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ORIGINAL ARTICLE

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Nonmedical use of benzodiazepines and Z-drugs in the UK

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Aims: To estimate prevalence of last 12-month nonmedical use (NMU) of benzodiazepines and Z-drugs (the nonbenzodiazepine hypnotics zaleplon, zolpidem and zopiclone) in the UK.

Methods: Data were collected using the Non-Medical Use of Prescription Drugs survey with poststratification weighting applied to be representative of the UK population (≥16 years). Participants were questioned about whether they had nonmedically used benzodiazepines and/or Z-drugs in the last 12-months and from where they had obtained the drug (including via a prescription, or illicitly from a friend/family member, a dealer or via the internet). Additional questions were asked about last 12-month use of illicit drugs (cannabis, cocaine, 3,4-methylenedioxymethylamphetamine [MDMA], non-pharmaceutical amphetamine, *crack cocaine* and/or heroin).

Results: The study included 10 006 eligible participants representing approximately 52 927 000 UK adults. The estimated prevalence of past 12-month NMU of any benzodiazepine and/or Z-drug was 1.2% (95% confidence interval: 1.0–1.5) corresponding to approximately 635 000 adults; amongst this group only an estimated 4.6% (1.2–8.0) had NMU of both a benzodiazepine and a Z-drug. The highest prevalence of NMU for only Z-drugs was among those who had used heroin in the last 12-months (5.4%, 2.7–10.5), whilst the highest prevalence of NMU for only benzodiazepines was among those who had used illicit stimulants in the last 12-months: cocaine (5.9%, 3.8–8.9), amphetamine (5.6%, 3.1–10.0) and MDMA (5.2%, 3.1–8.8). The drug non-medically used was more commonly acquired without than with a prescription for both only benzodiazepines (70.2%, 59.4–81.1 compared to 51.3%, 41.5–64.6) and only Z-drugs (75.6%, 61.6–89.7 compared to 33.9%, 16.9–51.0).

Conclusion: There is little overlap between benzodiazepine and Z-drug NMU suggesting distinct nonmedical use of the drugs; future studies need to explore whether this relates to personal preference, drug availability or other factors. A significant proportion are acquiring these drugs for NMU without a prescription, so without guidance and monitoring from a medical practitioner. While the dangers of mixing benzodiazepines and heroin/other opioids are well documented, there is a

The authors confirm that the PI for this paper is Paul I. Dargan and that he had direct clinical responsibility for patients.

paucity of data regarding concomitant NMU of benzodiazepines and stimulant drugs, or NMU of Z-drugs and opioids, and, given the prevalence of these combinations, this requires further investigation.

KEYWORDS

benzodiazepines, drug abuse, public health

1 | INTRODUCTION

The global concern regarding nonmedical use (NMU) of prescription medicines is well documented.[1] Over a decade ago, the International Narcotics Control Board warned that the misuse of prescription drugs could exceed illicit drug use.[2,3] Much of the attention is devoted to the NMU of prescription opioids; however, the United Nations Office on Drugs and Crime warned in 2017 that polydrug use, particularly with sedatives/hypnotics, may be linked to an observed rise in prescription opioid deaths and that NMU of benzodiazepines is a growing threat to public health.[4] The United Nations Office on Drugs and Crime Global Drug Report 2018 states that benzodiazepines are the most commonly misused type of prescription drug with approximately 60 countries ranking benzodiazepines among the 3 most commonly misused substances (both recreational and prescription).[1]

In a recent UK review of the scale, distribution, and causes of prescription drug dependence, Public Health England acknowledged a lack of available UK-focused data.[5] The findings of the review showed that while the number of prescriptions in England was falling, 1.4 million adults had been prescribed a benzodiazepine and 1.0 million adults had been prescribed a nonbenzodiazepine hypnotic Z-drug (3.1 and 2.3% of the adult population, respectively) between 2017 and 2018. Benzodiazepines and Z-drugs are prescribed as short-term treatments for anxiety and insomnia, but, due to concerns over their dependence potential, are only recommended for use for a maximum of 2–4 weeks. However, a study by Davies *et al*. found that it is likely that more than a quarter of a million people in England are taking these drugs longer than the recommended time with 35% of all benzodiazepine or Z-drug users taking the drugs for at least 12 times the recommended duration of treatment.[6] Also, a cause for concern is concurrent use of benzodiazepines by heroin users and increased risk of emergency department visits, overdose and death.[7,8]

The available data suggest that benzodiazepines encountered on the illicit drug market are primarily diverted from legitimate sources rather than being counterfeit medicines and that diversion can occur at all points along the pharmaceutical supply pathway from manufacturing sites and distributors to patients themselves.[4] A 2016 report by the UK Advisory Council on the Misuse of Drugs on *Diversion and Illicit Supply of Medicines* found that within the UK the most prevalent diverted drugs are opioids and benzodiazepines, with benzodiazepines and Z-drugs being the most common medicines illegally diverted from the regulated supply chain.[9] The UK Medicines and Healthcare Products Regulatory Agency estimated that between 2013 and 2016 up to £200 million worth of prescription medicines, including **diazepam** and **zopiclone**, had been diverted to the criminal market for supply.[10]

What is already known about this subject

- Benzodiazepines and Z-drugs have addiction and dependence potential.
- They are among the most common medicines illegally diverted from the regulated supply chain in the UK.

What this study adds

- Our study suggests nonmedical use of benzodiazepines and Z-drugs in the UK is a significant issue, but there is little overlap between the 2 drug groups.
- Nonmedical use of Z-drugs is most prevalent among heroin users.
- Nonmedical use of benzodiazepines is most prevalent among illicit stimulant users.

Most previous studies have reported the prevalence of NMU for benzodiazepines or Z-drugs in subpopulations that are not representative of the entire UK and/or only focused on lifetime NMU of drugs.[11–13] Information focusing on the situation in the UK is needed for development of public policy to assess and intervene in benzodiazepine and Z-drug NMU. In this study, we measured the prevalence of NMU of benzodiazepine and Z-drugs within the last 12 months in the UK and the source of acquisition of drugs utilising data from the UK Survey of Non-Medical Use of Prescription Drugs (NMURx) programme.

2 | METHODS

The NMURx programme is part of the Researched Abuse, Diversion and Addiction Related Surveillance (RADARS) system methodology, which has been described in detail elsewhere.[14,15] Data used in this analysis were collected from an online survey between 23 March and 23 April 2018. Poststratification weights were applied the survey population based on region, sex and age to be representative of the demographic distribution of the adult UK population.[14] NMURx was approved by the Colorado Multiple Institutional Review Board (Protocol Number: 13–2394).

Respondents were asked if they had ever used benzodiazepines or Z-drugs in their lifetime. If respondents reported lifetime use, they were asked about whether this included NMU; NMU was defined as "*using a medication without a doctor's prescription or for any reason other than what was recommended by their doctor*". If respondents reported lifetime NMU they were asked to select which specific drug substance they had nonmedically used and if that was within the last 12 months.

Basic demographics (age, sex, residential region) were collated together with data on the last 12-month NMU of prescription medications. Drug groups included were benzodiazepines (**alprazolam**, bromazepam, **chlordiazepoxide**, **clobazam**, **clonazepam**, diazepam, **flurazepam**, loprazolam, **lorazepam**, lormetazepam, **midazolam**, nitrazepam, **oxazepam** or **temazepam**) and Z-drugs (**zaleplon**, **zolpidem** or zopiclone). NMU of any benzodiazepine and/or Z-drug, any NMU of benzodiazepines but not Z-drugs (called *only benzodiazepines*), and any NMU of Z-drugs but not benzodiazepines (called *only Z-drugs*) were examined. Additionally, use of illicit drugs in the last 12 months (defined by cannabis, cocaine, 3,4-methylenedioxymethylamphetamine [MDMA], non-pharmaceutical amphetamine, *crack cocaine* or heroin) was collected along with last 12-month co-use of benzodiazepines/Z-drugs and illicit drugs or any NMU of an prescription opioid (buprenorphine, codeine, diamorphine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, pethidine, sufentanil, tramadol or tapentadol). Co-use represents those who have used both drug groups in the last 12 months and does not necessarily represent concomitant use at the same time.

Respondents reporting last 12-month NMU were then asked questions about how they obtained the drug that they nonmedically used. Multiple options on the survey for methods of drug acquisition could be reported. The following categories of methods of drug acquisition were included: (i) prescribed by a medical practitioner; and (ii) acquired without a prescription. Methods that were not acquired with a prescription were further broken into: (i) given by or took from family/friends; (ii) bought from a dealer; and (iii) bought via the internet without a prescription.

The weighted proportion and 95% confidence intervals (CIs) of select demographic characteristics were calculated to describe the population and weighted prevalence estimates and 95% CIs were calculated for last 12-month NMU of prescription drugs. The prevalence of prescription drug NMU in the last 12 months was estimated by sex and age (among those aged 34 years and younger compared to those aged 35 years and older, based on the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) definition of *young people*.[16] Prevalence by illicit drug use in the last 12 months and the proportion of adults reporting benzodiazepine and/or Z-drug NMU and co-use of illicit drugs or last 12-month NMU of any prescription opioid were also calculated. The estimated proportion and 95% CI of each method of drug acquisition for NMU of the drug groups were calculated; multiple response options are available; therefore, proportions may not sum to 100%. Analyses were conducted in SPSS Version 25.0 (Armonk, NY, USA).

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

In total, 10 006 eligible surveys, which, after poststratification weights were applied, represented approximately 52 927 000 UK adults (aged ≥16 years). Weighted demographic characteristics of the population are described in Table 1 and are representative of the UK population (Eurostat).[17]

The estimated prevalence of past 12-month NMU of any benzodiazepine and/or Z-drug in the UK population 16 years or older was 1.2%, corresponding to approximately 635 000 adults, Table 2. Among this group, an estimated 4.6% (95% CI: 1.2–8.0) had nonmedically used both a benzodiazepine and a Z-drug in the last 12 months. The prevalence of only benzodiazepine NMU was 0.7% corresponding to approximately 350 000 adults and only Z-drug NMU was 0.5% corresponding to approximately 250 000 adults. For comparison, last 12-month use of any illicit drug was 8.9% (8.3–9.6).

Although no significance testing was conducted due to descriptive nature of the study, NMU of both only benzodiazepines and only Z-drugs was estimated to be more common among females than males, Table 2. Additionally, those who were 34 years or younger had a higher prevalence of NMU of only benzodiazepines than those who were 35 years or older.

NMU of benzodiazepines/Z-drugs was estimated to be higher among those who also reported last 12-month use of illicit drugs than amongst all adults, Table 2. Whilst the highest prevalence of NMU for only Z-drugs was among heroin users (5.4%, 2.7–10.5), the highest

TABLE 1 Weighted demographic characteristics of population

Characteristic	% (95% confidence interval) weighted *n* = 52 927 002
Age, y	
16–24	13.7 (12.9–14.6)
25–34	16.9 (16.1–17.7)
35–44	15.8 (15.1–16.5)
45–54	17.5 (16.7–18.2)
55–64	14.5 (13.9–15.2)
65+	21.6 (20.1–23.3)
Sex	
Male	49.1 (47.8–50.4)
Female	50.9 (49.6–52.2)
Residential region	
London	12.9 (12.1–13.7)
England (excluding London)	71.4 (70.2–72.5)
Northern Ireland	2.7 (2.3–3.2)
Scotland	8.2 (7.5–8.9)
Wales	4.8 (4.3–5.4)

TABLE 2 Prevalence of last 12-month nonmedical use of benzodiazepines and Z-drug by age, sex and illicit drug use in the UK

Characteristics	Any benzodiazepine and/or Z-Drug % (95% CI)	Only benzodiazepine % (95% CI)	Only Z-drug % (95% CI)
All adults	1.2 (1.0–1.5)	0.7 (0.5–0.8)	0.5 (0.3–0.7)
Prevalence by age			
≤34 y	1.3 (1.0–1.9)	0.9 (0.6–1.3)	0.5 (0.3–0.8)
≥35 y	1.1 (0.8–1.5)	0.6 (0.4–0.8)	0.5 (0.3–0.8)
Prevalence by sex			
Male	1.0 (0.8–1.4)	0.5 (0.4–0.8)	0.4 (0.3–0.7)
Female	1.4 (1.0–1.9)	0.8 (0.6–1.1)	0.5 (0.3–1.1)
Prevalence among illicit drug users (last 12-month illicit drug use)			
Any illicit drug use	6.1 (4.7–7.8)	3.6 (2.6–5.1)	2.1 (1.3–3.3)
Cannabis	5.4 (3.9–7.3)	3.3 (2.2–4.9)	1.8 (1.1–3.1)
Cocaine	8.7 (6.1–12.1)	5.9 (3.8–8.9)	2.4 (1.2–4.7)
MDMA	8.4 (5.5–12.7)	5.2 (3.1–8.8)	3.2 (1.6–6.5)
Crack cocaine	9.3 (6.1–14.0)	4.4 (2.3–8.1)	4.1 (2.1–7.8)
Amphetamine	9.7 (6.1–14.9)	5.6 (3.1–10.0)	4.0 (1.9–8.2)
Heroin	11.5 (7.4–17.3)	4.6 (2.4–8.8)	5.4 (2.7–10.5)

CI, confidence interval

prevalence of NMU for only benzodiazepines was amongst illicit stimulant users: cocaine (5.9%, 3.8–8.9), amphetamine (5.6%, 3.1–10.0) and MDMA (5.2%, 3.1–8.8).

Among adults with last 12-month NMU of any benzodiazepine and/or Z-drug, 45.0% had also used an illicit drug in the same time frame, Table 3. Use of cocaine was more prevalent among those who had nonmedically used only benzodiazepines (32.9%) compared to only Z-drugs (19.0%), while use of heroin was more prevalent among those had nonmedically used only Z-drugs (19.0%) compared to only benzodiazepines (11.5%). Last 12-month NMU of any prescription opioid was common for both NMU of only benzodiazepines and NMU of only Z-drugs (78.6 and 70.4% respectively).

Drugs were acquired primarily without a prescription, Table 4. A prescription was identified as the source of drug acquisition by only 44.3% of those who had nonmedically used any benzodiazepines or Z-drug in the last 12 months. When the drug was not sourced by a prescription, the most common method of drug acquisition was being given the drug by, or taking the drug from, family or friends. Benzodiazepines were more commonly bought from a dealer than Z-drugs, whilst Z-drugs were more commonly bought via the internet without a prescription than benzodiazepines.

4 | DISCUSSION

The findings of this study suggest that over 600 000 UK adults (1.2% of the population) have taken a benzodiazepine and/or Z-drug for nonmedical reasons in the past 12 months. Data from the 2018 US National Survey on Drug Use and Health found that approximately 2.0% of the US population aged 12 or older reported misuse of benzodiazepines in the past year.[18] The Crime Survey of England and Wales 2018 reported that 0.6% of respondents (adults aged

TABLE 3 Last 12-month use of illicit drugs or last 12-month NMU of any prescription opioid among those reporting last 12-month NMU of benzodiazepines and/or Z-drugs

Co-use of another drug in last 12 months	Any benzodiazepine/Z-drug % (95% CI)	Only benzodiazepine % (95% CI)	Only Z-drug % (95% CI)
Any illicit drug use	45.0 (34.7–55.7)	48.3 (36.8–60.0)	39.1 (21.9–59.5)
Cannabis	32.1 (23.5–42.2)	35.6 (25.0–47.8)	27.7 (14.5–46.4)
Cocaine	27.2 (19.2–37.0)	32.9 (22.6–45.3)	19.0 (8.7–36.5)
MDMA	19.0 (12.4–27.9)	21.0 (12.7–32.8)	18.2 (8.1–36.0)
Crack cocaine	14.9 (9.5–22.4)	12.5 (6.7–22.2)	16.6 (7.7–32.1)
Amphetamine	15.7 (9.8–24.1)	16.4 (9.1–27.6)	16.5 (7.3–33.3)
Heroin	15.9 (10.1–24.0)	11.5 (5.9–21.1)	19.0 (8.8–36.4)
Any prescription opioid	75.4 (63.2–84.5)	78.6 (67.3–86.3)	70.4 (43.8–87.9)

CI, confidence interval

TABLE 4 Estimated percentage of method of drug acquisition among those with last 12-month nonmedical use of benzodiazepines and/or Z-drugs in the UK

	Any benzodiazepine/Z-drug % (95% CI)	Only benzodiazepine % (95% CI)	Only Z-drug % (95% CI)
Prescribed by medical practitioner	44.3 (34.2–55.0)	51.3 (41.5–64.6)	33.9 (16.9–51.0)
Acquired without a prescription	73.8 (64.4–81.4)	70.2 (59.4–81.1)	75.6 (61.6–89.7)
Given by or took from family/friends	53.5 (42.4–64.2)	55.9 (44.4–67.4)	48.0 (26.1–69.8)
Bought from a dealer	17.9 (11.7–26.3)	18.4 (9.4–27.4)	12.8 (1.8–23.7)
Bought via the internet (without a prescription)	16.5 (8.5–29.6)	6.9 (1.5–12.4)	28.6 (6.3–50.9)

16–59 years living in England or Wales) had used a *tranquiliser* (including benzodiazepines and barbiturates) not prescribed by a doctor or other healthcare professional in the previous year and the Global Drug Survey 2018, while not representative of general populations, found that 5.7% of respondents had used a benzodiazepine in the previous year.[12,19]

Previous studies have suggested that Z-drugs have a relatively low risk of misuse compared to benzodiazepines but this study shows only a small difference between the prevalence of last 12-month NMU for only benzodiazepines (0.7%, 0.5–0.8) or only Z-drugs (0.5%, 0.3–0.7) in the UK.[20–22] This study also shows that there is little overlap between benzodiazepine NMU and Z-drug NMU suggesting that there are distinct groups nonmedically using the drugs whether that be by personal preference or drug availability.

NMU of both only benzodiazepines and only Z-drugs were estimated to be more common among women and only benzodiazepine NMU was estimated as more common among those younger than 34 years than older adults; although significance testing was not conducted. While data are conflicted on whether benzodiazepine/Z-drug NMU is associated with sex,[23] it is known that women are more likely to be prescribed prescription sedatives and some studies suggest that women are at increased risk of misusing medicines and are also more likely to use drugs to cope with anxiety issues.[24–26] In the UK, data show that young adults are more likely to report anxiety or depression but also as a generation it is more acceptable to admit to mental health issues and there is less stigma attached to medication use.[27] It is recognised that young adults are more likely to misuse illicit and prescription drugs in general.[19,28] Additionally, young adults are exposed to pop culture with content that is open about taking drugs to self-medicate mental health issues, particularly alprazolam, so may be normalised to NMU of benzodiazepines.[29]

The prevalence of last 12-month NMU of both only benzodiazepines and only Z-drugs were higher among those who had also used illicit drugs in the last 12 months than the general population. This pattern has also been seen in people with substance use disorders in the USA, with rates of benzodiazepine misuse 3.5–24 times higher than the general population.[23] The prevalence of only benzodiazepine NMU in our study was most prevalent among illicit stimulant users. A survey of methadone treatment patients in Israel found that while the most common motivation for taking benzodiazepines was *to improve emotional state or problems* (87.1% of respondents), 18.6% reported taking benzodiazepines *to reduce the effect of amphetamines or cocaine*.[30] While there are no data available regarding simultaneous use of illicit stimulants and benzodiazepines in general populations, it is probable that benzodiazepines are used for their sedative properties to *come down* from adverse effects of the illicit stimulants. The prevalence of NMU of only benzodiazepines was also higher among heroin users, but co-use of heroin was most prevalent among those who had nonmedically used only Z-drugs. Co-use of both benzodiazepines/Z-drugs and illicit drugs within the last 12 months was common, but considerably more widespread was NMU of prescription opioids as well in the last 12 months. A Swedish survey of individuals receiving opioid maintenance therapy found that 81% also reported lifetime NMU of benzodiazepines and 60% lifetime NMU of Z-drugs with the majority reporting potentiating effects from combined use.[31] Motivations for co-use of benzodiazepines and prescription or illicit opioids include a desire to increase the sedative effects of the opioids, to achieve a greater level of euphoria, as well as to decrease symptoms of opioid withdrawal.[32–34] Combining opioids and sedatives increases the risk of respiratory depression, overdose and death.[7,8,35] While data regarding co-use of Z-drugs and prescription opioids are limited, it has been suggested that the main attractions of zopiclone for drug users is that, unlike benzodiazepines, they do not cause amnesia and may not be detected during standard illicit drug screening.[36,37]

Acquisition of benzodiazepines/Z-drugs for NMU was more common without a prescription than with a prescription and obtaining the drugs from family/friends was the most common source of acquisition for both drug groups. This supports previous indications that diversion of medication is a major contributor to the ease with which individuals are able to obtain prescription drugs for NMU.[38] In our study, we observed acquiring the drug via a dealer was also a notable source, while procuring the drugs from the internet was more common for NMU of only Z-drugs than for only benzodiazepines. The UK Advisory Council on the Misuse of Drugs review of diversion of prescription drugs noted that while benzodiazepines were being diverted from the legitimate supply chain, much is obtained via the internet or imported in bulk by dealers. [9] An investigation by Ho *et al*. in 2015 revealed that zopiclone was freely available to buy online without a prescription.[39] While medicines obtained through diversion are likely to be pure and unadulterated, those from illicit sources may be counterfeit, contaminated or contain adulterants.[9] There are reported cases of products appearing to be diazepam which were actually found to contain more

potent benzodiazepines, including etizolam or phenazepam.[40] These substances, etizolam in particular, have been linked to many deaths in Scotland, which has the highest rate of drug-related deaths in Europe and almost 3 times the rate of the UK as a whole.[41,42] Therefore, purchasing benzodiazepines or Z-drugs from illicit sources places additional danger on the consumer and ultimately increases the risk of adverse reactions, overdose or death.

As acknowledged by the EMCDDA, there is a lack of self-reported prevalence data on the misuse of benzodiazepines in the general population in Europe.[7] The 2019 UK Public Health England prescription drug review highlights the misuse of potentially addictive drugs as a serious cause for concern.[5] Both benzodiazepines and Z-drugs are known to have dependence potential and withdrawal and may be associated with premature mortality.[43–45] A study in the USA found that NMU of prescription sedative/tranquiliser drugs signalled a risk for future abuse of other substances.[46]

This investigation, to our knowledge, is the only general population study to examine last 12-month NMU of both benzodiazepines and Z-drugs collecting data from the entire UK. The relatively large sample size and applied weighting allows for prevalence estimates that are representative of the national population. However, there are some limitations that apply to this study. Apart from the standard limitations that apply to all online survey-based studies, such as unknown selection bias for an opt-in sample,[47–50] data are based on self-report of potentially aberrant behaviours, so we may underestimate the true prevalence. However, the confidential nature of the survey should alleviate some of this bias. While we identified a high proportion of NMU of benzodiazepine/Z-drugs combined with illicit drug use or NMU of prescription opioids within the same time frame, it is not possible to identify whether the drugs were taken concurrently. NMU of prescription drugs has also been reported to occur as a substitute for illicit drugs when unavailable, such as the increased benzodiazepine NMU observed during the global heroin shortage in the early 2010s.[51] Additionally, the study only included benzodiazepine drugs available via prescription in the UK. In recent years *designer* benzodiazepines (such as etizolam) have emerged onto the UK illicit drug market and have become available to purchase online. [52,53] In Scotland especially, these drugs have been associated with a high number of drug-related deaths. [42] Designer benzodiazepines, not available as prescription products in the UK, while outside the scope of the current study should be included in future research.

In conclusion, this study shows that NMU of benzodiazepines and Z-drugs are a cause for concern in the UK. It is of particular concern that a significant proportion are acquiring these drugs for NMU without a prescription, so without guidance and monitoring from a medical practitioner, and/or obtaining counterfeit products with a greater risk that there are unknown ingredients. The risks of health effects are increased for those taking the drugs in conjunction with other substances. Whilst the dangers of mixing benzodiazepines and heroin/other opioids are well documented, there is a paucity of data regarding concomitant NMU of benzodiazepines and stimulant drugs or NMU of Z-drugs and opioids, and therefore this requires further investigation. While NMU of benzodiazepines has long been noted, this study suggests that NMU of Z-drugs is also a significant issue that may need more attention. Further studies examining differences between benzodiazepine and Z-drug NMU including regional differences within the UK and the motivations for NMU of these drugs would provide further valuable information to influence public health decisions and inform measures to address this issue.

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COMPETING INTERESTS

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CONTRIBUTORS

J.H. prepared the manuscript. J.C.B., J.H. and K.R. conducted statistical analysis. All authors reviewed the final manuscript.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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