzodiazepine-related hospital stays by age, gender, deprivation profile and NHS board

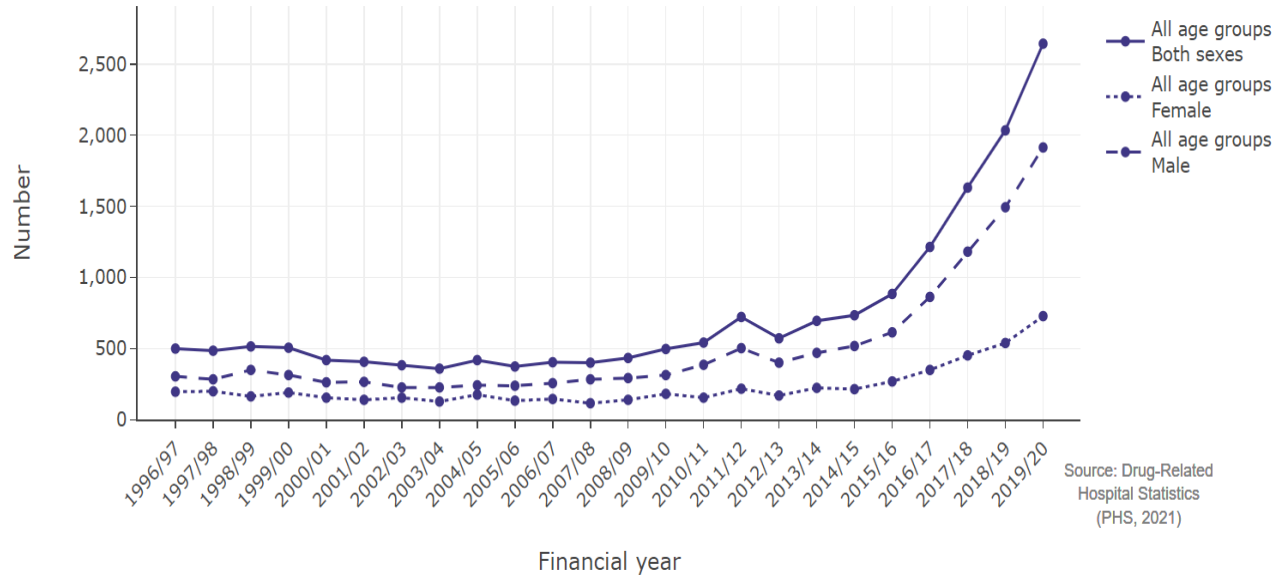
General drug-related hospital stay data for 2019/20 reflect similar trends to drug-related deaths, evidencing highest rates among those aged 35-44. Stay rates specific to sedatives/hypnotics (including benzodiazepines) show an increase across all age groups, with the highest rates belonging to the 35-44 age bracket, closely followed by the 45-54 age bracket (Figure 6). Those aged 45-54 years evidenced the sharpest rise in rates between 2018/19 and 2019/20, with rates increasing from 55.54 per 100,000 population to 87.88 per 100,000.

Figure 6. Stay rates for selected age group/sex 1996/97 to 2019/20 (Scotland; Any hospital type; Any diagnosis; Sedatives/Hypnotics).



Men accounted for 72.5% of patients (1,914) who had a sedative/hypnotic-related hospital stay in 2020/21, and women for 27.5% (729), figures broadly consistent with rates for all substances. Between 2010/11 and 2018/19, the rate of sedative/hypnotic-related stays for men was consistently more than double that of women, before beginning to increase more sharply. The rate of stays is now 2.5 times higher for men than women (Figure 7).

Figure 7. Stay numbers for selected age group/sex 1996/97 to 2019/20 (Scotland; Any hospital type; Any diagnosis; Sedatives/Hypnotics).



57.8% of patients whose stays were related to sedatives/hypnotics in 2020/21 were from the most deprived quintile, consistent with rates across the time series. In 2020/21, these patients were 25 times as likely to be from the most deprived quintile as from the least deprived, compared with 16 times as likely when considering rates for all substances.

Broken down, by NHS Board, the area with the highest rates of hospital stays for sedatives/hypnotics were Greater Glasgow and Clyde, which accounted for 41% of all stays across Scotland relating to sedatives/hypnotics, or 93.49 per 100,000 population. This was followed by Ayrshire and Arran (61.45 per 100,000); Fife (55.59 per 100,000) and Forth Valley (53.91 per 100,000), while the lowest rates per 100,000 population belonged to the Western Isles (0 per 100,000), Grampian (11.97 per 100,000); and Shetland (17.78 per 100,000).

2.4 Benzodiazepine supply and seizure data

Between April 2019 and March 2020, approximately 5.3 million benzodiazepine tablets were seized in total by Police Scotland for both supply-related crimes and possession-related crimes, compared with 2.1 million tablets seized in 2018/19.[33] For comparison, in England & Wales, 1.1 million doses of benzodiazepines were seized by police forces and Border Force between April 2019 and March 2020, presenting a stark contrast to figures for Scotland.[34] [35] It should be noted that seizures are not an accurate indicator of supply, and that figures are prone to substantial fluctuation year on year, as single instances of drug seizures can dramatically affect annual statistics. Seizure quantities in Scotland are, however, consistently higher than England & Wales, especially when taking population size into account.

Etizolam accounted for an estimated 94% of benzodiazepine seizures in Scotland in 2019/20, and was also the second most commonly seized drug, following herbal cannabis. It is not possible to provide a breakdown of the number of seizures that occurred in Scotland in 2019/20, although Police Scotland have previously stated that seizures are often connected to large scale, industrial pill presses.[36] The EMCDDA have similarly noted that the demand for tablets in Scotland has resulted in, “several large-scale producers setting up illicit production sites in the west of Scotland” and that the “detection of these production sites illustrates that professional equipment (such as multi-station rotary pill presses) [are] being used by illicit manufacturers to enable quick and efficient large-scale production.[37]

[33] Scottish Government (2021). Available at: drug seizures and offender characteristics, 2018-19 and 2019-20 (pdf).
[34] UK Government (2022). Available at: Seizures of drugs in England and Wales, financial year ending 2021 - GOV.UK (www.gov.uk)
[35] It should be noted that some difference in figures between Scotland and England & Wales may be accounted for by different measurements used to quantify drugs seized, as well as data quality issues in some areas, for which seizure figures were estimated.
[36] Police Scotland (2020). Available at: National serious and organised crime disruption operation - Police Scotland.
[37] EMCDDA (2021) New benzodiazepines in Europe – a review (europa.eu).

For supply-related crimes in 2019/20, benzodiazepines comprised the main Class C drugs seized by Police Scotland, totalling 4.9 million benzodiazepine tablets (the vast majority of which were etizolam, although it is not possible to present separate figures for etizolam, diazepam and other benzodiazepines).[38]

From a sample of drug possession crime, it was estimated that 14% of drug possession crimes in 2019/20 involved etizolam, compared with 48% involving herbal cannabis, 9% involving cocaine and 8% involving heroin. This again reflects an upward trend since the mid-2010s; for example there were no etizolam-related possession crimes recorded up to and including 2016/17. There were a total of 4,300 possession crimes relating to etizolam in 2019/20. Contrastingly, diazepam accounted for only a very small proportion of seizures for drug possession crimes, not reaching the level required to be reported in 2018/19 and 2019/20.

It is not possible to provide a breakdown of the characteristics of offenders by specific substances, however 85% of overall offenders were male, with a median age of 29.

2.5 Prescribing practices

2.5.1 Prescribing trends for the adult population in Scotland

Data from PHS reveal that in 2019/20, 5% of the adult population in Scotland (225,000 in total) received a benzodiazepine prescription in the last year, compared with, for example, 21.6% of the population receiving antidepressants; 17.8% receiving opioid pain medications; and 3.2% receiving z-drugs.[39] In 83.8% of cases for new patients – those who had not had a prescription prior to 2015 – benzodiazepines were not prescribed for less than three months.

There has been a broad decrease in benzodiazepine prescription trends over the past ten years, with 265,000 adults receiving at least one prescription for benzodiazepines in 2010/11 compared with 240,000 in 2014/15 and 225,000 in 2019/20. Prescription rates for z-drugs have conversely broadly increased in the past ten years, from 120,000 people in 2010/11 to 145,000 people in 2019/20. However, this is a drop from 2018/19 in which 150,000 people were prescribed z-drugs.[40]

2.5.2 Prescribing trends for the adult population in Scotland by age, gender and deprivation profile.

Data available for the general adult population in Scotland demonstrate a pattern of increasing benzodiazepine use up until age 49 on average, followed by a period of slight decline and then increasing use in older age.[41]

[38] The main Class A drugs were heroin, cocaine and ecstasy tablets, while Class B drugs were largely herbal cannabis, cannabis resin and amphetamines.
[39] Scottish Government (2021): Short Life Working Group On Prescription Medicine Dependence And Withdrawal: consultation - gov.scot (www.gov.scot).
[40] Ibid.
[41] Ibid.

Women are currently 1.8 times more likely to receive a prescription for benzodiazepines than men. 6.3% of the adult female population in Scotland in 2019/20 received a benzodiazepine prescription, compared with 3.6% of the adult male population. However, in 2019/20, men were up to 1.2 times more likely to receive long term prescriptions (12 months or more) than women were.

Deprivation has a consistent effect across all classes of prescription, with higher proportions of those in the most deprived quintiles receiving at least one prescription throughout the year. Although not as high as other drug classes, those from the most deprived areas are more than twice as likely to receive benzodiazepines than those in the least. Deprivation is also associated with longer treatment duration, with those from the most deprived areas being between 1.3 times as likely to receive benzodiazepine prescriptions for 12 continuous months or more, than those in the least. Trends for benzodiazepine prescribing according to deprivation quintile have been stable for the past ten years.[42]

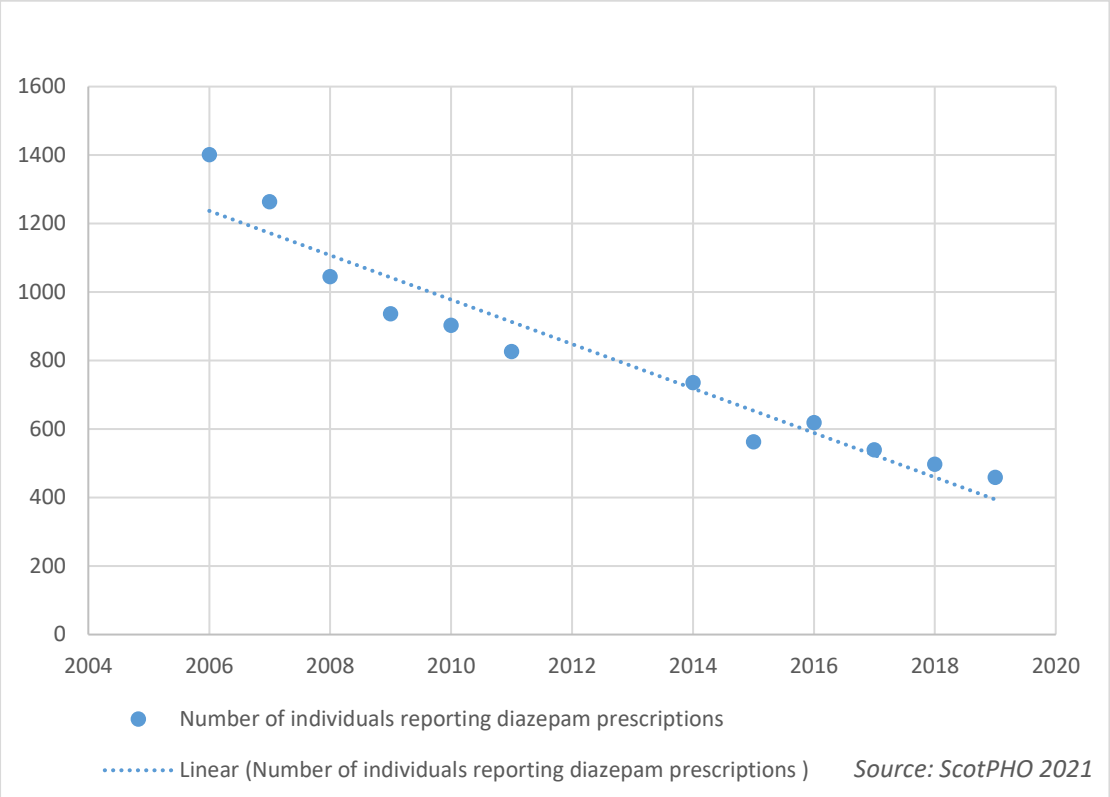
2.5.3 Prescribing trends for specialist drug treatment

The Scottish Drug Misuse Database (SDMD) shows that up until 2011/12, diazepam was the most commonly prescribed non-Opioid Substitution Therapy (OST) drug in specialist drug treatment.[43] [44] Diazepam prescriptions for specialist drug treatment have markedly decreased since 2006/07 (before which data is not available) (Figure 8).

For instance, in 2006/07, 27% of people who reported receiving prescriptions for the treatment of addiction reported a prescription for diazepam. In 2019/20, 9% reported a prescription for diazepam, following a consistent decrease across the time series.

[42] Ibid.
[43] ScotPho (2021). Available at: Treatment for drug misuse - ScotPHO
[44] It should be noted that SDMD data may be affected by data quality issues.

Figure 8. Number of individuals reporting diazepam prescriptions at assessment prior to treatment, 2006 to 2020.



Though now dated, the 2018 report on the National Drug-related deaths database (NDRDD) evidences similar trends.[45] 15% of people who had a DRD in 2016 were prescribed diazepam in the 90 days prior to death compared with 24% in 2013, following a decreasing trend since 2009.

Recent diazepam prescribing decreased over the time series (2009-2016) among individuals prescribed OST, while there was no clear trend among the non-OST group. Between 2009 and 2016, those prescribed OST were more likely to be prescribed diazepam (23%) than those who were not (15%).

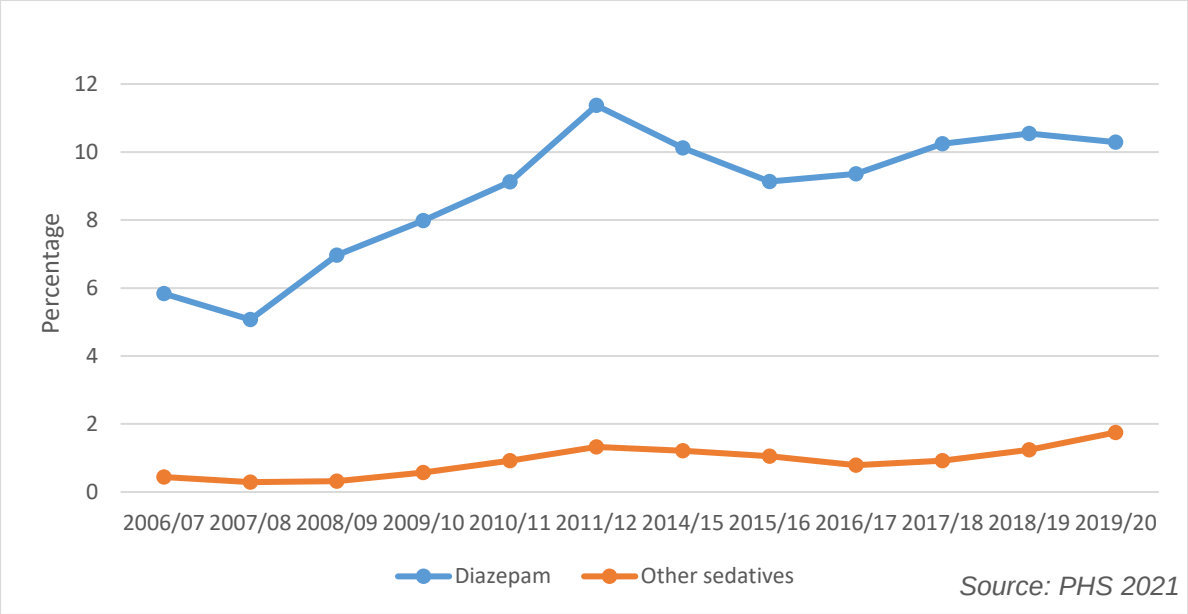
2.5.4 Drug use prior to treatment

Data available for those assessed for specialist drug treatment in 2019/20 show patterns of illicit drug use in the month prior to treatment.[46] Out of 10,900 people recorded on SDMD, 8,573 (79%) used illicit drugs in the month before entering treatment, with 2,495 (29%) using diazepam. Other benzodiazepines used prior to treatment are not recorded. For comparison 3,561 (42%) reported using heroin; 3,060 (36%) using cocaine/crack cocaine, and 2,486 (29%) using cannabis.

[45] Information Services Division (2018). Available at: The National Drug-Related Deaths Database (Scotland) Report (isdscotland.org)
[46] Public Health Scotland (2021). Available at: Scottish Drug Misuse Database (publichealthscotland.scot)

In 2019/20, 882 people out of 8,573 individuals assessed for a new specialist drug treatment episode (or 10%) recorded diazepam as the main drug for which they were seeking treatment, with the most common drug being heroin (3,109 people or 36%), followed by cocaine/crack cocaine (1,760 or 21%) and cannabis (1,544 or 18%). Reporting of diazepam as the main drug increased from 6% in 2006/07 to 11% in 2011/12, and has since remained in the range of 9% to 11% (Figure 9).[47]

Figure 9. Percentage of people reporting diazepam and other sedatives as main drug for which seeking treatment (2006/07 to 2019/20).



3. Considerations and concerns in treatment for problem benzodiazepine use

The data presented in this paper outline some of the key trends in benzodiazepine use in Scotland; the role of benzodiazepines in drug-related deaths; hospital stay rates, police seizures and prescribing practices. The data highlight the immense scale of benzodiazepine-related harms in Scotland and the challenges that exist in both tackling illicit supply and providing appropriate, evidence-based treatment for benzodiazepine use.

Benzodiazepine use among problem substance using populations has a longstanding history in Scotland, interwoven with complex polydrug use patterns. The approach to reducing harms and mortality related to benzodiazepines is not straightforward and existing clinical guidance on best approaches to harm reduction and treatment often remains conflicting. At present, there continues to be little

[47] Public Health Scotland (2021). Available at: Scottish Drug Misuse Database (publichealthscotland.scot).

consensus among experts and stakeholders on the safety, efficacy, benefits and harms of benzodiazepine prescribing as a treatment for substance dependency.[48]

Current UK clinical guidelines on the treatment of substance dependency **suggest minimising the long-term prescription of benzodiazepines,** except in exceptional circumstances.[49] Exceptional circumstances are given as previous long-term benzodiazepine prescriptions; clear evidence of relevant comorbid mental health problems; and clear 'deterioration' following previous benzodiazepine detoxification. Robust evidence exists to suggest that long-term benzodiazepine prescribing has serious repercussions for health, and that there is increased risk of mortality when co-prescribed with opioids.[50] However, at present there is a lack of published research that explicitly compares the risks and outcomes associated with benzodiazepine prescribing in the treatment of substance dependency against those of street benzodiazepine use, particularly in a Scottish context.

Benzodiazepine prescribing is alternatively often advocated for within a harm reduction approach, acknowledging the crisis posed by the prevalence of street benzodiazepines.[51] In 2020, the Drug Deaths Taskforce developed a set of principles and guidance for benzodiazepine prescribing, which offers direction for assessment, treatment planning and prescribing practice. The guidance acknowledges an inherent level of risk to the patient, which nonetheless may be comparatively lower than harms associated with street benzodiazepines.[52] It further emphasises the importance of needs-based assessments tailored to the individual; the weighing and documentation of risks associated with both pharmacological intervention and use of street benzodiazepines; and that new benzodiazepine prescribing may stabilise street benzodiazepine use in the short-term.

Despite reductions in benzodiazepine prescriptions for the treatment of substance use disorders in Scotland since 2006, there has not been an equivalent fall in prescribable benzodiazepine-related deaths (which have remained stable) or sedative-related hospital stay rates (which have seen an increase). This must be viewed in the context of the proliferation of street benzodiazepines since the mid-2010's which have significantly increased the availability and affordability of these drugs over the same period. The EMCDDA does, however, highlight the potential relationship between reduced prescribing and the rising prevalence of new benzodiazepines, stating that 'the increase in new benzodiazepines might […] be partially related to well-intentioned restrictions in the legal supply of authorised benzodiazepine medicines and the introduction of prescription limits in order to prevent or reduce harms among patients, such as dependence.'[53]

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[48] Drug Deaths Taskforce (2021). Available at: MAT Standards Informed Response for Benzodiazepine Harm Reduction, interim guidance, august-2021 (drugdeathstaskforce.scot).
[49] Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group (2017). Available at: Drug misuse and dependence (publishing.service.gov.uk)
[50] MacLeod et al. (2019). Available at: Prescription of benzodiazepines, z-drugs, and gabapentinoids and mortality risk in people receiving opioid agonist treatment: Observational study based on the UK Clinical Practice Research Datalink and Office for National Statistics death records (plos.org)
[51] Drug Deaths Taskforce (2021). Available at: MAT Standards Informed Response for Benzodiazepine Harm Reduction, interim guidance, august-2021 (drugdeathstaskforce.scot)
[52] Ibid.
[53] EMCDDA (2021). Available at: New benzodiazepines in Europe – a review (europa.eu)

Further work is therefore required to determine quality prescribing practice and review the safety and efficacy of benzodiazepine prescribing as a treatment option for substance dependency, particularly if being co-prescribed with OST. In support of this aim, the Scottish Government is currently funding research through the Drug Deaths Taskforce Research Fund that explores the safety of benzodiazepine prescribing with OST.[54] Researchers from the University of Stirling have undertaken a multicentre retrospective cohort study that aims to describe the prevalence, characteristics and patient outcomes associated with benzodiazepine prescribing among 1,350 people receiving OST in Scotland; work that is expected to inform future policy and practice.

[54] Drug Deaths Taskforce (2020). Available at: Drug Deaths Task Force: Research Fund | Drug Deaths Taskforce.

Annex A[55]

Table 1. Scotland specific literature

Author/ Year	Aim	Methods	Results	Conclusions	Observations/ Recommendations for practice
Prevalence and drug seizure					
Deeb et al. 2020 [1]	Evaluate prevalence and abuse potential of anti-epileptic drugs (AEDs) among prison populations in Scotland	Analysed 904 urine samples of admitted and released prisoners over 1 month period	81% of samples found illicit/non-prescribed drugs. Most frequently detected non-prescribed drugs were Benzodiazepines (61%); opiates (54%) and cannabis (47%).	High prevalence of illicit substances, particularly benzodiazepines, and AEDs, with majority of AED positive samples containing at least one other illicit substance.	Authors note that there is often over-prescribing of gabapentin to individuals who do not meet prescribing criteria.
Information Services Division (ISD) 2019 [2]	Provide estimates of national and local/national prevalence of problem drug use in Scotland, for ages 15-64. (Defined as opiate/benzodiazepine use).	Estimates drawn from clients in drug treatment services; drug-related hospital admissions; criminal justice social work (CJSW) reports in 2015/16.	Estimate range of 55,800 – 58,900 (giving rate of 1.62%). 94% admitted to hospital related to opioids, compared with 82% of all those identified through CJSW, which observed much higher use of benzodiazepines.[56]	N/A	N/A
Information Services Division (ISD) 2021 [3]	Report on hospital stays in relation to drug use diagnosis, including information on number of stays; age; sex; deprivation profile; substances involved and geographical variations across Scotland.	Data obtained from general acute inpatient and day case records, and psychiatric inpatient and day case records, from 1996/97 to 2020/21	In 2020/21: 14,310 drug-related hospital stays among 10,437 patients. 270 stays per 100,000 people (decreased from 284 per 100,000 in 2019/20). Sedative/hypnotic stay rate was 54 per 100,00 (increase from 50 stays 2019/20).	In 2020/21 sedative/hypnotic stays highest across the time series. Opioid-related stays were lower than average, but still accounted for almost half of stays each month.	Reductions in number of stays likely influenced by COVID-19 pandemic.

[55] The annotated bibliography is intended to give a general overview of the evidence and guidance relating to benzodiazepines in Scotland and is not intended to be exhaustive.
[56] Report by PHS estimates prevalence at 1.91% when cocaine and amphetamines are included: Prevalence of problem drug use in Scotland: 2015/16 Estimates (PublicHealthScotland.scot)

			Highest rate among 35-44 year olds, although still decreased from previous year. Approx half live in most deprived areas in Scotland. 71% male.		
National Records of Scotland 2021 [4]	Provide statistics of drug-related deaths in 2020, broken down by age, sex, substances implicated, underlying cause of death and NHS Board.	N/A	1339 drug-related deaths in 2020. 93% had more than one substance implicated. Broken down by following: Opioids (implicated in 89% of deaths); benzodiazepines (73%); gapapentin/pregabalin (37%); cocaine (34%);	Sharp rise in benzodiazepine-related deaths in past 5 years, from fewer than 200 deaths per year prior to 2016 to nearly 1000 in 2020. 'Street' benzodiazepines implicated in 66% of deaths.	N/A
Scottish Government 2019 [5]	Presents Official Statistics on drug seizures made by the police in Scotland and the characteristics of those found in possession of drugs.	N/A	Approx. 354,000 diazepam tablets seized in 2017-18, compared to 2.2 million in 2016-17. Approx. 326,000 etizolam tablets were seized in 2017-18. 6% of drug supply crimes involved diazepam/etizolam.	N/A	N/A
Scottish Government 2021 [6]	Presents Official Statistics on drug seizures made by the police in Scotland and the characteristics of those found in possession of drugs, 2018/19 and 2019/20.	N/A	Main class C drugs seized in 2019/20 were 4.9 million benzodiazepine tablets, majority of which were etizolam (compared with 1.8 million in 2018/19). Main Class A drugs seized were heroin (23kg); cocaine (131kg); ecstasy-type tablets (approx. 28,800 tablets). Main Class B were herbal cannabis (921kg); cannabis resin (649kg) and amphetamines (143kg).	N/A	N/A
Patterns and motivations of use					

McAuley et al. 2021 [7]	Commentary on role of benzodiazepines in Scotland's drug-related deaths.	N/A [commentary]	N/A	Authors note market now dominated by NPS-type benzodiazepines/ 'street benzos' as opposed to diverted prescription medications, which have increased risk environment for PWUD.	Implement safer supply, drug testing and drug consumption rooms, in addition to addressing socioeconomic inequalities.
MacLeod et al. 2016 [8]	Present findings on patterns of NPS use, motivations for use, treatment/legislative consequences.	Mixed methods, incl. qualitative interviews and focus groups; two surveys (424 NPS users and 184 service staff). Survey data, SDMD and needle exchange data for Glasgow/Lothian. [technical report].	41% of survey respondents used benzo NPSs, cited positive effects on sleep and mental health. People who used benzodiazepines emphasised prescription substitution.	High prevalence of NPS use and high poly-substance use, with reasons relating to pleasure, price, potency, ease of access, curiosity and influence of peers.	Workforce development may benefit from systems approach, involving improving training on NPS and other issues such as mental/sexual health, homelessness etc., along with embedding NPS in development strategies. Improve service engagement of vulnerable populations.
Roe 2020 [9]	Explore lived experiences of substance use in Scotland; understand how experiences of time/memory impact on substance use, relationships, treatment engagement.	12 month ethnography using participant observation; qualitative interviews with 15 people; unstructured conversations [PhD thesis].	Frequent use of non-prescribed benzodiazepines among small group of people actively injecting drugs, most commonly with heroin, methadone, alcohol, and cocaine.	Motivations for 'street' benzodiazepine use included anxiety management; trauma and PTSD symptom management; management of opiate and/or prescription benzodiazepine withdrawal; pleasure; boredom; price; ease of access and availability.	Improve trauma-informed care, including definitions of trauma-informed and its application in practice; strengthen harm reduction approaches not focused on abstinence; embed socio-historical perspectives of drug use/addiction in treatment and recovery services.

Prescribing practices					
Counter et al. 2016 [10]	Assess prevalence of potentially inappropriate medication (PIMs) in population of community-based multicompartment compliance aid (MCA) users in north-east Scotland.	Recorded data for MCAs dispensed by 48 of 50 community pharmacies between June-Oct 2014, with concurrently prescribed medications, patient demographics and Carstairs index of multiple deprivation.	25% of patients prescribed over 10 medications. Significant increase in the risk for at least one PIM associated with female sex; those aged under 80; those living in deprived areas (prescription of >10 medications and prescription of long-acting benzodiazepine).	Signficant proportion of MCA users were prescribed PIMs, including drug-drug interactions, with those younger than 80 and those living in poorest areas at greatest risk.	Authors state need for more aggressive multidisciplinary approach (involving prescriber, dispending pharmacist and patient) to the review of medications prescribed to MCA users.
Hughes et al. 2016 [11]	Explore impact of questions around clinical efficacy, dependence, tolerance and adverse effects of hypnotic and anxiolytic medications on clinical prescribing practice.	Review of community-dispensed prescribing data for patients on the East Practice Medical Center list in Arbroath, Scotland, in 2007, 2011 and 2015.	Proportion of patients prescribed benzodiazepines decreased between 2007 and 2015: 83.8% (n = 109) in 2007, 70.5% (n = 122) in 2011, and 51.7% (n = 138) in 2015 (P = 0.006). Proportion of these patients prescribed a non- benzodiazepine drug increased between 2007 and 2015: 30% (n = 39) in 2007, 46.2% (n = 80) in 2011, and 52.4% (n = 140) in 2015 (P = 0.001).	Changes in this prescribing practice may reflect the medicalization of insomnia, local changes in prescribing practice and alongside national recommendations.	Authors note that locally available Scottish prescribing data can be utilized to look in more detail in primary care prescribing practice, at a single practice level.
Johnson et al. 2018 [12]	Identify pattern of benzodiazepine and z-hypnotic prescribing in psychiatric inpatients at discharge and 12 months post-discharge.	Retrospective observational longitudinal cohort study of two adult psychiatric wards prescribed benzodiazepine/z-hypnotic drug, June-November 2012,	30% of 74 (n=22) patients were prescribed at discharge, 14 of whom were prescribed long-term.	One in three patients prescribed a benzodiazepine or z-hypnotics at discharge, with 1 in 5 receiving continuous long-term treatment (prescriptions) for 12 months post-discharge.	Authors note that future strategies using routine patient-level prescribing data may support prescribers to review and minimise inappropriate long-term prescribing.
Scottish Drug Deaths Taskforce 2021 [13]	Provide MAT Standards informed response for Benzodiazepine harm reduction	N/A [guidance document]	N/A	N/A	Guidance recommends more discussion of benzodiazepine use; empathetic listening; needs based-

					assessment; establishing a zone of accepted risk; improved benzodiazepine harm reduction (including supported self-reduction, medication assisted detox/stabilisation); prescribing where appropriate; establishment of shared goals.
Torrance et al. 2018 [14]	Examine variations in national opioid prescription rates, indicators of prescribing quality, co-prescribing of benzodiazepines and relationship with pain severity.	Electronic linkages of opioid prescribing determined from (i) national data from ISD, NHS Scotland and (ii) individual data from Generation Scotland: Scottish Family Health Study. Descriptive analyses performed on national data, multilevel modelling to examine factors associated with prescribing variation.	Patients in most deprived areas 3.5 times more likely to receive a strong opioid than least deprived. Significant variation in prescribing rates between geographical areas related to deprivation. Of women aged 25-40 prescribed a strong opioid, 40% were also prescribed a benzodiazepine.	Increasing primary care prescriptions of opioids (which may be appropriate for pain management) and common co-prescribing of opioids and benzodiazepines.	Authors highlight importance of guidance/protocols for safe/person-centred prescribing; and of continued development of alternative interventions to long-term opioids in chronic pain management.
Torrance et al. 2020 [15]	Examine national and regional prescribing rates (2006-2016); identify sociodemographic factors, co-prescriptions and mortality.	Analysed data from ISD, NHS Scotland, Health Informatics Centre, National Records of Scotland and Tayside Drug Death Databases.	Across period, 4-fold increase of.; 16-fold increase of pregabalin. In 2016 ‘recurrent users’ (three or more prescriptions) had mean age 58.1 yr, were mostly females (62.5%), and were more likely to live in deprived areas. Of these, 60% were co-prescribed an opioid, benzodiazepine, or both (opioid 49.9%, benzodiazepine 26.8%, both 17.1%).	Significant increase in gapapentinoid prescribing between 2006-2016, alongside mortality. Most likely to be prescribed were older people, women, and those living in deprived areas. Contribution to DRDs may be more related to illegal use with diversion of prescribed medication.	More attention needed to gabapentinoid prescribing, and public health approaches to common factors underlying the aetiology of chronic pain, substance misuse, and drug-related deaths.

Weatherburn et al. 2019 [16]	Evaluate impact of protocol to reduce prescribing of benzodiazepines and non-benzodiazepine hypnotics in Dundee practices.	Analysed quarterly prescribing data from ISD, NHS Scotland between 2015-2018. Data split into four clusters and standardised to Defined Daily Dose (DDDs) per 1000 registered patients. Interrupted Time Series analysis performed to assess prescribing one year after protocol introduced.	Reduction in prescribing of BZDs and Z-drugs across all GP practice clusters, but this related to an ongoing downward trend in prescribing.	No significant reduction in prescribing as a result of the protocol.	Key point is attention to past/contemporary trends in data. And attention to variables that might be hidden such as variation in intervention application by individuals (GPs here). Future studies could look at impact of utilising electronic decision support at time of prescribing and measure workload.
Harms and mortality					
Johnson et al. 2016 [17]	Systematic review by ScotPHO to investigate role of benzodiazepines in drug-related mortality.	Systematic review of literature from 1970 – 2015, with following inclusion criteria: benzodiazepine supply issues; pharmacokinetic and pharmaco dynamic effects and interactions; adverse drug effects; polydrug use and interactions; toxicology; comorbidity; mortality; fatality and non-fatality information; and acute pharmacological overdose treatment.	Increasing availability of unregulated benzodiazepines of unknown content and quality. Evidence of self-medication for anxiety with prescribed and/or illicit benzodiazepine-type drugs.	Difficult to understand role in DRDs due to supratherapeutic megadoses; use and polypharmacy further complicating adverse drug effects; low and high drug blood concentrations being present in DRDs; and benzodiazepine-type drugs being associated with increased mortality when used at routine doses.	Authors highlight areas for further investigation, including: increasing availability of unregulated benzodiazepines of unknown content/quality; self-medicating use of benzodiazepine (prescribed and non-prescribed); unclear role in DRDs; risk to short/long-term mental health/cognitive problems.
McAuley et al. 2015 [18]	Explore circumstances surrounding, and characteristics	Exploratory descriptive analysis of DRDs involving	Majority of NPS-implicated DRDs involved benzodiazepine type drugs,	Prominent role of unlicensed	A range of harm reduction strategies

	of individuals involved in, NPS deaths at population level.	NPS recorded by Scottish National Drug Related Death Database (NDRDD).	mainly Phenazepam. Most involved males, older adults, and polydrug use (mostly opioids. No stimulant drugs were co-implicated).	benzodiazepines in mortality.	are needed to prevent future deaths. Consistency of how different pathologists/labs interpret drugs as implicated merits further investigation.
McAuley et al. 2019 [19]	Conduct epidemiological analyses of association of NPS injecting (including benzodiazepines) and Hepatitis C virus (HCV) among population level sample of PWID to explore increased risk of BBV to NPS injectors.	5 cross sectional surveys of approx. 13,000 PWID attending services providing equipment, between 2008 and 2016. Logistic regression applied to determine associations of NPS injecting and HCV.	Proportion of PWID reporting injecting NPS in previous six months increased from 0.2% to 11% in 2015/16. High prevalence in Lothian NHS Board area and recent experience of homelessness. Significant likelihood of NPS injectors to be HCV positive.	NPS injecting likely to increase risk of HCV.	
Van Amsterdam et al. 2021 [20]	Systematic review to attempt to explain difference in opioid overdose deaths between Scotland and England/Wales.	Systematic review	Relatively higher polydrug use, particularly benzodiazepines (esp. etizolam). Etizolam manufactured domestically, but benzodiazepines and gabapentinoids are often prescribed together with opioids and partly diverted to the black market.	No concrete explanation in literature for higher polydrug use in Scotland.	Recommendations are to carefully restrict prescription of opioids and other depressants where not needed for essential medication.
Detection					
O'Conner et al. 2016 [21]	Evaluate whether the Immunalysis® Benzodiazepines ELISA kit could detect phenazepam, etizolam, pyrazolam, flubromazepam, diclazepam and its metabolite delorazepam.	Cross-reactivity was assessed by comparing the absorbance of the drug with that of oxazepam, the reference standard.	Uncontrolled benzodiazepines cross-react sufficiently to produce a positive result with the Immunalysis® Benzodiazepine ELISA kit. Cross-reactivity ranged from 79 to 107% for phenazepam, etizolam, pyrazolam, flubromazepam, diclazepam and delorazepam fortified into blood.	It is possible to detect these newer benzodiazepines with traditional forensic toxicology laboratory tools	Authors emphasise importance of including these benzodiazepines in confirmation tests
O'Conner et al. 2020 [22]	Explore scale of designer benzodiazepine use in different Scottish sub-populations, and detection of drugs in post-	Two Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) methods developed.	Designer benzodiazepines detected: Diclazepam (212 cases); Delorazepam (339 cases); Lormetazepam (144 cases);	Benzodiazepines and designer benzodiazepines are widely used in the	Results not reflective of wider general inmate population and not every post-

	mortem cases for both drug-related and non-drug related deaths.	Total of 2,582 samples analysed. Of these, 893 were urine samples from living participants and 1691 were blood samples from deceased individuals. All blood samples were from the post-mortem (PM) cohort and 369 (22%) of the cases were positive for the designer benzodiazepines tested [PhD thesis].	Flubromazepam (18 cases); Pyrazolam (9 cases).	Scottish population. he Immunalysis® Benzodiazepine ELISA kit can positively identify phenazepam, etizolam, diclazepam, delorazepam, pyrazolam and flubromazepam in blood.	mortem case was tested for designer benzodiazepines.

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