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A multifactorial critical appraisal of substances found in Drug Facilitated Sexual Assault cases

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Highlights

- Trend data from DFSA cohort studies is reported for the first time.
- Why certain compounds are detected in the DFSA cases is explored in detail.
- The mechanism of action of drugs associated with DFSA is reported.
- Attempt is made to identify compounds more likely to be used in predatory DFSA.
- A critical multifactorial review of compounds detected in DFSA cases is included.

Abstract

Drug-Facilitated Sexual Assault (DFSA) is a sexual act in which the victim is unable to give or rescind consent due to intoxication with alcohol and/or drugs that have been self-administered (opportunistic DFSA) or covertly administered by the perpetrator (predatory DFSA). The drugs that are most commonly associated with DFSA are flunitrazepam and gamma-hydroxybutyric

acid (GHB). They cause sedation and amnesia, are readily dissolved in beverages and are rapidly eliminated from the system. However, drugs such as amphetamine and cocaine, which are central nervous system (CNS) stimulants, have also been encountered in DFSA cases.

This paper critically evaluates trend data from cohort studies, identifying drugs that have been detected in DFSA cases and reports on the differences in drugs used between opportunistic and predatory DFSA. This is the first time that a critical multifactorial review of drugs used in DFSA has been conducted. The pharmacology of each identified group of drugs is presented, showing why these compounds are of interest and used in the perpetration of DFSA. Furthermore, the pharmacology and mechanisms of action are described to explain how the drugs cause their effects. It is also apparent from this study that if meaningful data is to be exchanged between law enforcement agencies then it is necessary to agree on protocols for the collection of evidence and the drugs for which analysis should be performed and indeed on the analytical methods used.

Abbreviations

ATS	amphetamine-type stimulants
CNS	central nervous system
DFC	drug-facilitated crime
DFSA	drug-facilitated sexual assault
GABA	gamma aminobutyric acid
GHB	gamma hydroxybutyric acid
GBL	gamma butyrolactone
MDA	3,4-methylenedioxyamphetamine
MDMA	3,4-methylenedioxymethamphetamine
PMA	para-methoxyamphetamine

PMMA	para-methoxymethamphetamine
SNRI	serotonin/norepinephrine reuptake inhibitors
SSRI	selective serotonin reuptake inhibitors
TCA	tricyclic antidepressants
UNODC	United Nations' Office on Drugs and Crime

Introduction

DFSA is defined as a sexual act in which a person (female or male) is incapacitated (unable to give or rescind consent) due to intoxication with alcohol and/or drugs [1]. These substances may be self-administered by the victim (opportunistic DFSA) or administered by the offender (predatory/ pro-active DFSA). It is estimated that there are about half a million sexual offences (including DFSA) each year in England and Wales but only 1% end in convictions [2]. There are several factors leading to the low conviction rate - the most crucial one being low reporting rate.

As part of the Crime Survey for England and Wales (combined data from 2007-12), 136 female victims (16-59 years old) of the most serious sexual offences (*rape, attempted rape and sexual assaults by penetration*) responded to a question regarding telling others about their experience [2]. This survey data shows that a quarter of female victims told no one about the sexual assault they had experienced; more than a half told someone but not the police and only 15% of the respondents told the police about the assault [2]. The reasons for this were given as feelings of self-blame, guilt, shame, embarrassment, fear, helplessness and even denial [2,3]. Other factors included being silenced by fear of the offender's retaliation and not being believed by others, including the authorities [3].

The same reasons were given for male victims of sexual assaults, i.e. embarrassment and social stigma, as well as fear of not being believed [4]. However, lack of information on sexual assault on men and lack of an appropriate support system were also cited as reasons for under-reporting by male victims. A study published in 2016 and based on 98 male respondents (19 to 58 years old) to an online survey showed that even though they disagreed with the majority of sexual assault/penetration/rape myths, they still believed that men can defend themselves from sexual assault and that the police will not take it seriously if a woman sexually assaults a man [4].

A recent study showed that some victims, who were sexually assaulted in the past and reported the sexual offence, expressed their unlikeliness in reporting another assault [5]. The reasons cited were mainly around negative experiences with the authorities and the justice system. Furthermore, a series of newspaper articles published in 2015 regarding a survey held among 1000 undergraduate students of universities across the UK reports that a third (33.3%) of female students and one in eight (12.5%) male students in the UK are sexually assaulted or abused [6].

Only 10% of reported sexual assaults (i.e. 1% of all sexual assault) end in conviction in court [2]. Low conviction figures are attributed to a number of determinants. In some cases, it is impossible to identify the offender. In other cases the offender is identified but the victim refuses to press charges. Sometimes charges are put forward but the evidence is not sufficient and the charge is dismissed [2].

In DFSA cases, by the time the victim reports the case, the drug(s) has (have) cleared away from the system and testing of the victim's blood and urine are of no use. Even though they are used to administer the drugs, the drinks themselves which are associated with such cases

are rarely used as evidence. It could be argued that suspected drinks should be collected and analysed and the knowledge of the chemical decomposition of any drug in a drink may become important [7].

In the *Guidelines for the Forensic analysis of drugs facilitating sexual assault and other criminal acts* published by the United Nations' Office on Drugs and Crime (UNODC) a number of substances are identified as having been used to perpetrate DFSA. These include GHB, benzodiazepines, antihistamines, barbiturates, opioids, cannabis, cocaine, amphetamines, piperazines and alcohol [1]. Drugs used in DFSA need to have certain characteristics both in terms of how they are administered and the effect they cause on the victim including (i) causing sedation and/or anterograde amnesia; (ii) being odourless and tasteless; (iii) dissolving readily in beverages; (iv) being rapidly absorbed after oral administration, and (v) being rapidly cleared from the body (within 24 hours) [8].

A term that is used to describe drugs associated with DFSA is "*date-rape drugs"*. However this description of substances used to spike drinks and/or food to incapacitate the victim is misleading as spiking is not limited to dates.

In speaking to law enforcement agencies in the UK, the authors have found that there is no unanimous view about the analysis of suspected spiked drinks and residues in the investigation of alleged DFSA cases. Protocols ranged from the analysis of all types of case related items, including suspected spiked beverages and food as important through to relying on already established means (e.g. blood and urine) of evidence gathering and not regarding the drink residues as relevant.

This paper reviews the reported prevalence and use of drugs in DFSA in different countries for the first time bringing together and comparing data from across the globe. It then goes on to explain why the reported drugs may be used in such offences. Finally, recommendations are made as to the sources of evidential types that may be available to law enforcement agents and which should be considered when a scene is being investigated or an offence is thought to have occurred.

Materials and Methods

A thorough literature review was carried out to identify studies where drugs had been detected from a number of suspected DFSA cases. Numbers and trends were derived from the data presented in those studies. Besides published research articles, we also examined various reports from governments and other organisations (e.g. UNODC, UK's National Health Service), newspaper articles, websites and other secondary sources. The data on the principle drugs reported to have been found in DFSA cases were collated and a comparative overview is provided. The mechanism of action and pharmacology of these drugs was determined to provide possible explanations for why these drugs may have been identified in the cases reported.

Results and discussion

DFSA cohort studies

There have been a number of cohort studies that report DFSA figures and drug use [9-13] (Fig 1).

One of the first reports on DFSA, carried out in the USA, resulted from the analysis of urine samples from 3303 cases of investigated sexual assaults [9]. Urine samples were collected within 72 hours of the alleged incident and on arrival at the laboratory, refrigerated and

analysed within a week. The report found that 2026 tested positive for alcohol and/or drugs (Table 1). A similar cohort study was published in the United Kingdom by the Forensic Science Service in 2005 [10]. Their results consisted only of samples that tested positive for drugs and/ or alcohol both from blood and/or urine. In 2008, a study using retrospective data from Forensic Science Northern Ireland, collected between 1999 and 2005, was published [11]. The data that were taken into consideration were cases in which blood samples had been collected within 12 hours of the alleged sexual assault. 294 cases were investigated, 200 of which were positive for drugs and/or alcohol. Another study which tried to assess covert drugging, published in 2010, was carried out in Ontario, Canada [12]. Urine was the matrix which was screened for the presence of drugs. Drugs can be detected in urine samples for a longer time (72 h or more) in comparison with blood samples (24 – 48 h). Data was collected for almost two years, from June 2005 to April 2007. Of 977 people reported to have been sexually assaulted, about a fifth of them were suspected to be victims of DFSA (178 participants) and 135 were positive for drug presence. A more recent study from women consulting at the Norwegian Sexual Assault Centre also made an attempt to estimate number of predatory DFSA cases [13]. This study is different to those previously described in that it only focussed on female victims. The data was collected between 1 July 2003 and 31 December 2010 and 264 biological samples (urine and/or blood) were included in the study.

Table 1 summarises positive results (sample tested positive for drugs and/or alcohol) of the five cohort studies. The USA study had the largest positive dataset, with over two thousand samples. Clearly, alcohol and cannabis are the two most commonly encountered substances in DFSA, except for Norway and Northern Ireland where benzodiazepines were featured as the second most detected drugs. In the USA, cocaine appeared as the second most commonly detected (15.4%) followed by amphetamines (13.8%) and then cannabis (10.9%). GHB, a compound associated with DFSA was detected in all studies except for Norway and Northern Ireland, even though it was included in the screening. However, due to rapid elimination of

GHB – the half-life of this compound ranges from 20 minutes to 1 hour [14] – it could have been eliminated before the sample was collected.

All studies found benzodiazepines, amphetamines and opioids. The Norwegian study did not include antidepressants and cocaine in their screening process. Antidepressants were not included in the US study. This demonstrates that if data is to be exchanged on a global scale, an agreed set of drugs must be screened for using agreed methodologies.

Opportunistic vs predatory DFSA

Even though all suspected DFSA cases should be investigated and prosecuted with the same amount of diligence, it is important to distinguish between opportunistic DFSA (the victim self-administered the substance/-s) and predatory DFSA (the perpetrator covertly administered the substance/-s). This distinction is made in an attempt to target compounds that are more likely to be used in predatory DFSA (Table 2). Furthermore, predatory DFSA implies intent on perpetrator's part which is vital in criminal prosecution. In Table 2 the distinction between drugs in opportunistic and predatory DFSA cases, based on classifications made by the respective research groups, is shown.

Findings from the US and Northern Ireland studies are difficult to interpret as they give no indication about the drug use habit of the victims, self-administration resulting in opportunistic DFSA or covert administration resulting in predatory DFSA. Each of the remaining research groups have applied different tools to identify the covert drug administration. These range from information obtained from police officers [10], comparison with victim's drug use history [12] and victim's suspicion of having been drugged [12,13].

In the UK study, based on information given by police officers, the authors identified only 21 cases (2.1% of positive samples) as deliberate spiking by the perpetrator (predatory DFSA).

However, this number might be underestimated due to insufficient information obtained. Even though diazepam was the most prevalent benzodiazepine, temazepam was the drug more associated with deliberate drink spiking with six cases out of 12 thought to be such. Diazepam was only attributed to three such cases. However, temazepam is an active metabolite of diazepam, therefore some of the temazepam-positive samples might have been cases of the administered diazepam being metabolised to temazepam. Such doubt could be unravelled if samples of spiked beverage/ foodstuff had been collected from scene and analysed. Both cases in which GHB was detected, were attributed to drink spiking. Ecstasy was also found in three cases of suspected intentional drink spiking cases.

In an Australian study published in 2006, cases in which drugs were detected but not expected to be there were classified as predatory DFSA [15]. 22 cases were suspected to be predatory DFSA cases, out of these in 15 cases unexpected drugs were detected. In five cases antidepressants were found, followed by cannabis, benzodiazepines, amphetamines and opioids (four cases each); and in one of the suspected predatory DFSA an antipsychotic was detected.

The largest number of estimated predatory DFSA cases – 137 out of 178 – was identified in the Canadian study. This classification was made based on interviews, when at least one of the following were true: (i) the victim had no previous history of CNS active drug use and this type of drug had been found during analysis; (ii) the CNS active compounds found in the analysis were different than those declared as having been used by the participant. Almost half of the cases reviewed fitted the set criteria for suspected predatory DFSA (87 cases out of 135; 48.9% of positive samples). The drugs that had the highest scores for being unexpectedly found in the victims were: cannabis (35 cases; 25.9% of positive samples), cocaine (28 cases; 20.7% of positive samples), amphetamines (20 cases; 14.8% of positive samples) and opioids (20 cases; 14.8% of positive samples). Other drug groups that were

identified as suspected predatory DFSA cases include antihistamines (18 cases; 13.3% of positive samples) and benzodiazepines (13 cases; 9.6% of positive samples). Noteworthy, contrary to UK findings, diazepam was detected in only one case with lorazepam being the most prevalent benzodiazepine (4.4% of positive samples) and no data on temazepam is given.

However, due to drug adulteration and impurities present in street samples or metabolism resulting in pharmacologically active metabolite (e.g. diazepam and its metabolite temazepam) the data acquired might be misleading in terms of identifying *de facto* predatory DFSA drugs and/or cases.

According to data shown in Table 2, cocaine is associated with opportunistic DFSA, not predatory DFSA. This might be due to the effect that cocaine is a stimulant and therefore lowers inhibitions and increases libido. However, amphetamines, also CNS stimulants, were found in both predatory and opportunistic DFSA. Similarly, benzodiazepines were detected in both types of DFSA. There is no specific amphetamine type of drug that was detected in all of the cohort studies, whereas diazepam (prescribed in cases of anxiety, muscle spasms and seizures, as well as during alcohol withdrawal) was identified in all cohort studies both as a substance used in predatory and opportunistic DFSA.

Although not as clearly, alcohol is also more likely to be found in opportunistic DFSA (Table 2). The general scenario for a DFSA assault includes the victim being drugged and severely incapacitated, usually in a situation that the victim perceives as non-threatening (at a party, in a restaurant or club, on a date, etc.). Therefore, the presence of alcohol, in an amount that could incapacitate the victim, is easily explained.

However, it needs to be emphasised that a drug not being detected in DFSA victim's system does not mean that no drugs had been administered to the victim. There are several reasons for this, for example, when the sample was collected for analysis, if there was a delay in reporting, the drug might have had already metabolised or be excreted. Another possibility is that the concentration of the drug present in the system was lower than the limit of detection set for the analytical method and/ or the extraction method was not specific. This shows the importance of developing a standardised method for the extraction and simultaneous detection of drugs from various types of evidence, including suspected spiked drinks.

Why are these drugs found in DFSA cases?

CANNABIS

According to data from the Crime Survey for England and Wales 2014/2015 and National Drug Treatment Monitoring System regarding adults who received specialist substance misuse interventions [16,17], cannabis is the most commonly misused substance. Table 2 shows that cannabis is very often found in DFSA cases, even in predatory DFSA. This paints a picture of two scenarios of possible cannabis misuse in DFSA. Scenario one, in which the victim consciously agrees to participate in a gathering where cannabis is used (or food containing cannabis) and the perpetrator takes advantage of the situation and the victim's reduced inhibitions; scenario two, in which the offender covertly administers the drug (e.g. brownies).

The high prevalence of cannabis might be due to relatively easy accessibility and the perception that it is harmless. Cannabis can be found in three forms - marijuana, hashish and hash oil [18,19]. The most prevalent form – marijuana, is dried plant material that is smoked in a cigarette form, the so-called *joint.* Hashish is the resin from the dried plant, usually mixed with tobacco or added to food. Hash oil is a dark and viscous liquid, usually added to tobacco and smoked [20].

However, given the form in which cannabis usually appears, i.e. dried plant or resin, and its physical properties, i.e. dark colour and either solid or water insoluble liquid, it is less likely to be used to spike drinks as it does not dissolve easily in beverages. Its liquid form – hash oil, is soluble in water and ethanol, but due to its colour and odour it is an unlikely candidate for drink spiking. The onset of action for cannabis depends on the administration route, i.e. 1 – 10 minutes when smoked and 30 – 120 minutes when administrated orally [21].

AMPHETAMINE TYPE STIMULANTS (ATS)

Amphetamine type stimulants refers to a group of drugs that show similarities in both structure and pharmacological effects to (and including) amphetamine and methamphetamine [22,23]. ATS include amphetamines, cathinones and piperazines with the most often reported in DFSA being amphetamine, methamphetamine and MDMA, as well as methylphenidate, mephedrone and 3-CPP [1,9,10,12,13,24]. ATS, especially amphetamine and ecstasy, are the most commonly abused drugs among young people [25] and young adults [16]. Even though ATS are CNS stimulants, i.e. cause increased alertness and euphoria, they are encountered in DFSA as they lower inhibitions, increase susceptibility to suggestion and in some cases increase sex drive. Given their similar chemical structure, ATS share similar physical properties, which are summarised in Table 3.

ATS pharmacology slightly varies. Half-lives range from 2 h (methylphenidate) up to 12 h (amphetamine). Similarly, pharmaceutical doses range from 2.5 – 25 mg for methamphetamine to 750 – 1000 mg for mephedrone. Onset times are more concise and usually do not exceed one hour. This means that it takes up to an hour for the drug to start its effect on the victim. For example, the time between administration of amphetamine and the resulting stimulation is 15-30 minutes. Detailed information is given in Table 4.

COCAINE

Cocaine is another CNS stimulant encountered in DFSA which increases motor activity, talkativeness and euphoria, stimulating the brain's pleasure and reward centres [32]. Although oral administration is possible, cocaine is usually administered nasally (by snorting) which produces sought behavioural changes within 15 minutes. Cocaine usually is a white powder but can also be in form of white lumps (crack) [27] and is soluble in both water and ethanol [33] and therefore meets the criteria for DFSA drink spiking.

Oral administration of cocaine results in less toxicity than nasal administration due to hydrolysis and rapid metabolism (plasma half-life $t_{1/2}$ = 0.7 – 1.5 h) [14] and onset of action is within minutes [21]. All major metabolites of cocaine, i.e. benzoylecgonine, ecgonine and ecgonine methyl ester, are pharmacologically inactive.

Similar to ATS, cocaine is not an obvious candidate for DFSA due to stimulant properties. However, the presence of cocaine may be an indicator of the abuse of other drugs (including DFSA drugs) and may also suggest risk taking behaviour of the victim [34]. Cocaine can induce good mood (happiness, confidence, feeling energised), increased libido and indifference to pain [19]. These mood alterations seem to be exploited for opportunistic DFSA as cocaine was only detected in cases classified as opportunistic DFSA (Table 2). However, cocaine can also cause unpredictable, violent and aggressive behaviour.

GHB and GBL

GHB is usually encountered as a colourless liquid or crystal and is soluble in water. The effects of GHB, a CNS depressant, which are exploited in DFSA are: increased sex drive; lowered inhibitions; memory lapses; drowsiness and dizziness [19].

GHB is metabolised very quickly with a half-life between 20 minutes and 1 hour [14]. It is converted into GBL (an active metabolite). GHB is used in treatment of amnesia at a dose of 50 mg/kg, as well as an analgesic at 10 – 20 mg. Intoxication might occur from a dose of 15 mg/kg and doses above 50 mg/kg are considered toxic, whereas a dose of 4 g is considered lethal [14]. The onset times for GHB and GBL are 20 – 60 minutes and 10 – 30 minutes, respectively [21].

BENZODIAZEPINES

Benzodiazepines are a group of drugs exhibiting depressant properties on CNS, having a sedative effect. As a result, they are used for medical purposes in treatment of anxiety and insomnia. Benzodiazepines most often associated with predatory DFSA are flunitrazepam and diazepam. Other benzodiazepines that have been associated with predatory DFSA include temazepam, lorazepam and nitrazepam.

The properties that are applicable for DFSA exhibited by benzodiazepine intake are: confusion, impaired thinking and memory loss; drowsiness, sleepiness and fatigue; impaired coordination and dizziness [19]. Benzodiazepines are found in forms of tablets, capsules and injectables [27]. Benzodiazepines are lipophilic compounds and therefore less soluble in polar solvents such as water and ethanol. More detailed information is given in Table 5.

There is a link between lipid solubility and onset time, i.e. the more lipid soluble the drug is, the faster the onset time (Table 6). Onset times range from a few minutes (e.g. lorazepam, nitrazepam) up to 1.5 h (e.g. diazepam, temazepam). This means that drinks spiked with benzodiazepines such as lorazepam and nitrazepam start acting more quickly than when

spiked with diazepam. Their half-lives vary from short-term acting flunitrazepam (3 h) to long-term acting diazepam (up to 100 h). The effect of diazepam is longer than that of lorazepam. Toxicological data for selected benzodiazepines is given in Table 6.

OPIOIDS

Opioids are a class of drugs used in treatment of severe pain (pain-killers) and are represented by: morphine, diamorphine, codeine and methadone. Prescription-only opioid painkillers are the second group of drugs reportedly most commonly abused by adults [16]. Respondents of the 2014/2015 Crime Survey reported that the painkillers they abused were not prescribed for them. This shows that there is a big problem with the diverted use of prescription medications.

Codeine is used in relief of dry irritating cough, as well as cold and flu (combined with antihistamines and decongestants) [19]. Methadone, on the other hand, is also used in treatment of opioid addiction due to its properties including: (i) it is unlikely to result in an overdose; (ii) the effects are long lasting which reduces the number of in-takes; (iii) it reduces symptoms of physical withdrawal. Effects that result from opioid intake which are exploited in DFSA include sedation, dizziness, sleepiness, tiredness, confusion and difficulty concentrating and blurred vision [19]. Opioids are available in various forms ranging from white powders to injectables (usually only administered in hospitals) as summarised in Table 7.

Table 8 summarises pharmacological information of selected opioids. Their half-lives are relatively short-term, with diamorphine having the lowest half-life and a rapid onset. The selected opioids indicate that there is a significant difference between dosages needed for medical purpose, depending on the individual built up and tolerance. Methadone has the longest half-life and is primarily used for opioid dependence treatment. It is safer and more long-lasting which results in less frequent visits to the treatment centre.

OTHER PHARMACEUTICAL COMPOUNDS

Although not as prevalent in DFSA as other drug classes, pharmaceutical compounds such as barbiturates, antihistamines and antidepressants have been reported.

BARBITURATES

Barbiturates exhibit similar pharmacological properties as benzodiazepines, with benzodiazepines having been introduced to replace barbiturates [27]. These include drowsiness and sedation as well as confusion and memory impairment. Additionally, there might be some residual impairment of judgment and fine motor skills the following day of barbiturate intake [27].

Barbiturates that feature in DFSA cases include phenobarbital, pentobarbital, amobarbital, barbital and secobarbital and are listed by UNODC in their 2011 guidelines [1]. Barbiturates are still in use as medicine for treatment of insomnia, sedation and seizures, as well as epilepsy (e.g. phenobarbital) [27]. Similar to benzodiazepines, barbiturates are found in forms of tablets, capsules and injectables [27] (Table 9).

Their half-lives vary from short-term acting amobarbital (8 h) to long-term acting phenobarbital (up to 100 h). Onset of action within barbiturates is comparable and ranges from 15 minutes (10 minutes for amobarbital) to 1 hour. Toxicological data for selected barbiturates is given in Table 10.

ANTIHISTAMINES & ANTIDEPRESSANTS

Antihistamines are medicinal compounds used most commonly in treatment of allergies. As they can induce sedation they have been encountered in DFSA cases (chlorpheniramine and diphenhydramine, i.e. first-generation antihistamines) [34]. Furthermore, antihistamines co-administered with alcohol may have an additive pharmacological effect [34].

Antidepressants are compounds used in treatment of mood disorders, including depression, obsessive compulsive disorder and post-traumatic stress disorder [40]. Generally, antidepressants can be divided into following groups: selective serotonin reuptake inhibitors (SSRI); serotonin/norepinephrine reuptake inhibitors; tricyclic antidepressants (TCA), monoamine oxidase inhibitors. Antidepressants commonly encountered in DFSA are citalopram, an example of SSRI, and amitriptyline, an example of TCA. Antidepressants can impair pain signals which is why they are used in treatment of long-term pain [40]. However, the effects of antidepressants which are exploited in DFSA are dizziness and drowsiness, sleepiness and blurred vision. Antihistamines can be found in various forms including tablets, capsules, syrups, lotions, gels, eye drops as well as nasal sprays [41], whereas antidepressants usually are available as tablets (Table 11).

Toxicological data for selected antihistamines and antidepressants is given in Table 12. Their half-lives vary from 2-9 h (e.g. diphenhydramine) to 33 h (citalopram). Onset of action ranges from 15 minutes to 1 hour except amitriptyline and citalopram where onset is variable.

Mechanisms of action

Intercellular communication between neurones requires the release of chemical messengers called neurotransmitters [46]. All neurotransmitters follow a similar scheme of activity:

1. Synthesis and storage in presynaptic neurons (the starting point of signalling);
2. Release from the presynaptic neuron;
3. Binding to receptors on the postsynaptic neuron (receiving end of signalling);
4. Clearance from the synaptic cleft.

Four groups of neurotransmitters have been defined in accordance with their structure. These include: (i) amino acid neurotransmitters, which participate in a wide range of signalling (e.g. GABA); (ii) monoamine neurotransmitters, which regulate attention, cognition and emotion (e.g. serotonin and dopamine); (iii) peptide neurotransmitters for pain reception (e.g. opioids);

and (iv) other neurotransmitters (e.g. acetylcholine) [46]. In Table 13 we discuss the neurotransmitters that are involved in the effects caused by drug classes associated with DFSA.

AMINOACID NEUROTRANSMITTERS

Benzodiazepines and barbiturates act on gamma-aminobutyric acid (GABA) receptors. GABA is the most common neurotransmitter in the CNS (cortex and limbic system), and reduces neuron excitability, resulting in an inhibitory or calming effect [47]. There are three classes of GABA receptors: GABA-A, GABA-B, GABA-C [47]. Benzodiazepines bind to the GABA-A receptor inhibiting GABA signalling and producing a calming effect. Benzodiazepine sensitivity depends on the molecular constitution of the cognate receptor. The a1 subunit (present in 60% of GABA receptors), designated as BZ1, is responsible for the sedative effect and anterograde amnesia, whereas the a2 isoform (BZ2) is responsible for anxiolytic and myorelaxant effects. The amnesic effect is enhanced with lipid solubility of the benzodiazepine, e.g. lorazepam which - has low lipid solubility therefore it is less likely to cause amnesia than other high-potency benzodiazepines (midazolam, alprazolam) [47].

Barbiturates also bind to the GABA-A receptor and alter the duration of the GABA channel (i.e. chloride channel) opening [49]. When barbiturates bind to the GABA channel, chloride ions will enter to the brain cells changing the voltage and because of this, brain cells are depressed. The mechanism of action of barbiturates is dose-dependent. At small concentrations barbiturates enhance activity of GABA. At high doses, barbiturates can activate GABA-A receptors without GABA being present. At higher concentrations, barbiturates inhibit current flow through the chloride channel.

A major difference in mechanism of action between benzodiazepines and barbiturates is that benzodiazepines bind specifically to GABA-A receptors, whereas barbiturates can also target other receptors in the periphery (e.g. heart) [48]. Additionally, barbiturates alter the duration of the chloride channel's opening, whereas benzodiazepines modify the frequency of the opening [47,48].

MONOAMINE NEUROTRANSMITTERS

Drugs of abuse stimulate the brain reward pathway by triggering release of the monoamine neurotransmitter, dopamine. Drug use results in the generation of neuronal active potentials, which triggers dopamine release in synaptic clefts. Dopamine binds to receptors on the surface of post-synaptic neurons, resulting in signal transmission and an increase in pleasurable feeling. Dopamine is subsequently transported to the pre-synaptic neurons by dopamine transporter for their re-use. Most drugs (e.g. amphetamine, cocaine) increase the level of dopamine in this reward pathway resulting in a euphoric effect [49].

Amphetamines are structurally similar to monoamine neurotransmitters (noradrenaline, dopamine and serotonin), and therefore compete with endogenous monoamines for monoamine reuptake transporters. At lower doses, amphetamines block transporter cells, i.e. reuptake of dopamine which is similar to the mechanism of action of cocaine [50]. At higher doses, amphetamines cause the release of more dopamine into the synapse, which subsequently becomes trapped, owing to prevention of dopamine reuptake. This results in the build-up of dopamine, and subsequent continuous stimulation or overstimulation, resulting in prolonged euphoria and addiction [51]. Diamorphine also indirectly excites dopamine producing neurons therefore increasing the level of dopamine.

Antihistamines act by competing with histamine for sites on histamine receptors [52].

There are 4 types of histamine receptors (H1, H2, H3, H4), which differ in their tissue localisation and function. For example, H1 is responsible for the contraction of nonvascular smooth muscles and H3 inhibits the synthesis and release of histamine [53]. When activated, H1-receptors are stimulated resulting in improvement of learning and memory and control of cardiovascular system etc. [54]. Daytime release of histamine causes increased mobility and arousal, therefore blocking histamine receptors leads to sedation, fatigue, impaired concentration and memory.

PEPTIDE NEUROTRANSMITTERS

Opioids act via a family of G-protein coupled receptors, known as opioid receptors [55]. Three types of opioid receptors (mu, delta, and kappa) have been identified [56]. Opioid receptors are involved in signalling in the limbic system (emotions and feelings of pleasure), the brain stem (basic bodily functions, e.g. heartbeat, breath), the spinal cord (pain) and the hypothalamic–neurohypophyseal system (releasing of hormones/neurotransmitters) [55]. These receptors bind to opioid like structures (i.e. β-endorphins, enkephalins and dynorphins) and reduce pain perception and act in a similar manner to opiates.

Opioids are also classified according to their opioid receptor action [55,57] as:

- Agonist: morphine, diamorphine;
- Partial agonist: buprenorphine;
- Antagonist: naloxone.

In the brain reward pathway, opioid receptors are stimulated by endogenous opioids (β-endorphins). When someone uses opiates, this stimulation is caused by the drugs resulting in the activation of dopaminergic neurons. This results in higher levels of dopamine release causing euphoria.

Conclusion

Substances used to spike drinks and/or food to render the victim incapacitated are commonly known as *date-rape drugs*, a term which is misleading as spiking is not limited to dates. These drugs exhibit specific properties which make them undetectable by the victim prior to the assault and afterwards by the forensic service providers. Substances commonly associated with DFSA are GHB and flunitrazepam (Rohypnol). However, cohort studies discussed in this paper show alcohol and cannabis as the most prevalent DFSA related substances, followed by benzodiazepines, amphetamines and opioids. Attempts have been made to distinguish between opportunistic and predatory DFSA drugs. Amphetamines and benzodiazepines as well as cannabis and opioids have been identified as drugs used for both predatory and opportunistic DFSA, whereas alcohol and cocaine as substances more likely to be self-administered by the victim. The pharmacology and mechanism of action of these different drug groups is presented to explain their effects and application in DFSA.

Due to the properties that the DFSA drugs exhibit, most of them are CNS depressants, i.e. they cause sedation, confusion and loss of consciousness. However, CNS stimulants such as amphetamines and cocaine have also been identified in DFSA as they lower inhibitions and increase sex drive, as well as make the person who took them more susceptible to suggestion. This paper provided a review of drugs reportedly associated with DFSA and critically discussed key properties of these substances which may result in them being identified as part of the investigation in DFSA cases.

Given that by the time the victim reports the assault, time will have passed and testing of the victim's blood and urine might lead to a negative result as the drug will have been metabolised and cleared from the body. Even though the drinks are entry points for the drugs, the drinks themselves are rarely ever used as evidence in DFSA cases as they are rarely collected since

when the victim reports 1) they may not know where the drug was administered, 2) it was in a public place (pub or club) and the glasses/ bottles would have been cleared or there is no way to identify the specific vessel, 3) the suspect has cleared and washed all drinking vessels. Consequently, the analysis of suspected drinks (in cases where they are collected) and knowledge of the behaviour of a drug in a drink becomes important as this provides useful information on any drugs used in the alleged assault. Therefore, it is recommended that a standard set of drugs should be screened for using a standard, harmonised, battery of screening techniques if data is to be exchanged around the drugs used in DFSA between different law enforcement agencies.

Author contributions

Michael D. Cole
Helped in design and interpretation

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Design, interpretation and finalising the manuscript

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Fig 1. Distribution of samples (cases; positive and negative) in suspected drug facilitated sexual assault cases from US, UK, Canada, Northern Ireland and Norway [9-13].

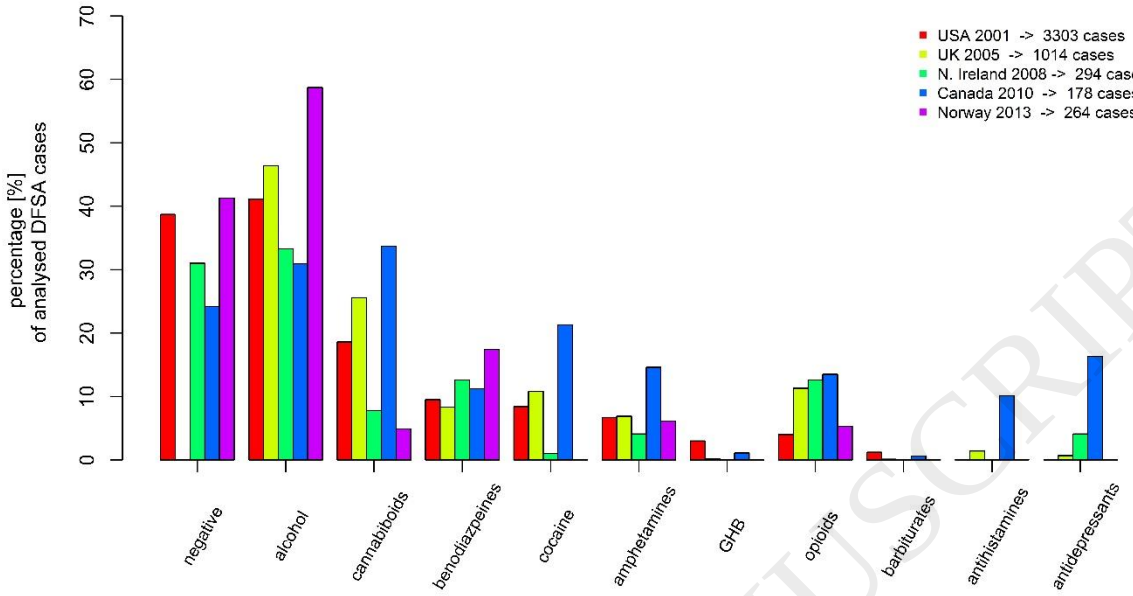

Table 1. Drug prevalence in reviewed DFSA cases.

	USA		UK		Northern Ireland		Canada		Norway	
No. of positive samples	2026		1014		200		135		155	
Alcohol	1358	**67.0%**	470	**46.4%**	98	**49.0%**	55	**40.7%**	119	**76.8%**
Cannabis	613	**10.9%**	260	**25.6%**	23	**11.5%**	60	**44.4%**	13	**8.4%**
Benzodiazepines	313	**2.0%**	84	**8.3%**	37	**18.5%**	20	**14.8%**	46	**29.7%**
Cocaine	279	**15.4%**	110	**10.8%**	3	**1.5%**	38	**28.1%**	Not included	
Amphetamines	220	**13.8%**	70	**6.9%**	12	**6.0%**	26	**19.2%**	16	**10.3%**
Opioids	131	**6.5%**	103	**10.2%**	37	**18.5%**	24	**17.8%**	14	**9.0%**
GHB	100	**4.9%**	2	**0.2%**	0	**0**	2	**1.5%**	0	**0**
Antidepressants	Not included		74	**7.3%**	12	**6.0%**	29	**21.5%**	Not included	

Table 2. Distribution of estimated predatory and opportunistic drug facilitated sexual assault cases based on data from Australia, UK, Canada and Norway (✓ indicates that the substance was classified in the group; × indicates that the substance was not classified in the group) [10,12,13,15].

	Predatory				Opportunistic			
	UK	AUS	Canada	Norway	UK	AUS	Canada	Norway
Alcohol	×	×	✓	×	✓	no data available	✓	✓
Cannabis	×	✓	✓	✓	✓		✓	✓
Benzodiazepines	✓	✓	✓	✓	✓		✓	✓
Cocaine	×	×	×	×	✓		✓	×
Amphetamines	✓	✓	✓	✓	✓		✓	✓
GHB	✓	×	✓	×	×		✓	×
Opioids	×	✓	✓	✓	✓		✓	✓
Barbiturates	×	×	✓	×	✓		×	×
Antihistamines	✓	×	✓	×	✓		×	×
Antidepressants	✓	✓	✓	×	✓		✓	×
Ketamine	×	×	✓	×	✓		×	×

Table 3. Physical forms of selected ATS [19,26,17] and their solubility (✓: soluble).

Compound		Form	Solubility	
			Water	Ethanol
Amphetamines	Amphetamine	powder; tablets; crystals; capsules colour ranges from white to brown (including grey and pink)	✓	✓
	Methamphetamine	clear crystals white or brownish crystal-like powder	✓	✓
	MDMA	white or off-white powder tablets, capsules or crystals in various colours	✓	✓
Cathinones	Cathinones (general) Mephedrone	white or brown amorphous or crystalline powder; capsules, pills white powder with a slight trace of yellow	✓	✓
Piperazines (general)		tablets, capsules; powder	✓	✓

Table 4. Half-life, onset and applied doses for selected ATS drugs [14,21,27-31].

Compound		Onset [min]	Half-life [h]	Major metabolites	Dose	
					Pharmaceutical/ therapeutic	Toxic
Amphetamines	Amphetamine	15 – 30	12 (4 – 8 h if urine pH < 7)	1-phenyl-2-propanone (active); 4-hydroxyamphetamine (active)	20-100 mg (treatment of narcolepsy)	200 mg
	Meth-amphetamine	20 – 70	9	4-hydroxymethamphetamine (active); amphetamine (active)	2.5 – 25 mg	1 g
	MDMA	20 – 70	6 – 7	MDA (active)	80 – 200 mg	300 mg
Cathinones	Mephedrone	15 – 45	2	nor-mephedrone (active); 4-OH-mephedrone (active); dihydromephedrone (active)	from 100 – 250 mg up to 750 - 1000 mg	NA
Piperazines	3-CPP	20 – 60	4.5	hydroxy-mCPP (active); N-(3-chlorophenyl)ethylenediamine (inactive); 3-chloroaniline; hydroxy-3-chloroaniline (inactive)	8 – 80 mg	NA

NA = not available

Table 5. Physical properties of selected benzodiazepines and their solubility [14,27,35].

Compound	Form	Solubility	
		Water	Ethanol
Diazepam	Tablets, capsules, injectables	Slightly soluble	Soluble
Flunitrazepam		Sparingly soluble	Slightly soluble
Lorazepam		Insoluble	Sparingly soluble
Nitrazepam		Practically insoluble	Slightly soluble
Temazepam		Practically insoluble/ very slightly soluble	Soluble/ freely soluble

Table 6. Half-life, onset and applied doses for selected benzodiazepines (toxic doses are not known) [14,21,27].

Compound	Onset [min]	Half-life [h]	Major metabolites	Pharmaceutical/ therapeutic dose
Diazepam	30 – 90	20 – 100	Desmethyldiazepam (active); oxazepam (active); temazepam (active)	5 – 30 mg
Flunitrazepam	15 – 30	16 – 35	Desmethylflunitrazepam (moderately active) 7-aminoflunitrazepam (inactive)	0.5 – 2 mg
Lorazepam	5 – 30	9 – 24	Glucuronide conjugate of lorazepam (inactive)	1 – 10 mg
Nitrazepam	10 – 40	18 – 38	7-aminonitrazepam (inactive); 7-acetoamidonitrazepam (inactive)	5 – 10 mg
Temazepam	20 – 90	8 – 15	Glucuronide conjugate of temazepam (inactive)	1 – 20 mg (insomnia); 20 – 40 mg (premedication)

Table 7. Physical forms of selected opioids and their solubility [14,19,35,36].

Compound	Form	Solubility	
		Water	Ethanol
Morphine	Tablets, capsules, suppositories; injectables (only in hospitals)	Very slightly soluble	Slightly soluble
Diamorphine	Fine white powder; off-white granules; light brown lumps	Very slightly soluble	Sparingly soluble
Codeine	Tablets; capsules; suppositories; liquids	Slightly soluble	Freely soluble
Methadone	Syrup (opioid addiction); injection and tablets (pain relief)	Soluble	Freely soluble

Table 8. Half-lives and applied doses for selected opioids [14,21,37,38].

Compound	Onset [min]	Half-life [h]	Major metabolites	Dose	
				Pharmaceutical/ therapeutic	Toxic
Morphine	15 – 60	2 – 3	Morphine 3-glucuronides (active); morphine 6-glucuronides (active); normorphine (active); codeine (active); morphine ethereal sulphate (active)	5 – 20 mg	200 mg but higher in addicts
Diamorphine	Not available	3 min	INTRAVENOUS ADMINISTRATION 6-monoacetylmorphine (active); normorphine (active) ORAL ADMINISTRATION morphine (active)	5 – 10 mg (intravenous administration) 50 – 70 mg (oral administration)	From 200 mg (no dependence) up to 10 g (high tolerance)
Codeine	30 – 45	2 – 4	Morphine (active); norcodeine (relatively inactive)	30 – 60 mg	800 mg
Methadone	45 – 120	10 – 25	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrolidine (inactive); 2-ethyl-5-methyl-3,3-diphenylpyrroline (inactive)	2.5 – 10 mg, up to 30 mg (pain relief); 10 – 60 mg (opioid dependence)	50 mg; 200 mg and higher for addicts

Table 9. Physical properties of selected barbiturates and their solubility [14,27].

Compound	Form	Solubility	
		Water	Ethanol
Amobarbital	Tablets, capsules, injectables	Very slightly soluble	Freely soluble
Barbital		Slightly soluble	Soluble
Pentobarbital		Very slightly soluble	Freely soluble
Phenobarbital		Slightly soluble	Freely soluble
Secobarbital		Very slightly soluble	Freely soluble

Table 10. Half-lives and applied doses for selected barbiturates [14,21,27,39].

Compound	Onset [min]	Half-life [h]	Major metabolites	Dose	
				Pharmaceutical/ therapeutic	Toxic
Amobarbital	10 – 30	8 – 40	3'-hydroxyamobarbital (moderately active)	30 – 240 mg	1.5 g (lethal)
Barbital	15 – 30	48	Excreted almost entirely as unchanged drug	300 – 600 mg	2 g (lethal)
Pentobarbital	15 – 60	15 – 50	(1′S,3′R)-, (1′S,3′S)-, (1′R,3′S)-, and (1′R,3′S)-5-ethyl-5-(3′-hydroxy-1′-methylbutyl)barbituric acids (relatively inactive)	100 mg (as hypnotic)	1 g (lethal)
Phenobarbital	15 – 45	90 – 100 (adults) 65 – 70 (children)	N-glucopyranosylphenobarbital (inactive); 4-hydroxyphenobarbital (inactive); glucuronide conjugate of phenobarbital (inactive)	60 – 180 mg	1.5 g (lethal)
Secobarbital	15 – 30	19 – 34	Hydroxylation of both side-chains at the C5-position with further oxidation of the omega-position on the butyl side-chain (inactive)	100 mg	2g (lethal)

Table 11. Physical properties for selected antihistamines and antidepressants [35,41].

	Compound	Form	Solubility	
			Water	Ethanol
Antidepressants	Amitriptyline (as hydrochloride salt)	Tablets	Freely soluble	Freely soluble
	Citalopram (as hydrochloride salt)	Tablets, drops	Very soluble	Freely soluble in anhydrous ethanol
	Citalopram (as hydrobromide salt)		Sparingly soluble	Sparingly soluble in anhydrous ethanol
Antihistamines	Chlorpheniramine (as maleate salt)	Tablets, capsules, syrups, lotions, gels, eye drops as well as nasal sprays	Freely soluble	Soluble
	Diphenhydramine (as hydrochloride salt)		Very soluble	Freely soluble
	Promethazine (as hydrochloride salt)		Very soluble	Freely soluble

Table 12. Half-lives and applied doses for selected antihistamines and antidepressants [14,21,27,42-45].

Compound	Onset [min]	Half-life [h]	Major metabolites	Dose	
				Pharmaceutical/ therapeutic	Toxic
Amitriptyline	variable	9 – 26 (higher in cases of overdose)	Nortriptyline (active)	50 – 150 mg max. 300 mg	1 g (intoxication) 2 g (severely toxic/ lethal)
Citalopram	variable	33 (3.75 days in elderly)	desmethylcitalopram (moderately active), didesmethylcitalopram (moderately active), citalopram-N-oxide (moderately active), propionic acid derivative (moderately active)	20 mg – 60 mg	Not know
Chlorpheniramine	30 – 60	2 – 43	Monodesmethyl and didesmethyl metabolites (inactive)	8 – 12 mg	25 – 50 mg/kg (lethal)
Diphenhydramine	15 – 60	2 – 9	Monodesmethyl and didesmethyl metabolites (inactive)	75 – 200 mg	3 g (lethal)
Promethazine	15 – 30	10 – 15	Promethazine sulfoxide (inactive)	20 – 100 mg	200 mg/kg (lethal)

Table 13. Overview of mechanism of action for drugs targeting neurotransmitters [47- 49,52,55,58].

Neurotransmitter type	Drugs	Properties	Mechanism of action
Monoamine	Amphetamines	CNS stimulant	Low dose: blockage of transporter cells i.e. reuptake of dopamine High dose: high level of dopamine is released from cell leading to high level of dopamine in synapse
	Cocaine	CNS stimulant	Blockage of transporter cells resulting in high level of dopamine in synapse.
	Diamorphine	Narcotics	Indirectly excites dopamine
	Antihistamines	Sedative	Blocking histamine action on receptor
GABA	Benzodiazepines and barbiturates	CNS depressants	Inducing the inhibitory effect of GABA
Peptide	Opioids	CNS depressants	Interaction with the opiate receptors to reduce pain perception