

Z-Drugs and their use in Drug-Facilitated Crimes: a review of the literature

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Abstract

Background. Z-Drugs are a category of non-benzodiazepine sedative-hypnotic drugs that include Zolpidem, Zopiclone and Zaleplon. They are all rapidly adsorbed and have a very short half-life, features that make them first-line treatment of insomnia and, in the meantime, first-choice drugs in cases of poisoning for criminal purposes. Z-drugs are frequently used in Drug Facilitated Crime cases (DFC) and Drug Facilitated Sexual Assault (DFSA), namely crimes, robberies, extortion and sexual violence committed after administration of incapacitating substances able to induce sedative-hypnotic effects. In these circumstances, the psychoactive substance is considered as a weapon and constitutes an aggravating circumstance in the criminal act: accordingly, judicial authority legitimates the analytical determination of these substances. Currently, few tests able to detect such drugs are available in daily clinical practice.

Aim. The aim of this work is to evaluate the effective utilization of Z-Drugs.

Methods. We have analyzed the literature, focusing on cases in which the criminal use of such incapacitating substances has been demonstrated. Relevant scientific articles were identified from PubMed, Cochrane Central, Scopus, Web of Science, Science Direct, EMBASE up to December 2022 using the following keywords: "z-drugs", "drug facilitated crime", "forensic toxicology". The resulting references were screened to exclude duplicates. In addition, non-English papers were excluded. This evaluation left 10 articles (8 case reports and 2 original studies) divided as follows: 1 case report of a DFC (robbery), 6 cases of confirmed DFSA, 3 cases of suspected DFSA, 2 original studies about DFC.

Results. The totality of the selected cases showed positive toxicological tests for a single intake of z-drugs.

Conclusions. This work has shown the limitations of screening tests currently in use in the emergency rooms. Forensic toxicology tests should be introduced in daily clinical practice. *Clin Ter* 2023; 174 (5):461-468 doi: 10.7417/CT.2023.2465

Key words: Drugs Facilitated Crime, Z-Drugs, sedative-hypnotic, forensic toxicology

Background

Use of incapacitating substances for the purpose of committing crimes is not a newly discovered phenomenon. Reports and complaints have increased significantly from the 1990s to the present day and much data has been collected.

The term Drug Facilitated Crime (DFC) includes robbery, money extortion, maltreatment of vulnerable people, rape and sexual assault (Drug Facilitated Sexual Assault, DFSA). Such criminal acts are carried out by administering covertly a psychotropic substance to a victim: drugs assist or facilitate the crime or the sexual assault (1).

Prescription drugs and over-the-counter medications are the most frequently used in DFC: benzodiazepines and Z-drugs, antihistamines, non-benzodiazepine sedatives, some neuroleptics and gammahydroxybutyric acid (GHB). All these molecules have to be considered alone or in conjunction with alcohol, cannabis, 3,4-methylenedioxy-N-methylamphetamine (MDMA), cocaine and other drugs of abuse.

They are generally hidden in drinks such as coffee or water, or more frequently alcoholic drinks; they can also be hidden in food (2).

The most important property that the drug used for these purposes must possess, is to cause retrograde or antegrade amnesia. This translates into the delayed denunciation of the crime, with eventual loss of crucial evidence. Moreover, such substances have a short half-life: if victim denounces the fact beyond a certain period of time, these drugs, and their metabolites, can no longer be traced within the body, making forensic toxicological investigations vain (3).

Biological samples conventionally used in order to determine a possible assumption in the previous 24 hours, are blood and urine. However, in such cases where victims often come late to physician's attention, the biological matrix left to test is keratin. Therefore, targeted analytical methods and sophisticated instrumentations, such as Gas Chromatogra-

phy/Mass Spectrometry (GC/MS), Liquid Chromatography/Mass Spectrometry (LC-MS), Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS), will be required, allowing maximum sensitivity and specificity.

So-called “Z-drugs” (Zolpidem, Zopiclone and Zaleplon) are chemically different from benzodiazepines but have the same mechanism of action. In fact, both potentiate the inhibitory effect of gamma-aminobutyric acid (GABA) on nerve transmission, binding to specific sites present on brain GABA-A receptors. Although dispensing of these drugs is subject to medical prescription and controlled by the health authorities it is now possible to obtain them through the underground market and online sales.

Z-Drugs pharmacology

Pharmacodynamics

Zolpidem is the progenitor of the emerging class of the new nonbenzodiazepine hypnotics: imidazopyridines. It exerts an anticonvulsant, sedative and central depressant action (4).

The fundamental difference between zolpidem pharmacological profile and benzodiazepines one is given by dose-effect relationship. In fact, zolpidem has a sedative-hypnotic activity at much lower doses than those necessary to obtain the anticonvulsant and muscle relaxant effect. This is the main aspect that makes it the first choice in what are the crimes induced by taking drugs.

Zopiclone represents the first exponent of a class of drugs, cyclopyrrolones, whose pharmacological action is dominated by the sedative effect (5). It has a different chemical structure than zolpidem, BDZ or other CNS antidepressants. It is active as a raceme of two enantiomers. Zopiclone enhances the function of the GABAergic synapses, binding on a receptor site which, according to some studies, would be similar but not identical to those of benzodiazepines. It also has been shown to bind competitively to the benzodiazepine site itself. The anxiolytic, anticonvulsant and muscle relaxant effect are less pronounced than the sedative effect.

Zaleplon is classified as pyrazolopyrimidine, and it has unique qualities for both receptor affinity and pharmacokinetics, increasing its potential in the use of sleep disorders where it is mainly indicated as a short-term treatment (6). In fact, it has an extremely rapid absorption and a half-life of about 1 hour.

Route of administration

As regards the route of administration both from a clinical and forensic point of view, the most common is oral and, secondly, the intramuscular one. Intravenous administration, which allows to have more immediate effects, is reserved for emergency treatments, and in anesthesiology. The effect onset after a single oral administration depends on the gastrointestinal rate of absorption of the molecule, which in turn is essentially regulated by the drug formulation and its physico-chemical properties. The duration of pharmacological effect after administration of a single dose depends on

multiple factors: speed and degree of drug distribution in body tissues, hepatic microsomal system metabolism, the presence of active metabolites.

Pharmacokinetics

All compounds belonging to the Z-drugs family have a very similar pharmacokinetics. They are all rapidly absorbed and have very short half-lives; they also have rapid peak concentration levels and minimal residue after elimination. Zolpidem, Zopiclone, and Zaleplon are rapidly absorbed following oral administration. Fat solubility plays an important role in determining the speed at which a given sedative-hypnotic enters the central nervous system. This property is responsible for the rapid onset of the central effects of Z-Drugs (7).

Zolpidem has a half-life between 1.5 and 2.5 hours after a single oral administration of 20 mg. It binds up to 90% to plasma proteins and it is extensively metabolized to inactive metabolites by the liver CYP450, mainly from the CYP3A4 isoform (US Food and Drugs Administration, 2013). The absorption of zolpidem is rapid and complete. The absolute bioavailability is 70% after 30 minutes from oral administration, with plasma peak between 120 and 60 minutes after a single administration of 20 mg.

Zopiclone has longer half-life and latency time than other Z-drugs, with potential residual effects. 4-5% of the single dose is excreted unchanged through urine; in 24-48 h after administration 100% of the drug is eliminated. Side effects of zopiclone are similar to those of “short acting” benzodiazepines, with minimal diurnal residual effects, mainly represented by metallic taste, dry mouth, asthenia, nausea, nightmares, gastralgia, restlessness and headache (8).

The pharmacokinetic characteristics of Zaleplon are not dependent on gender and age. As mentioned, half-life is approximately one hour after administration of a single oral or IV dose, and it is not dependent on the dose. The drug produces several active metabolites but there is no evidence that they affect behavior (9).

Interaction with alcohol

Fundamental feature to consider is the interaction of Z-Drugs with other substances, taking into account pharmacodynamic and pharmacokinetic characteristics. In fact, particular interactions with alcohol are noted, mainly in cases where they are used as a “medium” to facilitate a criminal event (10, 11). This interaction is pharmacodynamically manifested through an enhancement of the “depressogenic” effect that alcohol exerts on the central nervous system. In mild cases, there may be simple impairment of psychomotor performances, while in severe cases, phenomena of respiratory and cardiovascular depression may appear up to the exitus (12). At the pharmacokinetic level, it has been shown that high alcoholemia following acute ingestion can inhibit the metabolism of benzodiazepines and derivatives with a parallel increase in plasma concentrations and elimination time (13).

Table 1. Summarizes the pharmacokinetic properties of Z-drugs

	Zolpidem	Zopiclone	Zaleplon
Half-life (t 1/2)	1.5 – 3.5 hours	6 hours	1 – 2 hours
Oral bioavailability	70%	80%	30%
Time to maximal concentration	1 – 2 hours	1 – 1.5 hours	1 hour
Dose range	5 – 10 mg	3.75 – 7.5 mg	5 – 20 mg

Objective

The aim of this work is to evaluate the effective utilization of Z-Drugs through the analysis of literature, focusing on cases in which the criminal use of such incapacitating substances has been demonstrated.

Methods

Rationale for literature review is the scarcity of available tests for identification of these substances in medical practice. In fact, only screening devices are currently available in first aid facilities, aimed at identifying the most common substances of abuse such as: benzodiazepines, cocaine, opiates, methadone, barbiturates, antidepressants and alcohol.

Blood represents the most suitable biological matrix for assessing the actuality of use of the substance, but it allows the identification of the analytes only within 48 hours of intake, forced or voluntary. The use of urine samples has the advantage of non-invasiveness and a time window between 24 and 48 hours but its main limitation is related to the inability to determine the amount of substance consumed and the time of its intake. The need to increase time window for detecting these substances has paved the way towards toxicological analysis on the hair matrix; in fact, depending on the length of the hair, it is possible to detect an exposure temporally close or distant to the analysis. The analysis of segmentation of the hair allows, unlike blood and urinary matrices, to distinguish the intake or administration in single dose of the substance from a chronic exposure to the substance itself.

Relevant scientific articles were identified, independently by different authors, from PubMed, Cochrane Central, Scopus, Web of Science, Science Direct, EMBASE up to December 2022 using the following keywords: “z-drugs”, “drug facilitated crime”, “forensic toxicology”. The resulting references were screened to exclude duplicates. In addition, non-English papers were excluded. This evaluation left 10 articles (8 case reports and 2 original studies) divided as follows: 1 case report of a DFC (robbery), 6 cases of confirmed DFSA, 3 cases of suspected DFSA, 2 original studies about DFC.

The selected studies refer to a period from 2004 to 2022. It was considered appropriate the division of the cases into three groups. Firstly, is reported the only one case of DFC (robbery) published in Italy in 2016. In the second, fall all cases of confirmed DFSA, in which the victims declared that

they had never taken the drug belonging to the z-drugs and whose instead, the presence was established in the biological fluids examined. The analyses have, in fact, confirmed occasional use and thus limited exposure to the substance detected (cases 1 to 6). The third group includes all suspected cases of DFSA in which the analyses toxicology did not demonstrate a hypothetical single intake, showing instead a chronic exposure, not denied by the victims (cases 1 to 3). The last is about original DFC studies published in France between 2003 and 2007 (studies 1 to 2).

Results

Table 3 illustrates reasons for eligibility and for exclusions of evidence screened.

DFC (robbery)

This case is described in Italy and published in 2016. The victim is a 33-year-old man who presented at the emergency room in a fugue state, reporting that he had been robbed after accepting a coffee from a stranger. Given his altered mental state, he could not exactly remember the dynamic of the event. All clinical and hematological parameters were negative, as well as the toxicological screening performed on urine. Subsequently, at the local forensic toxicology laboratory, more sensitive and accurate analytic methods such as GC/MS and LC-HRMS highlighted the presence of zolpidem in blood at a concentration of 180 ng/ml (14).

Confirmed DFSA

Case 1

The first case of this series was published in 2004. The victim was a 21-year-old woman who reported that during a hospital stay she was offered a coffee by a nurse. After waking up in a state of confusion and lightheadedness, she noticed signs of violence. After 6 days from discharge, she reported the fact and, after 15 days from the alleged violence, a hair sample was collected and analyzed in different segments in LC-MS/MS. Zolpidem was found at a concentration of 4.4 pg/mg in the segment corresponding to the moment of the alleged violence. This result was also consistent with a limited and occasional exposure to the drug (15).

Table 2. illustrates the results of the review.

	Year of publication	Type of crime	People Involved / Sex	Substance	Delay in hair sampling	Drug Concentration (Hair)	Drug Concentration (Blood/Urine)	Analytical Technique
Villain et al.	2004	Confirmed DFSA	1 / Female	Zolpidem	15 (days)	4.4 pg/mg	-	LC-MS/MS (Hair)
		Suspected DFSA	1 / Female	Zolpidem	28 (days)	22 – 47 – 67 – 9 pg/mg	390 ng/ml (Blood)	LC-MS/MS (Hair)
Villain et al.	2004	Confirmed DFSA	1 / Female	Zopiclone	63 (days)	4.2 – 1.0 pg/mg	-	LC-MS/MS (Hair)
		Suspected DFSA	1 / Male	Zopiclone	28 (days)	21.3 – 21.5 pg/mg	-	LC-MS/MS (Hair)
Kintz et al.	2005	Confirmed DFSA	1 / Female	Zolpidem	49 (days)	0.10 – 0.7583 pg/mg	16 pg/ml (Blood) – 32 pg/ml (Urine)	LC-MS/MS (Hair)
Maravelias et al.	2009	Suspected DFSA	1 / Female	Zolpidem	-	-	47 µg/L (Blood)	GC-MS (Blood)
Djezzar et al.	2009	DFC / DFSA	158 (89 Female)	Zolpidem (20)	1 to 110 (hours)	-	-	LC-MS (Blood) / LC-MS + LC-DAD (Hair)
				Zopiclone (9)	5 to 120 (hours)			
Cheze et al.	2010	Confirmed DFSA	2 / Female	Lorazepam / Zolpidem	2 (months) / 1.5 (months)	< 2 pg/mg / 19 pg/mg	- / -	LC-ESI-MS/MS
		DFC (robbery)	8 / -	Zopiclone	3.5 (months) / 3 weeks to 8.5 months	13pg/mg / 15 – 16 – 19 – 20 – 42 pg/mg	- / 56 ng/mL (Blood) + 331 ng/mL (Urine)	LC-ESI-MS/MS
		DFC (extortion)	22 / -	Zolpidem (among other 7 substances)	1 to 4 months / 3 weeks to 18 months	8-74 pg/mg / 18-81 pg/mg	5.3 ng/mL (Blood) + 20 ng/mL (Urine) / -	LC-ESI-MS/MS
Salomone et al.	2012	Confirmed DFSA	1 / Female	Zolpidem	5 to 17 (months)	2.8 – 1.6 – 0.9 pg/mg	-	LC-MS/MS
			1 / Female	Diazepam	-	-		
Rocca et al.	2016	DFC (robbery)	1 / 1	Zolpidem	-	-	180 ng/ml (Blood)	GC-MS + LC-HRMS (Blood)
Wiedfeld et al.	2021	Confirmed DFSA	1 / Female	Zolpidem	122 (days)	0.125 pg/segment	-	LC-MS/MS (Hair)
Carfora et al.	2022	Confirmed DFSA	1 / Female	Zolpidem	7 (months)	0.70 – 1.06 – 0.91 pg/mg	-	LC-MS/MS (Hair)

Case 2

The second case examined was published in 2004. The victim is a 16-year-old girl who claimed to have suffered sexual violence after being narcotized (method of administration of the substance is not specified). The girl reported the fact 6 days after the alleged event. No blood and urine tests were performed but, after 9 weeks from the event, victim's hair was collected for a segmental assessment in LC-MS/MS. The first segment (0-3 cm) showed a Zopiclone concentration of 4.2 pg/mg; the second (3-5 cm) of 1.0 pg/mg; the remaining parts (5-7 cm) were devoid of it. These results seemed consistent with a single exposure to the drug (16).

Case 3

This case was described in a study published in 2005. The victim was a 23-year-old woman who reported an as-

sault after 6 days. The victim said that during a house party, after drinking "something that made her different", she had a discussion with a man. She also claimed to have woken up the next day naked in the man's bed, without remembering other details. Given the delay in reporting the incident, clinical investigations revealed no signs of violence. Blood and urine samples were collected and analyzed in LC-MS/MS: a concentration of Zolpidem equal to 16 and 32 pg/ml respectively was highlighted. Although these low concentrations, they are consistent with a drug exposure dating back several days. Seven weeks after the alleged crime, two hair strands were also analyzed. Results revealed 0.10 pg/mg of Zolpidem in the first segment (0-2cm), 0.785 pg/mg in the second (2-4 cm) and no traces were found in the last segment (4-5 cm). The detected concentrations were close to those observed after single exposure to the drug (17).

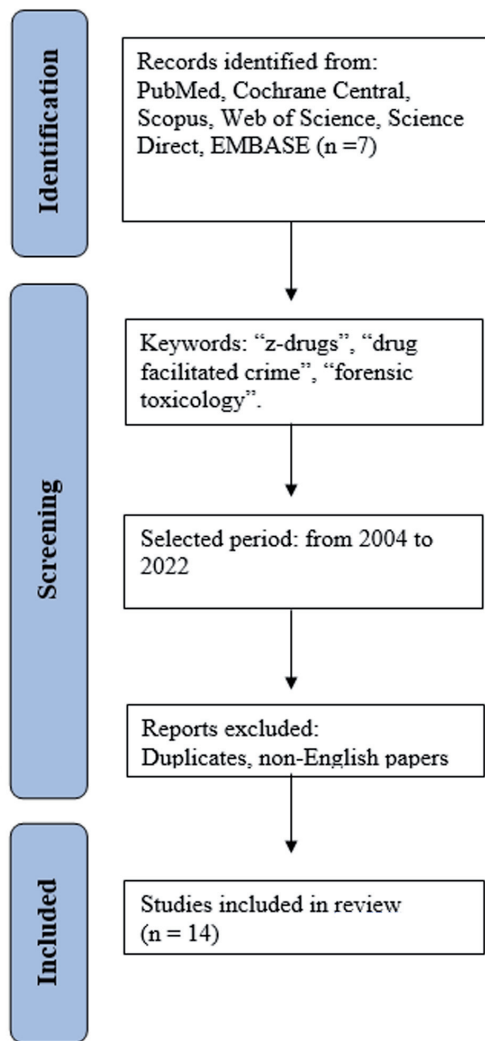


Table 3. Illustrates reasons for eligibility and for exclusions of evidence screened

Case 4

This case is described in a 2012 Italian publication. Two women reported to the police that they suffered sexual violence after accepting a drink from the same man at different times. The first victim tested positive for Zolpidem, while the second showed positive reactions to Diazepam. The first victim was a 26-year-old woman, showing to the hospital after 3 days from the incident. Blood and urine toxicological analysis showed a THC-COOH concentration of 7.4 ng/ml and 108 ng/ml respectively; hair test results confirmed that the woman was a chronic cannabis user. Between 5 and 17 months from the event hair samples were collected, and a total of 16 cm were analyzed: zolpidem was present in the 2 to 3 cm segment at a concentration of 2.8 pg/mg; 1.6 pg/mg in the 5 to 6 cm segment and, 0.9 pg/ml in the 6 to 8 cm segment. All tests were performed in LC-MS/MS. Zolpidem positivity, found in 2 consecutive segments, allows to say

that the victim was not a regular user, more likely, it was a single exposure (18).

Case 5

This case report was described in a study published in 2021. An 11-year-old girl was suspected of having been sexually abused by a man. Circumstantial evidence pointed to several incidents within the course of a few weeks. A clinical immunoassay performed one day after the last alleged incident gave a positive result for benzodiazepines in a blood sample of the girl, thus indicating that the man might have used these substances to facilitate the crimes. When forensic toxicologists were involved in the investigations, hair analysis was performed to prove the accusations. The hair sample (29 cm in length) was collected 122 days after the last assumed incident and all tests were performed in LC-MS/MS. The lower limit of quantification (LLOQ) and limit of detection (LOD) of the relevant analytes were as follows: bromazepam, 1.25 and 0.5 pg/segment; lorazepam, 2.5 and 1.25 pg/segment; mirtazapine, 0.125 and 0.05 pg/segment; Zolpidem, 0.125 and 0.05 pg/segment, respectively. Bromazepam, mirtazapine, and Zolpidem showed the same distribution pattern along all hairs analyzed, so it was likely that all three substances might have been co-administrated. In particular, the calculated time point of the last administration was very close to the suspected time point of 122 days before sampling, thus corroborating the accusations against the man.

Case 6

This case is described in a study published in 2022. In this case report, a 56-year-old female tourist claimed that, during a holiday night in Italy, she was sexually assaulted by five men, all of them employees of the hotel, after accepting a drink from one of them. In her native country, approximately after 35 hours after the assault, she reported the event to the authorities and a standard protocol for the rape cases was applied. Urine samples were collected at 38, 44 and 45 hours after the alleged rape and tested for GHB, Z-drugs, barbiturates, benzodiazepines, hypnotics, antipsychotics and drugs of abuse. The tests were performed by gas chromatography/mass spectrometry (GC-MS) and by liquid chromatography-tandem mass spectrometry (LC-MS-MS). Toxicological analyses performed on the urine samples showed inconclusive findings so, 7 months after the assault, hair strands (28 cm in length) were also sampled to perform the segmental hair testing. LC-MS-MS were applied for the qualitative and quantitative analysis. Zolpidem, flunitrazepam and oxazepam were detected in the hair segments corresponding to the time frame of the alleged assaults. No other illicit drugs or pharmaceuticals were detected in the other proximal and distal hair segments. So, although the urine analysis was inconclusive, the detected levels of Zolpidem, flunitrazepam and oxazepam in hair are consistent with the previously published DFSA cases and considered enough evidence for a DFSA.

Suspected DFSA

Case 1

This is a case published in 2004. A 50-year-old professor attended a student party and during the night he was hospitalized: his alcoholemia was 3 g/l; when he woke up the following day he did not recall of the previous night. He was accused of inappropriate behavior with female students; trying to exonerate himself from this accusation he privately requested analysis of hair, about 4 weeks after the event. Two segments were analyzed using LC-MS/MS: the first segment (0-2 cm) showed a Zopiclone concentration of 21.3 pg/mg; the second (2-4 cm) a concentration of 21.5 pg/mg. These results ruled out a hypothetical single exposure to Zopiclone, not demonstrating the alleged poisoning by third parties (16).

Case 2

This is a French case, reported in 2004. The victim was a 37-year-old woman who claimed a sexual harassment by an acquaintance who offered her a drink. She referred to a local hospital 9 hours after the incident, and a blood sample was analyzed in LC-MS/MS. Results revealed the presence of Zolpidem at a concentration of 390 ng/ml. After about 4 weeks from the alleged crime, a hair removal was also performed for a segmental analysis. All segments from 0 to 8 cm tested positive for Zolpidem (22, 47, 67, and 9 pg/mg respectively). Thus, while blood result demonstrated recent exposure to zolpidem, hair data revealed a regular intake was occurring (15).

Case 3

This case was described in a Greek study published in 2009. The victim was a 35-year-old woman who complained to her doctor for about 10 days, reporting dizziness, memory loss and vaginal irritation. She also reported being under therapy with Losec (omeprazole) for several weeks because of a gastric ulcer, as well as being in a period of abstinence from sexual intercourse for forty days. After 11 hours from taking the last Losec capsule, blood tests were performed in GC/MS, showing 47 µg/L of Zolpidem and the absence of omeprazole. The woman said that the only drug she took at that time was Losec and that it was normally provided by her husband, which aroused the for medicinal replacement. To confirm this hypothesis, the Losec capsules taken from home were analyzed, revealing a second smaller capsule containing Stilnox (Zolpidem). The lady's husband was forced to confirm that he had replaced his wife's Losec capsules with the hypnotic drug to have sex with her, as the woman did not voluntarily show herself available due to religious observance (19).

Original studies about DFC

Study 1

The study was carried out in France between 2003 and

2007. 309 cases were included, only 158 of which proved to be certain cases of DFC and DFSA. The victims were mostly women with an average age of 31. The symptoms reported were anterograde amnesia in most cases, then a disturbance of consciousness and finally the symptoms related to the violence or trauma suffered. The crimes committed were sexual violence, robberies, in some cases committed simultaneously. The toxicological analysis performed on blood, urine and hair showed the presence of Benzodiazepines and to a lesser extent also other substances including Zopiclone and Zolpidem. In particular, Zolpidem analyzed with LC-MS technique, was found in 20 cases, with positivity in 7 blood samples, 11 urine samples and 6 hair samples. Zopiclone, analyzed with LC-MS and LC-DAD method, was found in 9 cases, with positivity in 3 blood samples, 3 urine samples and 3 hair samples. (20)

Study 2

This paper describes the return of DFC in the area of Paris, reporting three series of cases.

Case 1: two women, aged 25 and 27 years, were raped and each victim reported eating a suspected strawberry tablet and suddenly after fallen asleep. Blood and urine tests were performed on the first victim, revealing 16 ng/mL and 1041 ng/mL of Lorazepam, respectively. Lorazepam was detected at trace level (<2 pg/mg) in her hair only in one segment. The second victim received only hair test (because she lodged her complaint more than 5 days after the event): 19 pg/mg of zolpidem were found in the hair segment corresponding to the period of the offence.

Case 2: the victims are eight, men and women, all over the age of 50. They said they suffered a robbery on a return trip from North Africa. They also reported having eaten a dessert and/or drinking coffee offered by the offender himself and falling asleep immediately afterwards. The first series of robberies (3 cases) occurred in France, in a railway station. Two blood samples were collected within nine hours after the accident: 51 ng/ml and 192 ng/ml of Zopiclone were found. No urine samples were collected. Three months later, hair tests showed a concentration of 13 pg/mg and 20 pg/mg (on pubic hair). The investigations were performed with the LC-ESI-MS/MS technique. The second series of robberies took place in an airport between 2006 and 2007 in France, with 5 victims involved. After 9 hours, blood and urine sample were taken: 56 ng/ml and 33 ng/ml of Zopiclone were found, respectively. Toxicological analyses were carried out on 7 hair samples which showed variable concentrations of zopiclone: 15, 16, 19, 20, 42 pg/mg. The technique used was LC-ESI-MS/MS. Zopiclone was detected only in the segment corresponding to the period of the offence in all individual's hair collected (7 victims)

Case 3: victims are 22, neither sex nor age are specified. This is a case of extortion: victims said they all had a dark drink offered by the alleged robber. All the victims showed a difficult awakening and were affected by anterograde amnesia. The offender prepared a cocktail of 6 active ingredients: flunitrazepam, clonazepam, doxylamine, cyamemazine, zolpidem, and lorazepam. Three blood samples were positive for zolpidem (5.3 ng/ml the first, lower than 1 ng/ml the other two). Urine tests showed the presence of zolpidem

in 3 samples (20 ng/ml in the first, lower than 1ng/ml the other two). Zolpidem was found in 15 hair samples: in 10 samples the concentration was between 18 and 81 pg/mg; in 3 samples the concentration was between 8 and 74 pg/mg, and in 3 samples it was less than 2 pg/mg (21).

Data obtained from the review of literature cases, confirmed that z-drugs are used in this type of crime. Delay between crime and reporting was found in most cases. Blood and urine samples were often found to be of limited interest in documenting drug exposure; analysis of the hair performed between 4 and 8 weeks after the alleged crime, proved to be a valuable solution. In all cases where the presence of z-drugs is demonstrated, the analyses were performed with specific and sensitive methods (GC/MS-LC/MS).

Discussion

The term Drug Facilitated Crime (DFC) refers to all those criminal actions that involve the use, by the aggressor, of psychoactive substances with the aim of subjugating the will of the victims, creating in them a state of semi-unconsciousness and anterograde amnesia (22). The administration of these substances, which always takes place without the victim's knowledge, to induce the latter inability to react and thus facilitate criminal action, is called chemical administration (CS) (20). Different types of crime fall into this category: aggression, theft, extortion, rape, and sexual abuse, in the latter case we will speak of Drug Facilitated Sexual Assault (DFSA) (23, 24). Generally, subjects over the age of 18 years seem to be involved in these types of crimes, and the female victims are younger than the male ones (25). There may be several events that lead to the intake of these substances:

- voluntary ingestion of substances that induce disinhibition;
- forced or hidden ingestion of substances that induce disinhibition;
- voluntary and forced ingestion of substances that induce disinhibition.

Research carried out in 2006 in England, from the combined work between Association of Chief Police Officers (ACPO), Forensic Science Service (FSS) and Sexual Assault Referral Centers (SARCs), have suggested a redefinition of the types of DFSA in:

- a) Proactive DFSA: if the crime is committed as a result of forced ingestion of substances;
- b) Opportunistic DFSA: if the crime is committed by taking advantage of the victim's state of intoxication.

Although known for some time, DFC cases are difficult to identify, both because physicians are not fully aware of the phenomenon and because the toxicological analyses, performed in the emergency room or in other first aid centers, are not able to detect all the substances potentially involved. Further complicating the picture, are the amnesic effects of the drugs used which prevent the victim from clearly remembering the events previous to the attack; this leads to a delay in reporting, also due to the "sense of guilt and shame" felt by the victims (26).

Data obtained from this review have made it possible to underline the great use of Z-Drugs for criminal purposes, on an international scale.

The case studies analyzed were divided as follows:

1. case of DFC of robbery, in which thanks to sensitive and accurate analytic methods such as GS/MS and LC-HRMS, an occasional positivity to zolpidem was found.
4. cases of full-blown DFSA, in which the victims declared that they had never taken a Z-Drug before and whose presence in the biological liquids examined was verified.
3. cases of suspected DFSA, in which the toxicological analyses have not shown a hypothetical single intake, highlighting instead a chronic exposure, not denied by the victims.
2. original studies about DFC.

Examining the eight cases of DFSA, women are most frequently involved (7 cases), the most represented age is between 16 and 37 years; the method of administration of the offending drug is - in most cases - through drinks (coffee and other) and just in two cases through a cake and the substitution of a drug. Among studied victims no Intellectual and Developmental Disability (IDD) was detected (27).

Amid Z-Drugs administered, zolpidem turned out to be the most frequently used, followed by zopiclone, while there was no administration of zaleplon. These drugs are used precisely for their side effects, especially amnesia: once the victim regain consciousness it is habitually difficult to remember what happened, this leading to a delay when asking for help. Accordingly, is not always possible to ascertain the occurrence of violence or to trace the substance in biological liquids, such as blood, and to demonstrate alteration during the alleged assault (28, 29, 30).

Failure to find the Z-Drugs through the first level analytical techniques (especially in Emergency Room) makes it difficult today to quickly identify the facilitating role of these substances in cases of DFC and DFSA. In fact, the identification of these substances requires a chromatographic analysis associated with mass chromatography, methods difficult to perform and not immediately usable.

The analysis of hair segmentation allows, unlike blood and urinary matrices, to distinguish the intake or administration in single dose from a chronic exposure to the substance itself.

Targeted research of these substances should be included in the management of victims who enter emergency departments and in whom the administration of incapacitating substances is suspected.

Conclusions

This work has shown how little is investigated on substances used for the purpose of crime: in fact, given the availability in the emergency room of screening devices able to detect only the most common substances of abuse (benzodiazepines, cocaine, opiates, methadone, barbiturates, antidepressants and alcohol), it is clear that it will be at least difficult to find other analytes. Forensic toxicology tests able to analyze biological liquids and keratin matrices in subsequent times, should be introduced in daily clinical practice, especially in emergency rooms (31, 32). In conclusion, the implementation of instrumental toxicological

analysis systems represents an important help for forensic toxicology and could be a relevant tool from the medico-legal point of view.

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