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BDZs and Z-drugs: pharmacology and misuse insights

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Abstract: Benzodiazepines (BZDs) are a widely prescribed class of sedative-hypnotics compounds for the treatment of a broad range of conditions as anxiety and obsessive-compulsive disorders, phobias, sleep related problems associated with insomnia and for the management of alcohol and GHB withdrawal.

Zolpidem, zopiclone and zaleplon, commonly known as Z-drugs are non-benzodiazepine hypnotic drug with pharmacology similar to BDZs. Despite their usefulness, BDZs and Z-drugs present a potential for abuse and dependence. Moreover, the non-medical use of BDZs is a well-known phenomenon and represents an increasingly widespread public health problem since is associated with an elevated risk of serious health consequences or fatal overdose, especially among specific group of users. The spectrum of BDZs and Z-drugs misuse is extended by new synthetic BDZs, which may pose high risks to users, since the majority have never undergone clinical trials or tests and consequently their pharmacology and toxicology is largely unknown.

Keywords: BDZs, Z-drugs, new BDZs, diversion, abuse, misuse, pharmacology

1. INTRODUCTION

Benzodiazepines (BZDs) are a widely prescribed class of sedative-hypnotics compounds for the treatment of a broad range of conditions as anxiety and obsessive-compulsive disorders, phobias, sleep related problems associated with insomnia and for the management of alcohol and GHB withdrawal [1, 2].

BDZs were discovered in the mid-1950s and quickly replaced previous sedative-hypnotics medications such as chloral hydrate, meprobamate and barbiturates, because of their high safety profile [1]. Compared to other drugs, BZDs were considered harmless, with a low toxicity profile and less side effects, so during the 1960s and early 1970s their use dramatically increased worldwide. Despite the usefulness of BDZs, their potential abuse and dependence was discovered as early as 1967 and they were placed as controlled substance on the Food and Drug Administration (FDA) restricted list in 1975 [2]. In the 1980s, long-term BDZs users became aware that the efficacy of these drugs decreased over the course of time and many patients noticed multiple adverse effects and reported that it was difficult to stop taking BDZs due to the onset of a pharmacological and physiological dependence. Controlled clinical trials confirmed that withdrawal symptoms reported by patients were authentic, and that these compounds could produce pharmacological dependence leading to addiction in long-term users [4].

In the late 1980s the introduction of the selective serotonin reuptake inhibitors (SSRi) that were safer, more effective and better tolerated than BDZs, led to a gradual decrease in BDZs prescription.

Although BDZs were indicated for a short treatment of 2-4 weeks [5], physicians continued to prescribe them for months or years: this situation resulted in an increasing trend in BDZs long-term consumption between 1999 and 2014 and a sharp rise of users with drug tolerance and withdrawal syndrome occurred [6-8].

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According to the National Institute on Drug Abuse (NIDA) data obtained from 102,000 adults who participated to the National Surveys on Drug Use and Health in the 2015-2016, about 30.5 million people used BDZs in USA (12.5% of adult population) and among BDZs users 17.1% misused them at least once and fewer than 2% presented benzodiazepine use disorders [9]. Donoghue *et al.*, by the analysis of the surveys about BDZs use reported in the scientific literature reviewed data from UK, Europe and North America, highlighted that the long-term use of BDZs is widespread in all the countries, and despite the exhortations to limit their use often represents the normal intake. The study also shows that official recommendations are often ignored and the prescription of these drugs sometimes occurs without following the guidelines and without evaluating the real risk/benefit ratio [10].

In addition to prescribed BDZs users, there is a subpopulation of subjects at risk for an inappropriate use of these medications, as polydrug abuse (mainly co-abused with alcohol, opiates or cannabis), or their recreational consumption [4].

The non-medical use of BDZs represents an increasingly widespread public health problem: the available information is limited as few countries reported data on this issue, but according to the World Drug Report 2019 in South and Central America more than 2 per cent of the population misused tranquilizers. In North America, the non-medical use of sedative and tranquilizers in 2017 was the 0.2 per cent of the adult population (older than 15 years) and in Western and Central Europe it ranged from 19.5 per cent in Czechia to less than 1 per cent in Portugal [11].

Recently, according to the data reported by the United Nations Office on Drugs and Crime (UNODC) there has been an increase in counterfeit BDZs in the illegal drug market with the rise of designer BDZs, new psychoactive substances not approved for their use in the pharmaceutical industry due to their safety profile or low degree of efficacy [12]. These fake or diverted medicines, together with the self-administration of BDZs for recreational purposes, represent an international concern frequently associated with abuse, dependence and with a growing number of accesses in the Emergency Departments for adverse events (falls, fractures, road accidents and cognitive impairment) [13] and overdose-related deaths due also to the illicit and uncontrolled trade of these compounds.

1.1. BDZs structure and mechanism of action

BDZs are a class of two-ring heterocyclic compounds whose core chemical structure is constituted by the fusion of a benzene and a 7-member diazepine ring with different side chains that affect the binding ability of the molecules to the gamma-aminobutyric acid A (GABAA) receptors modulating the pharmacological (e.g., potency and duration of the effects) and the pharmacokinetics (e.g., distribution, rate of elimination) properties [14].

The GABAA receptors are the major inhibitory neurotransmitter receptors of the central nervous system, mainly distributed at the neuronal synapses. After the BDZs binding, GABAA receptor undergoes conformational variations with an increase of GABA affinity for its binding site, increasing the total flow of chloride ions across the neuronal cell membrane with a consequent hyperpolarization of the neuron and a decrease of the neuronal ability to generate an action potential with consequent inhibitory effects [15, 16].

BDZs are the only drugs that enhance GABA affinity for its binding site acting as positive allosteric modulator: so BDZs do not provide a higher activation respect to GABA itself and this explains their elevated therapeutic index and the low risk of respiratory depression, unlike barbiturates that act directly on the GABA system maintaining chloride channels opened and increasing the risk of toxicity [14, 16].

BDZs tolerance is the result of complex neuroadaptive changes, and it develops as the consequence of their chronic or long-term use that lead to multiple adaptive processes as compensating variations in subunit expression and GABAA receptor coupling (e.g., uncoupling of the allosteric linkage of BDZ-GABA receptor complex), intracellular alterations (e.g., changes in receptor subunit turnover) and changes in neurotransmitter system (e.g., glutamatergic system) [17, 18]

The development of tolerance and the presence of withdrawal symptoms are both signs of physical and psychological dependence whose onset is also related to the dosage and potency of the drug and to the duration of therapy [19].

The onset of tolerance is often associated with an increase in the number of self-administrations which may be nearly undetectable and therefore confused with an appropriate use of the drug [20].

In some cases the patients take BDZs in combination with alcohol to achieve the desired therapeutic effects due to tolerance while others get diverted medications from the illicit prescription drug market, often provided by other patients [17].

1.2. Diversion of Prescription BDZs

1.2.1. Epidemiological Data

Misuse of prescription drugs means using a medication in an uncommon way (e.g., in combination with alcohol) or with a different dosage than prescribed for recreational purposes or to moderate the side effects of other drugs [17].

BDZs misusers or abusers obtain extra medications both by legitimate means (healthcare-related sources) and from the black market (e.g., street dealers, theft from hospitals, clinics or pharmacies, altered prescriptions, illicit trading or sharing with friends or family members) or through the Internet [21].

The most widespread healthcare sources of BDZs diversion are represented by script doctors (the prescriptions are issued by the physicians after a fee or provided by pharmaceutical suppliers), doctor shopping (simultaneous visits to several physicians for multiple prescriptions) and pharmacy diversion (medications theft by pharmacy staff or undercounting of pills) [17, 21, 22].

Although BDZs diversion is widespread worldwide, it is still difficult estimating the magnitude of the issue mainly due to the lack of monitoring and data collection systems that would be able to provide precise estimates of the extent and distribution of the problem.

In the United States, alprazolam is not only the most frequently prescribed benzodiazepine [23] but one of the three most diverted medications as well. In 2011, the Drug Enforcement Administration (DEA) stated that almost 40,000 alprazolam reports were produced by federal, state, and local forensic laboratories.

In the UK, the diversion of benzodiazepine prescriptions is also a widespread phenomenon and the Medicines and Healthcare products Regulatory Agency (MHRA) in 2016 carried out extensive investigative activities that led to the dismantling of an illicit prescription drug diversion network involving drug wholesalers and even some pharmacies [12].

The UNODC World Drug Report 2019 has reported interesting information about the global manufacturing and the seizures of BDZs carried out in recent years all over the world [11].

In 2016 the licit production of BDZs was reported by 21 countries. In 2017 Italy, India, China and Brazil were responsible together of more than 85 percent of global benzodiazepine manufacturing. The most legally produced BDZs in 2017 were diazepam with 47 tons, chlordiazepoxide (19 tons), and oxazepam (14 tons): these drugs were also the most used for medical purposes. Alprazolam together with diazepam were among the most counterfeited medications, often sold in the illicit drug market at very low prices with an increased risk of overdose due to the variable dosages and the presence of contaminants [24].

The illegal market is also involved in the BDZs diversion. The data related to the global quantities of BDZs seized from 2010 to 2017 has highlighted that most of the seizures were carried out in 2010 and 2015 in Asian territory and involved mainly alprazolam, nimetazepam, and diazepam. In 2016 the most seizures were carried out in Africa and involved mainly diazepam (6.3 tons), whereas in 2011, 2014 and 2017 the highest seizure rate was observed in the Americas, with nimetazepam and alprazolam as the most seizure substances [11].

Several clandestine laboratories illicitly manufacturing alprazolam have been recently dismantled in North America, Canada, India and Sweden. In 2011 and 2015 in Malaysia, East and South-East Asia clandestine laboratories producing nimetazepam, were discovered and seized [12].

1.2.2. Misuse Liability

The use of BDZs for non-medical purposes frequently co-occurs with other substances in a framework of poly-abuse: BDZs are often taken with opiates, amphetamines, cocaine and alcohol to enhance the drug effects, to get high or to be helpful with the 'come down' of stimulants or to relieve withdrawal symptoms [25].

These methods of abuse are associated with an elevated risk of serious health consequences or a fatal overdose, as occur with opioids. High-risk opioids users typically misuse BDZs orally, by snorting or by injection for self-medication or to manage the effects of the drug, exposing themselves to fatal interactions that can lead to decease [16, 26].

Diazepam, temazepam, lorazepam and alprazolam, are the substances most associated with misuse because of their pharmacokinetic and pharmacodynamic properties [19, 27, 28].

In fact, these BDZs are highly volatile and soluble in water (promoting the vaporization for smoking or the dissolution in water for intravenous administration) with a fast onset and brief duration of action, high potency and ability to cross the blood-brain barrier to obtain the most reinforcing effects.

Conversely, oxazepam, clorazepate and chlordiazepoxide appear to have lower reinforcing effects due to their scarce lipid solubility and low ability to cross the blood-brain barrier [19].

The potential misuse of alprazolam is probably related to its pharmacokinetic characteristics of low lipophilicity, short half-life and rapid onset of action; moreover, if compared to diazepam, it has a greater abuse potential because of its rapid metabolism and shorter duration of action. Alprazolam abuse potential is also due to its dopaminergic activity in the striatum that leads to an increase in extracellular dopamine concentrations with consequent stimulatory effects [23, 29, 30].

Although BDZs are rarely identified on their own as the cause of death in post-mortem toxicological investigations, there is evidence that they are involved in a large number of deaths recently occurred and induced by the concomitant use of opioids in North America and Europe [12]

Drug overdose related deaths involving BDZs in the United States reflect the latest trends exposed by UNODC in the Global SMART Update report, as the number of cases rose from 1,135 in 1999 to 11,537 in 2017 and from 2014 a continuous increase in death cases related to the concomitant use of opioids and BDZs has been observed [31].

The National Statistics of Scotland reported that BDZs were involved in, or potentially contributed to, 792 deaths (67%) in 2018. Moreover, the 57 per cent of all the drug-related deaths of the year (675 cases) were induced by "street" BDZs (e.g., etizolam, diclazepam and phenazepam). Prescribed BDZs were involved in fewer cases (238, approximately the 20 per cent of the total cases), most of which caused by diazepam misuse [32].

Polydrug abusers often misuse prescribed BDZs together with other drugs, mostly opioids and cannabis, and data reported by the emergency departments of ten European countries (belonging to the European-Drug Emergencies Network, Euro-DEN) from October 2013 to March 2014, revealed that the 22.8 per cent of the clinical cases involved cannabis use in combination with BDZs [12].

In Europe, BDZs with rapid onset of action, as diazepam, clonazepam, alprazolam, are more frequently related to deaths among the high-risk opioids users rather than slower BDZs as oxazepam and flunitrazepam, according also to their availability, legal status and costs [26].

In France, a shift in the use of substances was observed after limiting prescriptions for flunitrazepam with a consequent increase in clonazepam abuse [33].

Similarly, in the United Kingdom the restrictions of temazepam led to an increase in the spread of diazepam and so-called Z-drugs (e.g., zaleplon, zolpidem, zopiclone), together with a rapid rise in the use of phenazepam and etizolam, which were not initially under legal control [26, 34].

1.3. Z-drugs structure and binding activity

Zolpidem, zopiclone and zaleplon, commonly known as Z-drugs are non-benzodiazepine hypnotics advised for the short-term management of insomnia and anxiety.

Although Z-drugs are structurally different to BDZs, they share an analogous mechanism of action [35].

Like BDZs, they are agonists of the GABAA receptor complex and enhance GABA-mediated neuronal inhibition, but contrary to them, Z-drugs seem to have lower incidence of adverse effects as risk of abuse potential, withdrawal and next day sedation due to their improved pharmacokinetic profile (shorter half-life and duration of action) and their binding selectivity [35-37].

Zolpidem, was used in Europe as hypnotic agent by 1988 and approved by the US FDA in 1992. It belongs to the imidazopyridine class and it is recommended for the short-term treatment of insomnia related to sleep latency and sleep maintenance [35, 39].

Zolpidem is a full agonist for the benzodiazepine component of the GABAA receptor complex (α1-subtype) and it works by increasing the inhibitory neurotransmitter GABA resulting in sedation, anti-anxiety activity. It is characterized by a quick onset of action and a short elimination half-life (2.5 hours) [39].

Unlike the other Z-drugs, zolpidem has a greater ability to cause tolerance and dependence, and its spectrum of adverse events is comparable to BDZs when it is taken at higher doses than recommended, for long term treatments, or chronically as self-medication [40]. Additionally, zolpidem can be associated with complex behaviors and paradoxical reactions such as sleepwalking, sleep-driving, hallucinations, hyperactivity, vivid dreams, sexual disinhibition, anxiety and aggression [41].

Zaleplon is a quick-acting pyrazolopyrimidine compound with a fast onset, extremely short half-life (1 hour) and no active metabolites, used for the treatment of middle-of-the-night insomnia, that is characterized by difficulties in falling asleep or waking during the night without the risk of daytime hangover [35, 42-44].

Zalepon efficacy is similar to triazolam and zolpidem, but withdrawal symptoms and rebound effects, as the residual daytime sedation, have not been observed in patients. The lower affinity of binding to the subtype alpha-1 BDZ receptor sited on the GABAA receptor complex than other hypnotic agents ensure that zaleplon may be an advantageous therapy for patients who cannot be treated with BDZs [42].

Zopiclone was the first non-benzodiazepine hypnotic approved in 1986 in the European market. It is a cyclopyrrolone drug prescribed for the short-term treatment of sleep disorders related to the induction and sleep maintenance [35].

Zopiclone is chemically not related to zolpidem or other CNS depressants and it is marketed as racemic mixture. Zopiclone has an agonist activity mainly directed toward the α1 subunit of the GABAA receptor and its elimination half-life is the longest of the other Z-drugs (3.5-6.5 hours).

Therapeutic doses of zopiclone are not related to the onset of rebound insomnia, as it happens with zolpidem, but it has an increased risk for abuse potential, physical dependence and misuse after a long-term use, even if at prescribed doses, or when self-administered for recreational purposes [37].

1.3.1. Z-drugs Misuse and Diversion

Z-drugs are generally well tolerated and perceived to be safer than BDZs because of their favorable safety profiles; however, tolerance, dependence, and withdrawal syndrome are associated with their use, even though the symptoms seem to be less severe and with a lower incidence than those of BDZs [37, 39, 44].

There are many evidence that Z-drugs show a lower rate of misuse about one third that of BDZs suggesting that the abuse potential of BDZs is related to their affinity for the alpha-2 subtype of GABAA receptor complex [43, 45]. Nevertheless, because of their abuse potential, zolpidem, zopiclone and zaleplon, are placed in the same schedule of BDZs, as controlled substances [38].

To date, the phenomenon of abuse and diversion of these compounds remains understudied and unexplored because of the difficulties to find data related to the reasons and the frequency of misuse and the abusers' supply sources [46].

Kapil *et al.*, devised an online question-based survey to better understand the spread of the use and misuse of BDZs and Z-drug in the United Kingdom. The data collected from 1500 participants to the research, showed that diazepam (53.4%) and zopiclone (24.1%) were the most frequently misused medications followed by lorazepam (22.4%), alprazolam (17.2%), oxazepam (12.1%), zaleplon (11.2%), nitrazepam (10.3%), phenazepam (7.8%) and zolpidem (5.2%). The reasons of the misuse were mostly to induce sleep, to manage the stress, to get high or for social issues. Only a small number of subjects stated that these medications were misused out of curiosity, to facilitate come down caused by other drugs or because they felt safer to take these compounds rather than illegal or street drugs [47]. Other interesting remarks emerged from the statements regarding the supply sources of these substances: most declared that they obtained BDZs and Z-drugs from prescriptions of healthcare professionals (55.2%), friends or relatives (39.7%), the Internet (26.7%), drug dealers (19.8%) or elsewhere (11.2%). The authors conclude that the 7.7 per cent of the respondents declared an anxiolytics and hypnotics misuse.

These findings were consistent with those reported by the National Comorbidity Study in the USA, which showed that the incidence of sedative abuse among the adult population was approximately 7.1% [48].

The diversion of prescription drugs is challenging to evaluate both in qualitative (type of drug) and quantitative terms (due to the numerous diversion sources).

In this regard, a study was conducted in France to get information on the drugs more susceptible to diversion through the analysis of prescriptions falsified by patients and collected in a national program (OSIAP, Ordonnances Suspectes Indicateur d'Abus Possible) implemented by the French Addictovigilance Network and in collaboration with the community pharmacies. These data were gathered in three different periods from 2001 to 2012 and were used to

set up three different diversion patterns. Data obtained show that most of the falsified prescriptions for buprenorphine, flunitrazepam and morphine involved young men with a system of overlapping prescriptions. Women aged between 43 and 59 years old were related to the falsification of simple prescriptions for alprazolam, bromazepam, zolpidem, and codeine/acetaminophen. Elderly patients, instead, used modified prescriptions for purchasing acetaminophen and lorazepam. A cross profile to those up described can be identified for zopiclone, clonazepam, clorazepate and dextropropoxyphene (33).

Zolpidem diversion was the most frequently observed in OSIAP program with a steady increase in the examined period: a similar situation was observed for alprazolam, whereas zopiclone seemed to be not related to a misuse [49].

Some cases of abuse, intoxication, overdose and death caused by Z-drugs misuse are reported in the international scientific literature.

Emergency room accesses resulting from Z-drugs abuse are mostly related to the concomitant use with other CNS depressants (alcohol, BDZs, antidepressants and opioids), road accidents, falls and fractures, mainly between elderlies, or suicide attempts [33, 40, 50, 51].

This situation is widespread all over the world and affects both Europe and non-European countries with a similar incidence [52].

The risk of injuries associated with the use of Z drugs closely related to their sedative properties which arise as depression of mental activity and of alertness, loss of memory, and amnesia. The acute adverse effects of these drugs can affect also the mood with expression of drowsiness, lethargy, disinhibition, chaotic paranoid, and violent behavior and aggression [53].

Zosel *et al*. conducted a retrospective analysis of the intoxication cases involving zolpidem abuse reported to the Illinois Poison Center between 2004 and 2005. The Authors observed that zolpidem overdose was mainly related to the co-ingestion with other pharmaceuticals (over-the-counter flu medications, other psychotropic agents) or with alcohol that leaded to intensive care admission [54].

In France, Garnier *et al.* reviewed 344 cases of acute zolpidem poisonings occurred in 1994 and observed that in 91 per cent of cases the intoxication symptoms rapidly remitted and fatalities occurred in the 6 per cent of patients but none were directly linked to zolpidem consumption. The Authors concluded that their evidence confirmed previous published reports in which the cases of acute intoxication attributed to zolpidem taken alone were declared to be benign and did not require specific therapeutic measures [55].

An Australian study reviewed all the forensic cases involving zolpidem administration that showed up to the New South Wales Department of Forensic Medicine between 2001 and 2010. The Authors ascertained a total of 91 cases, and in 83.5% of them in addiction to zolpidem, other psychoactive substances were detected in biological matrices, such as antidepressants (46.2%), alcohol (39.6%), BDZs (35.2%) and opioids (26.4%). They concluded that zolpidem was not the predominant factor for deaths but only contributed to them [56].

Intoxication or death cases are rarely related to the use of Z-drugs alone, though many instances of psychosis, agitation and coma were published [57-59].

There also have been reported several fatalities due to zaleplon ingestion together with other drugs, none of which was exclusively attributable to zaleplon [60, 61].

The interpretation of Z-drugs role in drugs related deaths is challenging because of their short half-lives, inter patient variability and presence of co-ingestants. Moreover, in the cases of polydrug overdose the use of other substances together with Z-drugs is the major confounding factor [37, 62].

1.4. Z-drugs Vs BDZs: 'new drugs' for old crimes

Drug-facilitated crimes (DFCs) refer to a series of crimes, as robbery, sexual assault, money extortion or crimes against the person, committed after the surreptitiously administration of psychoactive drugs able to leave the victims in a weakness and/or unconscious state [63].

More than 50 drugs are known or suspected to have been used for criminal purposes. Most of them are prescribed medications or over-the-counter (OTC) pharmaceuticals acting as central nervous system (CNS) depressants that lead the victims to an apparent state of collaboration linked to the relaxation of the voluntary muscles, which prevents the reaction towards their attackers, and that is characterized by rapid drowsiness up to loss of consciousness and anterograde amnesia [64, 65].

The anterograde amnesia induced by BDZs, zolpidem and zopiclone is dose-dependent. This phenomenon probably related to the disruption of long-term memory consolidation through shortened sleep latency, because an awakening decisive period is necessary for the long-term memory consolidation process [66].

The memory impairment is more severe with 1,4-BDZs as flunitrazepam, especially if administered together with alcohol: in this case not only amnesia occurs but also loss of inhibition. Because of its ability to incapacitate the victims of offence, flunitrazepam is frequently linked to drug-facilitated sexual assaults (DFSAs): its hypnotic effects occur in 15-30 minutes and are enhanced by the concomitant use of alcohol or other psychoactive substances leading the person to become confused and sleepy up to a complete sedation after a short time [64].

Salvaggio *et al.* investigated flunitrazepam abuse, often associated with alcohol, cocaine and other CNS depressants, in heroin addicts. The Authors observed the diffusion of a specific type of amnesia called "automatism amnesia" syndrome characterized by an increased feeling of power often resulting in severe violent assaults (e.g., robbery, acts of physical violence, assaults, car crash) that subjects really did not remember [67].

The spread of aggressive behavior in benzodiazepine abusers was also observed in a study conducted by Albrecht *et al.* about the BDZs use among violent offenders. The participants were engaged through drug diversion and treatment programs of Melbourne, and only those who had committed a crime (property offence, drug dealing, violent crime and fraud) in the six months, and declared benzodiazepine use at least in the previous month before, were selected [68].

The most commonly used BDZs were diazepam, temazepam and alprazolam. The 91.5 percent of participants claimed to

purchase drugs without prescription whereas over the 70 percent obtained them from both medical and alternative sources. Moreover, most of them reported the use of BDZs (mainly diazepam and alprazolam) before committing a crime with a high rate of violence, usually in combination with other substances [68].

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) suggests that there is an underestimation of the involvement of alcohol and BDZs in these crimes and that the abuse of these pharmaceuticals is widespread [69]. Discerning between the stealthy administration of the substances for robbery or violence and their self and voluntary intake in concomitance with alcohol or other substances can be complicated [70].

Segmental hair analysis can be helpful to discriminate a prolonged drug intake from the single exposure, as reported in the study of Wang *et al.*, which analyzed hair samples collected in 25 DFCs cases occurred in Denmark from 2009 to 2016. Among the substances detected (e.g. barbiturates, antihistamines, antipsychotics, opioids analgesics, illicit drugs), they disclosed the presence, after a single administration, of clonazepam, diazepam, nordiazepam, temazepam, oxazepam, triazolam, zolpidem and zopiclone [71].

Generally BDZs and Z-drugs (zopiclone and zolpidem) are administered to the victims orally in food (e.g., cream cakes, couscous or pizza), into beverages (e.g., soda, cola or flavorful ones as tea, fruit juices) or in alcoholic drinks (mainly beer, whiskey or vodka) [72]. In most cases, the attackers mix the psychoactive drugs to the drinks with a high alcohol content because the combination with alcohol has a synergistic action and enhances the depressant effects of these substances [64].

In 2007 a survey research conducted by the French Agency Health Products Safety Agency (AFSSAPS) on chemical-induced submission cases showed that in France the most frequently identified substances in DFCs were in order: clonazepam, zolpidem, bromazepam, nordiazepam, zopiclone, flunitrazepam, alprazolam and diazepam [73]. The use of these substances closely related to their availability, cost, formulation (drops or tablets) and rapid onset and duration of effects [64].

1.5. Diversion from the illicit market: the evolution of the new psychoactive substances (NPS)

Since 2008, the globalization and the use of the internet allowed many countries, firstly China and India, to produce, sell, and distribute new psychoactive substances (NPS) on large scale in the illegal drugs market and in "cryptomarkets" in which anonymous sellers peddle these substances using untraceable cryptocurrencies [74-75].

NPS are de novo designed molecules or are created by manipulating already existing psychoactive substances, to mimic or enhance the effects of illegal drugs of abuse and they are sold as "research chemicals" or labeled as products "not for human consumption" in order to circumvent national narcotics legislation or international control [76]. Since 1997 to date, the EU Early Warning System formally notified 731 new psychoactive substances in Europe and 899 are those reported from 2008 to 2019 by the United Nations Office on Drugs and Crime (UNODC) [77].

These new substances belong to several classes of compounds as synthetic cannabinoids, cathinones, phenethylamines, opioids, tryptamines, arylalkylamines, BDZs, piperazines, plants and extracts, etc.

Initially, the problem related to the diffusion of the new BDZs, known as 'designer BDZs' (DBZDs) was underestimated but in the last 5 years many of them have been detected and seized on the illegal drug market and/or were identified by analysis of biological matrices of intoxicated users [78-85].

The first benzodiazepine identified in Europe in 2007 by the EMCDDA and illicitly sold by the Internet was phenazepam [26]. Originally developed in 1978 in the Soviet Union, phenazepam (also known as 'Bonsai') is a long-acting benzodiazepine belonging to the 1,4-benzodiazepine group along with diazepam, nordiazepam, oxazepam and temazepam [86].

Phenazepam is used as prescribed medication for the treatment of epilepsy, insomnia, alcohol withdrawal syndrome, anxiety and sleep disorders in the Russian Federation and in other commonwealth of independent state (CIS) countries [87].

However, phenazepam is illicitly used for recreational purposes to enhance the effects of opioids and alcohol, to reduce withdrawal symptoms and to better manage cocaine highs [88].

In the last ten years phenazepam increased its popularity all over the world: it can be purchased via the Internet as powder, tablets, blotters and be taken orally, transdermally or intravenously (after breaking the tablets), sniffed or snorted and by spraying into the mouth [89]. In 2009, the first use of phenazepam was reported in the UK and in the following years a boost in the illicit use of the drug was registered in several countries as USA, New Zealand, Finland, Norway and Sweden [90]. In March 2016 phenazepam was added to the Schedule IV of the Convention on Psychotropic Substances of 1971 [90].

Etizolam, a thienodiazepine derivative chemically related to BDZs, was the subsequent compound to be detected by the EMCDDA in 2011 [94]. It was introduced in Japan in 1983 for the treatment of sleep disorders and anxiety and it is currently used as a prescription medication in Japan, India and Italy.

Beyond its medical use, it can be purchased via the Internet as "research chemical" for recreational purposes and it has been seized in the form of powder (often white), in tablet form (blue, pink or white depending on the seller) sold also as 'street Valium', or spiked onto blotter paper [94]. Etizolam is generally consumed orally, sublingually, by snorting and rectally although these two last route of administration seem to be rare (91). In March 2020, Etizolam was added to the Schedule IV of the Convention on Psychotropic Substances of 1971 [92].

As a concluding remark, it is worth noting that at the end of 2019 the EU Early Warning System was monitoring 30 new BDZs, 21 of which were first detected in Europe since 2015 [93]. Most of them have never undergone clinical trials or tests. However, since they are readily available via the internet or sold on the illicit market, they may provide an attractive alternative too prescribed BDZs. The major issue is that the pharmacology and toxicology of new BDZs is largely unknown, and they may pose higher risks to users.

Another question that has emerged is that new BDZs have been found mixed with other new psychoactive substances, including synthetic cannabinoids [94]. Not only this, since it has been recently reported that counterfeit diazepam tablets have been seized in Europe while they contained a new potent synthetic opioid, oxycodone. These counterfeit tablets pose an additional serious risk to users, who cannot possibly be aware that they are using a potent opioid [93].

CONFLICT OF INTEREST

None

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