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A review on the forensic toxicology of global drug-facilitated sexual assaults

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Abstract. – OBJECTIVE: Drug-facilitated sexual assault (DFSA) is an act of sexual violence towards a victim who is incapacitated due to the voluntary or involuntary consumption of intoxicating substances. Sexual assaults are generally considered underreported and the toxicological analysis of DFSA cases is particularly challenging when there is a time delay from assault to medical examination. The aim of this review was to investigate typical toxicological findings in global DFSA cases and describe a typical DFSA case.

MATERIALS AND METHODS: A database search was conducted in PubMed using relevant search terms in order to identify studies reporting toxicological results in DFSA cases.

RESULTS: In total, 22 studies were included, covering toxicological findings in DFSA cases in North America, Europe, Asia, South Africa and Australasia from 1996 to 2018. Biological matrices used for analysis included blood, urine and hair. Toxicological findings were comparable among countries, with ethanol, cocaine, cannabis, benzodiazepines, amphetamines and analgesics being among the most frequently detected substances. Ethanol was frequently detected in combination with one or more drugs. A variety of benzodiazepines were observed, with the most common being diazepam, clonazepam, alprazolam, and oxazepam. The majority of cases involved women (87%-100%).

CONCLUSIONS: The findings suggest that a diverse range of substances are associated with DFSA and that victims are rendered vulnerable through recreational substance consumption at social events. As such, typical DFSA cases appear to be opportunistic in nature and primarily involves women in their mid-twenties and an acquaintance as the perpetrator.

Key Words:
Drug-facilitated sexual assault, Forensic toxicology, Date rape, Chemical submission, Drugs, Benzodiazepines.

Introduction

Drug-facilitated sexual assault (DFSA) is a term used to describe an act of sexual violence towards an individual who is incapacitated or unable to provide consent due to the influence of intoxicating substances[1-4]. DFSA can be either opportunistic or proactive in nature. In opportunistic DFSA, the victim is affected by the voluntarily ingestion of intoxicating substances, while in the proactive approach, the perpetrator covertly administers intoxicating substances to the victim with the intention of committing sexual violence[1,2,4-6].

Sexual assault cases are generally considered underreported and toxicological analysis of DFSA is particularly challenging if the assault is not reported early on. Many of the drugs associated with DFSA are potent in small quantities, rapidly metabolized by the body, and often possess sedative, hypnotic, and/or anterograde amnesiac properties – the very same attributes that make these drugs appealing to the assailant[5]. Substances related to DFSA are often named "date-rape drugs". However, the term can be misleading and limiting, as it suggests that drink spiking only occurs in dating scenarios[5,7]. Some date-rape drugs have very subtle organoleptic characteristics and can be bought in liquid solutions, which can make them nearly imperceptible in drink spiking[5]. When the victim recovers and reports the assault, it can be too late for toxicological analysis to confirm any forensic evidence of the DFSA. Blood is most often the biological matrix of choice when performing most toxicological analysis. However, the often-associated time-delay from assault to sample collection makes both urine and hair important additions to toxicological screening processes in DFSA cases[8-10]. The drug's short half-life and their ongoing metabolism make it difficult to quantify drug concentration in biological fluids collected several days after an assault[2,5,11]. Consequently, sensitive analytical methods are essential for detection of the drugs and their metabolites.

Toxicological findings revealing high levels of ethanol in combination with illicit drugs sug-

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gest that many victims are rendered vulnerable through recreational substance consumption[2,12]. Indeed, ethanol appears to be the most commonly detected substance in DFSA cases, as reported in earlier reviews[1,2,5,13]. In addition, benzodiazepines and gamma-hydroxybutyrate (GHB) are often implicated in DFSA, but a broad range of drugs has the potential for misuse in the facilitation of sexual assault[1,6,7,11,14].

In recent years, the occurrence of DFSA has received increased attention in the field of forensic science[1,2,5,13]. Thus, the objective of this review was to examine toxicological findings in global DFSA cases, identify any new trends in drug use and characterize a typical DFSA case.

Materials and Methods

A literature review was conducted to investigate the toxicology and global prevalence of DFSA. The electronic database PubMed was searched in the time-period of September to November 2020 using the search terms "DFSA," "drug-facilitated sexual assault," "date-rape drugs," "chemical submission," "date rape," "drink spiking," and "rape drugs." Articles were assessed for eligibility, and the database search was followed by a manual review of the relevant articles' reference lists. Epidemiological studies reporting toxicological findings related to DFSA were included in the review. Studies were excluded if they did not report any toxicological findings or if they were not available in English. Additionally, reviews, commentaries, letters, and single case reports were excluded. In the event of multiple papers using the same dataset from ongoing investigations, only the latest paper with the complete dataset was included.

Results

DFSA Studies and Positive Findings

The initial database search generated 467 peer-reviewed publications. Of these, the majority was not relevant to DFSA, and 445 were excluded as per the inclusion and exclusion criteria. Consequently, a total of 22 published studies were included in the review covering toxicological findings for 10680 cases from 16 countries ranging from 1996 to 2018. As some studies included findings from sexual assault cases in general, it was not possible to estimate the exact number of DFSA cases. The 22 studies included four studies conducted in the United States, two in Denmark, two in Spain, two in Sweden, one in South Africa, one in Australia, one in Canada, one in China, one in France, one in Italy, one in the Netherlands, one in New Zealand, one in Northern Ireland, one in Norway, one in Taiwan, and one in the United Kingdom (Table I).

DFSA Definition and Estimates of Proactive Approach

Proactive DFSA was estimated to contribute to a total of 2%-22% of cases in five studies from the United Kingdom[15], Australia[8], Denmark[16], Norway[17] and Spain[9]. No other studies reported an estimate of the level of proactive DFSA (Table I). While most studies generally agreed on the overall definition of DFSA, a complete comparison of data was limited by different inclusion criteria and incomplete data regarding voluntary substance ingestion. In the United Kingdom, Scott-Ham and Burton[15] categorized detected drugs according to their potential to cause incapacitation and compared to information on self-reported intake to estimate proactive DFSA, which accounted for 2% of total cases. In Australia, Hurley et al [8] also compared toxicological findings with self-reported drug use and prescription medication. Their toxicological findings were considered unexpected if a drug with potential psychoactive properties was detected and it did not align with the medical record. Unexpected toxicology was observed in 20% of cases, providing evidence of possible covert drug administration. In the United States, Juhascik et al[10] classified cases as DFSA if toxicological analysis detected a drug capable of compromising the ability to provide consent and if the sample was collected within 72 hours of the assault. Through this classification, 43% of 144 sexual assault cases were considered DFSA. However, an estimate of proactive DFSA was not provided since self-reported drug use was considered unreliable[10]. Two Spanish studies defined DFSA cases based on the criteria set by Du Mont et al[18]: (1) the victim reported suspicion of having been drugged in combination with at least one of 16 symptoms (e.g., amnesia) associated with DFSA, (2) having a valid reason for suspecting sexual assault (e.g., clothing in disarray) and (3) presented within 72 hours of the assault. Based on these criteria, Xifró-Collsamata et al[19] reported that 30.7% of 114 cases were suspected to be DFSA. Similarly, Caballero et al[9] reported 34.1% of sexual assault cases as probable DFSA cases. Of these, 13.2% were assumed to be proactive DFSA.

Other studies classified cases based on reported suspicion of DFSA. In South Africa, 12% of 908 sexual assault cases were suspected DFSA by the victim and/or medical practitioner[20]. In Denmark, 12% of 167 sexual assault victims suspected DFSA. Toxicological findings confirmed one or more drugs of abuse and/or medicinal drugs in 45% of these cases[16]. In Norway, Hagemann et al[17] reported that 22% of sexual assault cases suspected proactive DFSA. Of these, 61.4% were positive for ethanol and/or drugs, though none could be explicitly attributed to proactive DFSA.

Victim Characteristics and Circumstantial Data

Fifteen studies provided information on victim characteristics. The mean age of the victims varied from 23.7 to 31.4 years across studies[8,9,16,17,19-27]. Hagemann et al[17] included cases where the victim was 12 years of age or older and Du Mont et al[26] included those above 16 years. In contrast, age ranges of 2-90, 4-60 and 1-64 years were observed in France[25], the Netherlands[27], and the United States[22], respectively. The majority of victims were women (87%-100%), while men were affected in 0% to 13% of cases[9,15,16,19,20,22-29]. In several cases, the perpetrator was a recent acquaintance of the victim. Five studies included data concerning victim-assailant relationships and found that in 48% to 85.2% of cases, the victim knew the perpetrator[8,9,17,19,20]. Tiemensma and Davies[20] reported that most DFSA in South Africa occurred in the home of the offender or victim rather than in public places. In Spain, Caballero et al[9] found that the assault most often occurred in entertainment venues (42.3%), homes and hotels (34.2%) and other public places (23.4%). In contrast, a different Spanish study reported that 72.7% of assaults occurred in a private place and that 91.4% was preceded by a social activity with the presence of alcohol[19]. In Norway, most DFSA occurred at night, specifically between midnight and 7 am[17]. This was also reported by studies in South Africa and Spain[19,20]. Other studies found seasonal variations, with an increase in DFSA cases during the summer months in Sweden and Spain[21,24,27].

Sample Type and Time-Frame for Collection

In the present review, the majority of studies reported combined toxicological findings for both blood and urine samples (n=11). However, none of them had both blood and urine samples available for all cases (Table I). Four studies only reported findings for urine samples. Birkler et al[16] only reported findings for blood samples, while Wang et al[28] focused on hair samples. Five studies reported combined toxicological findings for urine, blood and hair samples, though hair samples were only included in a few of the cases (0.4%-6.5%)[10,24,25].

Most studies reported decreasing positive test results with increasing time-delay from assault to sample collection[9,20,26,27,29,30]. In Italy, Bertol et al[29] reported that 81.8% of positive results were from samples collected less than 24 hours after the assault. Correspondingly, a South African study by Tiemensma and Davies[20] found most positive toxicology results in urine samples collected less than 48 hours after suspected drug administration. In Northern Ireland, Hall et al[31] reported that 44%-74% of toxicology results from 1999 to 2005 were negative when time delay exceeded 12 hours. In Spain, Caballero et al[9] found that positive toxicology results decreased considerably for delays longer than 12 hours. With delays less than six hours and between 6 to 12 hours, the percentages of positive cases were 100% and 91.6%, respectively. The amount of positive cases decreased to 64.5% when the delay exceeded 12 hours.

In the Netherlands, Bosman et al[27] looked into the distribution of sample type, time delay, and positive toxicology. When time delay was greater than 24 hours and blood alone was collected, 100% of cases had negative toxicology results. In contrast, only 36% of cases had negative toxicology results when urine samples had been obtained with a delay of more than 24 hours. In Denmark, Birkler et al[16] found that victims suspecting DFSA underwent medical examination later than the total study population of sexual assault victims. While the average time lapse from assault to medical examination was 12.8 hours (median 7.3) for all sexual assault victims, the average time lapse for DFSA victims was 23.5 hours (median 22).

Analytical Methods

Fifteen studies used immunoassays in the initial screening for drugs of abuse, including cannabis, cocaine, amphetamine and benzodiazepines (Table I). Studies screening for GHB used gas chromatography-mass spectrometry (GC-MS) or gas chromatography-flame-ionization detection (GC-FID). Additional drug screening was performed by either GC-MS, ultra-high pressure liquid chromatography-mass spectrometry (UHPLC-MS) or ultra-high performance liquid chromatography time-of-flight

mass spectrometry (UHPLC-TOF-MS). Positive cases were verified by either GC-MS, liquid chromatography-tandem mass spectrometry (LC-MS/MS), high-pressure liquid chromatography-diode-array detection (HPLC-DAD) or gas spectrometry-nitrogen phosphorous detection (GC-NPD)[8-10,15,17,19,21-24,27,29,32-34]. The majority of studies used GC-FID for ethanol detection, which is also the recommended method by the United Nations Office on Drugs and Crime (UNODC)[35]. However, Birkler et al[16] used GC-MS whereas Tiemensma and Davies[20] used a breath analyzer for ethanol detection. Approximately half of the studies did not state which limits of detection (LOD) were used and in many of those that did, the LOD were not similar to the recommended minimum performance limits set by the Society of Forensic Toxicologists (SOFT). Concerning sample preparation, a total of four studies stated that urine samples were treated with β-glucuronidase prior to analysis[10,15,27,32].

Toxicological Findings

A broad range of substances relevant to DFSA were detected, including ethanol, cannabinoids, cocaine, benzodiazepines, amphetamines, GHB, opioids, hypnotics, MDMA, heroin, antihistamines, methaqualone, antidepressants, antipsychotics, hallucinogens (ketamine, phencyclidine), cathinones, and new psychoactive substances (NPS) (Table I). Across studies, the most frequently detected substances included ethanol, cannabinoids, benzodiazepines, cocaine, amphetamine, analgesics, and antidepressants (Figure 1).

Benzodiazepines and Hypnotics

Hypnotics were found in 10 studies primarily as zopiclone or zolpidem[15,17,19,21,22,24,25,27,28,34]. Hypnotics where the most common drug group (63.6%) found in a Danish study by Wang et al [28].

Benzodiazepines were detected in all studies with a range from 3.5% to 82% of total cases (Table I). In Europe, benzodiazepines were detected in 5.1% to 82.0% of cases. The highest prevalence was found in France (82.0%) followed by Denmark (36.4%), while the lowest prevalence was observed in Italy (5.1%) and the United Kingdom (9.0%) (Table I). Asia accounted for some of the highest prevalence of benzodiazepines, rates of 43.7% and 77.8% being detected in Taiwan and China, respectively. Studies from the United States and South Africa reported some of the lowest detected percentages of benzodiazepines at 3.5% and 3.7%, respectively (Table I). However, prevalence varied from 3.5% to 20.0% in the United States[10,22,32,33]. New Zealand (13%), Norway (12%), Northern Ireland (11.6%), the Netherlands (10%) and Canada (11.2%) detected similar

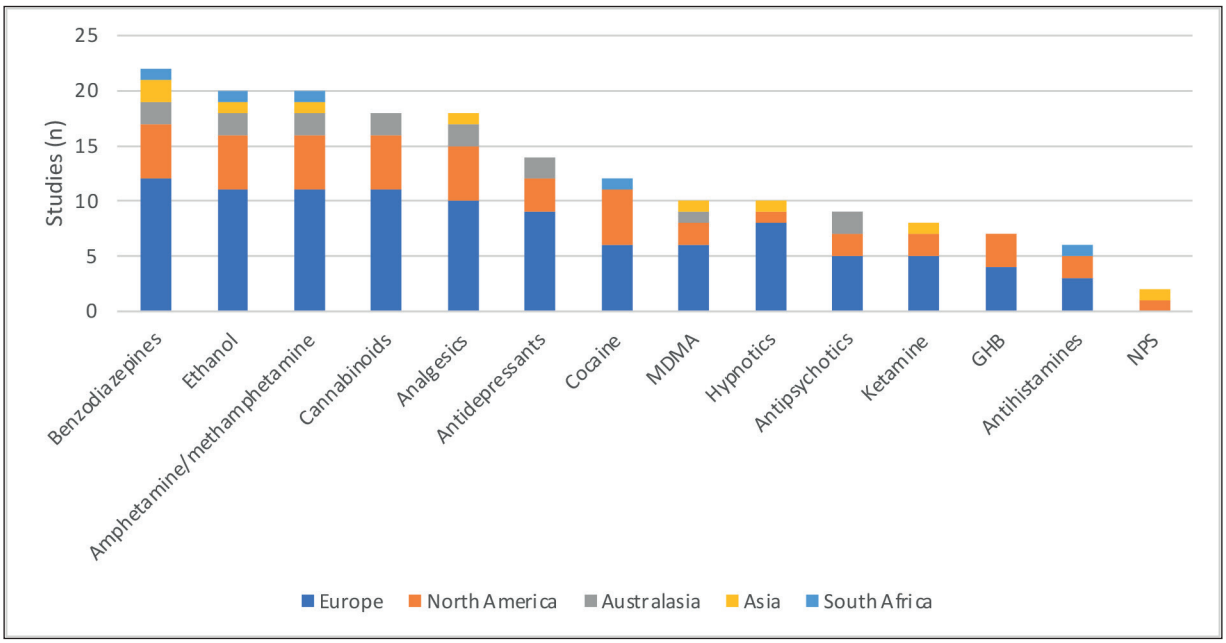

Figure 1. Common substances and drug groups detected in DFSA cases across the 22 studies. The figure shows number of studies detecting the substances and origin of the studies.

Table I. Summary of studies on toxicology in DFSA cases ordered by publication year. Positive toxicology for each study is shown in order of most prevalent detection.

Reference, country	Duration	Cases (n)		Type of biological sample (% of cases)	Time frame for collection (% of cases)	Analytical method	Positive toxicology (% of total cases)	
		Total cases included	Estimated proactive DFSA cases (%)				Ethanol	Drugs
Hindmarch et al[32] (2001) United States	June 1996–February 2000	3303 alleged DFSA cases	N/A	Urine	<24 h (73.0%) <72 h (98.8%)	Screening: immunoassay Verification: GC–MS Ethanol: GS–FID	41.1%	Cannabis (18.6%) Benzodiazepines (9.5%) Cocaine (8.4%) Amphetamine (6.7%) GHB (3.0%) Opiates (2.6%) Propoxyphene (1.3%) Barbiturates (1.2%) Phencyclidine (<0.1%)
Scott-Ham & Burton[15] (2005) United Kingdom	January 2000–December 2002	1014 alleged DFSA cases	21 (2%)	Blood (13%) Urine ± blood (87%)	<24 h (72.0% urine and 84.0% blood samples)	Screening: immunoassay Verification: GC–MS Ethanol: GS–FID	46%	Cannabis (26.0%) Cocaine (11.0%) Non-opiate analgesics (11.0%) Benzodiazepines (9.0%) Antidepressants (7.5%) MDMA (5.0%) Antihistamines (1.4%) Amphetamine (2.0%) Heroin (1.0%) Hypnotics (0.8%) Ketamine (0.5%) Antipsychotics (<0.5%)
Hurley et al[8] (2006) Australia	April 2002–April 2003	76 alleged DFSA cases	15 (19.7%)	Urine (if >24 h) Urine ± blood (if <24 h)	2–106 h (median 20 h)	Screening: immunoassay, GC–MS Verification: MS	37%	Cannabis (5.3%) Antidepressants (5.3%) Benzodiazepines (5.3%) Amphetamine (3.9%) Opioids (3.9%)
Juhascik et al[10] (2007) United States	January 2002–March 2004	144 sexual assault cases incl. 62 (43%) suspected DFSA	N/A	Urine Hair	<72 h (N/A)	Screening: immunoassay, MS Verification: GC–MS	9.7%	Cannabis (32.6%) Cocaine (18.1%) Amphetamine (6.9%) Opiates (6.9%) Benzodiazepines (3.5%)
Jones et al[24] (2008) Sweden	2003–2007	1806 sexual assault cases	N/A	Blood (11.5%) Urine (9.4%) Blood + urine (78.8%) Hair (0.4%)	N/A	Screening: immunoassay Verification: GC–MS Ethanol and GHB: GC–FID	55%	Cannabis (5.5%) Amphetamine (4.8%) Benzodiazepines (N/A) † Anticonvulsants (N/A) Antidepressants (N/A) Opioids (N/A) Hypnotics (N/A)
Hall et al[31] (2008) Northern Ireland	1999–2005	294 sexual assault cases	N/A	Blood Urine	<12 h (N/A) >12 h (N/A)	N/A	55%	Opioids (18.0%) Benzodiazepines (11.6%) Cannabis (8.2%) Antidepressants (4.4%) MDMA (2.7%) Cocaine (0.7%) Amphetamine (0.3%)

Table continued

Table I. ***(Continued).*** Summary of studies on toxicology in DFSA cases ordered by publication year. Positive toxicology for each study is shown in order of most prevalent detection.

Reference, country	Duration	Cases (n)		Type of biological sample (% of cases)	Time frame for collection (% of cases)	Analytical method	Positive toxicology (% of total cases)	
		Total cases included	Estimated proactive DFSA cases (%)				Ethanol	Drugs
Djezzar et al[25] (2009) France	October 2003–December 2007	158 DFC cases incl. 79 DFSA cases ‡	N/A	Blood Urine Hair	<12 h (17.0%) 13–24 h (25.0%) 25–72 h (33.0%) >72 h (18.0%) N/A (6.0%)	LC–DAD LC–MS LC–MS/MS GC–MS	49%	Benzodiazepines (82%) Antihistamines (10%) Antipsychotics (6.9%) Opioids (5.1%) Anesthetics (3.8%) GHB (3.2%) MDMA (2.5%) Antidepressants (1.9%) Cannabis (0.6%) Cocaine (0.6%)
Du Mont et al[26] (2010) Canada	June 2005–March 2007	178 DFSA cases	N/A	Urine	<72 h (N/A)	N/A	30.9%	Cannabis (33.7%) Cocaine (21.4%) Antidepressants (16.4%) Analgesics (13.5%) Benzodiazepines (11.2%) Amphetamine (7.3%) MDMA (7.3%) Antipsychotics (3.4%) GHB (1.1%) Ketamine (1.1%)
Bosman et al[27] (2011) Netherlands	January 2004–December 2006	135 alleged DFSA	N/A	Blood (21.0%) Urine (37.0%) Blood + urine (42.0%)	<12 h (40.0%) 12-24 h (20.7%) >24 h (22.2%) N/A (17.0%)	Screening: immunoassay, GC–MS and HPLC–DAD. Verification: GC–MS, HPLC–DAD, LC–MS/MS. Ethanol: GC–FID.	47%	Paracetamol (20.0%) Cocaine (14.0%) Benzodiazepines (10.0%) MDMA (10.0%) Cannabis (10.0%) Amphetamine (4.0%) GHB (2.0%) Ketamine (1.0%)
Jones et al[21] (2012) Sweden	2008–2010	1460 sexual assault cases	N/A	Blood Urine	N/A	Screening: immunoassay Verification: GC–MS, LC–MS, GC–NPD Ethanol and GHB: GC–FID.	54%	Cannabis (5.8%) Amphetamine (3.8%) Benzodiazepines (N/A)[&] Anticonvulsants (N/A) Antidepressants (N/A) Opioids (N/A) Hypnotics (N/A)
Birkler et al[16] (2012) Denmark	June 2007–December 2009	20 alleged DFSA	N/A	Blood	Average time delay = 12.8 h (median 7.3)	Screening: UPLC–TOF–MS. Verification: LC–MS/MS.	20%	Benzodiazepines (25%) Cannabis (15%) Meprobamate (5%) Oxycodone (5%) Methylphenidate (5%) Amphetamine (5%) Citalopram (5%) Paracetamol (5%)

Table continued

Table I. ***(Continued).*** Summary of studies on toxicology in DFSA cases ordered by publication year. Positive toxicology for each study is shown in order of most prevalent detection.

Reference, country	Duration	Cases (n)		Type of biological sample (% of cases)	Time frame for collection (% of cases)	Analytical method	Positive toxicology (% of total cases)	
		Total cases included	Estimated proactive DFSA cases (%)				Ethanol	Drugs
Hagemann et al[17] (2013) Norway	July 2003–December 2010	264 sexual assault cases	57 (22%)	Blood Urine	<12 h (48%) <72 h (90%)	Screening: immunoassay Verification: LC–MS, GC–MS	45%	Benzodiazepines (12%) Central stimulants (5.7%) Cannabis (5.4%) Opioids (3.6%)
Xifró-Collsamata et al[19] (2015) Spain	January 2011–December 2011	35 alleged DFSA	N/A	Blood Urine	<12 h (45.7%) <24 h (77.1%)	Screening: immunoassay Verification: GC–MS. Ethanol: GC–FID.	48.4%	Cocaine (39.4%) Opioids (27.3) Amphetamine (12.1%) MDMA (12.1%)) Cannabinoids (12.1%) Benzodiazepines (12.1%) Antidepressants (9.1%) Hypnotics (3.2%) Antipsychotics (3.0%)
Hagan & Reidy[33] (2015) United States	2013	45 sexual assault cases	N/A	Urine	<12 h (45.7%) <24 h (77.1%)	Screening: immunoassay, GC–MS. Verification: GC–MS	43%	Cannabis (58%) Other (33%) Cocaine (26%) Amphetamine (13%) Methylone (13%) Benzodiazepines (11%) Opiates/oxycodone (11%) Methamphetamine (5%)
Caballero et al[9] (2017) Spain	January 2010–December 2013	152 alleged DFSA cases	20 (13.2%)	Blood (28.9%) Urine (15.8%) Blood + urine (53.9%)	<6 (21.01%) 6–12 h (40.33%) 13–24 h (26.05%) 25–36 h (5.04%) >36 h (7.56%)	Screening: immunoassay, GC–MS, HPLC–DAD. Verification: GC–MS, LC–MS/MS Ethanol: GC–FID.	65.7%	Benzodiazepines (23.0%) Antidepressants (13.8%) Others (9.2%) Cocaine (17.1%) Cannabinoids (11.2%) Amphetamine (5.9%) Ketamine (1.9%)
Tiemensma & Davies[20] (2018) South Africa	October 2013–June 2016	107 alleged DFSA cases	N/A	Blood (37%) Urine (90%) Hair (2%). Breath (54%)	<24 h (73%) 24–72 h (18%) <72 h (91%)	Screening: HPLC–MS, LC–MS/MS. Ethanol: breath measurements	14%	Methamphetamine (28.0%) Cocaine (9.3%) Methaqualone (14.0%) Doxylamine/diphenhydramine (12.1%) Benzodiazepines (3.7%)
Wang et al[28] (2018) Denmark	2009–2016	11 alleged DFSA cases ¶	N/A	Hair	1–2 months (range 29–180 days, median 38 days)	Screening: UHPLC–-TOF-MS or UHPLC–-Xevo G2-S QTOF-MS. Verification: UHPLC–MS/MS.	N/A	Hypnotics (63.6%) Opioids (36.4%) Benzodiazepines (36.4%) Ketamine (18.2%) Amphetamine (9.1%) Antipsychotics (9.1%) Antihistamines (9.1%) MDMA (9.1%)

Table continued

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Reference, country	Duration	Cases (n)		Type of biological sample (% of cases)	Time frame for collection (% of cases)	Analytical method	Positive toxicology (% of total cases)	
		Total cases included	Estimated proactive DFSA cases (%)				Ethanol	Drugs
Lee et al[34] (2018) Taiwan	January 2011–December 2015	126 sexual assault cases	N/A	Urine	N/A	Screening: immunoassay Verification: LC–MS/MS.	N/A	Benzodiazepines (43.7%) NPS (9.5%) Ketamine (7.9%) Amphetamine (4.8%) Hypnotics (4.0%) MDMA (2.4%) Morphine/codeine (0.8%)
Bertol et al[29] (2018) Italy	January 2010–July 2018	256 alleged DFSA cases	N/A	Blood Urine	<24 h (66%), 24–48 h (12.1%) >48 h (14.5%) N/A (7.4%)	Screening: immunoassay Verification: GC–MS, LC–MS/MS. Ethanol: GC–FID	22.2%	Cannabis (7.4%) Cocaine (5.6%) Benzodiazepines (5.1%) Opioids (4.7%) Amphetamine (0.8%) GHB (0.4%)
Fiorentin & Logan[22] (2019) United States	March 2015–June 2016	1000 alleged DFSA	N/A	Blood (11.6%) Urine (51.3%) Urine + blood (15.5%)	N/A	Screening: immunoassay, LC–QTOF-MS. Verification: GC–MS, LC–MS/MS. Ethanol: GC–FID.	30.9%	Cannabinoids (28.8%) Stimulants (24.1%) Benzodiazepines (20.9%) Antidepressants (17.3%) Opioids (12.8%) Cocaine (10.4%) Antihistamines (10.2%) Anticonvulsants (5.2%) Antipsychotics (1.8%) Antiepileptics (3.4%) GHB (0.7%) Barbiturates (0.5%)
Pan et al[36] (2019) China	February–December 2017	35 alleged DFSA cases	N/A	Blood (51.6%) Urine (37.5%) Hair (6.5%)	N/A	Screening: GC–MS and LC–MS/MS. Ethanol: GC–FID.	11.1%	Benzodiazepines (77.8%) Dexmedetomidine (11.1%)
Poulsen et al[23] (2020) ‖ New Zealand	2015–2018	162 alleged DFSA	N/A	Blood Urine	<24 h (81.2%), range 2–93 h, average 16 h, median 10 h.	Screening: immunoassay, LC–TOF-MS. Verification: LC–MS/MS. Ethanol: GC–FID.	46.9%	Antidepressants/antipsychotics (25.3%) Paracetamol (14.2%) Opiates (13.6%) Benzodiazepines (13.0%) Methamphetamine (11.1%) Cannabis (9.3%) MDMA (1.2%)

N/A: not available; DFC: drug-facilitated crime; DFSA: drug-facilitated sexual assault; h: hours; LC–MS: liquid chromatography–mass spectrometry; GC–MS: gas chromatography–mass spectrometry; GC–FID: gas chromatography–flame-ionization detection; LC–TOF-MS: liquid chromatography–time-of-flight-mass spectrometry; LC–MS/MS: liquid chromatography–tandem mass spectrometry; LC–QTOF-MS: liquid chromatography quadrupole time-of-flight mass spectrometry; UHPLC–TOF-MS: ultra-high performance liquid chromatography time-of-flight mass spectrometry; UHPLC–Xevo G2-S QTOF-MS: ultra-high pressure liquid chromatography coupled with orthogonal acceleration quadrupole time-of-flight mass spectrometry; UHPLC–MS/MS: ultra-high pressure liquid chromatography–tandem mass spectrometry; HPLC–DAD: high pressure liquid chromatography–diode-array detector; GC–NPD: gas spectrometry–nitrogen phosphorous detection.

†Percentages for benzodiazepines, anticonvulsants, antidepressants, hypnotics and opioids not possible to estimate from article. ‡The study included 309 cases divided into two groups: (A) 158 DFC cases including 79 DFSA cases and (B) 151 non-specific cases. Percentages shown are from group A, and it was not possible to distinguish between toxicological results for DFSA and DFC cases. §Percentages for benzodiazepines, anticonvulsants, antidepressants, hypnotics, and opioids not possible to estimate from article. ¶ Wang et al[28] included results for 25 DFC cases (11 DFSA and 14 DFC), but only results for the 11 DFSA cases are shown here. ‖Ethanol and drug percentages are shown for urine samples only.

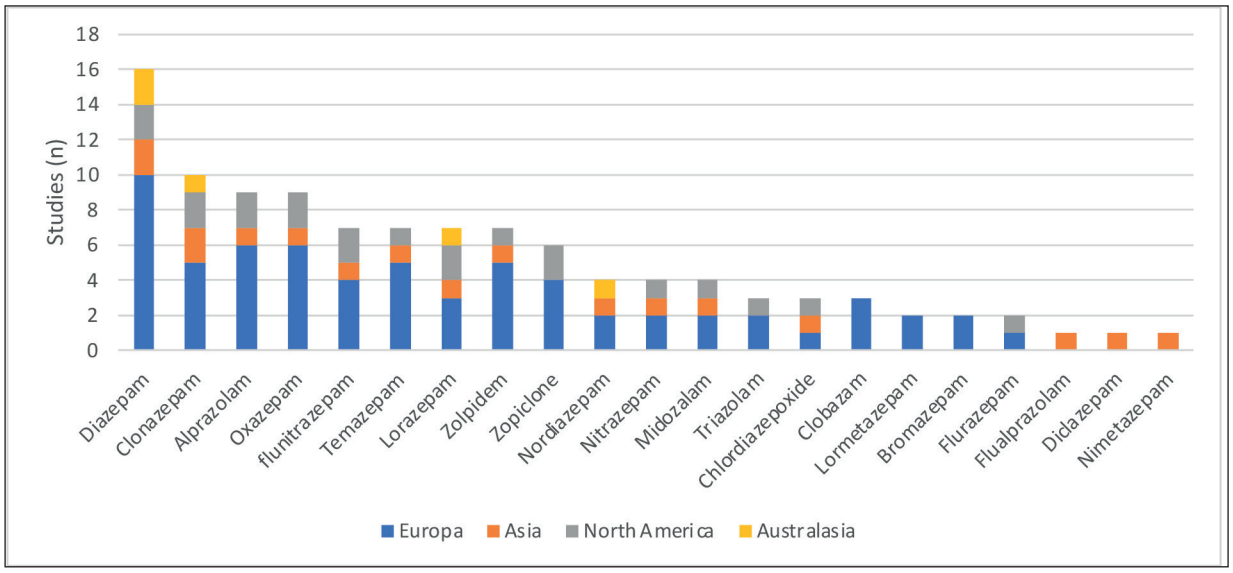

Figure 2. Benzodiazepines, designer benzodiazepines and hypnotics detected in toxicological analysis of DFSA cases.

percentages of benzodiazepines (Table I). Across studies, various benzodiazepines were detected with the most common being diazepam, clonazepam, alprazolam and oxazepam (Figure 2).

In Europe, the most frequently detected benzodiazepines and hypnotics were diazepam, alprazolam, oxazepam, clonazepam, temazepam, and zolpidem (Figure 2). 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[26], while diazepam was the most common found in Australia[8] and New Zealand[23].

Ethanol

In nearly all studies, ethanol was the most commonly detected substance (11.1%-65.7%) and it was commonly detected in combination with one or more drugs[8,9,15-17,19,21-24,27,29-32]. Some of the highest percentages of ethanol (>45%) were detected in studies from Spain[9,19], the United Kingdom[15], Sweden[21,24], France[25], Northern Ireland[31], the Netherlands[27] and New Zealand[23]. The lowest percentages (<30%) were observed in China[36], Italy[29], the United States[22], and Denmark[16]. Pan et al[36] and Juhascik et al[10] were the only studies where ethanol was not the most commonly detected substance. In China, Pan et al[36] reported that ethanol was observed in 11.1% of cases. In the United States, Juhascik et al[10] detected ethanol in 9.7% of cases, but self-reported use (45.8%) suggested that actual alcohol consumption was higher than confirmed by toxicological analysis. Similarly, Birkler et al[16] reported that in 85% of cases, victims stated that they had consumed alcohol prior to the assault. However, toxicological findings were only able to confirm four positive cases of ethanol consumption (20%).

Amphetamine, Methamphetamine and MDMA

Amphetamine was found in 18 studies in 0.8% to 20% of samples. The lowest prevalence of amphetamine was observed in Northern Ireland (0.3%) and Italy (0.8%), while the highest prevalence was observed in Spain (11.4%), the United States (16.5%) and Australia (20%)[8,19,22,29,31]. The highest prevalence of methamphetamine was observed in South Africa by Tiemensma and Davies[20]. Contributing to 28% of positive samples, it was also the most common drug observed in the study. Poulsen et al[23] detected methamphetamine in 18.5% of samples in New Zealand. MDMA was observed in 10 studies in 1-11.4% of samples[15,19,22,23,25-28,31,34]. The highest percentages were observed in Canada[26] (7.3%), the Netherlands[27] (10%) and Spain[19] (11.4%), while the lowest were observed in the United States[22] (1%), New Zealand[23] (1.4%) and Taiwan[34] (2.4%).

Analgesics

A total of 19 studies observed analgesics in DFSA cases. It was the most common drug group

(18.0%) found in alleged cases of DFSA in Northern Ireland, where some of the most frequently observed were codeine (6.8%) and morphine (2.4%)[31]. Bosman et al[27] found the most common drug group to be non-opiate analgesics in Dutch cases of DFSA[27]. In Canada, Du Mont et al[26] detected analgesics in 13.5% of positive samples. Codeine was the most frequently observed analgesic (4.5%), followed by morphine (3.9%), oxycodone (3.4%), methadone (1.1%) and hydromorphone (0.6%). In the United Kingdom, Scott-Ham et al[15] found sedative analgesics in 10.2% of cases and these included codeine/morphine (5.3%), dextropropoxyphene (2.1%), dihydrocodeine (1.5%) and methadone (1.3%). In Australia, Hurley et al[8] observed analgesics in 20% of cases, which included tramadol, oxycodone, and codeine.

Cannabinoids

Cannabinoids were observed in 19 studies[10,15,22-24,29,30,32] with a range of 0.6% to 33.7% of samples. It was the most prevalent drug found in nine studies, with the highest percentage of 33.7% was detected in Canada by Du Mont et al[26]. The highest prevalence of cannabinoids was detected in studies from Canada, USA, New Zealand and the United Kingdom (18.6%-33.7%)[8,10,15,22,23,26,32]. In contrast, the lowest prevalence of detected cannabinoids (0.6-11.4%) occurred in France, Norway, Sweden, Northern Ireland, the Netherlands, Spain and Italy[9,17,19,24,27,29]. In Taiwan, Lee et al[34] found no samples positive for cannabinoids.

Cocaine

Cocaine was observed in 11 studies where it was detected in 0.6% to 37.1% of cases. The highest prevalence of cocaine was reported in studies from Canada[26] (21.4%) and Spain[9,19] (17.1%-37.1%), while the lowest prevalence was detected in France[25] (0.6%), Northern Ireland[31] (0.7%), and Italy (5.8%)[29]. Cocaine was not detected in any cases in Taiwan[34], China[36] or New Zealand[23].

Antidepressants and Antipsychotics

Antidepressants were found in 13 studies with citalopram, fluoxetine and venlafaxine being the most common[8,9,15,16,19,21-27,31]. In Australia, Hurley et al[8] found antidepressants in 26.6% of cases. These were not accounted for by the victims' medical records and included citalopram, clozapine, mirtazapine, moclobemide and venlafaxine. In Canada, Du Mont et al[26] reported that antidepressants were detected in 16.4% of samples. Of these, citalopram (6.7%) and venlafaxine (4.5%) were the most commonly detected. Fluoxetine, mirtazapine, bupropion, sertraline, paroxetine, desipramine and amitriptyline were observed to a lesser extent (0.6-1.1%)[26]. In New Zealand, Poulsen et al[23] found citalopram and fluoxetine to be the most commonly detected antidepressants in 167 DFSA cases over a three-year period. In Northern Ireland, Hall et al[31] found antidepressants in 4.4% of cases with citalopram and venlafaxine being the most common.

Antipsychotics were detected in nine studies and quetiapine was the most common, being reported in five studies from Denmark[28], the United States[22], Spain[19], Canada[26], and New Zealand[23]. Olanzapine was detected in three studies from the United Kingdom[15], Netherlands[27] and the United States[22]. Other detected antipsychotics included chlorpromazine, clozapine, methotrimeprazine, risperidone and thioridazine[8,15,22,23,26].

GHB

Seven studies detected GHB in 0.2% to 5.9% of their samples. The lowest percentages were observed in Canada[26] (1.1%), the United Kingdom[15] (0.2%), and Italy (0.4%)[29]. The higher percentages were observed in the United States[22] (5.9%), France[25] (3.0%) and the Netherlands (2.0%)[27]. Fiorentin and Logan[22] reported the highest prevalence (5.9%) of GHB found in samples, using a cut-off of 2 mg/L in both blood and urine. However, when using the recommended cut-off levels of 10 mg/L in urine and 5 mg/L in blood, the percentage of samples containing GHB was only 0.7%[37].

Antihistamines

Antihistamines were observed in six studies with doxylamine, diphenhydramine and chlorpheniramine being the most common[15,19,20,22,25,26]. The highest prevalence was observed in South Africa, where Tiemensma and Davis[20] detected doxylamine and diphenhydramine in 12.1% of cases. A similar detection rate was observed in France (10.0%) and the United States (10.2%), while the lowest prevalence was observed in the United Kingdom (1.4%) (Table I).

New Psychoactive Substances (NPS)

While most studies carried out broad toxicological screenings, Hagan and Reidy[33] focused primarily on the detection of synthetic cathinones in DFSA cases in the United States. Toxicological analysis detected methylone in 13% of 45 samples. Methylone was also detected in Taiwan in 2.4% of samples. Additionally, Lee et al[34] detect-

ed 2C-B, PMA, mephedrone, 5-MeO-AMT and 5-MeO-DIPT, which were not detected in other studies.

Other Drugs

In China, Pan et al[36] found dexmedetomidine to be the third most commonly detected drug (11.1%). In South Africa, methaqualone was observed in 14% of cases[20].

Discussion

Toxicological Findings in DFSA Cases

In the current review, 22 studies were identified, covering 10680 cases from 16 countries over a 23-year period from 1996 to 2018. Although a small number of cases included male victims, it is clear that the majority of DFSA cases across studies involved women with a mean age of 23.7 to 31.4 years. A wide variety of substances relevant to DFSA were found and detection of more than one drug in combination with ethanol was common in most studies. As ethanol enhances the sedative effects of some drugs, the combined intake of alcohol and drugs could further increase vulnerability to opportunistic DFSA. The variety of drugs found indicates that there is not typically a single substance associated with DFSA. Toxicological findings differed slightly between studies, suggesting that there may be intercultural variations in relation to the most commonly used drugs in different countries[20,32,34]. The toxicological findings observed in South Africa differed from the rest of the studies, with methamphetamine, methaqualone, diphenhydramine and doxylamine being the most common drugs found[20]. Tiemensma and Davies[20] recognized that these findings illustrated the widespread use of methamphetamine and Mandrax in the Western Cape. Additionally, Asian studies detected a range of NPS and the sedative dexmedetomidine, which were not detected in any other studies[34,36]. Methylone was detected in a study in the US[33] and though NPS were only detected in few studies overall, the use of NPS for DFSA has previously been reported in a case study[38]. The continuous emergence of more NPS represent additional challenges and a constantly changing list of potent NPS to screen for in toxicological analysis[39]. Thus, it is important to take this ever-growing list of NPS into account when performing toxicological analysis of DFSA cases.

GHB is often mentioned in relation to DFSA, but it was detected in very few cases in the studies included (0.2%-3.0%). However, the endogenous nature of GHB requires toxicological findings to be carefully interpreted, and rapid sample collection is essential to distinguish between exogenous and endogenous concentrations[1,40]. As GHB can only be detected in blood samples for up to four to five hours and urine samples for up to 8 to 12 hours, it is plausible that use of GHB is underestimated in the literature[6,40-42].

Even though ethanol was found to be the most prevalent substance in a majority of studies, these results were still considered to be underestimated because toxicological results were usually lower (9.7%-65.4%) than self-reported consumption (64%-100%)[8,16,17,19,20]. As such, it is likely that the rapid metabolism of ethanol causes an underestimation of its prevalence in many DFSA cases. Furthermore, the number of cases positive for ethanol suggests that social situations involving alcohol consumption precedes many DFSA scenarios. The pronounced prevalence of cannabinoids, cocaine, and ethanol also implies that DFSA often occurs in settings involving recreational drug use. Though all studies detected benzodiazepines, it was not always reported which type of benzodiazepines were found. Diazepam, clonazepam, alprazolam and oxazepam were the most commonly detected benzodiazepines across studies, though this could be due to their long half-life. Consequently, it is difficult to estimate whether these are indeed the most common benzodiazepines used in DFSA. While most studies reported drugs of abuse and benzodiazepines to be the most prevalent in toxicological findings, the limited contextual information makes it complicated to interpret the toxicological findings and estimate level of covert drug administration.

Biological Matrices, Time Delay and Analytical Methods

Across studies, there were variations in biological matrices used for toxicological analysis. This could be for several reasons; First, different inclusion criteria for each study defined their choice of biological matrix. While most chose to include both urine and blood, some studies explicitly choose to only include urine samples or exclude blood samples that exceeded a fixed time span. Hurley et al[8] only considered blood samples to be appropriate if collected within 24 hours of the assault, whereas UNODC[35] recommends collection of blood samples within 48 hours. Second, some studies included samples based on availability. Thus, an unequal percentage of urine and blood

samples were provided. Variations in sample availability could be due to late reporting, different sample collection protocols or inconsistencies in procedures for handling DFSA cases. Several studies stated that samples were collected at different emergency departments, sexual assault centers, and medical clinics[10,15,19,26,32]. Potential inconsistencies in protocols make the estimation and analysis of DFSA cases challenging. If urine samples are not included in the toxicological analysis, it is possible to miss important metabolites, thus generating a possible underestimation of DFSA cases. Hair testing can further increase the detection window of drugs in cases where collection of blood and urine has been delayed. However, in order to be able to measure a single dose of a certain drug in hair, careful sample preparation is required to extract the drug from the complex hair matrix and very sensitive instrumentation such as target UHPLC-MS/MS are essential to detect the low drug levels in hair following a single dose. Juhascik et al[10] collected hair samples 5-7 days after the initial medical examination, a timespan that was chosen for the convenience of the victims. However, with the sample collection after only 5-7 days, any positive toxicology likely reflected drug use in the weeks and months prior to the assault.

Six studies did not provide specific information regarding time delay between the assault and sample collection[21,22,24,31,34,36]. Missing information about sampling time is problematic, as it can lead to an underestimation of positive toxicology cases. Specifically, unknown sampling times or too great a time delay from assault to sample collection could generate false-negative toxicology results. Several studies found that increased time delay from assault to sample collection was correlated with decreased positive toxicology. Specifically, a delay of more than 12-24 hours seemed to lead to a notable decrease in positive toxicology results[9,29,31]. The association between negative toxicology and time delay was more prominent in blood samples, as reported by Bosman et al[27]. Thus, a shorter time delay increased the chances of ensuring forensic evidence, stressing the importance of a timely medical examination and rapid sample collection. Additionally, collection of both blood and urine samples may further enable detection of substances in cases where time delay leads to negative results in blood. Birkler et al[16] reported that time delay was greater (median time delay 15 hours longer) for cases suspecting DFSA compared to other sexual assault cases. Consequently, the toxicological analysis of DFSA cases is particularly challenging and demands appropriate sensitive analytical methods. Moreover, broad screening methods are necessary to ensure that a large number of both drugs and their metabolites are included. The majority of studies used immunoassay and GC-MS as screening methods followed by verification with GC-MS and/or LC-MS/MS. However, the use of immunoassay has its limitations, as the technique is less sensitive and nonspecific and can present either false positives or false negatives[43,44]. Therefore, UNODC[35] recommends performing the screening with more sensitive and specific techniques such as GC-MS, liquid chromatography-high resolution mass spectrometry (LC-HRMS) or targeted LC-MS/MS, which can cover a broader range of drugs and metabolites in low concentrations. Prior to analysis, an enzymatic hydrolysis of urine samples may be required to ensure the detection of drugs and/or conjugated metabolites[35]. However, only four studies mentioned that samples were enzymatically hydrolyzed prior to analysis[10,15,27,32]. With the wide use of immunoassay across studies, it is plausible that some drugs commonly associated with DFSA were missed during screening, thus creating an underestimation of DFSA cases and misrepresentation of toxicological findings. To improve the consistency in results generated by toxicology laboratories performing analyses of urine samples from DFSA victims, SOFT[14] presented a guidance document with recommended minimum performance limits for common drugs and metabolites in urine samples, which all laboratories can follow when dealing with these cases. However, it is very plausible that those studies that relied on immunoassay for initial screening did not meet the testing recommendations of SOFT.

Definitions of DFSA and Characterization of a Typical Case

There were variations in how each study defined DFSA and reported their toxicological findings. While some studies had very specific criteria for a case to be categorized as DFSA, others made estimates based on self-reporting by the victim or the notion of medical personnel. Also, many studies reported all positive toxicology, while others primarily reported findings for drugs with potential to facilitate sexual assault. Juhascik et al[10] reported toxicological findings for 144 sexual assault cases and six illustrative DFSA cases. Consequently, their overall toxicological findings connected to DFSA were difficult to esti-

mate. Similarly, Djezzar et al[25] did not distinguish between DFC and DFSA in their results, making it impossible to estimate which drugs were directly associated with DFSA. This made a full comparison between studies challenging as some toxicological results might provide a picture of recreational use before and/or after the assault or leave out results because they were not considered related to DFSA drugs. Additionally, some studies had specific inclusion criteria, which left out any victims that reported the assault after more than 72 hours[9,10,19]. This could potentially cause an underestimation of DFSA cases. However, including cases with a time lapse of more than 72 hours creates a need for more sensitive toxicological analysis in order to confirm any forensic evidence. In general, proactive DFSA was estimated to occur in 2% to 22% of DFSA cases, suggesting that opportunistic DFSA is more common[8,9,15,17].

Based on the present review, the typical DFSA case appears to involve women in their mid-twenties who are rendered vulnerable through voluntary consumption of alcohol and/or illicit drugs at social events. The assault typically takes place during the night at private places and the perpetrator often seems to be an acquaintance of the victim. Though there is no single drug associated with DFSA, most cases involve cannabis, cocaine, benzodiazepines and or amphetamines. Consequently, the present compilation indicates that the consumption of alcohol and illicit drugs constitutes a risk factor for DFSA. It is generally assumed that sexual assaults cases are highly underreported and since those who report DFSA seem to have a greater time delay from assault to medical examination, it further complicates the estimation of the prevalence of DFSA as well as which drugs are found in these types of cases. Underestimations in toxicological findings and prevalence of DFSA seems very much apparent due to the plausibility that some drugs are not detected, and some cases are unreported. While the present findings do not provide major new insights regarding DFSA, the toxicological findings over the years suggests that there is still a need for more sensitive analytical methods, protocol consensus and advanced educational measures to ensure that victims report the assaults and receives timely medical examination.

Conclusions

Globally, toxicological analyses of DFSA cases reveal the use of similar drugs groups, but with some variations between countries. While cases in Europe, the United States and Australasia provides comparable prevalence of ethanol, cannabis, cocaine and a variety of benzodiazepines, results from Asia and South Africa differ slightly by including some drugs not detected elsewhere. These differences possibly reflect variation in drug use and/or availability between countries. Among the most commonly detected benzodiazepines were the long-acting diazepam, clonazepam, alprazolam and oxazepam. The limited knowledge of recreational and prescription drug use complicates an estimate of proactive DFSA compared to opportunistic DFSA. However, the common detection of ethanol and stimulants suggests that the majority of DFSA cases are opportunistic in approach. Consequently, a typical DFSA case seems to involve women who are rendered vulnerable through voluntary substance consumption. These findings shows that the challenges of DFSA are still very much present, and that continual advancement of sensitive analytical methods is essential.

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Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

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