From the clinic to the street

From the clinic to the street: the changing role of benzodiazepines in the Scottish overdose epidemic

A McAuley[a*], C Matheson[b], JR Robertson[c]

a. School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, UK
b. Faculty of Social Sciences, University of Stirling, Stirling, UK
c. Usher Institute, College of Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh, UK

*Corresponding author: School of Health and Life Sciences, Glasgow Caledonian University, Cowcaddens Road, Glasgow, G4 0BA
andy.mcauley@phs.scot

Abstract

Drug-related deaths in Scotland increased for seven years in a row between 2014 and 2020 consolidating Scotland's place at the top of the United Kingdom and European drug-related mortality charts. One of the defining features of this recent and rapid rise has been the role of benzodiazepines which are now involved in two-thirds of all cases. Policy decisions over four decades have contributed to the supply and demand drivers of this unique element of the Scottish overdose crisis. An illicit market once populated by diverted prescription medications is now dominated by a toxic supply of NPS-type benzodiazepines or so-called 'street benzos' which have increased the risk environment for people who use drugs. In response, Scotland needs to urgently expand its harm reduction infrastructure and implement safer supply, drug testing and drug consumption rooms. Such a response should be made in parallel to addressing the socioeconomic inequalities which are fuelling an epidemic of global significance.

Keywords: Overdose; Benzodiazepines; Etizolam; Mortality; Drugs; Prescribing

Introduction

Drug-related deaths in Scotland increased for seven years in a row between 2014 and 2020 and have risen by nearly 450% since records began in 1996 (National Records of Scotland, 2021a) (Figure 1). In 2020, there were 1339 drug-related deaths recorded, all involving persons aged 15-64 years (National Records of Scotland 2021a). By comparison, in 2020 a total of 650 persons aged 15-64 died from COVID-19 (National Records of Scotland 2021b). The annual number of drug-related deaths in Scotland now exceeds the annual number of alcohol-specific deaths (National Records of Scotland 2021c). Scotland's rate of 327 deaths per million population consolidates its place at the top of the British (88 per million[1]) and European Union (15 per million[2]) drug-related mortality charts.

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Root causes of drug-related death: poverty, policy, population, prescribing and polydrug use

Scotland's unacceptably high rates of drug-related deaths are complex and deep-rooted. Although not exclusively, much of Scotland's overdose excess can be explained through poverty, policy, population, prescribing and polydrug use (House of Commons Scottish Affairs Committee, 2019).

Poverty is strongly associated with drug use and related harms. People living in the most deprived communities are more likely to engage in problematic drug use and, in turn, more likely to be affected by drug-related morbidity and mortality. In 2000, people living in the most deprived communities in Scotland had a 10-fold greater risk of drug-related death than those living in the least deprived communities (National Records of Scotland 2021a). By 2020, this ratio had almost doubled to an 18-fold greater risk reflecting the widening inequalities in this epidemic (National Records of Scotland 2021a).

Policies at both UK Government (where drug laws are reserved and largely operate under the 1971 Misuse of Drugs Act) and Scottish Government (where health policy is devolved from the UK Government) have contributed to a crisis which has been developing for over 30 years. The rapidly changing social, economic and political context of the 1980s contributed to a cohort effect of increased drug-related death rates during the 1990s, especially among males living in the most deprived areas born between 1960 and 1980 (Parkinson et al, 2018). Additionally, Scottish Government funding decisions, alongside the UK Government austerity drive from 2010, contributed to a decade of budget cuts to frontline drug treatment services which disproportionately affected the poorest and most vulnerable communities (McPhee & Sheridan, 2020). These cuts were compounded by a further 22% cut in funding in 2015 from £69 million to £53 million (Audit Scotland, 2019).

Budget cuts directly impacted a range of services including those where the evidence is strongest for preventing drug-related deaths such as opioid agonist therapy (Sordo et al, 2017). Moreover, policies

[1] Based on 2018 data
[2] Based mainly on 2019 data

and funding cuts were implemented against a backdrop of Scotland having one of the highest prevalence rates of 'problem drug users' anywhere in the world (Information Services Division, 2019) and at a time when drug-related death rates were already increasing. The proportion of people at risk of overdose engaged with drug treatment in Scotland is unacceptably low, especially in comparison to neighbouring countries (House of Commons Scottish Affairs Committee, 2019). In Scotland, around 40% of people with drug problems are engaged in drug treatment compared to around 65% in England and over 70% in Norway (Selin et al, 2015). In addition, those who are engaged in treatment tend to cycle in and out frequently, thereby increasing their risk of overdose due to fluctuating tolerance levels.

Although Scotland has always had high rates of drug-related mortality, since 2013 these rates have begun to accelerate at a pace no other country in Europe has matched. It is only really in North America, where overdose death rates have been fuelled by a triple-wave epidemic (Ciccarone, 2019), where one can draw comparison with such a dramatic rise. One of the key features of this recent Scottish increase has been the changing profile of substances involved in deaths and an increase in the average number of substances involved in deaths. In 2008, one or two drug types were implicated in 86% of drug-related deaths; by 2020 three or more substances were involved in 61% (Schofield, 2021). Whilst cocaine, gabapentinoids and alcohol have a part to play in the high risk poly-drug using picture alongside opioids, it is benzodiazepines in particular which have changed the most.

Benzodiazepine use among people who use drugs

Globally, benzodiazepines are among the most widely prescribed psychotropic drugs with over 30 different variations, each with common mechanisms of action which produce a range of similar effects for individuals. They can be categorised based on their pharmacokinetic profile and chemical structure. For example, shorter-acting drugs such as temazepam are mainly used as hypnotics at night in the treatment of insomnia, whereas medium-acting drugs such as diazepam are typically used as anxiolytics. They are prescribed for the management and treatment of a range of conditions including anxiety, seizures and musculoskeletal pain and are frequently used as hypnotics in minor surgical procedures (e.g. midazolam). People who use drugs may also seek illicit benzodiazepines to reduce and self-manage anxiety, insomnia and withdrawal symptoms (Ford & Law, 2014). They also report using supra-therapeutic ['mega'] doses of benzodiazepines to enhance the effects of opioids (Jones et al, 2012).

Benzodiazepine prescribing and use in Scotland: a brief history

Since the 1980s, Scotland's relationship with the misuse of benzodiazepines has been prominent, initially through the use of temazepam, diazepam, and triazolam (Green et al, 1992; Hammersley et al, 1995; Robertson & Ronald, 1992; Strang et al, 1994). Prior to then, prescribing of benzodiazepines for the general population of Scotland had increased over the 1960s and 1970s. Benzodiazepines were originally marketed as a safer alternative to barbiturates. However wide availability resulted in leakage into the illicit market which became problematic in the 1980s when it emerged that liquid filled temazepam capsules were being injected (Strang et al, 1992). Seizures of industrial quantities of

temazepam demonstrated new levels of availability in drug markets reflecting a shift from the previous sources, largely diversion from prescribed sources.

Patterns of illicit use changed in the 1990s following the withdrawal of temazepam liquid capsules which were replaced with gel capsules which, in turn, were associated with a range of injecting-related harms. Removing temazepam gel capsules from the market was subsequently associated with a reduction in benzodiazepine-related deaths in the UK (Buckley & McManus, 2004). Following the withdrawal, many people who used drugs shifted to oral temazepam or diazepam as an alternative. It was diazepam, however, which quickly established itself as the most popular benzodiazepine among prescribers owing to its more predictable effects and the range of tablet strengths which facilitated clinical flexibility, and relatively cheap costs per dose.

As prescribing of diazepam increased in the general population, so too did diversion into the illicit market. Diazepam was mainly consumed alongside other depressant drugs, typically opioids and alcohol, thus increasing risk of heavy sedation and respiratory depression (Ford & Law, 2014). As Scotland's drug-related death numbers continued to increase throughout the 2000s the role of diazepam came under scrutiny and the long term trend of increased prescribing peaked around 2006/07 followed by a steady reduction which has persisted to the present day. This change in policy was partly due to concerns about increasing levels of benzodiazepine dependence among people who use drugs and inappropriate prescribing but also the increasing pressure on primary care prescribers to supply escalating demand. Anxiety about the evidence of increased tolerance to previously unseen doses and the spectre of alleged withdrawal seizures caused a new level of resistance to prescribing benzodiazepines in primary care. At the peak of diazepam prescribing in Scotland, it was involved in around one in five drug-related deaths with annual numbers less than 500.

Benzodiazepine use in Scotland: the emergence of NPS

While restrictions on benzodiazepine prescribing addressed issues related to supply and diversion, insufficient attention was paid at the same time to demand. People who use drugs in Scotland had been using benzodiazepines (one way or another) for 30 years therefore a huge market existed. At the same time prescribing was curtailed in the mid to late 2000s, new/novel psychoactive substances (NPS) began to take a foothold in global drug markets including in the UK (Shapiro, 2016). The United Nations Office on Drugs and Crime (UNODC) define NPS as "substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat" (UNODC, 2021). This includes those that are *new* to the illicit market, including both substances synthesised decades ago and more recent creations.

Driven by the enhanced accessibility and affordability afforded by the internet, suppliers began to import a whole range of NPS into the UK market including synthetic cathinones, cannabinoids and benzodiazepines. A sea change occurred during this period, taking benzodiazepine use in Scotland to a new, and extraordinarily high, level. Supply generated a new market in the same way that heroin

availability had in the early 1980s. This may have been further exacerbated by a national drugs policy in 2008 based on achieving abstinence from all drugs (Scottish Government, 2008). By discouraging agonist treatment a potential unintended consequence was that people who use drugs looked for supplements to diminishing prescriptions doses of methadone and buprenorphine.

As the number of diverted benzodiazepine prescriptions on the illicit market began to decrease suppliers looked to alternatives offered by NPS. The EU early warning system operated by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) gave an indication of the NPS-type benzodiazepines appearing on the market across Europe with phenazepam and etizolam two of the first drugs detected (Figure 2). NPS-type benzodiazepines have been labelled using a variety of terms including ‘designer benzodiazepines’, ‘NPS benzodiazepines’ and, ‘synthetic benzodiazepine analogues’ (EMCDDA, 2021). In Scotland, they are often referred to as ‘street benzos’ (Matheson, 2021).

Phenazepam is a long-acting benzodiazepine developed in the 1970s in the former Soviet Union (Corkery et al, 2012). It is available on prescription in Russia and a number of ex-Soviet states. It was first detected in Scotland from police seizure operations in 2008 and considered to be potentially harmful given its increased toxicity (Kyle et al, 2012). The Scottish Government issued a public information warning regarding the availability and risks related to phenazepam consumption following an increase in associated hospital admissions (Williams, 2010). Soon after, the first phenazepam-related deaths in Scotland were recorded in 2011 (13/584; 2%) (National Records of Scotland, 2012). In the same year there were 123 diazepam-related deaths (29% of the total in that year). Notably, seizures of phenazepam at the time identified the drugs to have features similar to diazepam (Corkery et al, 2012). The UK Government subsequently controlled phenazepam as a Class C drug in June 2012 and its impact on drug-related mortality in Scotland diminished over the next few years after peaking in 2013 (34/527 deaths; 6%) (National Records of Scotland, 2014). Phenazepam was brought under international control in 2016 (UNODC, 2016), but is still viewed as an NPS-type benzodiazepine by institutions including the EMCDDA (EMCDDA, 2021).

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In the same way phenazepam appeared to have plugged the gap created by restrictions on diazepam prescribing, etizolam emerged as the natural successor to phenazepam. Indeed, seizure data also suggested that etizolam was similarly being prepared and branded to look like other drugs including diazepam (Advisory Council on the Misuse of Drugs, 2016). Etizolam is an anxiolytic which has been available for prescription in Italy, India and Japan for almost 40 years, but is a controlled drug in many other countries including the UK (Nielsen & McAuley, 2020). It was brought under international control in 2020 (United Nations, 2020) and has a half-life of 5-7 hours making it much shorter-acting than other benzodiazepines. In lab studies, etizolam has not been shown to be more deadly than other benzodiazepines including diazepam, typically requiring larger doses for lethality (Nielsen & McAuley, 2020). However, as an anxiolytic, etizolam is estimated to be 5-10 times more potent than diazepam

(Nielsen & McAuley, 2020). Studies of etizolam use among human subjects are lacking, in particular studies of use at supratherapeutic doses and/or in combination with other drugs.

Prevalence data on trends of etizolam use over time in Scotland are not yet available, however the mortality data paint a stark picture of how the drug has quickly become one of the most prominent influences on drug-related deaths in recent years. When first detected in 2012, it was involved in one death representing just 0.2% of the total that year (1/581) (National Records of Scotland. (2021a). By 2015 this had increased to 6% (43/706). In the most recent figures for deaths recorded in 2020, etizolam was involved in 60% (806/1339) representing a 19-fold increase in just five years (Figure 3). By comparison, in 2020 diazepam was involved in 14% of drug-related deaths (194/1339). The prevalence of NPS-type benzodiazepines is also related to the ability of available analytical methods to detect these molecules. Etizolam, for example, was not available as a raw material when it was sold in large quantities on the street. In 2012 and even much later, very few laboratories were able to detect these molecules.

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In Scotland, etizolam is mainly consumed alongside other drugs in the same way benzodiazepines have historically been used. These polydrug combinations typically involve other central nervous system depressants such as opioids and alcohol, and increasingly cocaine and gabapentinoids. Mortality data confirm this, with only 8/806 (1%) etizolam-related deaths in 2020 involving etizolam alone (National Records of Scotland, 2021a). Although etizolam specific studies are lacking, the risks associated with consuming multiple depressant drugs in combination are well established (Ford & Law, 2014; Gudin et al, 2013). In addition, the illicit production of such drugs where contents are unknown and their appearance is designed to mimic other drugs leaves people who use drugs in a perpetual cycle of consumption roulette where they are unsure of the effect they may experience between different sessions or even pills. Given its shorter half-life, people who use etizolam may also re-dose more frequently than they would with other benzodiazepines, thus further increasing their risk of harms. These frequent consumption patterns are facilitated by its affordability; etizolam reportedly retails for around 50p per pill on the Scottish street market with people who use these drugs reporting using ‘handfuls’ of pills at a time (McGivern, 2020).

Domestic production

The onset of the Covid-19 pandemic posed major challenges for every aspect of society including illicit drug supply. Routes were hugely interrupted owing to the impact of pandemic restrictions on drug trafficking which relies heavily on routine trade to mask its processes as well as individuals to supply the market (United Nations Office on Drugs and Crime, 2020). While this was the case in many territories and for particular drugs, the street benzo trade in Scotland was largely uninterrupted. This is due in part to the shift to domestic production of etizolam in recent years, having previously been reliant on the importation of drugs from overseas. Increasingly, domestic suppliers are producing their own drugs in significant quantities to supply the substantial market that exists in Scotland. Seizures of etizolam have increased significantly in recent years as have interceptions of domestic industrial

laboratories capable of producing millions of pills per day (McGivern, 2018). It is perhaps unsurprising that etizolam has increased its influence in the Scottish drug-related death figures despite the Covid-19 restrictions imposed on society.

Tackling the benzodiazepine problem

As we have articulated in this paper, the benzodiazepine problem in Scotland is deep rooted and complex. Therefore, the response requires a broad range of strategies across the short, medium and longer terms involving a range of stakeholders at local, national and international levels.

The immediate focus has to be on harm reduction. Scotland has a good harm reduction infrastructure with availability of free to access opioid agonist therapy, needle and syringe provision and take-home naloxone. Given that overdoses involving benzodiazepines mainly involve opioids as well, then consolidation and scale up of these existing interventions remains critically important. However, the rapid rise in street benzo-related deaths (mainly via etizolam) in recent years necessitate urgent additional strategies to reduce harms; in particular, safe supply, drug checking facilities and drug consumption rooms (DCRs).

Safe supply initiatives aim to reduce the risk of drug-related harms including overdose by prescribing pharmaceutical grade medicines such as benzodiazepines and opioids to people at risk of such harms who are obtaining drugs from the illicit market (Ivsins et al, 2020). An unintended consequence of the move toward more limited benzodiazepine prescribing in Scotland has undoubtedly been its role in driving people who use illicit supplies from diverted prescriptions to a more dangerous array of street benzos, thus increasing the risk environment for those at-risk of overdose (Rhodes, 2002). This situation mirrors the experience from the USA where curtails on opioid prescribing drove the at-risk population toward street heroin and then synthetic opioids with disastrous consequences (Ciccarone, 2019). The aims of the decision to limit benzodiazepine prescribing in Scotland were well intentioned, however without simultaneously addressing demand reduction they triggered the onset of the street benzo market which dominates today. Demand reduction will require a long term strategy which addresses inequalities in health and society. Indeed, relative and absolute inequalities in premature mortality have widened in Scotland in recent years linked to Government austerity measures (Scottish Public Health Observatory, 2021). In the meantime, it is essential we urgently review the current strategy and consider prescribing benzodiazepines again (Robertson et al, 2021). This is not without risk and controversy, of course, but in the absence of evidence of risks associated with longer term use prescribers should assess what role they can play, and how to balance risk of harm from not prescribing, in addressing this critical aspect of the Scottish epidemic through facilitating safer supply. The Scottish Drug Death Taskforce, established by the Minister for Public Health in response to the overdose crisis in 2019, has recognised the need to consider safer prescribing as part of a harm reduction approach. In relation to benzodiazepines, the Taskforce plan includes guidance on clinical management for immediate risk reduction (Matheson, 2021).

Arguments for and against increasing prescribing of benzodiazepines to reduce harm are complicated. The absence of robust research on the long term effects of benzodiazepine use on

cognition is a major problem as is the understandable warnings from prescribers of escalating tolerance and associated demand for increasing doses, as well as the absence of an exit strategy supported by research on withdrawal effects. Often driven by supply of new substances, the opioid crises in North America took Governments and policy makers by surprise, although warning signs were there, and the Scottish benzodiazepine problem has, as we have outlined, deeper causation.

Drug checking facilities operate where people voluntarily submit drug samples and are provided with information about content, potency and purity for the purposes of harm reduction (Guirguis et al, 2020). They have significant potential to have a positive impact on the current crisis by allowing more real-time surveillance into the supply side which can better inform people who use drugs and practitioners as to what drugs are circulating in communities. This, in turn, can inform harm reduction strategies that are timely and localised and allow users to make more informed choices as to what drugs they are taking. Surveillance of street drugs in the UK is currently limited to police seizure data or health records. The former is limited in its reach and the latter suffers from significant time-lags challenging its ability to respond effectively to issues related to new or more toxic drugs within the supply chain. The experience of the NPS-type benzodiazepine market to date shows us that it is likely etizolam could soon be replaced by another, potentially more potent, NPS-type benzodiazepine drug in the same way that etizolam replaced phenazepam (EMCDDA, 2021). The EU early warning system (Figure 2) offers an important overview of what these might be, but drug checking can accelerate the identification of these new substances in real time. Moreover, drug-checking has potential to benefit wider surveillance of street drugs, including the ongoing threat of synthetic opioids which have yet to penetrate the UK market in any meaningful way.

Application of drug checking facilities in the UK is currently limited. The evidence base to date for drug checking is mainly derived from studies conducted within music festival settings (Wallace, 2020). Drug checking facilities at drug treatment services, which are more likely to engage with community populations at-risk of overdose, are much more limited although a recent UK pilot did provide proof of concept (Guirguis et al, 2020). There remain concerns about the role of drug checking in changing behaviours among these populations and the most appropriate technologies to utilise in such settings (Wallace, 2020). As such, implementation of drug checking facilities as a community overdose prevention initiative should be undertaken within a research environment. Indeed, Scottish pilots funded by the Taskforce are now underway across three cities (University of Stirling, 2021) with a view to establishing these services as more mainstream aspects of the harm reduction infrastructure.

Drug consumption rooms (DCRs) are facilities which allow the consumption of drugs within a safe and hygienic environment under supervision by staff (EMCDDA, 2018). Should someone suffer a drug overdose involving benzodiazepines within a DCR then the availability of immediate staff support (typically trained healthcare professionals) can reduce the risk of drug-related death. Although people who use such facilities mainly inject drugs, the significance of polydrug use in Scotland means that these services also have the potential to impact on benzodiazepine-related deaths. DCRs also provide a low threshold point of engagement with some of the most marginalised individuals in the at-risk population who may not be linked in to other services (EMCDDA, 2018). There are no legal drug

consumption rooms operating in the UK at present. The need to provide a DCR service has been described as extraordinary and indicates the 'moral-sidestep' given by Government to tackling drug-related deaths (Stevens, 2019).

Low threshold access to drug treatment, harm reduction advice and facilities, and trauma informed care are at the core of Taskforce led Medication Assisted Treatment standards (Scottish Government, 2021). Whilst realistically these may take time to embed, there are no legal or political impediments to implementation, unlike DCRs.

NPS-type benzodiazepines: a global threat

The use of NPS-type benzodiazepines, in particular alongside opioids, is now recognised as a global threat to public health (UNODC, 2017). A recent study by the EMCDDA investigating NPS' role in deaths across Europe in 2016 and 2017 found that they were involved in one in seven cases (2,300), and that etizolam accounted for just under a third (30%) of all cases, the overwhelming majority of which were from Scotland (López-Pelayoa, 2021). However, illicit etizolam use is not exclusive to Scotland or indeed Europe. In Ireland etizolam has been identified in urine samples among individuals in treatment for opioid dependence (McNamara et al, 2019) suggesting similar polydrug consumption patterns to those in Scotland. The NSW government in Australia issued a public information notice warning of the availability and risks associated with etizolam use after it was detected in pills designed to look like another benzodiazepine, alprazolam (New South Wales Ministry of Health, 2019). In the USA, the Drug Enforcement Agency National Forensic Laboratory Information has reported increasing detection of etizolam in recent years (Bollinger et al, 2021). Also in North America, an increase in etizolam (and other street benzos) has been detected within samples submitted to community drug checking programmes in Canada, mainly as part of adulterated opioids (Laing et al, 2021). This so called 'benzo-dope' product is increasingly associated with mortality, detected in 39% of drug-related deaths in British Columbia between July 2020 and May 2021 (BC Coroners Service, 2021). These examples from across the world illustrate the extent to which NPS-type benzodiazepines like etizolam have infiltrated different markets and increased risk of harm for people who use drugs, particularly when used concomitantly with opioids.

Conclusion

The role of street benzos in Scotland's drug-related death epidemic has become hugely significant in recent years and demands an especially urgent response from policymakers, practitioners and academics alike. A strategic response is demonstrated by the work of the Taskforce through focussing on reducing harms via safer supply, enhanced surveillance and clinical management. However, focussing on substances is just one part of the solution. Such a response should be made in parallel to addressing the socioeconomic inequalities which are fuelling an epidemic of global significance.

Prescribing for people who use drugs has always been contentious, as fluctuating Government policy demonstrates over several decades. National Guidelines (Clinical Guidelines on Drug Misuse and

Dependence Update 2017 Independent Expert Working Group, 2017) have helped, and recent renewed interest and investment in drug treatment services have focussed attention for the first time since previous crises sparked by HIV and Hepatitis C infection. A joined up approach is essential and optimising the more securely evidenced based Opioid Agonist treatment is fortunately a priority. Addressing coexisting substances such as benzodiazepines requires a strategy combining careful monitoring, robust research and inevitably serious investment if we are to impact on the death rate in a group who are among the most vulnerable members of our society.

References

Advisory Council on the Misuse of Drugs. (2016). *Designer Benzodiazepines A review of the evidence of use and harms.* London: ACMD. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/579352/ACMD_TCDO_Report_U47700_and_Etizolam_and_designer_benzodiazepines.pdf

Audit Scotland. (2019). *Drug and Alcohol Services in Scotland, An update*. Audit Commission, Edinburgh. https://www.audit-scotland.gov.uk/uploads/docs/report/2019/briefing_190521_drugs_alcohol.pdfHouse of Commons

BC Coroners Service. (2021, August). *Illicit drug toxicity type of drug data (data to Jan 31, 2021)*. www2.gov.bc.ca/assets/gov/birth-adoption-death-marriage-and-divorce/deaths/coroners-service/statistical/illicit-drug-type.pdf

Bollinger, K., Weimer, B., Heller, D., Bynum, N., Grabenauer, M., Pressley, D., et al. (2021). Benzodiazepines reported in NFLIS-Drug, 2015 to 2018. *Forensic Sci Int Synerg*., 3, 100138.

Buckley, N. A., & McManus, P. R. (2004). Changes in fatalities due to overdose of anxiolytic and sedative drugs in the UK (1983-1999). Drug Saf., 27(2), 135-41. doi: 10.2165/00002018-200427020-00004.

Burns, C. (2019). Scotland's first heroin-assisted treatment service launched in Glasgow. *The Pharmaceutical Journal*, 303, 7932, 303(7932). DOI:10.1211/PJ.2019.20207404

Ciccarone, D. (2019). The triple wave epidemic: Supply and demand drivers of the US opioid overdose crisis. *Int J Drug Policy*, 71, 183-188. doi: 10.1016/j.drugpo.2019.01.010.

Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group. (2017). *Drug misuse and dependence: UK guidelines on clinical management*. London: Department of Health. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/673978/clinical_guidelines_2017.pdf

Corkery, J.M., Schifano, F., & Ghodse, H. (2012). Phenazepam abuse in the UK: An emerging problem causing serious adverse health problems, including death. *Human Psychopharmacology Clinical and Experimental*, 27, 254-261.

European Monitoring Centre for Drugs and Drug Addiction. (2018). *Drug consumption rooms: an overview of provision and evidence*. Lisbon: EMCDDA. https://www.emcdda.europa.eu/system/files/publications/2734/POD_Drug%20consumption%20rooms.pdf

European Monitoring Centre for Drugs and Drug Addiction. (2021). *New benzodiazepines in Europe – a review*. Publications Office of the European Union, Luxembourg. https://www.emcdda.europa.eu/system/files/publications/13759/TD0221596ENN_002.pdf

Ford, C., & Law, F. (2014). *Guidance for the use and reduction of misuse of benzodiazepines and other hypnotics and anxiolytics in general practice*. www.smmgp.org.uk/download/guidance/guidance025.pdf

Green, S., Goldberg, D., Frsicher, M., & McKeganey, N. (1992). Triazolam as a substance of abuse by injecting drug users. *Br J Addict*, 87, 941-2.

Gudin, J.A., Mogali, S., Jones, J. D., & Comer, S. D. (2013). Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. *Postgrad Med*, 125, 115-30.

Guirguis, A., Gittins, R., & Schifano, F. (2020). Piloting the UK's First Home-Office-Licensed Pharmacist-Led Drug Checking Service at a Community Substance Misuse Service. *Behav Sci,* 10(8), 121. doi:10.3390/bs10080121

Hammersley, R., Cassidy, M. T., Oliver, J. (1995). Drugs associated with drug-related deaths in Edinburgh and Glasgow, November 1990 to October 1992. *Addiction*, 90(7), 959–65.

House of Commons Scottish Affairs Committee. (2019). *Problem drug use in Scotland: First Report of Session 2019*. https://publications.parliament.uk/pa/cm201919/cmselect/cmscotaf/44/44.pdf

Information Services Division. (2019). *Prevalence of Problem Drug Use in Scotland 2015/16 Estimates*. NHS National Services Scotland, Edinburgh. https://www.isdscotland.org/Health-Topics/Drugs-and-Alcohol-Misuse/Publications/2019-03-05/2019-03-05-Drug-Prevalence-2015-16-Report.pdf

Ivsins, A., Boyd, J., Beletsky, L., & McNeil, R. (2020). Tackling the overdose crisis: The role of safe supply. *Int J Drug Policy*, 80, 102769. https://doi.org/10.1016/j.drugpo.2020.102769

Jones, J. D., Mogali, S., & Comer, S. D. (2012). Polydrug abuse: A review of opioid and benzodiazepine combination use. *Drug and Alcohol Dependence*, 125(1–2), 8–18.

Kyle, P.B., Brown, K.B., Bailey, A.P., & Stevenson, J.L. (2012). Reactivity of commercial benzodiazepine immunoassays to Phenazepam *Journal of Analytical Toxicology*, 36, 207-209.

Laing, M. K., Ti, L., Marmel, A., Tobias, S., Shapiro, A. M., Laing, R., et al. (2021). An outbreak of novel psychoactive substance benzodiazepines in the unregulated drug supply: Preliminary results from a community drug checking program using point-of-care and confirmatory methods. *Int J Drug Policy*., 93, 103169.

López-Pelayoa, H., Vicente, J., Gallego,s A., McAuley, A., Büyüke, Y., White, M., et al. (2021). Mortality involving New Psychoactive Substances across Europe, 2016-2017. *Emerging Trends in Drugs, Addictions, and Health* https://doi.org/10.1016/j.etdah.2021.100016

Matheson, C. (2021, July). *Scotland's Benzo challenge and how we can meet it*. Scottish Drug Deaths Taskforce. https://drugdeathstaskforce.scot/scotland-s-unique-challenge/tackling-benzodiazepines/

McGivern, M. (2018, November 28). See inside Paisley 'Breaking Bad' pill factory after 'Blue Plague' gang busted. *Daily Record*. https://www.dailyrecord.co.uk/news/scottish-news/amazing-cop-footage-paisley-breaking-13654075

McGivern, M. (2020, October 18). Scots hooked on 50p 'benzo' pills 40 times stronger than Valium. *Daily Record*. https://www.dailyrecord.co.uk/news/health/scots-hooked-50p-benzo-pills-22863204

McNamara, S., Stokes, S., & Nolan, J. (2019). The emergence of new psychoactive substance (nps) benzodiazepines. A survey of their prevalence in opioid substitution patients using LC-MS. *Ir Med J*, 112, 970.

McPhee, I., & Sheridan, B. (2020). AUDIT Scotland ten years on: explaining how funding decisions link to increased risk for drug related deaths among the poor. *Drugs and Alcohol Today*, 20(4), 313-322. https://doi.org/10.1108/DAT-05-2020-0024

National Records of Scotland. (2012). *Drug-related Deaths in Scotland in 2011*. https://www.nrscotland.gov.uk/files/statistics/drug-related-deaths/2011/drug-related-deaths2011.pdf

National Records of Scotland. (2014). *Drug-related Deaths in Scotland in 2013*. https://www.nrscotland.gov.uk/files//statistics/drug-related-deaths/2013/drugs-related-deaths-2013.pdf

National Records of Scotland. (2021a). *Drug-related Deaths in Scotland in 2020*. https://www.nrscotland.gov.uk/files//statistics/drug-related-deaths/20/drug-related-deaths-20-pub.pdf

National Records of Scotland. (2021b). *Deaths involving coronavirus (COVID-19) in Scotland*. https://www.nrscotland.gov.uk/files//statistics/covid19/covid-deaths-21-report-week-34.pdf

National Records of Scotland. (2021c). *Alcohol-specific deaths 2020*. https://www.nrscotland.gov.uk/files//statistics/alcohol-deaths/2020/alcohol-specific-deaths-20-report.pdf

New South Wales Ministry of Health. (2019, December). *Drug warning - Non-pharmaceutical grade (counterfeit) alprazolam tablets containing etizolam*. https://www.health.nsw.gov.au/aod/public-drug-alerts/Pages/drug-warning-counterfeit-alprazolam.aspx

Nielsen, S., & McAuley, A. (2020). Etizolam: A rapid review on pharmacology, non- medical use and harms. *Drug Alcohol Rev*., 39(4), 330-336. doi:10.1111/dar.13052

Parkinson, J., Minton, J., Lewsey, J., Bouttell, J., & McCartney, G. (2018). Drug-related deaths in Scotland 1979–2013: evidence of a vulnerable cohort of young men living in deprived areas. *BMC Public Health*, 18 (357). https://doi.org/10.1186/s12889-018-5267-2

Rhodes, T. (2002). The 'risk environment': a framework for understanding and reducing drug-related harm. *Int J Drug Policy*, 13(2), 85-94.

Robertson, J. R., Ronald, P. J. M. (1992). Prescribing benzodiazepines to drug misusers. *The Lancet*, 339(8802), 1169–70.

Robertson, R., McAuley, A., & Matheson, C. (2021). Benzodiazepines: the time for systematic change is now. *Addiction*, 116, 2246– 2247. https://doi.org/10.1111/add.15488

Schofield, J. (2021, August 13). Personal communication.

Scottish Government. (2008). *The road to recovery: a new approach to tackling Scotland's drug problem*. Edinburgh: Scottish Government. https://www.gov.scot/binaries/content/documents/govscot/publications/strategy-plan/2008/05/road-recovery-new-approach-tackling-scotlands-drug-problem/documents/0060586-pdf/0060586-pdf/govscot%3Adocument/0060586.pdf

Scottish Government. (2021). *Medication Assisted Treatment (MAT) standards: access, choice, support*. The Scottish Government, Edinburgh. https://www.gov.scot/binaries/content/documents/govscot/publications/independent-report/2021/05/medication-assisted-treatment-mat-standards-scotland-access-choice-support/documents/medication-assisted-treatment-mat-standards-scotland-access-choice-support/medication-assisted-treatment-mat-standards-scotland-access-choice-support/govscot%3Adocument/medication-assisted-treatment-mat-standards-scotland-access-choice-support.pdf

Scottish Public Health Observatory. (2021, March). *Health inequalities: Scottish comparisons and trends*. Scottish Public Health Observatory. https://www.scotpho.org.uk/comparative-health/health-inequalities/data/scottish-trends/

Selin, J., Perala, R., Stenius, K., Partanen, A., Rosenqvist, P., & Alho, H. (2015). Opioid substitution treatment in Finland and other Nordic countries: established treatment, varying practices. *Nordic Studies on Alcohol and Drugs*, 32, 311-324.

Shapiro, H. (2016). *NPS Come of Age: A UK overview*. Drugwise. http://www.drugwise.org.uk/wp-content/uploads/NPSComeofAge.pdf

Sordo, L., Barrio, G., Bravo, M. J., Indave, B. I., Degenhardt, L., Wiessing, L., et al. (2017). Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ*, 357, j1550. doi:10.1136/bmj.j1550

Stevens, A. (2019). 'Being human' and the 'moral sidestep' in drug policy: Explaining government inaction on opioid-related deaths in the UK. *Addictive Behaviors*, 90, 444-450.

Strang, J., Seivewright, N., & Farrell, M. (1992). Intravenous and other novel abuses of benzodiazepines: the opening of Pandora's box? *Br J Addict*, 87(10), 1373-5. doi: 10.1111/j.1360-0443.1992.tb01916.x.

Strang, J., Griffiths, P., Abbey, J., & Gossop, M. (1994). Survey of use of injected benzodiazepines among drug users in Britain. *BMJ*, 308(6936), 1082.

Strang, J., Groshkova, T., Uchtenhagen, A., Van den Brink, W., Haasen, C., Schechter, M., . . . Metrebian, N. (2015). Heroin on trial: Systematic review and meta-analysis of randomised trials of diamorphine-prescribing as treatment for refractory heroin addiction. *British Journal of Psychiatry*, 207(1), 5-14. doi:10.1192/bjp.bp.114.149195

UK Government Committee on the Safety of Medicines. (1988). Benzodiazepines, withdrawal and dependence symptoms: UK Government Bulletin to Prescribing Doctors. *Current Problems*, 21, 1-2.

United Nations. (2020). *Commission on Narcotic Drugs Report on the sixty-third session.* Economic and Social Council. https://www.unodc.org/documents/commissions/CND/CND_Sessions/CND_63/E2020_28_e_V2001956_Advance_Version.pdf

United Nations. (2016). *Commission on Narcotic Drugs Report on the fifty-ninth session.* Economic and Social Council. http://www.undocs.org/E/2016/28

United Nations Office on Drugs and Crime. (2017). *Non-medical use of benzodiazepines: a growing threat to public health?* United Nations, Vienna. https://www.unodc.org/documents/scientific/Global_SMART_Update_2017_Vol_18.pdf

United Nations Office on Drugs and Crime. (2020). *COVID-19 and the drug supply chain: from production and trafficking to use*. United Nations, Vienna. https://www.unodc.org/documents/data-and-analysis/covid/Covid-19-and-drug-supply-chain-Mai2020.pdf

United Nations Office on Drugs and Crime. (2021). *What are NPS?* United Nations Office on Drugs and Crime. https://www.unodc.org/LSS/Page/NPS

University of Stirling. (2021, August). *Could drug checking help prevent harms in Scotland?* University of Stirling. https://www.stir.ac.uk/news/2021/august-2021-news/could-drug-checking-help-prevent-harms-in-scotland/

Wallace, B., van Roode, T., Pagan, F. et al. What is needed for implementing drug checking services in the context of the overdose crisis? A qualitative study to explore perspectives of potential service users. Harm Reduct J 17, 29 (2020). https://doi.org/10.1186/s12954-020-00373-4

Williams, M. (2010, August 24). Warning over online 'Valium'. *The Herald*.