Non-medical use of benzodiazepines and GABA analogues in Europe

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Aims: We investigated the prevalence of non-medical use (NMU) of benzodiazepines and GABA analogues in Europe.

Methods: Data were collected using the online Non-Medical Use of Prescription Drugs (NMURx) survey from France, Germany, Italy, Spain and the UK.

Results: The study included 55 223 eligible surveys which, after post-stratification weights were applied, represented approximately 260 million European adults. Lifetime NMU of benzodiazepines was highest in Spain (6.5%, 95% CI: 6.0-7.0) and lowest in Germany (1.7%, 1.5-2.0). Lifetime NMU of GABA analogues was highest in Germany (5.4%, 5.0-5.7) and lowest in France (2.2%, 1.9-2.5) and the UK (2.2%, 1.9-2.6). While no notable difference was observed for France or the UK, there was a higher prevalence of last 12-month NMU of benzodiazepines compared to GABA analogues in Italy (2.4 times higher) and Spain (3.0 times higher) and a higher prevalence of NMU of GABA analogues compared to benzodiazepines in Germany (2.6 times higher).

Conclusion: This study shows that there is variation in NMU of benzodiazepines and GABA analogues among countries. Of particular interest is the high incidence of GABA analogue NMU in Germany and benzodiazepine NMU in Spain. Further research to identify factors and motivations responsible for the higher prevalence observed are essential to inform public health policies in those countries.

KEYWORDS
addiction, drug abuse, public health

1 | INTRODUCTION

Non-medical use (NMU) of prescription medicines is a global issue and, while much of the attention is focused on NMU of prescription opioids, there are other drug classes that warrant investigation.1,2

A previous study by Novak et al. investigating NMU of prescription drugs in Denmark, Germany, Great Britain, Spain and Sweden found that, while opioids were the most commonly reported medication for lifetime NMU (13.5% of respondents after weighting, compared to 10.9% for sedative drugs [benzodiazepines and tranquillizers]), sedative drugs were most commonly reported for past-year NMU (5.8% compared to 5.0% for opioids).3

Benzodiazepines have been widely used for their sedative and anxiolytic properties globally for decades, while more recently the
gamma-aminobutyric acid (GABA) analogues gabapentin and pregabalin have become popular alternatives for anxiety and treatment of neuropathic pain. Baclofen, another GABA analogue, is currently used for the treatment of spastic movement disorders and also has potential in the treatment of alcohol and gamma-hydroxybutyrate/gamma-butyrolactone withdrawal syndrome. NMU of benzodiazepines has long been recognised and more recently NMU of pregabalin and gabapentin has been noted, along with deaths related to this NMU, particularly associated with concomitant opioid use. While concern regarding NMU of benzodiazepines and GABA analogues have been documented, there has currently been limited research focusing on the prevalence and causes of NMU of these drug classes within Europe.

The primary aim of this study was to determine the prevalence of use and NMU of benzodiazepines and GABA analogues through data collected by an online cross-sectional survey on drug use in five European countries. Additionally, we studied factors associated with NMU of these drugs to determine associations between person-specific factors (demographics, medical history and previous drug use) or place-specific factors (availability of drugs) and the prevalence of NMU of benzodiazepines or GABA analogues.

2 METHODS

2.1 Study design and population

The Researched, Abuse, Diversion and Addiction Related Surveillance (RADARS) System Survey of Non-Medical Use of Prescription Drugs (NMURx) Program collects data on respondent demographics and the prevalence, reasons, routes of administration and method of drug acquisition for NMU of prescription drugs across multiple countries. Post-stratification weights were applied to each survey population (based on region, gender and age) to be representative of the demographic distribution of the national adult populations. The methodology of this program has been described elsewhere. The countries included in this study are the five most populous located entirely within Europe: Germany, the United Kingdom (UK), France, Italy and Spain. Recruitment and data collection are delivered to country-based members through a global survey panel company, in the native language of the country where it is undertaken and in English, and targeted at the age group from 15 years (Spain), 16 years (UK) and 18 years (France, Germany, Italy) and older. Data used in this analysis are from the surveys launched in the second half of 2017.

Respondents were asked if they had ever used benzodiazepines or specific GABA analogues (baclofen, gabapentin or pregabalin) for any reason in their lifetime; a yes response classified lifetime use. If respondents reported lifetime use, they were asked about lifetime NMU, where 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 benzodiazepine NMU they were asked to select which specific drug substance they used. Respondents were then asked substance-specific questions including the frequency of recent NMU, motivations for NMU and methods of drug acquisition. The individual national surveys were tailored to specifically ask only about drugs available via prescription in that country (see Supporting information).

Basic demographics were collated together with data on prevalence of illicit drug use. Participants were asked about whether they had used a range of illicit drugs, which varied based on the drugs and slang terms specific to individual survey countries (see Supporting information). Additionally, the prevalence of respondents scoring six or greater out of ten questions used to identify problematic drug use (see Supporting information), indicating substantial or severe problematic drug use, or reporting they had sought professional help for substance abuse, was calculated. Respondents were also asked if they had ever been diagnosed with chronic pain or a mental health disorder (see Supporting information).

2.2 Drug utilisation analysis

Association between NMU and legitimate drug availability was investigated using drug utilisation data obtained from IQVIA (Durham, NC, USA). To create comparable timeframes, last 12-month NMU was correlated with 12-month drug utilisation data for quarter four 2016 to quarter three 2017 for the UK and quarter one to four 2017 for other countries. To enable comparison between types of units sold, number of standard units sold was used where a standard unit for a tablet was a single tablet, a standard unit for a patch was a single patch, and a standard unit for liquids was 5 ml of liquid. Sales data for available benzodiazepines and GABA analogues were analysed (with the exception of clorazepate which was not included for any country) and ranked to provide the top four benzodiazepine/GABA analogue drugs with the highest estimated standard units sold by country.
2.3 | Statistical analysis

The weighted proportion and 95% confidence intervals (CIs) of select demographic and respondent characteristics were calculated to describe the population. Weighted prevalence estimates and 95% CIs were calculated for lifetime use, lifetime NMU and last 12-month NMU of benzodiazepines and/or GABA analogues in each country. Additionally, characteristics of those endorsing lifetime NMU or lifetime use without NMU of benzodiazepines and/or GABA analogues were calculated and compared. Characteristics comprised the estimated proportion and 95% CIs by age, gender, previous history of a mental health disorder, chronic pain, lifetime illicit drug use, problematic drug use and seeking help for substance abuse. The prevalence and 95% CIs of last 12-month NMU of individual drugs were also calculated to identify the top four benzodiazepine or GABA analogue drugs reported for NMU per country. Analyses were conducted in SPSS Version 25.0 (Armonk, NY). In order to investigate association between drug availability and NMU, Spearmans correlation coefficient was used to measure the strength of a relationship between rank NMU prevalence and rank standard units sold for the top drugs reported for last 12-month NMU (alprazolam, bromazepam, diazepam, lorazepam, baclofen, gabapentin and pregabalin). Analysis was conducted in SAS Version 9.4 (Cary, NC). Statistical significance was determined by non-overlapping CIs.

2.4 | Ethical approval

NMURx was approved by the Colorado Multiple Institutional Review Board.

3 | RESULTS

3.1 | Characteristics of the study population

The final analytical dataset comprised 55,223 eligible surveys (France [n = 10,072], Germany [n = 15,051], Italy, [n = 10,019], Spain [n = 10,062], UK [n = 10,019]). As shown in Table 1, there is variation in the general population characteristics between countries, including higher prevalence of chronic pain in Germany and the UK and higher prevalence of mental health disorders in Spain and the UK.

3.2 | Prevalence of lifetime use and non-medical use

The prevalence of lifetime use of benzodiazepines was higher than lifetime use of GABA analogues in all countries (Figure 1). The overall lifetime prevalence estimates of benzodiazepine and GABA analogue

| Table 1 | Study population characteristics, results from the survey of non-medical use of prescription drugs (NMURx) from France, Germany, Italy, Spain and the United Kingdom |
|---------|--------------------------------------------------------------------------------------------------|
| Characteristic | France (weighted N = 50,374,980) | Germany (weighted N = 68,556,909) | Italy (weighted N = 50,496,389) | Spain (weighted N = 39,340,232) | United Kingdom (weighted N = 52,927,659) |
| Age, years | | | | | |
| <18 | N/A | N/A | 0.8 (0.61-1.0) | 1.9 (1.62-2.4) |
| 18-24 | 10.2 (9.61-11.0) | 8.9 (8.49-9.5) | 8.3 (7.88-8.9) | 10.6 (9.91-11.2) | 11.7 (10.81-12.6) |
| 25-34 | 15.5 (14.81-16.3) | 15.4 (14.81-16.0) | 13.5 (12.91-14.1) | 14.4 (13.81-15.0) | 16.8 (16.01-17.6) |
| 35-44 | 16.5 (15.81-17.2) | 14.5 (14.01-15.0) | 17.5 (16.91-18.2) | 19.8 (19.12-20.5) | 15.8 (15.11-16.5) |
| 45-54 | 17.3 (16.61-18.0) | 19.7 (19.12-20.3) | 19.2 (18.42-20.0) | 18.2 (17.51-19.0) | 17.4 (16.71-18.2) |
| 55-64 | 16.1 (15.41-16.8) | 30.1 (29.23-30.9) | 27.4 (26.28-28.6) | 26.8 (25.52-28.1) | 14.2 (13.61-14.8) |
| 65+ | 24.4 (23.32-25.4) | 11.5 (10.91-12.1) | 14.1 (13.21-15.0) | 9.5 (8.71-10.4) | 22.2 (21.32-23.0) |
| Gender | | | | | |
| Male | 47.7 (46.74-48.8) | 48.8 (47.94-49.6) | 48.1 (47.04-49.3) | 48.8 (47.64-49.9) | 48.7 (47.64-49.7) |
| Female | 52.3 (51.25-53.3) | 51.2 (50.45-52.1) | 51.9 (50.75-53.0) | 51.2 (50.15-52.4) | 51.3 (50.35-52.4) |
| Medical history | | | | | |
| Mental health disorder | 25.2 (24.32-26.1) | 25.8 (25.12-26.6) | 24.8 (23.82-25.8) | 31.6 (30.52-32.7) | 35.3 (34.33-36.3) |
| Chronic pain | 34.2 (33.23-35.2) | 40.1 (39.24-40.9) | 30.3 (29.23-31.4) | 31.2 (30.13-32.3) | 40.9 (39.94-41.9) |
| Illicit drug use | | | | | |
| Lifetime | 18.2 (17.41-19.0) | 25.5 (24.82-26.2) | 21.0 (20.12-21.9) | 24.5 (23.62-25.5) | 30.1 (29.13-31.1) |
| Past year | 8.2 (7.68-8.8) | 7.2 (6.87-7.7) | 6.0 (5.56-6.5) | 10.2 (9.61-10.9) | 9.8 (9.11-10.5) |
| DAST-10 score (6) | 1.4 (1.21-1.6) | 1.3 (1.11-1.5) | 1.1 (0.91-1.3) | 1.8 (1.62-2.1) | 2.1 (1.82-2.4) |
| Substance abuse help | 2.0 (1.72-2.3) | 1.9 (1.72-2.2) | 1.0 (0.81-1.2) | 2.3 (2.02-2.7) | 2.5 (2.22-2.9) |
use were similar in Germany but varied more among other countries. The prevalence of lifetime benzodiazepine use and NMU was highest in Spain and lowest in Germany. The prevalence of lifetime GABA analogue use was highest in Spain and lowest in Italy, while the prevalence of lifetime GABA analogue NMU was highest in Germany and lowest in France and the UK. Less than one in five of lifetime benzodiazepine users reported lifetime NMU, while over one in five of GABA analogue lifetime users reported lifetime NMU, two-thirds in Germany.

### 3.3 Factors associated with lifetime use and non-medical use

Among those reporting lifetime use but not NMU of benzodiazepines or GABA analogues, approximately 80% were aged 35 years or older (see Table 2). Among lifetime users, the proportion aged 34 or younger was significantly greater for those reporting NMU than no NMU especially for GABA analogues, accounting for approximately a half of reported lifetime NMU in France, Spain and the UK and a third in Germany and Italy. The proportion of those reporting lifetime NMU of benzodiazepines was similar among those aged 34 years or less and those aged 60 years or older in France, Germany and Italy but significantly greater in Spain and the UK. For GABA analogues, the proportion reporting NMU was significantly greater for those aged 34 years or less and those aged 60 years or older in all countries.

Lifetime use without NMU of benzodiazepines and GABA analogues was more common among females than males, significantly so in all countries except for GABA analogues in Germany (see Table 2). Lifetime NMU of benzodiazepines was also more common among females in all countries except the UK but only significantly so in France. Conversely, lifetime NMU of GABA analogues was more common among males than females, significantly different in all countries except Italy.

Mental health diagnoses and a history of chronic pain were significantly more common among those reporting both lifetime NMU and lifetime use without NMU of benzodiazepines or GABA analogues than among the general population (see Tables 1 and 2).

Mental health diagnoses were more common among those reporting lifetime NMU than lifetime use without NMU of benzodiazepines in all countries except Spain, although only significantly so in France (66.0 [60.371.2] vs. 53.9 [51.656.1]). Mental health diagnoses were also more common among those reporting NMU of GABA analogues in all countries with significant difference observed in France (67.8 [61.373.8] vs. 47.6 [43.152.2]), Germany (60.3 [56.663.8] vs. 42.3 [37.447.5]), and Italy (62.7 [55.569.4] vs. 42.2 [36.747.9]).
TABLE 2 Characteristics of respondents from France, Germany, Italy, Spain and the United Kingdom reporting yes or no lifetime non-medical use (NMU) among those reporting lifetime use of benzodiazepines or GABA analogues

| Country      | Benzodiazepine lifetime use | GABA analogue lifetime use |
|--------------|-----------------------------|-----------------------------|
|              | Nolifetime NMU% (95% CI) | Yeslifetime NMU% (95% CI) | Nolifetime NMU% (95% CI) | Yeslifetime NMU% (95% CI) |
| France       | n = 11 726 304 | n = 1 548 089 | n = 2 887 443 | n = 1 113 258 |
| Age 34 years | 12.2 (10.813.7) | 27.0 (22.032.5) | 16.8 (13.720.4) | 59.6 (52.866.0) |
| Age 3559 years | 45.6 (43.447.8) | 49.1 (43.454.9) | 44.5 (40.248.9) | 26.0 (20.831.9) |
| Age 60 years | 42.2 (39.944.6) | 23.9 (18.929.7) | 38.7 (34.143.5) | 14.4 (9.820.8) |
| Gender Male | 34.5 (32.436.5) | 43.9 (38.449.6) | 42.3 (38.046.8) | 74.2 (67.380.1) |
| Gender Female | 65.5 (63.567.6) | 56.1 (50.461.6) | 57.7 (53.262.0) | 25.8 (19.932.7) |
| Mental health disorder | 53.9 (51.656.1) | 66.0 (60.371.2) | 47.6 (43.152.2) | 67.8 (61.373.8) |
| Chronic pain | 57.4 (55.259.6) | 54.8 (49.160.4) | 65.7 (61.369.8) | 45.7 (39.252.4) |
| Lifetime illicit drug use | 21.8 (20.123.6) | 38.1 (32.843.8) | 24.3 (20.828.2) | 56.9 (50.263.4) |
| DAST-10 score (6) | 1.7 (1.32.3) | 5.5 (3.939.1) | 2.3 (1.43.9) | 13.9 (9.719.4) |
| Substance abuse help | 3.6 (2.94.4) | 9.6 (6.613.9) | 5.5 (3.97.6) | 14.8 (10.520.6) |
| Germany       | n = 5 742 507 | n = 1 188 750 | n = 1 897 515 | n = 3 669 185 |
| Age 34 years | 13.5 (11.615.7) | 21.1 (16.226.9) | 18.9 (15.223.3) | 32.6 (29.236.2) |
| Age 3559 years | 52.2 (49.255.2) | 56.1 (49.662.4) | 54.4 (49.259.5) | 49.5 (45.953.2) |
| Age 60 years | 34.3 (31.437.3) | 22.8 (17.621.9) | 26.7 (22.231.7) | 17.9 (15.121.1) |
| Gender Male | 41.7 (38.484.7) | 46.6 (40.353.0) | 45.1 (40.150.2) | 55.8 (52.159.4) |
| Gender Female | 58.3 (55.361.2) | 53.4 (47.059.7) | 54.9 (49.859.9) | 44.2 (40.647.9) |
| Mental health disorder | 60.9 (57.963.7) | 63.3 (56.969.1) | 42.3 (37.447.5) | 60.3 (56.663.8) |
| Chronic pain | 67.1 (64.369.9) | 66.4 (60.172.1) | 62.1 (57.066.9) | 66.7 (63.270.0) |
| Lifetime illicit drug use | 38.5 (35.641.4) | 64.5 (58.170.4) | 29.8 (25.334.6) | 36.3 (32.939.8) |
| DAST-10 score (6) | 2.1 (1.53.1) | 11.2 (7.716.0) | 3.2 (1.95.4) | 5.1 (3.77.0) |
| Substance abuse help | 6.3 (5.07.8) | 19.4 (14.825.1) | 4.5 (2.87.2) | 5.9 (4.47.9) |
| Italy         | n = 12 520 521 | n = 2 336 591 | n = 2 018 037 | n = 1 748 861 |
| Age 34 years | 14.3 (13.115.7) | 21.1 (17.824.9) | 16.4 (13.201.0) | 34.8 (28.841.3) |
| Age 3559 years | 54.7 (52.527.1) | 60.8 (55.765.7) | 60.6 (54.866.1) | 53.1 (46.065.0) |
| Age 60 years | 31.0 (28.633.5) | 18.0 (13.723.3) | 23.0 (17.929.0) | 12.2 (7.519.5) |
| Gender Male | 41.0 (38.743.3) | 46.8 (41.951.8) | 43.2 (37.948.8) | 55.8 (48.562.8) |
| Gender Female | 59.0 (56.761.3) | 53.2 (48.258.1) | 56.8 (51.262.1) | 44.2 (37.251.5) |
| Mental health disorder | 53.3 (50.955.7) | 55.9 (50.860.8) | 42.2 (36.747.9) | 62.7 (55.569.4) |
| Chronic pain | 45.7 (43.348.1) | 43.7 (38.848.8) | 54.6 (48.960.2) | 53.2 (46.260.0) |

Illicit drug use

| DAST-10 score (6) | 1.5 (1.12.1) | 5.5 (3.87.7) | 3.4 (1.96.1) | 6.2 (4.09.7) |
| Substance abuse help | 1.3 (0.91.9) | 4.5 (2.97.1) | 2.4 (1.24.8) | 7.1 (4.311.7) |

Spain

| DAST-10 score (6) | 1.8 (1.42.3) | 4.9 (3.56.8) | 2.5 (1.54.0) | 8.0 (5.511.4) |
| Substance abuse help | 2.7 (2.23.4) | 7.1 (5.49.3) | 4.3 (2.96.2) | 14.1 (10.718.3) |
There was no significant difference in prevalence of chronic pain between those reporting yes or no NMU of benzodiazepines in any country, while those not reporting NMU of GABA analogues had higher incidence of chronic pain in France (65.7 [61.3–69.8] vs 45.7 [39.2–52.4]), Spain (65.4 [61.1–69.5] vs. 57.4 [51.2–63.3]), and the UK (80.9 [77.5–84.0] vs. 63.1 [55.6–70.0]).

A history of lifetime illicit drug use, problematic drug use and seeking substance abuse help were significantly more common for lifetime NMU than for lifetime use without NMU of benzodiazepines in all countries (see Table 2). For GABA analogues, a history of lifetime illicit drug use, problematic drug use and seeking substance abuse help were also more common among those reporting NMU, although significant difference was observed only in France, Spain and the UK.

Lifetime illicit drug use was highest in the UK with approximately three-quarters of individuals reporting lifetime NMU of benzodiazepines or GABA analogues also reporting illicit drug use. The highest prevalence of problematic drug use and seeking substance abuse help was also observed in the UK with over a fifth of benzodiazepine/GABA analogue NMU endorsers having problematic drug use or having sought help for substance abuse.

### 3.4 | Prevalence of last 12-month non-medical use

While no notable difference was observed for France or the UK, there was a higher prevalence of last 12-month NMU of benzodiazepines compared to GABA analogues in Italy (2.4 times higher) and Spain (3.0 times higher) and a higher prevalence of NMU of GABA analogues compared to benzodiazepines in Germany (2.6 times higher) (see Figure 2). NMU of GABA analogues in Germany was at least double that seen in other countries.

### 3.5 | Association of 12-month non-medical use with legitimate availability

The highest selling benzodiazepine/GABA analogue drugs per country were examined from last 12-month sales data corresponding to each survey period. The top four selling drugs varied by country with gabapentin and pregabalin being the top two sold in Germany and the UK, while for other countries alprazolam featured in the top two along with oxazepam in France and lorazepam in Italy and Spain (see Figure 3). Pregabalin was the only benzodiazepine/GABA analogue that featured in the top four sold in every country.

Of the drugs examined, the four most reported drugs for past 12-month NMU in all countries comprised seven drugs; the three GABA analogues (baclofen, gabapentin and pregabalin) and four benzodiazepines (alprazolam, bromazepam, diazepam and lorazepam), although there was variation in the proportions of these drugs across the five countries (see Figure 4). Diazepam was the most common NMU benzodiazepine in all countries except France and Italy, where bromazepam and alprazolam were the most common
respectively (see Figure 3). In France, Italy and Spain, alprazolam and bromazepam were among the most commonly reported drugs for NMU but these two drugs did not feature for Germany or the UK. For Germany and the UK, all three GABA analogue drugs featured in the top four drugs, while in Spain and Italy no GABA analogue drugs featured in the top four. The UK was the only country where NMU of gabapentin was greater than NMU of pregabalin. The results of the correlation analysis suggest a positive strong relationship between drug availability and NMU. The UK (r = 0.96), Germany (r = 0.89) and Spain (r = 0.71), in particular, showed relatively high correlations, while weaker correlations were observed in Italy (r = 0.57) and France (r = 0.39).

4 | DISCUSSION

This study documents differences in the prevalence of lifetime and last 12-month NMU of benzodiazepines and GABA analogues across five European countries. While the prevalence of lifetime use of benzodiazepines is higher than lifetime use of GABA analogues in all countries and the prevalence of lifetime NMU of benzodiazepines is higher in France, Italy and Spain, the proportion of users that also non-medically used GABA analogues is higher in all countries. Therefore, while the absolute number of people non-medically using GABA analogues may be lower than for benzodiazepines in some countries, it is important to recognise that these
drugs potentially are more likely to be non-medically used if prescribed.

Among both benzodiazepine and GABA analogue lifetime users, the proportion aged 34 years or younger was higher for those who had non-medically used than those who had not, while the reverse was true for those over the age of 60 years. Lifetime NMU of GABA analogues was more common among males than females in all countries, while lifetime NMU of benzodiazepines was more common among females in all countries except the UK.

In most countries use of benzodiazepines increases with age and is more common among women. A systematic review by Votaw et al. found conflicting reports on whether benzodiazepine misuse was associated with age or gender. In contrast to the US, most studies outside of the US show greater likelihood of benzodiazepine misuse among females but, when controlled for a history of benzodiazepine prescription, which is higher among women, show higher misuse rates among men.

A systematic review by Evoy et al. found most studies documented abusers of gabapentin or pregabalin were typically young but, as with benzodiazepines, data regarding gender differences are conflicting. A study of adverse drug reactions recorded by the European Medicines Agency's EudraVigilance database found more reports of abuse, dependence or product misuse related to gabapentin or pregabalin among females than males, but the authors suggested this may be due to the fact that the indicated uses of GABA analogues (including neuropathic pain, generalised anxiety disorder and fibromyalgia) are more typically identified with female individuals.

General population estimates for a history of previous mental health or chronic pain diagnosis were approximately one in three to one in four, while lifetime illicit drug use was approximately one in four to one in five for all countries; these estimates are comparable to previous studies. Perhaps not surprisingly, due to their use to treat neuropathic pain or general anxiety disorder, a higher prevalence of mental health diagnoses and chronic pain were observed among those reporting both lifetime use but not NMU, and lifetime NMU of benzodiazepines or GABA analogues, than the general population.

No association was seen between NMU and a history of chronic pain for either benzodiazepines or GABA analogues, while mental health diagnosis was more common among lifetime users reporting NMU of benzodiazepines/GABA analogues, except for benzodiazepines in Spain. Previous studies have documented association between mood/anxiety disorders and NMU of both benzodiazepines and GABA analogue NMU. However, as suggested by Evoy et al., increased prevalence of NMU may be partially explained by use of the drugs to treat psychiatric conditions.

NMU of both benzodiazepines and GABA analogues were significantly associated with illicit drug use in all countries, supporting findings of many previous studies showing NMU of benzodiazepines or GABA analogues is associated with a history of substance use. Votaw et al. documented that individuals with substance use disorders in the US have rates of benzodiazepine misuse 3.524 times higher than the general population and that the misuse of other substances is the most consistent and robust correlate of benzodiazepine misuse, while Bastiaens et al. declared the most common risk factor for development of gabapentin abuse is past or current opioid use disorder. There is evidence that, like benzodiazepines, GABA analogues potentiate the effects of opioids and combining opioids with gabapentin or pregabalin potentially increases risk of acute overdose.

Documented risk factors for prescription opioid misuse include being male, younger age, any mental health diagnosis and current or past history of substance misuse. The findings of our study indicate that person-specific factors, to some extent, also apply for NMU of benzodiazepines and GABA analogues.

NMU is also at least in part linked to drug availability as previously noted by studies investigating risk factors for illicit drug use, NMU of prescription opioids and excessive use of prescription drugs. The top four benzodiazepine/GABA analogue drugs reported for last 12-month NMU were comparable to the top four benzodiazepine/GABA analogue drugs sold in the last year per country. Additionally, the UK was the only country where NMU of gabapentin was greater than pregabalin, reflected by also being the only country where sales of gabapentin were greater than sales of pregabalin. Location potentially also plays a part in NMU as the drugs most non-medically used in Northwestern Europe (Germany and UK) are similar, as are those most non-medically used in Southwestern Europe (Italy and Spain).

Spain had the highest prevalence of lifetime benzodiazepine NMU and also last 12-month NMU of benzodiazepines, particularly diazepam, while the highest prevalence of both lifetime and last 12-month NMU of GABA analogues was observed in Germany. A previous study noted a significant increase in tranquiliser, sedative and sleeping pill misuse among Spanish high-school students. German pregabalin-related studies have documented NMU among substance users, increased cases of abuse or dependence reported to the German Federal Institute for Drugs and Medical Devices (BfArM), and detection in post-mortem toxicology, especially in combination with opioids.

However, there is limited previous data published on the prevalence of NMU for benzodiazepines or GABA analogues among general populations. Additionally, it is problematic to compare to other studies due to differing definitions of misuse/NMU and the fact that some studies combine benzodiazepines with other sedative or hypnotic drugs. For example, data from the 2017 US National Survey on Drug Use and Health (NSDUH) show approximately 2.2% of the US population (aged 12 years and older) had misused tranquilisers in the last year and 0.5% had misused sedatives. A systematic review of benzodiazepine misuse reported only one European population-based study that indicated 2.2% of Swedish adults (aged 1564 years) had misused benzodiazepines and other sedatives in the previous year. The range of estimated prevalence of past year benzodiazepine NMU in our study (from 0.9% in the UK to 3.9% in Spain) incorporates the estimated prevalence of sedative NMU in these other general population studies. While, to our knowledge there are no studies documenting last 12-month NMU of GABA analogues,
the prevalence of lifetime NMU in the UK estimated in this study is comparable to a previous UK study from 2014 (2.2% compared to 2.5%).\textsuperscript{13}

The prevalence of lifetime and 12-month NMU in this study is lower than observed in the previous study of European NMU by Novak et al. (10.9% lifetime and 5.8% past year NMU of sedatives).\textsuperscript{3} However, that study targeted individuals aged 1249 years with characteristics associated with drug use (e.g. tobacco/cannabis users) and recruited from areas associated with high levels of drug use (e.g. needle exchanges, homeless shelters). Therefore, the survey was not representative of the general population even though the goal was to produce population-based estimates and post-stratification weights were applied to represent national demographics and substance use characteristics.

The major strength of this study is that it is representative of the national populations; the UK version of the survey has been shown to be comparable to the national Crime Survey of England and Wales (CSEW) cohort, in terms of illicit drug use.\textsuperscript{17} The main limitation with this study, as with all online surveys, is the reliance on participants providing honest, accurate answers. Additionally, there is a potential issue concerning confounding by indication as individuals with a history of chronic pain or mental health may use benzodiazepines or GABA analogues to treat the conditions. Another limitation is that the survey only covers members of the general population with access to the internet, which may exclude vulnerable populations, including prison inmates and individuals with no fixed abode, who are more at risk to NMU, addiction and overdose, so resulting in potential underestimation of prevalence estimates.\textsuperscript{49} High levels of pregabalin and gabapentin use and NMU in particular have been documented in UK prisons.\textsuperscript{50}

The NMURx surveys are one component of the RADARS system mosaic collecting data relating to NMU of prescription medicines. These data provide a greater insight into the prevalence of NMU of prescription medicines and the source of the drugs, together with other factors including the harms associated with NMU, association with illicit drug use and risk factors for NMU. Triangulation of the mosaic of data from the RADARS network, including the NMURx surveys reported in this paper, are important to inform appropriate prevention activities at both a national/international and practitioner level; from a clinical care perspective, it is important that clinicians are aware of the drugs associated with NMU in order that they can ensure appropriate oversight of prescribing and drug safety monitoring in their patients.

This study is the first to provide comparable estimates of lifetime and last 12-month NMU of benzodiazepines and GABA analogues across different European countries. Overall, this study shows that while there is variation among countries, the proportion of GABA analogue users taking the drugs for non-medical reasons is higher than for benzodiazepines. Prescribers should be aware of the potential of the drugs for NMU, especially among those with a previous history of illicit drug use. In particular, this study identifies some interesting observations, namely the high incidence of GABA analogue NMU in Germany and benzodiazepine NMU, especially diazepam, in Spain compared to the other European countries. Further research to identify factors and motivations responsible for the higher prevalence observed are essential to inform public health policies in those countries.

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**COMPETING INTERESTS**

The RADARS System is supported by subscriptions from pharmaceutical manufacturers, government and non-government agencies for surveillance, research and reporting services. The RADARS System is the property of Denver Health and Hospital Authority, a political subdivision of the State of Colorado. Denver Health retains exclusive ownership of all data, databases and systems. Subscribers do not participate in data collection nor do they have access to the raw data. We declare no competing interests.

**CONTRIBUTORS**

J.H. prepared the manuscript. E.A., J.C.B., A.F. and J.H. conducted statistical analysis. All authors reviewed the final manuscript.

**DATA AVAILABILITY STATEMENT**

Research data are not shared.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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