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[Review] Old and “New Designer” Benzodiazepines as Crime Facilitating Drugs: A Review of Toxicological and Analytical Aspects

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Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

Abstract

Introduction. Many crimes, especially of a sexual nature, are committed using sedative substances to reduce the victim's state of consciousness and reactivity and are defined as "drugs facilitated crimes". Among these, benzodiazepines (BDZ) and some new designer derivatives are widely used especially in liquid formulations added to other drinks. The purpose of this article is to analyze the chemical, toxicological and analytical characteristics starting from the alteration data and through in-depth analysis on dedicated databases.

Materials and methods. We conducted searches in PUBMED, PUBCHEM, CHEMID PLUS and GOOGLE SCHOLAR for papers and documents done on qualitative characteristics of the BDZ most commonly used as facilitating crimes. We have selected research articles and reviews from 2012 to 2022, with the primary endpoint relative to the typology of BDZ found in the samples examined in the various studies. We also researched their chemical and toxicological characteristics on the PUBCHEM and CHEMID PLUS international databases.

Discussion and conclusions. Benzodiazepines (BDZs) are among the most commonly used sedatives for illicit purposes, including their use to facilitate sexual crimes or robbery, alone or in co-administration with other substances, especially alcohol. In recent years there have been recorded cases of both classic BDZ intoxication, marketed as medicinal specialties, but also of new designer BDZs such as cinazepam, flualprazolam or phenazepam, less easily detectable in first-level toxicological tests and often much more potent than other more commonly used compounds. The analytical techniques in use, especially the first-level assays used in triages, can sometimes fail to cross-react and make these molecules invisible which, even in the most sophisticated confirmation tests such as techniques combined with mass spectrometry, do not always make these new psychoactive substances detectable.

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Keywords: drugs facilitated crimes, new psychoactive substances, benzodiazepines, designer drugs, forensic toxicology.

Introduction

Any criminal action in which an incapacitating agent is used to assist the perpetrator in committing the crime can be classified as "drug facilitating crime"; typically these include, in particular, sexual assault, robbery and other similar acts.[1] The incapacitating agent It is generally administered to the victim who involuntarily ingests it without immediately analyzing the consequences.[2] Sometimes victims are misled as to the true identity of the drug before consuming it. The media have described so-called drink spiking as a popular means by which a perpetrator secretly drugs his victims.Drug facilitated crimes present several challenges for forensic toxicologists and one is the large number of drugs that can be used in these crimes[3] Despite the popular belief that only two or three drugs serve as the primary chemical submission agents, any substance that depresses the central nervous system can be used.[4] They may also be co-ingested with one or more other CNS depressants like alcohol; the resulting effect can be severe, at times mimicking a general anesthesia, making the victim vulnerable and / or unable to consent to a sexual act.[5] The society of forensic toxicologists lists over 100 drugs that should be used.[6] Is important to recognize that most drugs facilitating crimes are not reported to law enforcement because victims are often incapable.[7] When drugs are used, it is not surprising that even fewer are reported due to the victim's uncertainty of many of the key aspects of the crime.[8] Because of the many challenges related to the toxicological analyzes in these cases, negative findings alone should not be used to rule out the occurrence of a crime.[9]

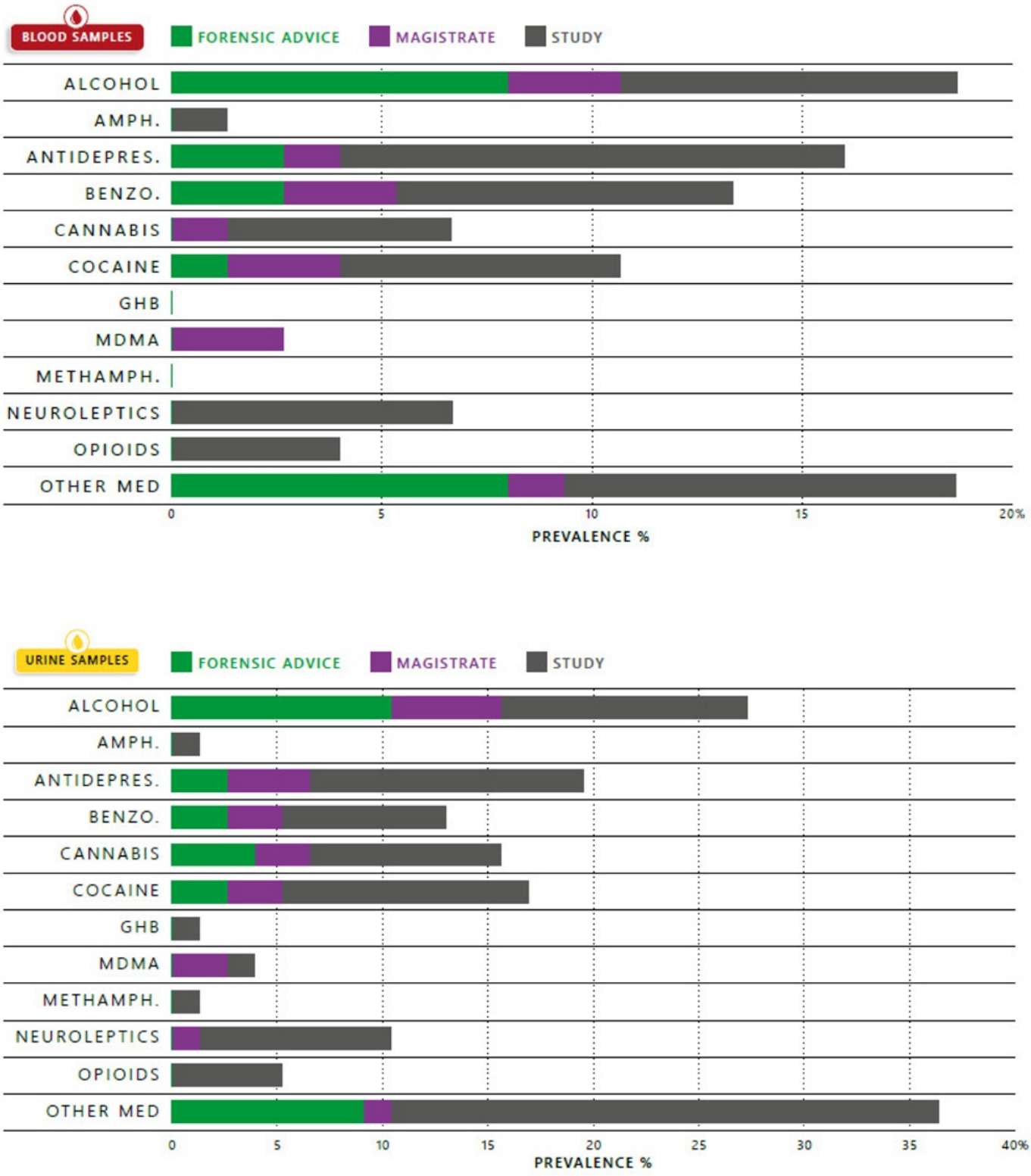

Figure 1. Prevalence of compounds in blood and urine samples indicated in percentage. FA: samples selected via forensic advice (n = 15); MAG: samples selected via magistrates (n = 13); study samples (n = 51); Amph: amphetamine; Antidepres: antidepressants; Benzo: benzodiazepines, Methamph: methamphetamine; Other Med: other medication—painkillers, heart-medication, anti-histaminics, antibacterial or antifungal medication, methylphenidate, diabetic medication. From: "The Interest of a Systematic Toxicological Analysis Combined with Forensic Advice to Improve the Judicial Investigation and Final Judgment in Drug Facilitated Sexual Assault Cases" (**doi.org/10.3390/ph14050432**)

Figure 1 lists the main substances that are found in the biological matrices of victims subjected to drugs: in this article we

want to focus on the characteristics of benzodiazepines (BDZ) and "Z-drugs", which as shown in the figure are at the top of the list. terms of use.[7] Benzodiazepines are one of the most prescribed drug classes in the world and therefore it is not surprising that they are commonly found in drug-facilitated crime victims.[10] Furthermore, the popularity of some Z drugs such as Zolpidem has meant that these are also frequently found in these cases. BDZs show pharmacological characteristics that make them very useful in those who want to commit crimes by sedating victims:

- easy to find in the legal and illegal market
- availability of liquid formulations, often themselves added to ethanol as an excipient and therefore easy to add to cocktails and alcoholic beverages without the victim being aware of it[11]
- high potency and rapidity of action of some of these compounds, which also have a short half-life and therefore rapid elimination after a few hours
- high therapeutic index with very limited risk of death from overdose
- ability to induce anterograde amnesia for many of them, with difficulty or inability to recall the exact events in the hours preceding intoxication[12]

In this article we want to describe the toxicological and analytical aspects of some compounds among those most detected in these poisonings. Starting from their chemical structure, we will focus in particular on the toxicological characteristics, stability in biological matrices and the main analytical instrumental methods used.[13]

Materials And Methods

We conducted searches in PUBMED, PUBCHEM, CHEMID PLUS and GOOGLE SCHOLAR for papers and documents done on the pharmaco-toxicological characteristics of the BDZ most commonly used as facilitating crimes. We have selected research articles and reviews from 2012 to 2022, with the primary purpose of evaluating which classes of compounds belonging to the BDZ genus are most frequently found in these cases, also including those belonging to the new psychoactive substances. A secondary endpoint was the frequency, in addition to the type, with which these substances were found in the cohorts examined. We also researched their chemical and toxicological characteristics on the PUBCHEM and CHEMID PLUS international databases. The stability characteristics in biological matrices and the detailed methodologies used for the purposes of laboratory analyzes are not covered in this article but the latter will be mentioned anyway.

Discussion

Benzodiazepines (chemical general structure in figure 2) and Z-drugs (zolpidem, zaleplon and zopiclone) are one of the most widely prescribed classes of drugs and it’s not surprising that they are also common findings in drug-facilitated crimes.[14] They, alone or in combination with other CNS depressants, can cause anterograde amnesia as well as complete unconsciousness.[15]

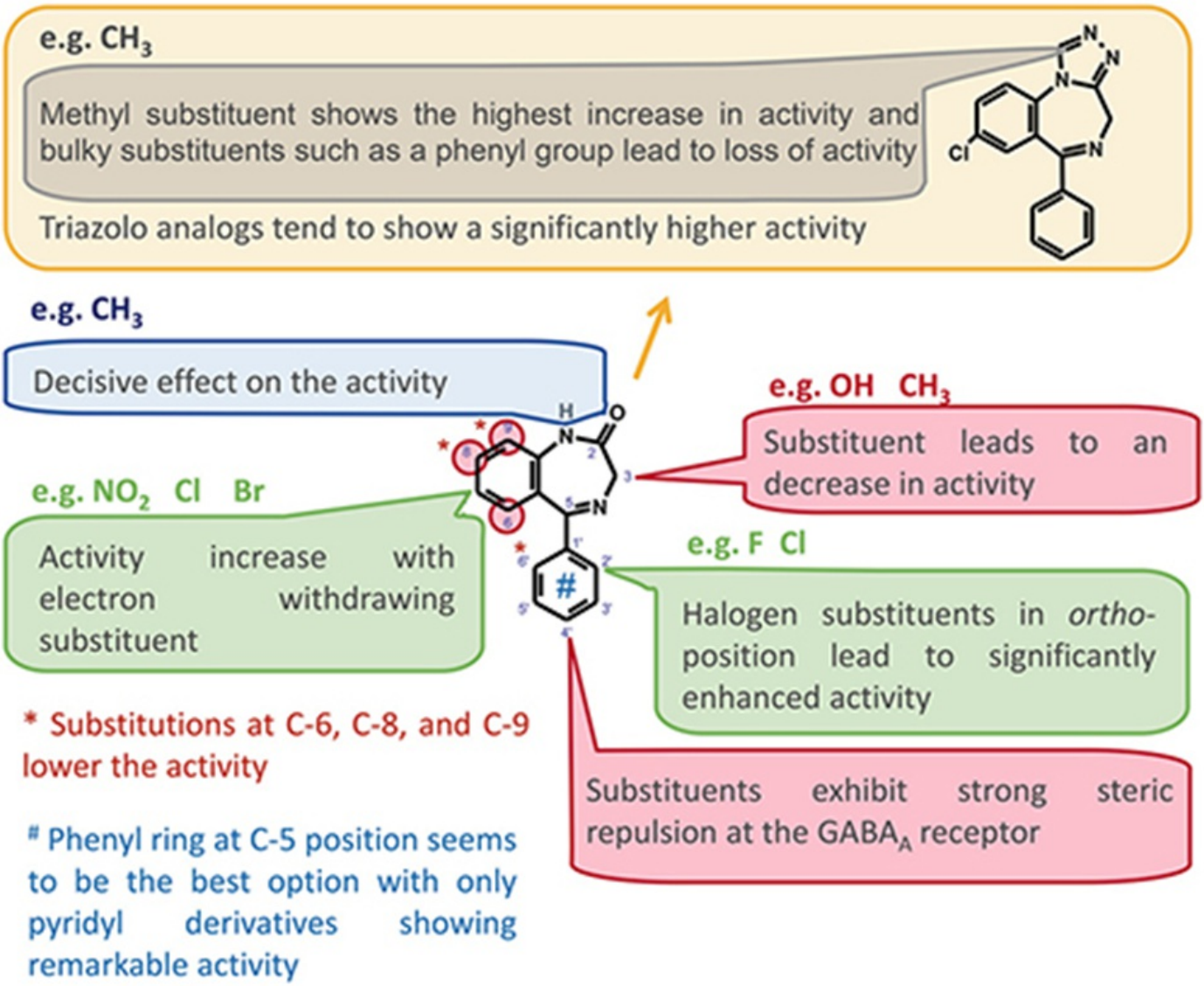

Figure 2. chemical structure-activity relationship of benzodiazepines: the basic structure is the combination of a benzene ring with a seven member diazepine ring with a phenyl ring in the 5- position of the diazepine.

Currently, approximately 30 BDZ (available in over 300 pharmaceutical packages, including generic and in various formulations, liquid and solid "fast" and "retard") are approved in Italy and prescribed as anxiolytics, muscle relaxants, antiepileptics, anesthetics adjuncts and hypnotics.[16] To these traditionals, in recent years, 'legal / designer BZDs' have recently emerged in the drug (mainly online / virtual) market (Figure 3). First designer BZDs appeared as NPS around 2007.[17] So far, 29 designer BZDs have been notified to the EMCDDA, being some of them extremely powerful, also at lower dosages. They are sold as tablets / powder / pellets / capsules / blotters / liquids, at very affordable prices, and variably administered. Some are also sold on the illicit drug market as counterfeit forms of traditional BZDs or as either adulterants or diluents in heroin or other synthetic opioids / cannabinoids.[18]

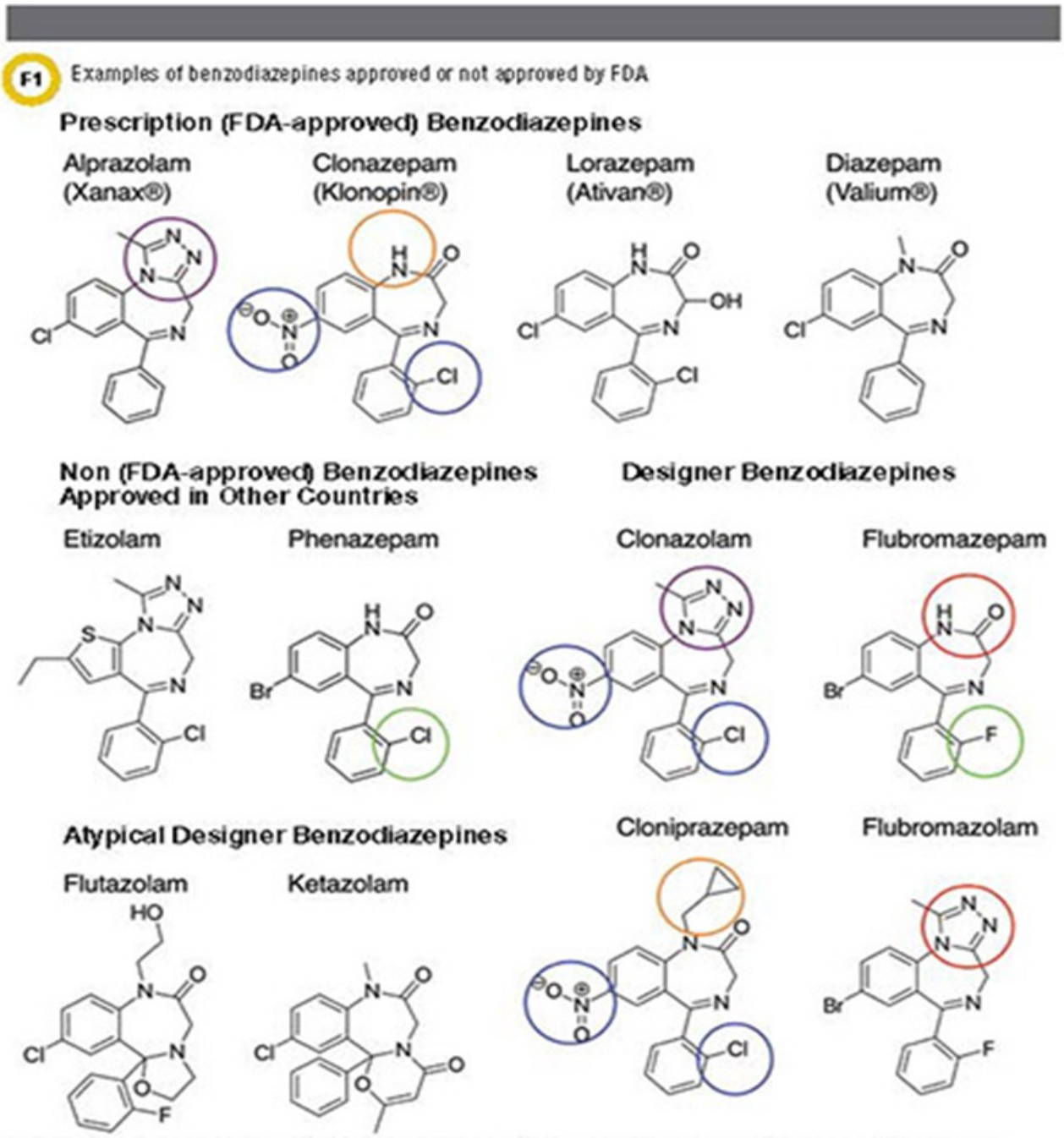

Figure 3. A few examples of old and new BDZ Cloniprazepam is metabolized into clonazepam by the removal of the cyclopropylmethyl group (circled in orange). Clonazolam can be considered a hybrid of clonazepam (functional groups circled in blue) and alprazolam (triazolo group circled in purple). Similarly, flubromazolam is a triazolo analog of flubromazepam (difference circled in red). Flubromazepam only differs from phenazepam by the substitution of the chlorine group by fluorine (circled in green). Adapted from Marin *et al.*

Starting from the basic chemical structure, potency can be improved by adding an electron- withdrawing group in the ortho-position on the phenyl ring (R2') (i.e. lorazepam, clonazepam, flunitrazepam), with also a greater amnestic effect. Other structural modifications are possible and can affect both potency and duration of action.[19] BDZ with smaller substituents on position N1 tend to have higher intrinsic activity; however some drugs with larger N1 substituents are effective (like flurazepam), largely due to metabolic dealkylation to an active metabolite.[20] Some of the newer "designer"

BDZ involve the replacement of the phenyl ring with a pyridine (like pyrazolam) or replacement of the benzene ring with thiophene ring (i.e. etizolam).[21] In addition to the therapeutic use, they can produce sedative and amnestics effects: an intravenous dose of short acting BDZ assists in the induction of surgical anesthesia. In a recent review by Skov *et al.*[22] on Drug-facilitated sexual assault (DFSA), with a total of 22 studies included, covering toxicological findings in DFSA cases in North America, Europe, Asia, South Africa and Australasia, a variety of benzodiazepines were observed, with the most common being diazepam, clonazepam, alprazolam, and oxazepam.[23] The majority of cases involved women (87% -100%). Specifically, hypnotics were found in 10 studies primarily as zopiclone or zolpidem. Benzodiazepines were detected in all studies with a range from 3.5% to 82% of total cases.[24] In Europe, benzodiazepines were detected in 5.1% to 82.0% of cases and the most frequently detected benzodiazepines and hypnotics were diazepam, alprazolam, oxazepam, clonazepam, temazepam, and zolpidem.[25] In Asia, it was nimetazepam, flunitrazepam, clonazepam, lorazepam, and the designer benzodiazepines diclazepam and flualprazolam. In the United States, it was oxazepam, diazepam, clonazepam, alprazolam and lorazepam. Lastly, lorazepam was the most common benzodiazepine detected in Canada, while diazepam was the most common found in Australia and New Zealand. In another review conducted by Xiang *et al.*[26] Hair concentrations of 35 psychoactive drugs given in 20 controlled dose studies are reviewed and compared to the 25 different drugs detected in reported case work. The most common drugs were benzodiazepines and related hypnotics and gamma-hydroxybutyrate (GHB), followed by ketamine and methamphetamine.[27] Those concentrations reported in DFC were mostly similar or higher than that seen in controlled dose studies. Similarly, a systematic review was undertaken to determine the current global prevalence of DFSA reported in adults in order to identify trends in the toxicology findings in DFSA around the world over the past 20 years, by Anderson *et al.*[28] The majority of studies included were published in the United States, followed by the United Kingdom, with only a single study dedicated to this area in both Australia and Europe.[29] Nonetheless, alcohol is the most commonly detected substance and co-occurrence with other drugs is common.[30]Aside from alcohol there was no other specific drug category associated with DFSA. Cannabinoids and benzodiazepines were frequently detected, but a lack of contextual information made it difficult to establish the extent that these substances contributed to suspected cases of DFSA. From both studies it is interesting that:

- alprazolam, diazepam, zolpidem and lorazepam are the absolute BDZs with the highest prevalence of use in these contexts[31]
- the emergence of many "BDZ designers" such as etizolam, cinazepam, fluorinated compounds (flualprazolam / flubromazepam), diclazepam, phenazepam and pyrazolam.[32]

The role of flunitrazepam (Roipnol®, Darkene® and others) should not be forgotten, now reduced, at least in Italy, by its arrangement in section A of the table of narcotic drugs, thus requiring a similar prescription and now no longer in use. Indeed, flunitrazepam was specifically associated with several cases of misuse and diversion with intent to use as a DFSA.[33]

Table 1. Chemical-toxicological characteristics of the compounds described in the studies

Alprazolam, an intermediate-acting triazolo-BDZ, has a potency about more than 20 times that of diazepam. Following oral administration, it is well absorbed with a bioavailability of 90% and is metabolized to alpha-hydroxyalprazolam and 4-hydroxyalprazolam by CYP3A4. Almost all of a single dose of alprazolam is excreted within 72h.[34] **Diazepam** is a long-acting 1,4-BDZ with an oral bioavailability about 100%; following administration is demethylated to form its primary active metabolite, nordiazepam, which accumulates in plasma.[35] The CYP2C19 and CYP3A4 enzymes mediate the demethylation of diazepam with the formation of oxazepam and temazepam.[36] The oxazepam glucuronide and the conjugation of temazepam, nordiazepam and oxazepam is the main mode of elimination. **Lorazepam** is also an intermediate-acting BDZ with a primary metabolic pathway of inactive glucuronide conjugate formation. Approximately 75% of a lorazepam dose is eliminated over 5 days as lorazepam-glucuronide in the urine and only a small amount of the drug is eliminated unchanged.[37] LORAZEPAM CAN BE DIFFICULT TO DETECT AS MOST COMMERCIALLY AVAILABLE IMMUNOASSAY SCREENING TESTS DON'T HAVE HIGH CROSS-REACTIVITY TO THIS DRUG. There are some BDZs that are more frequently found in post-mortem toxicological contexts or of subjects intoxicated after crimes of abuse or violence, which make these drugs a greater probability of illicit use than therapeutic ones.[38] **Temazepam** is a hypnotic agent indicated for the short-term treatment of insomnia (in Italy it is not available for medication use). Ix a white crystalline powder with a bioavailability of about 100% after oral administration). The major metabolic pathway for temazepam is glucuronidation and a smaller amount of oxazepam and its glucuronide is formed.[39] **Etizolam** is a thieno-triazolo-BDZ analog that is approved for clinical use, with an half-life of 7-15 hours and an extensive metabolism by hydroxylation and glucuronidation. The major phase 1 metabolite (hydroxyetizolam) significantly contributes to the CNS- depressant effects of the drug, due to its approximately equipotent pharmacological activity and longer life than etizolam.[40] **Phenazepam** is a BDZ that was developed in the Soviet Union in the 1970s and has been used in Russia to treat insomnia. Today is not approved in Europe and in the USA but is frequently used illicitly. After oral ingestion, the peak plasma concentration occurs at 4 hours and has a longer half-life than most BDZ (like 60 hours). Its main phase 1 metabolite, 3-hydroxyphenazepam, is also psychoactive.[41] **Pyrazolam** (Figure 4) is another designer-BDZ that in 2012 appeared on the illicit drug market. Is structurally similar to alprazolam, with pyrazolam having a bromine atom on the benzene ring of the benzodiazepine nucleus instead of chlorine and a pyridine ring instead of a benzene ring on C6 of the diazepine ring. The presence of the strong electron-withdrawing groups again leads to the potency of pyrazolam. Surprisingly, no excreted metabolites have been identified. [42]

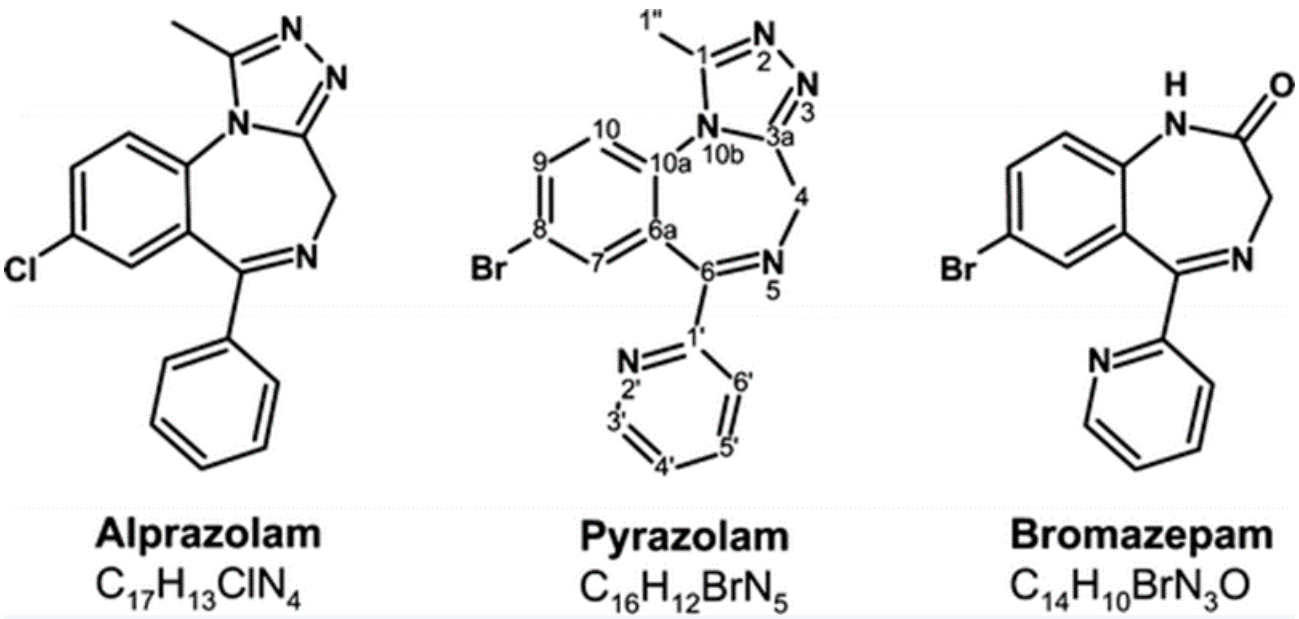

Figure 4. Chemical structures of some BDZ (note the comparison between alprazolam and pyrazolam, where the differences are the halogen substituent of the first ring and the nitrogen on the phenyl ring which makes it heterocyclic)

Regarding the detection methods, the use of mass spectrometry (Figure 5) combined with chromatographic techniques remains the reference method for confirmatory analyses. A study by Costa *et al.*[43] remembers how the use of LC-MS / MS for analysis of benzodiazepines in hair is recommended by UNODC. It also recommends the analytical laboratories efforts in detection of benzodiazepines in urine, considering the common use of this drug class in DFSA cases.[44] Several methods using LC-MS / MS have already been validated, differing as to the sample extraction procedure and the limits of detection. Quintela *et al.* 58 adopted a solid-phase extraction with a mixed-mode phase, reaching LODs lower than 0.05 µg / L, while Solomon *et al.* 59 obtained LODs ranged from 0.5 to 30 µg / L, using an enzymatic hydrolysis and liquid-liquid extraction in sample preparation.[45] Magalhaes *et al.* 60 adopted a method of extraction based on liquid-liquid extraction

with low-temperature partitioning and analysis using liquid chromatography combined with high-resolution mass spectrometry, obtaining LODs for benzodiazepines in urine lower than 5 µg / L.[46] The use of immunoassay methods for screening benzodiazepines in biological matrices of DFSA victims can be adopted as long as the cut-offs informed by the manufacturer are higher than those recommended in DFSA investigations or with the revalidation of the method for lower cut-offs.[47]

Figure 5. An example of a GC-MS instrument (tandem mass spectrometer with chromatography instrument)

Conclusions

Benzodiazepines (BDZs) are among the most commonly used sedatives for illicit purposes, including their use to facilitate sexual crimes or robbery, alone or in co-administration with other substances, especially alcohol.[48] In recent years there have been recorded cases of both classic BDZ intoxication, marketed as medicinal specialties, but also of new designer BDZs such as cinazepam, flualprazolam or phenazepam, less easily detectable in first-level toxicological tests and often much more potent than other more commonly used compounds.[49] The analytical techniques in use, especially the first-level assays used in triages, can sometimes fail to cross-react and make these molecules invisible which, even in the most sophisticated confirmation tests such as techniques combined with mass spectrometry, do not always make these new psychoactive substances detectable.[50] In addition to the need for more sensitive and specific analysis techniques, there is also the need to expand the monitoring and control of the marketing of these compounds, some of which are sold

as medicinal specialties in European and non-European countries, and in particular to implement controls in places of aggregation such as discos where these substances are more often used.[51]

Declarations

- **Ethics approval and consent to participate:** nothing to declare.
- **Consent for publication:** all authors have consented to the publication.
- **Availability of data and material:** nothing to declare.
- **Competing interests:** the authors declare that they have no conflicts of interest
- **Funding:** the authors declare that they have not received funds for the writing of this article.
- **Authors contributions:** all authors contributed to the writing of this article. E.M. had the initial idea and developed both the introduction and the conclusions while A.M., N.M., C.M. and A.C. developed materials and methods and all authors contributed to writing the discussion. C.T. supervised all the work and in particular the discussion part.
- **Acknowledgements:** nothing to declare.

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