separations

MDPI

Article

The Prevalence of Benzodiazepine Use among Italian Drivers in 15,988 Cases of Driving License Regranting from 2015 to 2023: Risks and Implications for Driving Fitness

Lucrezia Stefani [1,2,†], Federico Mineo [1,†], Leonardo Romani [1,2], Francesca Vernich [1], Carmelo Russo [1,2], Luigi Tonino Marsella [1] and Roberta Tittarelli [1,*]

[1] Laboratory of Forensic Toxicology, Section of Legal and Forensic Medicine, Social Security and Forensic Toxicology, Department of Biomedicine and Prevention, Faculty of Medicine and Surgery, University of Rome "Tor Vergata", Via Montpellier 1, 00133 Rome, Italy; lucrezia.stefani@students.uniroma2.eu (L.S.); f.mineo@med.uniroma2.it (F.M.); leonardo.romani.09@students.uniroma2.eu (L.R.); francesca.vernich@uniroma2.it (F.V.); carmelo.russo.01@students.uniroma2.eu (C.R.); marsella@uniroma2.it (L.T.M.)

[2] PhD School in Medical-Surgical Applied Sciences, University of Rome "Tor Vergata", Via Montpellier 1, 00133 Rome, Italy

* Correspondence: roberta.tittarelli@uniroma2.it

† These authors contributed equally to this work.

Abstract: The use of benzodiazepines is strongly associated with an increased risk of traffic accidents due to their side effects of sedation and drowsiness, which can significantly impair driving performance. The main aim of our study was to investigate the trend of benzodiazepine use over nine years (2015–2023) in a population of 15,988 subjects who had their license suspended for driving under the influence (DUI) of alcohol or drugs. Among the 15,988 users accessed to our laboratory, 924 tested positive for at least one benzodiazepine. An increase in the number of positive-testing users was observed in the period 2015–2018, followed by a slight decrease in 2019. Overall, the trend of benzodiazepine use was stable over the next four years (2020–2023), with the highest incidence in 2022. The most common benzodiazepines, and/or metabolites, found in urine samples were α-OH-alprazolam (28.66%; $n = 366$) and oxazepam (27.25%; $n = 348$). Several cases of mixed positivity were observed in the study population. The main substances taken with benzodiazepines were cocaine and Δ9-tetrahydrocannabinol. Our findings suggest that people taking benzodiazepines should be monitored, as these have a relevant impact on driving ability in addition to significant interindividual differences in the behavioral effects of benzodiazepines on driving performance.

Keywords: benzodiazepines; addiction; psychoactive drugs; abuse; driving license; screening; GC/MS

Citation: Stefani, L.; Mineo, F.; Romani, L.; Vernich, F.; Russo, C.; Marsella, L.T.; Tittarelli, R. The Prevalence of Benzodiazepine Use among Italian Drivers in 15,988 Cases of Driving License Regranting from 2015 to 2023: Risks and Implications for Driving Fitness. *Separations* **2024**, *11*, 169. https://doi.org/10.3390/separations11060169

Academic Editor: Katelynn A. Perrault

Received: 3 May 2024
Revised: 20 May 2024
Accepted: 22 May 2024
Published: 29 May 2024

1. Introduction

Benzodiazepines (BZDs) are a class of drugs commonly used to treat anxiety, insomnia and related sleep problems, muscle relaxation, and other psychiatric disorders such as depression and psychosis [1,2]. They act as positive allosteric modulators of gamma-aminobutyric acid (GABA) receptors, resulting in increased inhibitory neurotransmission in the brain. Although benzodiazepines are effective for treating these conditions, they are also associated with several adverse effects, including cognitive impairment, sedation, addiction, and withdrawal symptoms [1].

As stated by a report published by the World Health Organization (WHO) in 2019, the estimated number of people affected by anxiety, depression, and/or other mental disorders worldwide was 970 million—one in every eight people [3].

In Europe, the frequency of benzodiazepine use varies between countries and populations. According to data reported in 2021 by the European Monitoring Centre for Drugs

and Drug Addiction (EMCDDA), the prevalence of benzodiazepine use in the general population ranges from less than 1% to over 10%, varying by country [2].

The EMCDDA also reports that benzodiazepines are frequently used in combination with other drugs, particularly opioids and alcohol, which increases the risk of overdose and other adverse effects [2]. To date, it is very difficult to monitor the extent of their use, because so-called "new benzodiazepines" (or "designer benzodiazepines") are still widely available in several European countries, as they are uncontrolled substances. In 2022, Estonian police forces reported the seizure of several mixtures containing metonitazene and bromazolam a new synthetic opioid and a new benzodiazepine, respectively. These mixtures, known as "benzo-dope" or "tranq-dope", were responsible for many fatalities in the USA and Canada [4].

Between August and November 2023, "A Surveillance Study of Illicit Substance Toxicity" (ASSIST), conducted at the emergency department (ED) of the Queen Elizabeth University Hospital (QEUH), investigated the feasibility of introducing a surveillance system to detect the presence of attendances related to acute drug toxicity. Benzodiazepines were one of the most common classes of detected drugs and represented 59% of all determinations [5]. Temazepam was identified in 73 samples (10% of detections; 56% of samples); oxazepam was identified in 59 samples (8% of detections; 45% of samples); and diazepam was identified in 47 samples (7% of detection; 36% of samples).

According to data reported by the National Survey on Drug Use and Health (NSDUH), in 2020, an estimated 4.8 million people aged 12 years or older misused prescription benzodiazepines in the previous year. This survey included 1.1 million young adults aged 18–25 years, 3.5 million adults aged 26 years or older, and 157,000 adolescents aged 12–17 years [6]. In 2021, approximately 2% of people misused prescription benzodiazepines in the previous year [7]. Almost 4% of all drug reports in 2022 (45,916 reports) were documented by the NFLIS (National Forensic Laboratory Information System) concerned benzodiazepines. Alprazolam represented 31% of reported benzodiazepines, whereas clonazepam represented 10% [8].

Worldwide international guidelines regulate the long-term use of benzodiazepines, as the risks associated with their long-term use range from psychological side effects to addiction. In order to prevent this wide range of negative effects, monitoring the long-term use of benzodiazepines with targeted strategies to assess their efficacy is needed [9].

At present, for the treatment of generalized anxiety disorder, insomnia, panic attacks, and phobia-related disorders in adults aged 65 years or older, good practice guidelines involve only prescribing short-term treatments with benzodiazepines, with a maximum period between 2 and 4 weeks for insomnia and anxiety, and no more than 2 weeks for mixed anxiety–depressive disorders [10].

The potential risks associated with benzodiazepine use are well documented in the international literature. In 2023, a systematic review and meta-analysis by Lader et al. [11] reported that long-term benzodiazepine use was associated with cognitive impairment, an increased risk of falls and fractures, and a higher incidence of motor vehicle accidents. Similarly, a study by Olfson et al. [12] found that benzodiazepine use was associated with an increased risk of opioid overdose in patients receiving opioid therapy for chronic pain. The symptoms of depression, anxiety, and insomnia were related to the early stages of cognitive dementia. Conversely, in 2023, Wu et al., examined the association between benzodiazepine use and the risk of dementia. The authors highlighted the lack of strong and consistent data about the risks associated with the type of benzodiazepine and their dosage in both short- and long-term treatment [11].

In Italy, benzodiazepines are among the most prescribed drugs. An estimated 15–20% of the adult population reported being users of benzodiazepines in their lives [13]. In Italy, benzodiazepines are only available by prescription and are subject to strict regulations designed to ensure their safe and appropriate use. Moreover, such recommendations are meant to prevent misuse, the non-medical or recreational use of benzodiazepines, and emergency department admissions and related deaths. Reports from Italy and EMCDDA,

included in the 2022 Annual Report on Drugs to the Italian Parliament, concerned 113 new substances, including four benzodiazepines [14].

European data on the prevalence of new benzodiazepines associated with opioids also find confirmation in Italy. In 2022, among the new psychoactive substances identified in Italy and notified to the EMCDDA, bromazolam, previously mentioned for its dangerous association with the new synthetic opioid metonitazene, was reported and seized [14].

According to Italian statistics on benzodiazepine use in Italy in 2022, lormetazepam was the most consumed drug, followed by alprazolam and lorazepam [15]. The average level of benzodiazepine consumption varied considerably across regions. According to these data, Liguria was the region with the highest benzodiazepine use in 2022, followed by Piemonte and Veneto. Lazio was the twelfth region for benzodiazepine use, whereas Basilicata registered the lowest degree of use [16].

According to the National Report on Medicines Use in 2022, benzodiazepines with anxiolytic activity was the category with the highest expenditure in Italy, followed by paracetamol. Lormetazepam represented the most widely used substance in the population with 15.6 Defined Daily Dose (DDD)/1000 representative inhabitants per day, followed by alprazolam and lorazepam. The National Report also reported great variability between the northern and southern regions, with a 73% higher consumption rate for the former. At a regional level, data confirmed previous statistics, with Liguria recording a consumption three times higher than Basilicata. Nevertheless, the Report also registered a slight reduction in anxiolytic benzodiazepine consumption over the previous year, with 26.1 DDD/1000 inhabitants per day, describing a reduction of −4.4% between 2021 and 2022. In 2022, the total consumption of benzodiazepines reached 53.7 DDD/1000 inhabitants per day, registering −1.2% compared to the previous year; meanwhile, the last 8 years registered an increase of 34% with a mean annual change of +4.3% [17].

Moreover, data published by the Italian Medicines Agency (AIFA) also highlighted the finding that the use of benzodiazepines in Italy slightly decreased (−1.6%) between 2021 and 2022, likely due to efforts to promote safer prescribing practices. Nevertheless, an estimated range from 6% to 76% of benzodiazepine users become long-term users during the years of treatment, with 15% to 30% of users developing moderate to severe withdrawal and/or rebound symptoms [18].

The Italian Ministry of Health issued guidelines for the appropriate use of benzodiazepines and other sedatives, highlighting the importance of prescribing these drugs only for the short-term treatment of anxiety and insomnia and regularly reviewing the treatment plan. The guidelines also recommend caution in prescribing benzodiazepines to elderly patients and patients with a history of substance abuse [19].

Furthermore, AIFA implemented measures to monitor and control the use of benzodiazepines and other psychotropic drugs, establishing a national database to monitor the prescribing and dispensing of benzodiazepines and other controlled substances and improving the national electronic prescription systems to enhance their traceability.

In addition, Italian law requires that patients prescribed benzodiazepines receive detailed information about the risks and benefits of these drugs, as well as recommendations on how to use them safely and effectively. Patients are also advised to avoid drinking alcohol or taking other sedative drugs while using benzodiazepines, as this may increase the risk of adverse effects.

Like other countries in Europe, Italy is also grappling with the challenge of addressing the risks associated with the abuse and misuse of these drugs. The relation between benzodiazepine consumption, impaired driving, and the increased risk of car accidents has been widely reported in the international scientific literature [20–22].

Benzodiazepines may produce a moderate or severe impairment of driving performance [23]. The main effects able to affect driving performance include sedation and drowsiness. Benzodiazepines have a sedative effect and can make individuals feel somnolent or excessively tired, leading to reduced alertness and vigilance and slower reaction times while driving. The use of BZDs while driving may cause impaired coordination,

impaired judgment and decision making, and decreased concentration and attention. Specifically, benzodiazepines can affect motor coordination, making it more difficult to perform tasks that require accurate movements (e.g., steering, braking, or changing lanes), can compromise cognitive function, and can impair judgment, resulting in misjudging distances or risks.

Benzodiazepines can also make it challenging to pay attention and maintain focus, leading to inattentiveness and reduced awareness of the road and other vehicles [23,24]. The specific impact of benzodiazepines on driving ability can be very different depending on an individual's tolerance, dosage, and the period of use. Even though BZDs are commonly detected in drivers at sub-therapeutic or therapeutic concentrations, impaired driving, even at low concentrations associated with therapeutic dosages, cannot be ignored [25–27].

This is especially applicable to longer-acting benzodiazepines when tested in the morning after an overnight dose. The literature suggests that the greatest risk of accidents is associated with the use of long half-life benzodiazepines after dose escalation and in the first few weeks of use, whereas shorter-acting BZDs show minor adverse effects on psychomotor abilities in the morning after an overnight dose [28–30].

In this context, epidemiological evidence points to an increased risk of hip fractures and traffic accidents after using anxiolytic benzodiazepines; however, these effects were only significant for benzodiazepines with a long elimination half-life (>24 h) and not for those with a short half-life (<24 h). Additionally, combining benzodiazepines with alcohol or other drugs can further amplify their sedative effects and increase the risk of impaired driving. In Italy, subjects charged with drug-impaired driving must undergo a mandatory medico-legal and forensic toxicological examination in order to re-obtain their driving license [31].

The aim of our study was to examine the trend of benzodiazepine use in a population of 15,988 subjects who underwent toxicological investigations following license suspension for driving under the influence (DUI) of alcohol or drugs. In order to investigate the peculiarities of the socio-demographic phenomenon related to the use of benzodiazepines in the observed population, special attention was given to the evaluation of age and gender.

2. Materials and Methods

2.1. Samples Collection and Screening Analysis

A total of 15,988 urine samples collected between 2015 and 2023 at the Forensic Toxicology Laboratory of the University of Rome "Tor Vergata", were screened for ten classes of drugs and psychotropic substances (amphetamines, ecstasy, cocaine, opiates, methadone, cannabinoids, benzodiazepines, barbiturates, and alcohol). The subjects were also tested for carbohydrate-deficient transferrin (CDT) to determine a potential condition of chronic alcohol consumption. The tests were mandatory, and the data obtained were aggregated and anonymized, as they were collected for non-medical purposes.

The inclusion criteria focused on drivers, aged older than 18 years, who had a suspended license due to the violation of Articles 186 (Driving under the influence of alcohol), and 187 (Driving under the influence of drugs) of the Italian Highway Code. The exclusion criteria were as follows: subjects under the age of 18, applications for a firearm license, and requests for toxicological analysis from courts or hospitals.

Urine specimen collection required the acquisition of two samples with BD Vacutainer® tubes under a strict chain of custody procedure. Each sample was labelled with tamper-evident seals, separately identified with the letter "A" and "B", to ensure the integrity and the security of the specimens and to avoid manipulation and conduct or statements that could be viewed as offensive or inappropriate [32]. The collector reported the date on the seals, and the examined subject placed his or her signature on the seal followed by that of the collector. Then, the subject witnessed the sealing of the tubes.

The seal labelled "A" was placed on the primary tube, and the seal labelled as "B" was applied to the second tube, with both containing at least 10 mL of urine [33]. The sample

"A" was analyzed immediately, whereas the second one (sample "B") was frozen at −20 °C and stored for one year, as reported in our internal procedures [33].

After collection, screening analyses were carried out on samples "A" with a homogenous immunoenzymatic assay (ILab™ Taurus, Instrumentation Laboratory, Werfen Company, Barcelona, Spain).

To confirm the presumptive non-negative results obtained from the screening tests, confirmation analyses were carried out via gas chromatography/mass spectrometry (GC/MS) using an Agilent Technologies 7820A GC coupled with an Agilent Technologies 5975 MSD Series (Agilent Technologies, Palo Alto, CA, USA).

2.2. Sample Preparation and GC/MS Analysis

For the detection and quantification of benzodiazepines, the urine samples, after the addition of 200 ng of a mixture of deuterated benzodiazepines, were buffered with 1 M sodium acetate (pH 5) and incubated with 50 µL of Helix pomatia β-glucuronidase at 35 °C overnight for hydrolysis [34]. After cooling, 50 µL of 1 M sodium hydroxide and phosphate buffer were added to the samples to adjust the pH to 7.5.

Sample preparation consisted of liquid–liquid extraction (LLE), followed by derivatization with N,O-bis(trimethylsilyl)trifluoroacetamide plus 1% trimethylchlorosilane (BSTFA + 1% TMCS). The samples were extracted with 3 mL of ethyl acetate on a rotating mixer for about 20 min, aiming to ensure adequate mixing; the extraction resulted in centrifugation (4500 rpm, 5 min). The supernatants were collected and evaporated to dryness at the temperature of 40 °C under a gentle nitrogen flow. The dried samples were derivatized with 70 µL of BSTFA + 1% TMCS for 30 min at 70 °C.

The extracts were analyzed via GC/MS in a selected ion monitoring mode (SIM). GC/MS equipment consisted of an Agilent HP-5MS 5% Phenyl Methyl Silox capillary column (30 m × 250 µm I.D. × 0.25 µm thickness), and data analysis was performed with the Agilent MSD ChemStation Data Analysis Application (version G1701EAE.02.02.1431).

The ionization mode was an electronic impact at 70 eV, and the detector voltage was 0.9 kV. The injector temperature was 270 °C. The initial oven temperature was 130 °C for 1 min; then, it was increased by 25 °C/min to 300 °C and maintained for ten minutes. The transfer line temperature was maintained at 280 °C. The constant flow of carrier gas (He) was 1 mL/min. A splitless injection mode was used.

The total time of analysis was 15 min. A volume of 1 µL of each sample was injected into the GC/MS system.

2.3. Data Analysis

Data analyses and graph preparation were performed with Microsoft Excel® 2016 MSO (16.0.4738.1000) (Microsoft Corporation®, Redmond, WA, USA).

3. Results

Epidemiological Data

Among the 15,988 users accessed in our laboratory, 924 tested positive for at least one benzodiazepine, representing about 5.78% of the total (Figure 1). A total of 701 were males (75.87%), and 223 were females (24.13%).

The median age of the observed population was 46.74 years, with a maximum of 75 years and a minimum of 26 years (Table 1). Quantitative data were expressed as medians or means and ranges.

Among the positive-testing users included in this study, 430 (46.54%) had access to benzodiazepines via medical prescription or because of treatment in psychiatric settings, as shown in Figure 2. Of the remaining 494 users (53.46%), we lack information about any regular benzodiazepine prescription.

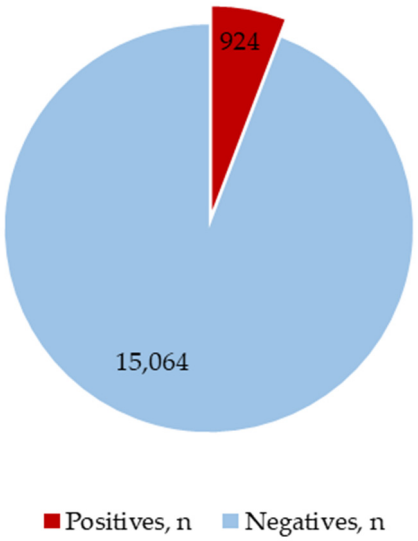


Figure 1. Number of positive subjects (red) compared to the total number of analyzed samples.

Table 1. Demographic data of the study population.

Study Group	Positives
n = 15,988	n = 924
Female, n (%)	223 (24.13)
Male, n (%)	701 (75.87)
Median Age	46.74

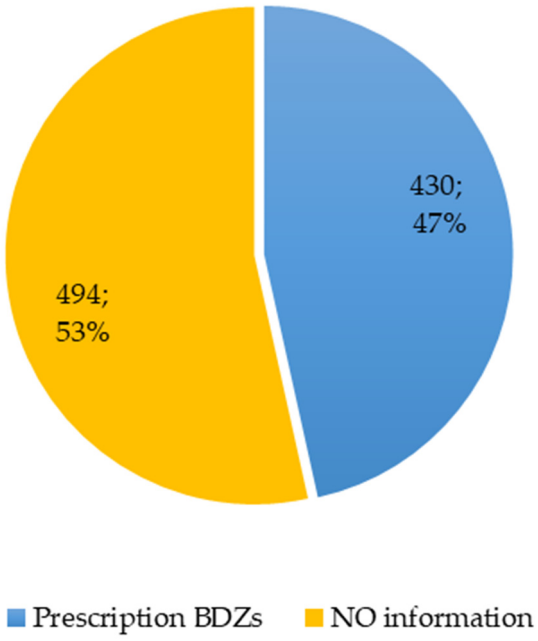
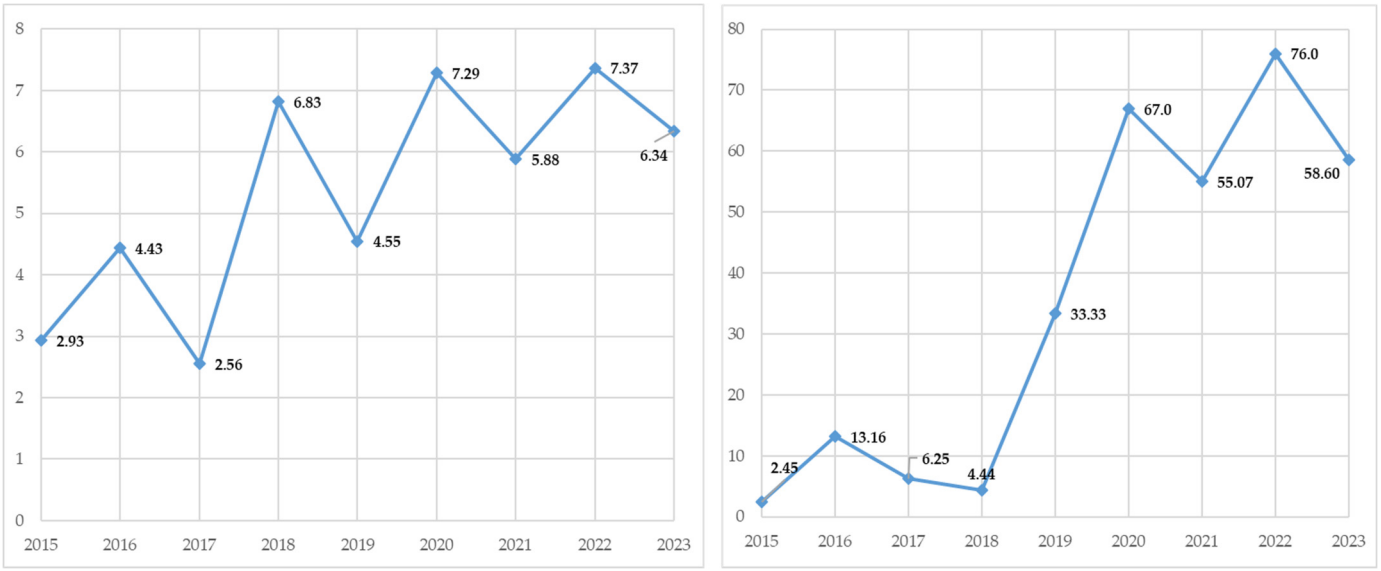


Figure 2. Percentage values of the total subjects who reported taking benzodiazepines related to the total number of positive-testing subjects (n = 924).

As shown in Figure 3A, we also evaluated the percentages of the subjects who tested positive compared to the total population, categorized by year.



(**A**) (**B**)

Figure 3. (**A**) Graph of the trend of the percentage ratio between total positive-testing subjects and total subjects per year. (**B**) Graph of the trend of the percentage ratio between the number of subjects who reported taking benzodiazepines compared to the number of positive-testing subjects per year.

In 2015, between September and December, the percentage stood at 2.93% (10 positives out of 341); an increase up to 4.43% was registered in 2016 (38 positives out of 857), whereas in 2017, the value fell to 2.56% (38 positives out of 1487). We observed an up and down trend, with increases and decreases in values that occurred in a 6-year period. In 2018, an increase in the number of users was registered, reaching a value of 6.83% (129 positives on 1890); in 2019, the percentage dropped to 4.55% (114 positives on 2507) and then rose in 2020 to 7.29% (100 positives out of 1372). A similar situation was observed in 2021, with a value of 5.88% (138 positives out of 2345) and in 2022, with a percentage equal to 7.37% (200 positives out of 2714). During 2023, the percentage stood at 6.34%, with 157 positive-testing users out of 2475 total subjects analyzed. The discontinuous trend shown in Figure 3A displayed a sharp increase (+2.74%) in the number of positive-testing users during the pre-pandemic year (4.55% in 2019) and the first year of the pandemic (7.29% in 2020). There is a significant relationship between these findings and the ones related to the increase in the number of benzodiazepines communicated by users during sample collection, as shown in Figure 3B. In the same period, we also highlighted a greater proportion of positive-testing users declaring a prescription of BZDs, from 33.33% in 2019 to 67.00% in 2020 (+33.67%), with a maximum peak of 76.00% in 2022.

The distribution of the most used benzodiazepines and/or their main metabolites are summarized in Figure 4. During data analysis, we considered that a subject could be positive for one or more benzodiazepines.

Figure 4 shows the distribution of each substance over the total number (n = 1277) of the drugs found during the observation period.

In this graph, it is interesting to note that the quantitative proportion of α-OH-alprazolam and oxazepam was similar—366 out of 1277 (28.66%) and 348 out of 1277 (27.25%), respectively. Temazepam, lorazepam, and nordiazepam were found in 149 (11.67%), 144 (11.28%), and 119 cases (9.32%), respectively. The remaining benzodiazepines were revealed less than 151 times (11.82%).

It was not uncommon to detect benzodiazepine along with other substances. Several cases of mixed positivity were also observed in the study population. Figure 5 reports the number of subjects who tested positive for benzodiazepines and also tested positive for other classes of substances.

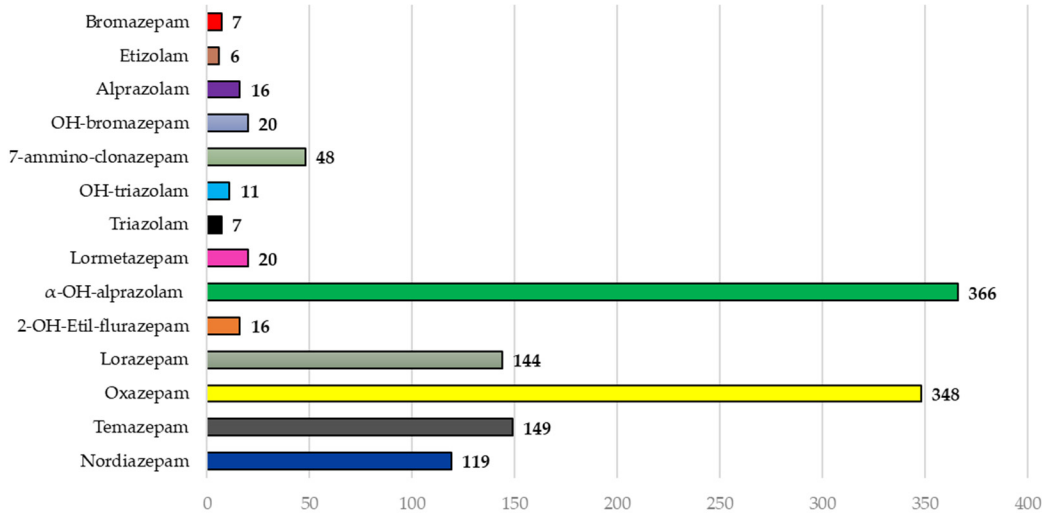


Figure 4. Types of BZDs and/or their main metabolites determined in positive-testing subjects (n, BZDs/metabolites).

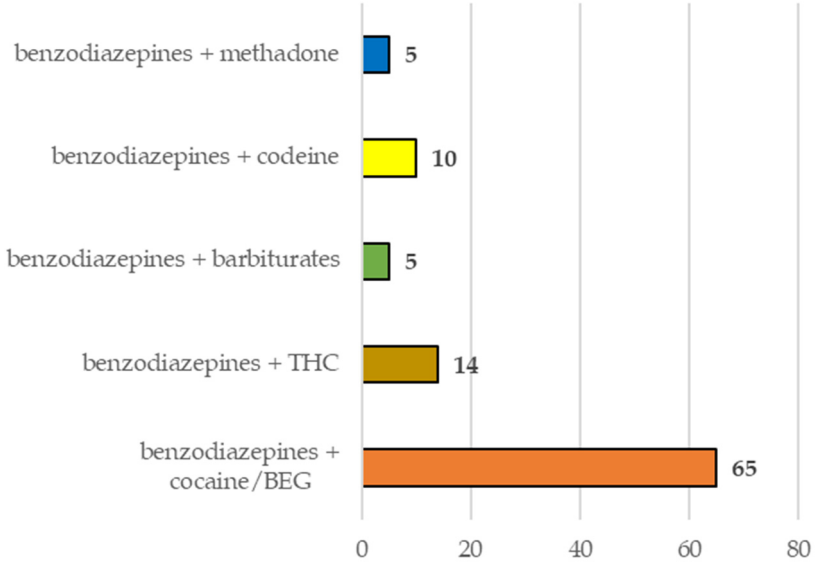


Figure 5. Cases who tested positive for BZDs with concurrent positivity for other drugs of abuse.

The graph in Figure 5 shows that 65 subjects tested positive for cocaine, 14 tested positive for Δ9-tetrahydrocannabinol (Δ9-THC), 10 tested positive for codeine, 5 tested positive for barbiturates, and 5 tested positive for methadone.

In Figure 6, the percentage values of the main detected BZDs are represented. α-OH-alprazolam was found to be the most widely revealed benzodiazepine metabolite (366 cases; 28.66%), followed by oxazepam (348 cases; 27.25%).

To a lesser extent, temazepam (149 cases; 11.67%), lorazepam (144 cases; 11.28%), and nordiazepam (119 cases; 9.32%) were detected.

Lastly, benzodiazepines found in a few cases, including 2-OH-ethyl-flurazepam, lormetazepam, triazolam, OH-triazolam, 7-aminoclonazepam, OH-bromazepam, alprazolam, etizolam, and bromazepam, were grouped for 151 cases (11.82%).

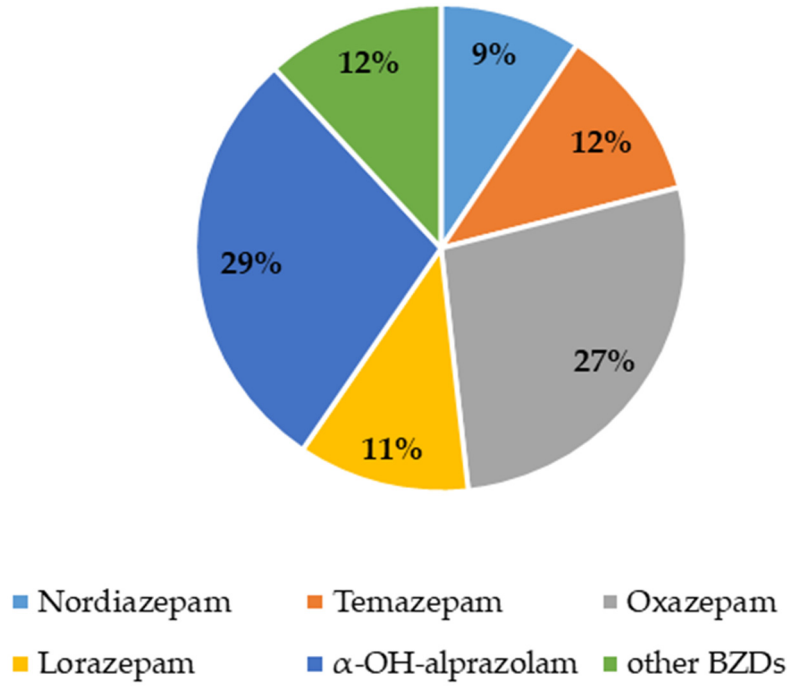


Figure 6. Percentages of the main detected benzodiazepines.

4. Discussion

Benzodiazepines are a worldwide-prescribed group of drugs ordinarily used to reduce anxiety, produce sedation, relieve muscle spasms and sleep-onset latency, and improve the quality of sleep by altering neuron activity [1].

BZDs have been used for their anxiolytic properties but also for their usefulness in treating insomnia, agitation, seizures, muscle spasms, and alcohol withdrawal, as well as surgical premedication. Over the years, several clinical trials have tested the effectiveness of benzodiazepines compared with other drugs. In this context, their side effect profiles appeared to be better than other psychotropic drugs. They are a versatile agent for short-term and long-term treatments, as they are effective in balancing the risks and benefits associated with treatments [35].

In Italy, among the top 20 highest-spending class C therapeutic categories under prescription in 2020, three were benzodiazepines (both anxiolytic and hypnotic-sedating compounds). Therefore, they are the highest purchasing category, representing 17% of expenditure and 22% of prescription class C DDDs. Italy registered a regional trend of weighted DDD/1000 inhabitants per day from 40.0% in 2015 to 49.3% in 2018, rising to 55.0% in 2020 and 53.7% in 2022 [17].

According to the OECD, symptoms of anxiety and depression among young people more than doubled in several European countries during the pandemic, increasing the demand for mental health supports. Over the past decade, the use of BZDs, both long-term and long-acting, decreased throughout EU countries. Large declines in long-term use occurred in Iceland, whereas Denmark and Iceland experienced a large decline in the use of long-acting benzodiazepines. On the other hand, the use of long-acting benzodiazepines in Estonia was the highest in the EU and 23-fold higher than in Finland [36].

Globally, benzodiazepine use has declined the most in high-income countries, which, historically, had the highest rates of use. According to data from IQVIA's Multinational Integrated Data Analysis (MIDAS) database between July 2014 and September 2020, the United States (U.S.) and Belgium experienced the largest decline in benzodiazepine use, with a percentage variation of −35% and −22%, respectively.

This wide variation between different countries is mostly explained by the differences in the prescribing policies for benzodiazepines, as well as differences in disease prevalence.

This finding is relevant because the slight global decrease in BZD use does not necessarily represent an improvement in mental health care but may be related to easier accessibility to these categories of drugs. For example, BZDs have relatively high rates of use in high-income countries such as the United States, France, and other European countries. However, these countries also have high rates of benzodiazepine abuse, especially among the elderly [37].

Our study aimed to produce a more comprehensive understanding of the trend of benzodiazepine use over 9 years (2015–2023), including the pandemic period, in a study group of subjects who had their driving licenses suspended due to DUI of alcohol or drugs. We observed the prevalence of benzodiazepine use increasing between 2015 and 2023. Benzodiazepine consumption was more common among males.

Oxazepam, α-OH-alprazolam, lorazepam, temazepam, and nordiazepam were the five most identified benzodiazepines. Among these drugs, α-OH-alprazolam (28.66%; n = 366) and oxazepam (27.25%; n = 348) were the most frequently found benzodiazepines in urine samples.

The key strengths of our study are the wide range of data collected and the study period of 9 years. It could be very interesting to expand the observation group to obtain a more detailed overview of benzodiazepine use and/or potential abuse.

Benzodiazepine use is strongly associated with the abuse of other substances [38]. For this purpose, in our study, a comparison with users who also tested positive for other psychotropic drugs of abuse was performed. The combined use of benzodiazepines and other substances can decrease performance in tasks that require brain–eye–hand coordination and may increase the risk of harmful outcomes, including impaired driving performance, reduced vigilance, and dangerous behaviors while driving, which are exacerbated if the doses are not stable [39].

Raising awareness of the fact that potential interactions between benzodiazepines and other drugs may result in a greater risk of experiencing adverse consequences is undoubtedly important.

In total, 7.03% of users also tested positive for more than one psychotropic substance, such as benzodiazepines and cocaine. Among 65 users, who tested positive for both BZDs and cocaine, we found a high frequency of association between cocaine and α-OH-alprazolam (n = 25), cocaine and oxazepam (n = 30), and cocaine and temazepam (n = 10).

Mixing cocaine and benzodiazepines can lead to the development of serious consequences for users. Benzodiazepines affect the organization of GABA output systems since they facilitate GABA neurotransmission [40], which is the SNC inhibitory neurotransmitter that aims to lessen nerve cells' ability to acquire, generate, or send chemical messages to other nerve cells. BZDs enhance gamma-aminobutyric-acid-mediated neural inhibition. Moreover, cocaine abusers show considerable reduction in brain striatal D2 receptors, reflecting postsynaptic elements on GABA cells [41]. Cocaine abusers manifest adaptive responses based on decreases in GABA activity; concurrently with benzodiazepines, this reinforces GABA-induced chloride flux at the GABA receptor [42]. Cocaine use could be related to the onset of anxiety, agitation, and panic attacks that are frequently managed by users with benzodiazepines. Some authors have demonstrated that cocaine abusers are more likely to take on BZDs in order to alleviate anxiety-associated symptoms [42].

Previous studies have highlighted the existence of poly-drug consumption also concerning alcohol and other different drugs. Considering the widely spreading incidences of drinking and driving, as well as the increasing use of benzodiazepines, it is not unusual that alcohol and benzodiazepines are found in combination in drivers' blood samples [43]. The association between benzodiazepines and alcohol emphasizes the decrease in cognitive performance and psychomotor skills [44]. Carbohydrate-deficient transferrin (CDT) has been widely investigated as the most relevant biological marker in the monitoring of heavy/chronic alcohol consumption [45]. Despite the lack of consistent information available related to chronic alcohol consumption and drug misuse, Appenzeller et al. col-

lected blood specimens from 210 drivers in Luxembourg between 2001 and 2002. They tested blood samples in order to investigate illicit drug use and chronic alcohol use via CDT quantification. According to statistics, benzodiazepines were rarely associated with chronic alcohol consumption [44]. This evidence is in line with our data, as we only observed 7 cases (0.04%) testing positive for the combined use of benzodiazepines and alcohol, as characterized by CDT testing (CDT values > 2%).

Furthermore, we separately analyzed pre-pandemic data, from January 2015 to December 2019, and post-pandemic data, from 2020 to 2023. As documented by the World Health Organization (WHO), the first year of the COVID-19 pandemic, with stay-at-home orders and health concerns, resulted in a marked increase of almost 25% for anxiety, depression, sadness, and mental health problems globally. The worsening of general psychiatric health conditions was likely associated with increased benzodiazepine prescriptions and/or use [46].

Before COVID-19, anxiety and depression in Europe were the most frequent mental health problems, followed by alcohol and drug use disorders, bipolar disorder, and schizophrenia. According to OECD data, during the same years in Europe, at least 84 million people suffered from mental health conditions. This number corresponds to more than 1 in 6 people in the EU (17.3%). Anxiety-related mental health disorders involved almost 25 million people (5.4% of the total population in Europe), followed by depressive disorders (21 million people, 4.5%), and drug and alcohol disorders (11 million people, 2.4%) [47]. In 2023, 1 in 2 subjects (46% of the total population) had experienced emotional or psychosocial problems, such as feeling depressed or anxious, in the previous 12 months [48].

In the same years in Italy, the National Statistics Institute (ISTAT) reported that 3.7 million people suffered from anxiety–depressive disorders [49].

In our study, an increase in users who tested positive for benzodiazepines was observed from 4.26% (mean value in the five-year period of 2015–2019) to 6.72% (mean value in the four-year period of 2020–2023), with the highest incidence of users testing positive for BZDs in 2022 (7.37%; 200 positive-testing users out of 2714).

The pandemic period was associated with a 57.75% increase in the number of positive-testing users compared with the prior years, and it was strictly related to the increased number of users per year, from 1487 in 2017 to 2714 in 2022.

Nevertheless, we described uneven percentages of positive urine samples related to the total population via analysis per year. Concurrently, an increase in the number of self-reported benzodiazepine use (from one subject in 2015 to 152 in 2022 and 92 in 2023), was registered. The widespread availability of benzodiazepines and their relatively low cost increases the potential for the non-medical use of these medications [50].

Our data on the rate of use of benzodiazepines was compared with users who declared a medical use of benzodiazepines. An overall percentage value of 46.54% of users declared a therapeutic and prescribed use of benzodiazepines, with a minimum value in 2016 (13.16%) and a maximum value of 76.00% in 2022. On the other hand, we have no information about any medical treatment patterns or prescriptions for the remaining 53.46% of users.

Our study has several limitations due to the limited cohort studied, composed of licensed drivers over the age of 18, as well as the discontinuous trend of users, resulting in considerable variability in the collection of samples both monthly and yearly. However, the data collected during the 9-year observational period suggests the need for further investigations of this topic, potentially involving the distinction between therapeutic doses of BZDs within medical treatment contexts and the abuse of BZDs within recreational and/or illicit use.

Future studies will be carried out to better evaluate the impact of these drugs on driving ability through assessing their prevalence in road traffic accidents classified as occurring under the effects of alcohol and drugs (Articles 186 and 187 of the Italian Highway Code).

5. Conclusions

Our findings suggest a strong relationship between benzodiazepine use and driving-related risks. The chromatographic techniques used in our study were a valuable tool for monitoring impaired driving, and in the future, will also allow for the rapid and effective testing of many other substances with a potential for abuse.

People taking medications, such as BZDs, should be monitored because of their significant impact on driving ability. An assessment of the possible side effects of these drugs on driving performance should always be carried out, both in cases where they have been regularly prescribed with a specific therapeutic regimen and also in cases where their intake could be associated with recreational and non-medical use.

Author Contributions: Conceptualization, L.S. and F.M.; methodology, R.T.; software, L.R.; validation, F.V., C.R. and F.M.; formal analysis, L.S.; investigation, F.V.; resources, C.R.; data curation, L.R.; writing—original draft preparation, R.T. and L.S.; writing—review and editing, L.T.M.; visualization, L.S.; supervision, R.T.; project administration, L.T.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Analyses were conducted as suggested by the World Health Organization and in conformity with the ethical guidelines of the 1975 Declaration of Helsinki.

Informed Consent Statement: Approval by an institutional and/or licensing committee was not required since experimental protocols were not applied in this study. Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Edinoff, A.N.; Nix, C.A.; Hollier, J.; Sagrera, C.E.; Delacroix, B.M.; Abubakar, T.; Cornett, E.M.; Kaye, A.M.; Kaye, A.D. Benzodiazepines: Uses, Dangers, and Clinical Considerations. *Neurol. Int.* **2021**, *13*, 594–607. [CrossRef] [PubMed]
2. EMCDDA New Benzodiazepines in Europe—A Review. Available online: https://www.emcdda.europa.eu/publications/rapid-communications/new-benzodiazepines-europe-review_en (accessed on 27 June 2023).
3. World Health Organization (WHO). Mental Disorders. Available online: https://www.who.int/news-room/fact-sheets/detail/mental-disorders (accessed on 27 June 2023).
4. European Monitoring Centre for Drugs and Drug Addiction. *European Drug Report 2023: Trends and Developments*; European Monitoring Centre for Drugs and Drug Addiction: Lisbon, Portugal, 2023.
5. Public Health Scotland Rapid Action Drug Alerts and Response (RADAR). *Quarterly Report*; Public Health Scotland: Edinburgh, Scotland, UK, 2024.
6. SAMHSA. National Household Survey on Drug Abuse (NHSDA). Annual Report. 2020. Available online: https://www.samhsa.gov/data/ (accessed on 8 February 2022).
7. SAMHSA. National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Services Administration. Available online: https://www.samhsa.gov/data/report/2021-nsduh-detailed-tables (accessed on 4 January 2023).
8. Diversion Control Division; National Forensic Laboratory Information System. *NFLIS-Drug 2022 Annual Report*; U.S. Department of Justice, U.S. Drug Enforcement Administration: Springfield, VA, USA, 2023.
9. Airagnes, G.; Lemogne, C.; Renuy, A.; Goldberg, M.; Hoertel, N.; Roquelaure, Y.; Limosin, F.; Zins, M. Prevalence of Prescribed Benzodiazepine Long-Term Use in the French General Population According to Sociodemographic and Clinical Factors: Findings from the CONSTANCES Cohort. *BMC Public. Health* **2019**, *19*, 566. [CrossRef] [PubMed]
10. Torres-Bondia, F.; de Batlle, J.; Galván, L.; Buti, M.; Barbé, F.; Piñol-Ripoll, G. Trends in the Consumption Rates of Benzodiazepines and Benzodiazepine-Related Drugs in the Health Region of Lleida from 2002 to 2015. *BMC Public Health* **2020**, *20*, 818. [CrossRef] [PubMed]
11. Wu, C.-C.; Liao, M.-H.; Su, C.-H.; Poly, T.N.; Lin, M.-C. Benzodiazepine Use and the Risk of Dementia in the Elderly Population: An Umbrella Review of Meta-Analyses. *J. Pers. Med.* **2023**, *13*, 1485. [CrossRef]
12. Olfson, M.; King, M.; Schoenbaum, M. Benzodiazepine Use in the United States. *JAMA Psychiatry* **2015**, *72*, 136–142. [CrossRef] [PubMed]
13. Hockenhull, J.; Amioka, E.; Black, J.C.; Forber, A.; Haynes, C.M.; Wood, D.M.; Dart, R.C.; Dargan, P.I. Non-medical Use of Benzodiazepines and GABA Analogues in Europe. *Br. J. Clin. Pharmacol.* **2021**, *87*, 1684–1694. [CrossRef] [PubMed]

14. The Department for Drug Policies (DPA)—Presidency of the Council of Ministers. *Report on Drug Addiction in Italy in 2023 (Data Collected in 2022)*; The Department for Drug Policies (DPA)—Presidency of the Council of Ministers: Rome, Italy, 2022.
15. Gagliardi, J. Consumption-Rate-of-Benzodiazepines-by-Active-Ingredient-in-Italy. Available online: https://www.statista.com/statistics/914467/consumption-rate-of-benzodiazepines-by-active-ingredient-in-italy/ (accessed on 30 August 2023).
16. Gagliardi, J. Consumption Rate of Benzodiazepines in Italy 2022, by Region. Available online: https://www.statista.com/statistics/915561/consumption-rate-of-benzodiazepines-by-region-in-italy/ (accessed on 30 August 2023).
17. The Medicines Utilization Monitoring Centre. National Report on Medicines Use in Italy—Year 2022. Available online: https://www.aifa.gov.it/documents/20142/2143103/Rapporto-OsMed-2022_EN.pdf (accessed on 1 December 2023).
18. Colizzi, M.; Meneghin, N.; Bertoldi, A.; Lugoboni, F. Further Evidence on the Interplay between Benzodiazepine and Z-Drug Abuse and Emotion Dysregulation. *J. Affect. Disord. Rep.* **2021**, *6*, 100234. [CrossRef]
19. Ministry of Health. *Allegato 1—Riassunto Delle Caratteristiche Del Prodotto*; Supplemento ordinario alla GAZZETTA UFFICIALE; Ministry of Justice: Rome, Italy, 1999; pp. 7–24.
20. Thomas, R.E. Benzodiazepine Use and Motor Vehicle Accidents. Systematic Review of Reported Association. *Can. Fam. Physician* **1998**, *44*, 799–808. [PubMed]
21. Smink, B.E.; Egberts, A.C.G.; Lusthof, K.J.; Uges, D.R.A.; de Gier, J.J. The Relationship between Benzodiazepine Use and Traffic Accidents: A Systematic Literature Review. *CNS Drugs* **2010**, *24*, 639–653. [CrossRef]
22. Orriols, L.; Gbaguidi, G.N.; Contrand, B.; Gadegbeku, B.; Lagarde, E. Trends in Benzodiazepine Anxiolytics and Z-Hypnotics Use among French Drivers Involved in Road Traffic Crashes from 2005 to 2015: A Responsibility Case-Control Study. *Inj. Epidemiol.* **2019**, *6*, 32. [CrossRef]
23. Van der Sluiszen, N.N.J.J.M.; Vermeeren, A.; Verster, J.C.; van de Loo, A.J.A.E.; van Dijken, J.H.; Veldstra, J.L.; Brookhuis, K.A.; de Waard, D.; Ramaekers, J.G. Driving Performance and Neurocognitive Skills of Long-Term Users of Benzodiazepine Anxiolytics and Hypnotics. *Hum. Psychopharmacol.* **2019**, *34*, e2715. [CrossRef] [PubMed]
24. Dubois, S.; Bédard, M.; Weaver, B. The Impact of Benzodiazepines on Safe Driving. *Traffic Inj. Prev.* **2008**, *9*, 404–413. [CrossRef] [PubMed]
25. Longo, M.C.; Hunter, C.E.; Lokan, R.J.; White, J.M.; White, M.A. The Prevalence of Alcohol, Cannabinoids, Benzodiazepines and Stimulants amongst Injured Drivers and Their Role in Driver Culpability. *Accid. Anal. Prev.* **2000**, *32*, 623–632. [CrossRef] [PubMed]
26. Longo, M.; Lokan, R.; White, J. The Relationship between Blood Benzodiazepine Concentration and Vehicle Crash Culpability. *J. Traffic Med.* **2001**, *29*, 36–43.
27. Jones, A.W. Driving Under the Influence of Drugs in Sweden with Zero Concentration Limits in Blood for Controlled Substances. *Traffic Inj. Prev.* **2005**, *6*, 317–322. [CrossRef] [PubMed]
28. Van der Sluiszen, N.; Vermeeren, A.; Jongen, S.; Vinckenbosch, F.; Ramaekers, J. Influence of Long-Term Benzodiazepine Use on Neurocognitive Skills Related to Driving Performance in Patient Populations: A Review. *Pharmacopsychiatry* **2017**, *50*, 189–196. [CrossRef] [PubMed]
29. Smink, B.E.; Lusthof, K.J.; de Gier, J.J.; Uges, D.R.A.; Egberts, A.C.G. The Relation between the Blood Benzodiazepine Concentration and Performance in Suspected Impaired Drivers. *J. Forensic Leg. Med.* **2008**, *15*, 483–488. [CrossRef] [PubMed]
30. Verster, J. Effects of Alprazolam on Driving Ability, Memory Functioning and Psychomotor Performance A Randomized, Placebo-Controlled Study. *Neuropsychopharmacology* **2002**, *27*, 260–269. [CrossRef] [PubMed]
31. Pascali, J.P.; Vaiano, F.; Palumbo, D.; Umani Ronchi, F.; Mari, F.; Bertol, E. Psychotropic Substance Abuse and Fitness to Hold a Driving License in Italy. *Traffic Inj. Prev.* **2019**, *20*, 244–248. [CrossRef]
32. Office of Drug and Alcohol Policy and Compliance. *DOT Urine Specimen Collection Guidelines*; United States Department of Transportation: Washington, DC, USA, 2018.
33. Strano Rossi, S.; Frison, G.; Chericoni, S.; Bertol, E.; Favretto, D.; Pichini, S.; Salomone, A.; Tagliaro, F.; Vignali, C. Linee Guida per La Determinazione Di Sostanze Stupefacenti e Psicotrope Su Campioni Biologici Con Finalità Tossicologico-Forensi e Medico-Legali. *La Riv. Ital. Della Med. Lab.* **2023**, *19*, 192–205. [CrossRef]
34. Uddin, M.N.; Samanidou, V.F.; Papadoyannis, I.N. Bio-Sample Preparation and Gas Chromatographic Determination of Benzodiazepines—A Review. *J. Chromatogr. Sci.* **2013**, *51*, 587–598. [CrossRef] [PubMed]
35. Balon, R.; Starcevic, V.; Silberman, E.; Cosci, F.; Dubovsky, S.; Fava, G.A.; Nardi, A.E.; Rickels, K.; Salzman, C.; Shader, R.I.; et al. The Rise and Fall and Rise of Benzodiazepines: A Return of the Stigmatized and Repressed. *Braz. J. Psychiatry* **2020**, *42*, 243–244. [CrossRef] [PubMed]
36. Organisation for Economic Cooperation and Development (OECD). *Health at a Glance: Europe 2022*; OECD: Paris, France, 2022; ISBN 9789264462113.
37. Alabaku, O.; Yang, A.; Tharmarajah, S.; Suda, K.; Vigod, S.; Tadrous, M. Global Trends in Antidepressant, Atypical Antipsychotic, and Benzodiazepine Use: A Cross-Sectional Analysis of 64 Countries. *PLoS ONE* **2023**, *18*, e0284389. [CrossRef] [PubMed]
38. EMCDDA Spotlight On. . . Non-Medical Use of Benzodiazepines. Available online: https://www.emcdda.europa.eu/spotlights/non-medical-use-benzodiazepines_en (accessed on 27 June 2023).
39. Leung, S.Y. Benzodiazepines, Opioids and Driving: An Overview of the Experimental Research. *Drug Alcohol. Rev.* **2011**, *30*, 281–286. [CrossRef] [PubMed]

40. Morrow, A.L.; Paul, S.M. Benzodiazepine Enhancement of Gamma-Aminobutyric Acid-Mediated Chloride Ion Flux in Rat Brain Synaptoneurosomes. *J. Neurochem.* **1988**, *50*, 302–306. [CrossRef] [PubMed]
41. Volkow, N.D.; Fowler, J.S.; Gatley, S.J.; Logan, J.; Wang, G.J.; Ding, Y.S.; Dewey, S. PET Evaluation of the Dopamine System of the Human Brain. *J. Nucl. Med.* **1996**, *37*, 1242–1256.
42. Volkow, N.D.; Wang, G.J.; Fowler, J.S.; Hitzemann, R.; Gatley, S.J.; Dewey, S.S.; Pappas, N. Enhanced Sensitivity to Benzodiazepines in Active Cocaine-Abusing Subjects: A PET Study. *Am. J. Psychiatry* **1998**, *155*, 200–206. [CrossRef]
43. Maxwell, H.G.; Dubois, S.; Weaver, B.; Bédard, M. The Additive Effects of Alcohol and Benzodiazepines on Driving. *Can. J. Public Health* **2010**, *101*, 353–357. [CrossRef]
44. Appenzeller, B.M.R.; Schneider, S.; Yegles, M.; Maul, A.; Wennig, R. Drugs and Chronic Alcohol Abuse in Drivers. *Forensic Sci. Int.* **2005**, *155*, 83–90. [CrossRef]
45. Fiorelli, D.; Romani, L.; Treglia, M.; Pallocci, M.; Passalacqua, P.; Coppeta, L.; Marsella, L.T.; Tittarelli, R. Carbohydrate-Deficient Transferrin (CDT) as a Biomarker of Alcohol Abuse: A Retrospective Study of the Italian Drinking Trend among Drivers from 2016 to 2022. *Toxics* **2023**, *11*, 914. [CrossRef]
46. World Health Organization (WHO). COVID-19 Pandemic Triggers 25% Increase in Prevalence of Anxiety and Depression Worldwide. Available online: https://www.who.int/news/item/02-03-2022-covid-19-pandemic-triggers-25-increase-in-prevalence-of-anxiety-and-depression-worldwide (accessed on 27 June 2023).
47. OECD. *A New Benchmark for Mental Health Systems*; OECD: Paris, France, 2021; ISBN 9789264710139.
48. European Commission; Directorate-General for Communication. *Flash Eurobarometer FL530: Mental Health, Version v1.00*; Directorate-General for Communication: Brussels, Belgium, 2023; Available online: http://data.europa.eu/88u/dataset/s3032_fl530_eng (accessed on 21 May 2024).
49. The Italian National Institute of Statistics. *Mental Health at Various Stages of Life*; The Italian National Institute of Statistics: Rome, Italy, 2018.
50. Zaami, S.; Graziano, S.; Tittarelli, R.; Beck, R.; Marinelli, E. BDZs, Designer BDZs and Z-Drugs: Pharmacology and Misuse Insights. *Curr. Pharm. Des.* **2022**, *28*, 1221–1229. [CrossRef] [PubMed]