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The prevalence of selected licit and illicit drugs in drug facilitated sexual assaults

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ABSTRACT

Little is known about the prevalence of incapacitating substances present in drug facilitated sexual assaults (DFSA). Presented here is a literature review conducted to provide background information, such as symptoms, exacerbations, and drug interactions, on drugs typically implicated in DFSA, namely gamma-hydroxybutyrate (GHB), gamma-butyrolactone (GBL), 1,4-butanediol (1,4-BD), ketamine, diazepam, oxycodone, methamphetamine, and alcohol.

Literature found through Scopus and Pubmed was reviewed to determine the current prevalence of these substances in DFSA with a focus on Australian data.

The global literature revealed that there is a wide variety of substances used in DFSA and the prevalence varied by country. For example, it was found that in Northern Ireland, opioids were most prevalent whereas in France, benzodiazepines were most prevalent. In Australia the review revealed a lack of contemporary data with the most recent report in Victoria using data collected during 2011–2013. The literature also revealed there can be an important difference between self-reported substance use and substances discovered via toxicological analysis. This can be due to the challenges of biological detection, reliability of self-reporting, and the possibility of a substance being introduced to a person's food or drink without their knowledge.

This review highlights the need for the collection and analysis of current data pertaining to DFSA reports and the drugs detected, and due to the constantly evolving picture of both licit and illicit drug use an assessment of the role of prescription medications in DFSA due to drug-drug interactions as well as potential to incapacitate is warranted.

1. Introduction

Drink spiking in social settings is one of the most pervasive forms of drug facilitated sexual assault (DFSA), particularly for young women [1]. However, despite media reports surrounding drink spiking over the years and the abuse potential of drugs, colloquially referred to as "date-rape" drugs (used to incapacitate an individual), little is known about the prevalence of substances present in drug facilitated sexual assaults. Sexual assaults are also a challenging crime for the criminal justice system to manage. There is often a lack of evidence such as independent witness testimony, as well as juror (and other criminal justice agents) preconceptions surrounding the subject of consent, what a typical assault looks like and how a victim of assault behaves [2,3].

This literature review presents a background on definitions, laws, and statistics of drink spiking and DFSA in an Australian context. There are many substances that have been implicated in DFSA and this review focussed on gamma-hydroxybutyrate (GHB), gamma-butyrolactone (GBL), 1,4-butanediol (1,4-BD), ketamine, diazepam, oxycodone, methamphetamine, and alcohol. Symptoms, exacerbations, and drug interactions are outlined and the prevalence of these substances in DFSA is reported. The implications to the criminal justice system and the impact on juror preconceptions of sexual assault are also discussed.

2. Methodology

In this review the literature published over the period 2001–2023 on the prevalence of different substances implicated in drug facilitated sexual assaults in an Australian context was reviewed. Scopus and

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Pubmed databases were searched using the search terms "Drug Facilitated Sexual Assault", "Drink Spiking", "Toxicology", "Prevalence", "Gamma (γ)-hydroxybutyrate", "GBL", "1,4-butanediol", "benzodiazepines", "Ketamine", "opioids", "illicit substances", "Australia", and a combination of these terms.

To obtain a comprehensive insight into the prevalence of different substances and trends in DFSA no limit was placed on publication date range for the literature search, and the oldest article reviewed was from 1997. The focus for this review was placed on articles that reported prevalence of suspected DFSA and toxicology results. Only articles published in English or having an English translation were used. To ensure quality control only articles published in a peer reviewed journal were used.

3. Drug facilitated sexual assault

3.1. Definitions

3.1.1. Sexual assault

The World Health Organisation (WHO) defines sexual abuse as "actual or threatened physical intrusion of a sexual nature, whether by force or under unequal or coercive conditions". In their definition, WHO includes sexual assault as an act of sexual exploitation and abuse. Countries across the world have adopted these definitions within the context of their legislature and created laws to enforce such acts within their criminal justice systems [4].

In Australia, sexual assault is "an act of sexual nature carried out against a person's will through the use of physical force, intimidation or coercion" [5]. In the authors' home state of Western Australia, *sexual assault* occurs when a person is forced, pressured, or tricked into sexual acts against their will or without their consent; gives consent as a result of intimidation or fraud; or is unable to give consent due to youth, mental incapacity or family connection [6].

Indecent assault is unwanted touching or a threat to touch someone else's body in a sexual manner without consent. This is not limited to kissing or inappropriately touching someone's breasts, buttocks, or genitals [6].

Importantly, the Western Australian Police Force has classified both sexual assault and indecent assault under the title of *sexual assault*. It describes *sexual assault* as a broad range of sexual crimes committed against a person. These crimes include sexual intercourse without consent and indecent assault [7]. In our review of definitions, this appears consistent across all Australian states.

3.1.2. Drug facilitated sexual assault

The term *drug facilitated sexual assault* (DFSA) commonly suggests a perpetrator drugging an individual, sometimes by introducing a drug into an unsuspecting victim's drink. However, there are complexities, for example in sexual assault cases where an individual may have voluntarily ingested substances leading to their inability to provide consent, highlighting that a comprehensive definition of drug-facilitated assaults is more complex [8–11].

In general drug-facilitated sexual assault is used to describe a scenario where an individual is incapacitated by a substance to a point where they are unable to give legal consent to a sexual act. This means that DFSA can have two different typologies, proactive or opportunistic [8–11].

Proactive DFSA involves the active or forcible administration of psychoactive or incapacitating substances with the intent to render an individual intoxicated or unconscious for the purposes of facilitating non-consensual sexual activity [11].

Opportunistic DFSA does not involve the perpetrator administering the incapacitating substance. The perpetrator engages in sexual activity with the self-intoxicated person while they are incapable of consenting to the sexual act [11]. Reported DFSA cases are mostly categorised as opportunistic DFSA as opposed to proactive where drink spiking may

have occurred [11]. This does not necessarily mean that there are fewer cases of proactive DFSA compared to opportunistic, a view supported by evidence that suggests that opportunistic DFSA is significantly under-reported [12].

It is important to recognise that whether the consumption of a substance is voluntary or not, it does not change the fact that the crime is classified as a drug facilitated sexual assault. This is crucial for investigators to understand as too often the credibility of the victim may be called into question if there are no "date rape drugs" found in their toxicology results [13].

3.2. Australian law

The Australian federal attorney general's office states that sexual assault laws are the responsibility of the governments of Australia's states and territories [14]. To create a harmonised approach, the state and territory governments and federal government are currently working on the 2022–2027 national work plan to strengthen criminal justice responses to sexual assaults [14]. The plan aims to strengthen legal frameworks across Australia to ensure improved outcomes and protections for victims and survivors as well as building better justice sector capability to help achieve this. The plan also aims to support research and collaboration to identify best practices and ensure actions are supported by a sound and robust evidence base [14].

The Criminal Code Act Compilation Act 1913 (WA), which was last updated April 2023, outlines some definitions about sexual assault and intoxication by deception [15]. Firstly, a person who indecently assaults and/or sexually assaults another person is liable. Secondly an incapable person is defined as a person who is so mentally impaired as to be incapable of understanding the nature of the act or guarding themselves against the act. Thirdly, harm to a person includes an impairment of the senses or understanding of a person, that the person might reasonably object to in the circumstances. Lastly that an intoxicating substance includes any substance that affects a person's senses or understanding [15].

Intoxication by deception is defined as a perpetrator giving a person or causing a person to be given drink or food that contains an intoxicating substance that the person is not aware of; or, containing more of an intoxicating substance than that person would reasonably expect it to contain [15]. The perpetrator intends a person to be harmed or knows/believes that consumption would cause harm [15].

This brings to light the fact that all aspects of drug-facilitated sexual assault are classified as an illegal criminal act and a perpetrator would be guilty with possible jail time of up to 14 years. Of significance is the fact that whether the offender has given an intoxicating substance or not, the victim is incapable of understanding the situation or guarding themselves against it.

3.3. Australian statistics

It is difficult to obtain statistics on drug facilitated sexual assault as most publicly available reports only report on sexual assault as a class and do not distinguish different types. This is further exacerbated by the underreporting of sexual assault cases. A Crime Victimisation Survey conducted by the Australian Bureau of Statistics in 2016 and reported by the AIHW showed that sexual assault is estimated to be underreported at a rate of 86.8 % [12]. The reasons provided by individuals for not reporting their assault to police were presented in the AIHW report and included reasons such as feeling ashamed or embarrassed. A summary is presented in Table 1 [16]. The data in these tables have been collected from females assaulted by male perpetrators and do not consider neither male victims nor female perpetrators [16].

AIHW also reported that in 2016 a total 23,040 people were recorded as victims of sexual assault [16]. Of this number 18,855 people were females and 4106 were males and the remainder 75 people did not specify sex. In 2021, this number rose to a total 31,118 people with 26,

Table 1
Reasons given by females in the Crime Victimisation Survey for not reporting their most recent sexual assault by a male perpetrator to the police [16].

Reason	Number ('000)	RSE (%)	Proportion (%)	95 % MoE
Felt they could deal with it themselves	189.4	8.1	34.2	4.0
Did not regard the incident as a serious offence	187.4	10.7	33.8	6.1
Felt ashamed or embarrassed	142.7	9.0	25.8	3.6
Did not think there was anything the police could do	122.0	11.6	22.0	4.4
Did not know or think the incident was a crime	118.9	12.0	21.5	4.5
Fear of the person responsible	102.1	13.4	18.4	4.4
Did not want the person responsible arrested	92.1	13.5	16.6	4.0
Felt would not be believed	89.3	11.4	16.1	3.2
Did not think the police would be able to do anything	80.3	12.1	14.5	3.1
Fear of legal processes	54.3	15.3	9.8	2.7
Did not want to ask for help	49.2	14.9	8.9	2.4
Did not trust the police	32.1	24.2	5.8	2.7
Workplace/on the job incident	10.3[b]	29.8	1.9	1.1
Cultural/language reasons	18.3[b]	28.4	3.3	1.8
Other	39.7	24.4	7.2	3.4
Not known	16.1[b]	28.6	2.9	1.6
Total[a]	553.9	5.4	100.0	0.0

Abbreviations.
RSE: Relative standard error (%).
95 % MoE: Margin of error of proportion (±).
[a] Components for all reasons police not contacted are not able to be added together to produce a total. Where a person has more than one reason, they are counted separately for each reason but are counted only once in the aggregated total.
[b] Should be used with caution because RSE is from 25 % to 50 %.

669 females and 4350 males and 99 of unspecified sex [16].

In early 2023 the Sexual Assault Reporting Option (SARO) was streamlined to make anonymous online reporting of sexual assault easier for victims in New South Wales (NSW) and can be performed through the NSW police website [17]. SARO is not the same as a formal complaint to the police and will not initiate a criminal investigation. However, SARO provides an option to create a record of the incident as well as provide police with more information about sexual offences and offending [17]. This option is not nationwide and, in most jurisdictions, the only option to report sexual assaults was to go to a police station or call their hotline. According to a report by the Sydney Morning Herald, over 300 reports had been made through SARO within 3 weeks of January 2023. This is almost a third of the 936 reports made in 2022 [17]. Caution should be taken when interpreting this data as it is possible there may be database accuracy problems such as the possibility of duplicate reports.

The Australian Bureau of Statistics (ABS) released a report on sexual violence in 2021 that included a report on women who have experienced sexual assault by a male perpetrator in the previous 10 years [18]. This reported data also included whether alcohol or other substances were a contributing factor. Of the 638,500 women who had experienced sexual assault it was estimated that 365,700 incidences had alcohol or other substances as a contributing factor and only 43,900 of these women reported the incident to the police [18].

4. Drink spiking

4.1. Definitions

Drink spiking, regardless of the intent of the perpetrator, is a distinct crime type, separate from drug facilitated sexual assaults [19]. Drink spiking is the intentional addition of a substance, be it licit or illicit to a person's drink without their knowledge or consent. The substance could even be the addition of more alcohol than what was expected in that drink [19,20].

4.2. Food and drink spiking laws in Australia

In most states and territories in Australia the food and drink spiking laws are grouped as the same law and the reported occurrences also fall under the same category, so separating drink spiking from food spiking is not possible [15,21–25]. Queensland is the only state in Australia that have specifically targeted drink spiking in their criminal code. This was brought into effect in 2006 [26,27]. These laws fall under the law about intoxication by deception as discussed under Australian law for DFSA.

4.3. Spiking statistics in Australia

In 2004 a paper was released from a national enquiry into drink spiking that was carried out over 2002–2003. The report was founded on data collected from a hotline that was setup for 1 month gaining a total of 201 people reporting drink spiking incidences [28]. Police data and sexual assault resource centre data were also utilised. The report roughly estimated that between July 1, 2002 and June 30, 2003 there were 3000–4000 drink spiking incidences, with approximately one third involving sexual assault [28]. This number was estimated by multiplying police report data by the rate of under-reporting calculated from victim self-report surveys [28]. Any further research into the rates of drink and food spiking was difficult to find and there have been no further investigations since the 2004 national report.

The NSW Bureau of Crime Statistics and Research (BOCSAR) released data showing that recorded drink spiking incidences had risen to 219 in 2022 compared to 128 in 2019 before Covid lockdowns [29]. Crime statistics on drink and food spiking are not publicly available from other Australian states and territories.

5. Symptoms and exacerbations

5.1. Symptoms

The point at which a person experiences adverse effects by any substance differs for everyone due to metabolic stability and pharmacodynamic response [30]. Therefore, it is difficult to determine from toxicological analysis of substances and their concentrations in samples collected from victims, whether they were incapacitated to the point they did not understand their situation or were unable to defend themselves.

5.1.1. GHB, GBL and 1,4-butanediol

Gamma-hydroxybutyrate (GHB) is an endogenous compound found in the central nervous system (CNS), specifically in the brain where it is a precursor to gamma-aminobutyric acid (GABA) an inhibitory neurotransmitter [31]. Gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) are industrial solvents that convert to GHB in the body and therefore have the same psychoactive effects [32]. It is the psychoactive effects that make these substances effective in DFSA.

Care must be taken with diagnosing GHB intoxication as the symptoms are similar to other CNS depressants and can easily be misdiagnosed [32]. Symptoms include euphoria, drowsiness, nystagmus, ataxia, memory loss, aggression, loss of consciousness, vomiting and apnoea [32,33]. Serious adverse effects include hypotension, hypothermia, bradycardia, respiratory depression, seizures, and coma [32,33]. Zaharna et al. also reported psychiatric effects such as anxiety, confusion, depression, suicidal ideation and abnormal dreams [34]. Due to the short elimination time of GHB most symptoms dissipate within 4–8 h. Withdrawal effects may include tremors, agitation, hallucinations, tachycardia, and hypertension [32,33].

5.1.2. Benzodiazepines and designer benzodiazepines

Benzodiazepines bind to the GABA-A receptor creating a conformational change and increasing the affinity for GABA [35]. This leads to a reduction in membrane potential and therefore neuronal firing. GABA-A receptors are located in the spinal cord, brain stem, cerebellum and limbic and cortical areas, and lower neuronal firing in these areas will result in CNS depression [35]. This is characterised by drowsiness, a relaxed state, slurred speech, confusion, disinhibition, and impairment of motor coordination and higher brain functions such as memory [35]. Their effects combined with their rapid action make benzodiazepines an ideal candidate to be used in DFSA. Furthermore, benzodiazepines that are eliminated quickly can also be difficult to detect in blood and urine samples [35].

In order to circumvent national and international drug laws, designer benzodiazepines have started to be synthesised with a rise in detection since 2014, for example etizolam and clonazolam in countries where these drugs are prohibited [35]. There is a lack of clinical or pharmacological data on such novel psychoactive substances (NPS) as they have not been approved for medical use [35]. Because their pharmacological effects and toxicity are largely unknown the effects of designer benzodiazepines are unpredictable [35]. Effects are further unpredictable when they are mixed with other substances and alcohol, and detection is hampered by the fact that there are no reference samples, and therefore they are not often screened for in analysis which leads to false negatives in DFSA cases [35]. Attempts are being made to alleviate these shortcomings, for example the Center for Forensic Science Research & Education NPS Discovery Program works in collaboration with forensic science, public health, emergency medicine, and criminal justice agencies to rapidly identify NPS associated with intoxications [36]. Additional analytical detection programs include The International Association of Forensic Toxicologists (TIAFT) HighResNPS high-resolution mass spectral NPS database [37].

Designer benzodiazepines are synthesised using varying methods such as selection of 1,4-benzodiazepines (Fig. 1) from literature or patent applications, or a logical combination of substituents; synthesis of active metabolites; addition of triazole groups or modification of etizolam [35]. While designer benzodiazepines are understudied, quantitative structure-activity relationship modelling suggests that their effects are also mediated through GABA-A receptors but that they have a higher affinity compared to prescription benzodiazepines [35]. Higher doses are correlated with a higher degree of impairment. Effects are increased by other CNS depressants such as alcohol [35].
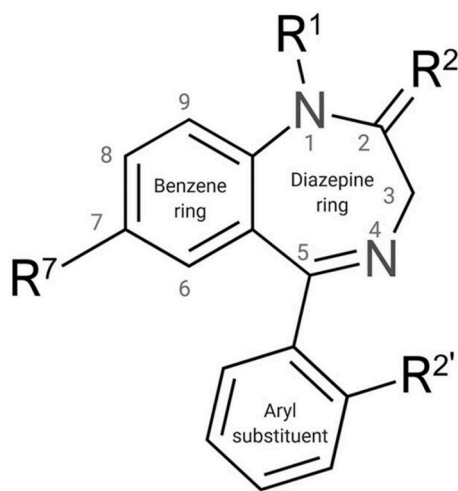
5.1.3. Alcohol

Alcohol, a neuro-inhibitor, is the most consumed and easily accessed psychoactive substance and is often involved in DFSA either alone or co-ingested with other substances [32]. How quickly alcohol exerts its effects is dependent on factors such as whether the person has any food in their stomach at the time [38]. This is because food can lower the efficacy of alcohol absorption due to prolonged gastric emptying duration and also due to Michaelis-Menten kinetic behaviour where lower amounts of alcohol are metabolised at a proportionately higher rate [38]. In some studies, fasting subjects have exhibited peak blood alcohol concentrations within 0.5–2 h (average 0.75–1.35 h), depending on dose and time since last meal. Non-fasting subjects exhibited peak levels within 1–6 h (average 1.06–2.12 h) [38].

Alcohol acts as a CNS depressant and depresses many other body functions. Alcohol can induce euphoria, altered vision, auditory discrimination, changes to decision making, alterations to response and reaction time [38]. The intensity of the side effects is proportional to the concentration of alcohol in the blood [38]. The different symptoms that may accompany the corresponding blood concentration of alcohol are outlined in Table 2 [38]. It should be noted that the impairment experienced while under the influence of alcohol can vary between individuals, since absorption, distribution, and elimination are affected by factors such as age, weight, and height [39].

Fig. 1. General chemical structure of a 1,4-benzodiazepine (core formed by the combination of a benzene ring and a diazepine ring) with a 5-aryl substituent. Image used under the Creative Commons Attribution – Non-Commercial License (CC BY NC 4.0) [35].

Table 2
Clinical symptoms at different blood alcohol concentrations [38].

Blood alcohol concentration (g/dL)	Stages of alcoholic influence	Clinical signs/symptoms
0.01–0.05	Subclinical	Influence/effects not apparent or obvious. Behaviour nearly normal by ordinary observation. Impairment detectable by special tests.
0.03–0.12	Euphoria	Mild euphoria, sociability, talkativeness. Increased self-confidence; decreased inhibitions. Diminution of attention, judgement, and control. Some sensory motor impairment. Slowed information processing. Loss of efficiency in critical performance tests.
0.09–0.25	Excitement	Emotional instability. Loss of critical judgement. Impairment of perception, memory, and comprehension. Decreased sensitory response; increased reaction time. Reduced visual acuity, peripheral vision, and glare recovery. Sensory motor incoordination; impaired balance. Drowsiness.
0.18–0.30	Confusion	Disorientation; mental confusion. Dizziness. Exaggerated emotional states (fear, sorrow, rage, etc). Disturbances of vision and perception of colour, form, motion, dimensions. Increased pain threshold. Increased muscular incoordination; staggering gait. Slurred speech. Apathy. Lethargy.
0.25–0.40	Stupor	General inertia. Approaching loss of motor functions. Markedly decreased response to stimuli. Marked muscular incoordination. Inability to stand or walk. Vomiting. Incontinence of urine faeces. Impaired consciousness. Sleep or stupor.
0.35–0.50	Coma	Complete unconsciousness; coma. Anesthesia; depressed or abolished reflexes. Subnormal temperature. Incontinence of urine and faeces. Impairment of circulation and respiration. Possible death.
0.45+	Death	Death from respiratory arrest.

5.1.4. Ketamine

Ketamine was first derived and administered to humans in the 1960s and produced a dissociative anesthetized state [40]. The (S)-ketamine isomer can produce especially dissociative properties and is known to be associated with the potential for abuse of ketamine. Ketamine is rapidly metabolised and its metabolites can be found in plasma as early as 40 min after administration [40]. Ketamine can produce illusory experiences, increases in perceptual acuity and paranoia within 10 min of intravenous (IV) administration showing its rapid entry into the brain [40]. Elimination half-life is between 2 and 4 h depending on route of administration [40].

Ketamine is an N-methyl D-aspartate receptor antagonist (NMDAR), which is likely to be responsible for its dissociative and psychotomimetic effects [40]. There is also evidence that the effects of ketamine on the monoamine system can produce its negative side effects such as acute psychosis, presumably through overactivation of 5-HT and D_2 receptor signalling [40].

These symptoms associated with ketamine can be dose-dependent with lower doses causing mood elevation, derealisation, depersonalisation, visual hallucinations and pleasant or unpleasant dreams, impairment of attention, learning ability and memory [41]. Higher doses of ketamine can cause vomiting, slurred speech, amnesia, impaired motor function, tachycardia, palpitations, agitation, and delirium. Flashbacks and visual disturbances can also occur days or weeks after exposure [41]. NMDAR blocking can lead to reductions in GABA release, which facilitates release of other neurotransmitters [40].

5.1.5. Oxycodone

Oxycodone belongs to the drug class of opiates and is a μ-opioid receptor agonist available in long and short acting forms [38,42]. The μ-opioid receptor is the main receptor responsible for CNS depression, euphoria, respiratory depression and decreased gastrointestinal motility [38]. Oxycodone produces drowsiness and muscle relaxation as well as pain relief via activation of the μ-opioid receptors in the CNS [38,42]. The respiratory depression caused by this activation is extremely dangerous especially for people with breathing difficulties. Death can result from respiratory failure or pulmonary aspiration of gastric contents or even noncardiogenic pulmonary oedema [42].

Oxycodone can cause effects such as a pleasant drowsy state, reduced anxiety, and a decreased sensation of pain in therapeutic doses [38]. Symptoms of oxycodone ingestion in a mild to moderate overdose include lethargy and pupils that are small and constricted [42]. Cognitive function, including memory, may be impaired [38]. Blood pressure and pulse rate may be decreased as well as bowel sounds being decreased and the muscles flaccid [42]. Risk of respiratory failure, apnoea, coma and death occur with higher doses and pulmonary oedema can still occur even after administration of naloxone to counteract the overdose [42]. Peak effects occur within 2–3 h but absorption may be slowed by gastrointestinal (GI) motility or effects may be delayed by slow-release forms [42].

5.1.6. Methamphetamine

Methamphetamine is a CNS stimulant that increases synaptic levels of monoamine neurotransmitters, mainly dopamine, through multiple pathways [43,44]. Methamphetamine can be used as a substance in DFSA due to the widespread belief that it lowers inhibitions and energises sexuality [43]. It is the release of monoamine neurotransmitters that cause the general effects of methamphetamine such as euphoria, alertness, improved athletic performance, improved attention and concentration, increased libido, thinking and problem-solving abilities and coordination [42–44]. Catecholamines are also released from the adrenal glands, which leads to adverse effects such as raised blood pressure, hyperthermia, haemorrhagic stroke and cardiac arrythmias [44]. Methamphetamine has also been reported to increase respiration rate, raise blood sugar levels, dilate the bronchi, divert blood flow from internal organs to skeletal muscle, constrict nasal mucous membranes and

reduce appetite [42,43]. Once the euphoria wears off psychological symptoms can include anxiety, insomnia, aggression, paranoia and hallucinations [44]. Methamphetamine is not commonly used for DFSA as it is not an incapacitating drug, but rather relies on the excitation of sexuality [42,43].

Acute clinical presentation of toxicity includes euphoria, talkativeness, anorexia, anxiety, restlessness, agitation, psychosis, seizures, and coma. Intracranial haemorrhage can also occur due to hypertension and cerebral vasculitis. Acute peripheral manifestations include sweating, tremor, muscle twitches and rigidity, grinding of teeth, tachycardia, hypertension, acute myocardial ischemia, and infarction [42]. Death may occur due to ventricular arrythmia, status epilepticus, intracranial haemorrhage, or hyperthermia [42].

5.2. Drug interactions and exacerbation of effects

Due to shared biochemical pathways and metabolising enzymes in the human body, the effects and efficacy of different substances and medications can be influenced by interactions with other food and chemical substances. One major potential for interactions is through the CYP450 enzymes. Different types of medications and substances available in Australia that are metabolised or affect metabolism through these enzymes are presented in Table A in appendix 1 [45]. Substances that lead to inhibition of CYP enzymes may lead to increased systemic exposure and therefore effects from the substance, whereas inducers will decrease exposure and effects of the parent compound, however some metabolites may be active [46].

In 2018, a study was performed to determine the daily use of prescription medication by Australians, and it was found that 9 million people used at least one prescription medication in one day [47]. The use of illicit drugs with prescription therapies has the potential to exacerbate or inhibit the effects of both the illicit drug and the prescription therapy and this can lead to toxic effects or a reduction in therapeutic activity [44]. Common interactions described in the reviewed literature are outlined in Table 3. It is not a complete and exhaustive list, and further investigations are needed specifically into the impact of the drug interactions in drink spiking scenarios.

5.2.1. The "problem" with alcohol

Alcohol has the potential for many interactions with other substances, and exacerbations of symptoms from both itself and other substances. Alcohol is metabolised by alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH) and CYP450 enzymes such as CYP2E1, CYP1A2 and CYP3A4 [32]. These enzymes are involved in the metabolism of many other substances and therefore inhibitors and inducers of these enzymes are influenced by alcohol. These interactions can affect the neuro-stimulatory or inhibitory effects of psychoactive drugs [32]. Ethanol also binds to the GABA-A receptors, which can cause interactions with other substances that also bind to this receptor or interact with the GABA pathway [35].

5.2.2. Gamma-hydroxybutyrate (GHB) and its precursors

Most orally ingested GHB undergoes first pass metabolism by CYP450 and the main biotransformation pathway is oxidation catalysed by GHB dehydrogenase [31]. Although it is known that up to 98 % of GHB is metabolised through the liver via first pass metabolism, not a lot is known about which specific enzymes and drug transporters are involved [49,50].

A double-blind study by Oliveto et al. extended findings of previous studies showing lower doses of GHB take effect faster and resolve faster than higher doses, which is consistent with non-linear pharmacokinetics [53]. However, they did note that behavioural side effects started at much lower doses (0.32 g/70 kg) than other studies [53]. The study performed was small with only 8 participants and only lower doses were examined, therefore some behavioural effects may have been potentially missed [53]. A review by Costa et al. concluded that the peak plasma

Table 3
Common interactions of drink spiking agents.

Spiking substance	Enzyme/Pathway involved	Interactions substance	Mechanism of interaction	Effect of interaction	Reference
GHB, GBL, 1,4-BD	CYP450 (we don't know specifically which enzymes) GABA pathway	Alcohol Sodium valproate Phenytoin Ethosuximibe Benzodiazepines	1,4-BD: ADH competition GABA-B (1,4-BD) GHB: CYP450 enzymes (possibility) These medications are GHB dehydrogenase inhibitors.	GHB and alcohol: ↑ gastrointestinal disturbances ↓ Blood pressure ↓O2 saturation ↑ C_{max} ↑ Half life ↑ Vomiting ↓ Consciousness ↑ Agitation 1,4-BD and alcohol: ↓ GHB concentration in brain and liver when alcohol given first. 25 % increase of exposure to sodium oxybate with GHB dehydrogenase inhibitors.	[31,32, 48–50] [51]
Ketamine and Esketamine	CYP2B6, CYP3A4, CYP2C9, CYP2A6	Methamphetamine Clarithromycin Clopidogrel Ketoconazole Grapefruit juice Orphenadrine St John's wort Lamotrigine	CYP3A inhibitor CYP2B6 inhibitor CYP3A4 inhibitor CYP3A inhibitor CYP2B6 inhibitor CYP3A4 inducer Prevents glutamate release	Additive hallucinations ↓in sedation ↑exposure to oral esketamine ↑plasma concentration of ketamine by 3.6 fold. ↓N-demethylation ↓N-demethylation ↑ C_{max} and half-life (by 24 %) of ketamine ↓N-demethylation ↓exposure and C_{max} ↓Memory impairment, perception abnormalities, psychotic symptoms.	[44] [46]
Benzodiazepines	CYP3A4, CYP2D6, GABA pathway	GHB, opioids Ethanol Cimetidine, fluvoxamine, tobacco	GABA pathway GABA-A receptors and CYP3A4 CYP enzymes	↑ CNS depression ↑ CNS depression Synergistic effect of symptoms Slower clearance of benzodiazepines Slower metabolism	[51,52] [35] [38]
Alcohol	CYP2E1, CYP1A2, CYP3A4, GABA pathway (binds to GABA-A receptors), ADH, ALDH	GHB, GBL, 1,4-BD Benzodiazepines	ADH competition, GABA-B (1,4-BD)	*See GHB, GBL and 1,4-BD* *See Benzodiazepines*	
Methamphetamine	CYP2D6	Morphine Ketamine *Theoretical/possible* Amitriptyline Doxepin Nortriptyline Imipramine Sodium oxybate (GHB) Moclobemide	Not indicated	↑ Morphine euphoria ↑Analgesia ↓ Respiratory depression from morphine Heart rate counterbalanced Pupil changes offset *See Ketamine* ↑Hypertension and CNS stimulation ↑Hypertension and CNS stimulation ↑Hypertension and CNS stimulation ↑Hypertension and CNS stimulation ↑ Seizures ↑ Hypertensive crisis	[44]

concentration is reached in 30–90 min and the half life is short at low doses and extended at higher doses [31].

In drink spiking, GHB, GBL or 1,4-BD are mostly used with alcohol [32]. The metabolic pathway of GHB and its precursors through the GABA receptors and where ethanol and ADH play a role is illustrated in Fig. 2 [32]. GHB has a high affinity for GABA-A receptors; however, its pharmacological and toxicological effects are attributed to its lower affinity binding at the GABA-B receptors [32]. Animal studies show that GHB can upregulate or downregulate the concentration of extracellular GABA, glutamic acid and dopamine in the brain, dependant on dose and the specific regions of the brain on which it acts [32].

Studies have shown that when GHB is used in combination with ethanol more side effects are seen even though there are no significant pharmacokinetic interactions [32,48]. In animal studies it was found that when ethanol was given before 1,4-BD the elevation of GHB concentrations in the brain and liver were inhibited due to competition for ADH by ethanol [32]. This further complicates clinical interpretation of GHB intoxication. Animal studies have revealed that co-administration of GHB and ethanol increases the half-life of GHB and inhibits its elimination by virtue of alcohol's inhibition of the oxidation metabolic pathways, thereby enhancing GHB's sedative effect [54].

As shown in Table 3, side effects include gastrointestinal disturbances, hypotension and decreased oxygen saturation levels as well as a small effect on clearance and bioavailability of GHB resulting in a greater maximum concentration (C_{max}) in the body and longer half-life [48]. The cardiac pharmacodynamic effects, decreased oxygen saturation levels and decreased blood pressure are statistically significant [32].

It should be noted that in the United States of America, GHB is legally available in a pharmaceutical formula referred to as sodium oxybate and used for the treatment of narcolepsy. Studies have shown that the concomitant use of GHB and some medications may have unintended effects. For example the combination of sodium valproate and sodium oxybate result in a 25 % increase in systemic exposure to sodium oxybate and in greater attention and working memory impairment and therefore this combination is discouraged [51].

5.2.3. Methamphetamine

When physiological measures were observed in the administration of morphine and amphetamines in combination, the effects of both were additive when they had common effects such as euphoria and analgesia [44]. They were antagonistic when they had opposing effects where
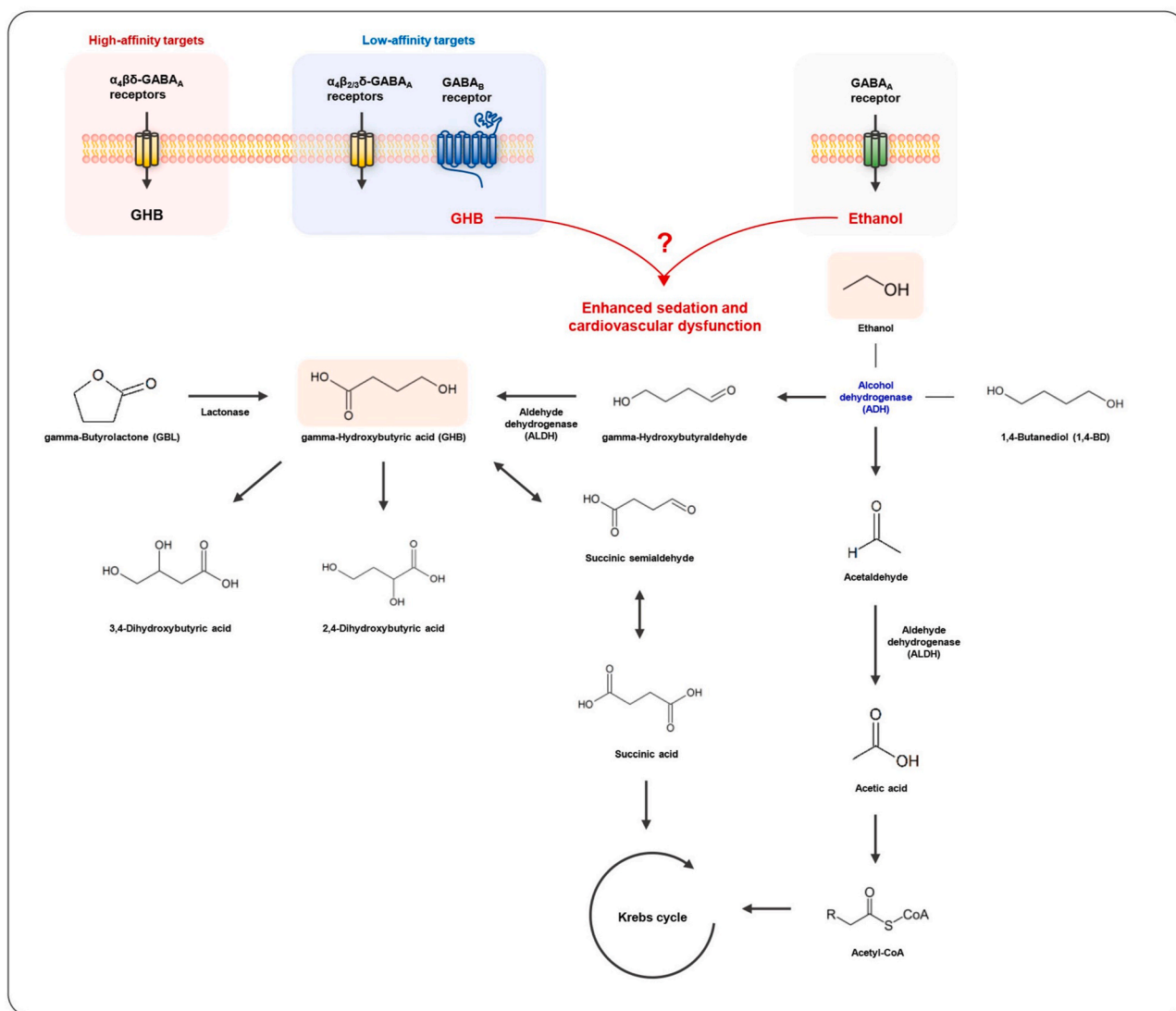
Fig. 2. The metabolic pathway of GHB and its precursors, GBL and 1,4-BD and the interaction of ethanol. Image used under the Creative Commons Attribution – Non-Commercial License (CC BY NC 4.0) [32].

heart rate, pupil changes, respiratory rate, respiratory depression and temperature were all offset [44].

The combination of amphetamine and ketamine did not produce a significant increase in euphoria compared to ketamine alone; however, it was significant compared to amphetamine use alone [55]. Hallucinations were significantly additive (p < 0.001). There was a clinically relevant reduction in the sedative effects of ketamine [44,55].

5.2.4. Benzodiazepines

Benzodiazepines, particularly diazepam and alprazolam, are the prescription medication most associated with concomitant use with GHB and its analogues [51]. Benzodiazepines are positive allosteric modulators and enhance the binding affinity of the GABA-A receptor for GABA [51]. Although GHB works on the GABA-B receptors it is known to be a precursor for GABA and therefore increases systemic GABA [52]. The risk of CNS depression is increased when substances such as GHB, ethanol or opioids are simultaneously consumed.

Alcohol also binds to the GABA-A receptor creating a synergistic effect with benzodiazepines and therefore more symptoms [35]. Both substances are also metabolised by cytochrome P450 enzymes creating slower clearance of benzodiazepines and therefore longer effects of the drug and higher chances of toxicity [35].

5.2.5. Ketamine

Metabolism of ketamine is through the intestines and first pass hepatic metabolism. Ketamine non-competitively antagonises the activation of NMDA receptors resulting in decreased synaptic plasticity [46]. GABAergic interneuron disinhibition and direct action of metabolites can play a part in drug effects [46].

Drugs that prevent glutamate release such as lamotrigine were shown to weaken dissociative symptoms such as learning and memory impairment, perception abnormalities and psychotic symptoms [46]. Other studies involving animal studies or human studies of small sample size also suggest pharmacodynamic interactions with memantine, clozapine, haloperidol and risperidone, however the clinical relevance still needs to be investigated [46].

An age and sex interaction with dissociative effects has also been observed [46]. At a dose of 0.5 mg/kg dissociative effects were observed in men but not women and a negative correlation between age and symptoms was observed in the male group [46]. Differences between the sexes could be attributable to the effects hormones have on induction of CYP enzymes involved in the metabolism of ketamine (i.e. E2 and progesterone cause induction of CYP2B6, CYP3A4 and CYP2A6) [46]. Another short term S-ketamine (also referred to as esketamine) clinical study revealed adverse effects such as dissociation, nausea, headache,

dizziness, and vertigo occurred in higher rates in women than men potentially due to higher plasma concentrations of S-ketamine active metabolites compared to males [46].

6. Biological detection

6.1. Body fluids

In DFSA cases that are reported within 48 h of the alleged assault it is recommended that both whole blood and urine samples should be collected. Protocols suggest that a minimum of two 50 mL samples of urine and two 5 mL samples of whole blood should be collected [56]. Analysis of these body fluids requires methodology and instrumentation that is highly sensitive and specific in order to detect substances used in DFSA [56]. Techniques recommended by the United Nations Guidelines for the forensic analysis of drugs facilitating sexual assault and other criminal acts are Liquid Chromatography-Mass Spectrometry (LC-MS), LC-MS-MS and Gas Chromatography-MS-MS (GC-MS-MS) [56].

6.2. Hair analysis

In cases of late reporting of the assault or if chronic exposure to a drug must be assessed, it is recommended that head hair should be collected at least 4 weeks after the alleged assault. Hair samples are an especially interesting matrix for drugs with a short half-life since hair provides a longer time window for their detection compared to blood and urine [35]. Qualitative analysis may be the only analysis possible if segmental analysis is not possible such as in the case of short hair. This shows that a drug was ingested but does not indicate dose or time ingested [56].

6.3. Factors affecting detection

Many of the drugs used in DFSA cause amnesiac effects which may cause a delay in the victim reporting the assault [56]. This causes complications in detection because many CNS depressants are not detectable after 24 h of ingestion, while some are detectable for four or more days [56]. Sample collection timeframes are critical. When a report has been made it is crucial that samples are collected immediately as even a delay of an hour or two can lead to substances being missed [56].

At the time of the incident report, it is important that a thorough list of any substances that the victim voluntarily ingested is collected [56]. This list should also include the estimate of the number of alcoholic drinks that the complainant consumed leading up to the assault [56]. This will help the laboratory staff account for any substances that should not be present but are being detected in analysis [56].

The CNS depressants that are sometimes used in DFSA, such as GHB, ketamine and some benzodiazepines, are potent and as such reports suggest that they may be administered in low doses [56]. The low doses and different physicochemical properties of many of these drugs create challenges for laboratories to be able to detect them using routine analytical methods [56]. GHB has a short half-life (30–50 min) and a low urine excretion rate (ca. 2 %) [32]. Combined with low levels of administration, these factors and the endogenous presence and post-mortem production of GHB, make the deliberate administration of GHB difficult to prove through quantification of GHB in biological samples such as blood and urine [32]. It may be postulated that if high levels of GHB have been administered its detection will be more obvious; however, the aforementioned factors affirm that collection timeframes will still play a critical role. It is therefore important that more sensitive methodology and instrumentation are used [56]. It is also possible that laboratory staff may not be aware of the broad range of drugs that are used in DFSA which means that targeted analysis may only focus on a small range of drugs and miss the ones that are used [56]. This is especially significant if the victim has consumed drugs (voluntarily or

spiked) purchased through illegal markets that are not available in Australia.

The presence of active metabolites can also complicate analysis, for example temazepam and oxazepam are metabolites of diazepam as shown in Fig. 3 [35]. The large number of benzodiazepines and designer benzodiazepines also creates analytical problems and requires highly selective techniques to determine which one is present. This is made even more difficult by many of the designer benzodiazepines being positional isomers [35]. Additional challenges include the lack of reference standards for analysis, lack of clinical data making it difficult to determine cut off values for one time drug intake, and lack of knowledge of metabolism and associated metabolites. This makes implementing methodology for analysis difficult especially for urine samples [35].

7. Prevalence of multiple substances

The prevalence of drugs most often detected in DFSA varied by country on a global level [1,57]. Reviews into the global epidemiology of toxicology analysis in DFSA found that alcohol and cannabis were generally the most prevalent substances around the world [1,57]. However, in some countries this did vary. For example, in Northern Ireland from 1999 to 2005 the most prevalent drug in DFSA was opioids, while in France from 2003 to 2007 the most prevalent drug was benzodiazepines [1,57].

The most recent Australian study that evaluated the presence of different substances detected in DFSA cases was released in 2019. This study evaluated data from 204 DFSA cases in Victoria Australia between January 2011 to December 2013 [11]. Upon review of the data, it was noted that this study reported on the presence of all substances that were detected and did not discriminate between substances that may have been used directly to perpetrate the assault from those that were present from self-use. Furthermore, the results highlighted the discrepancy between self-reported substance use and substances detected through toxicological blood sample analysis as shown in Fig. 4.

Of the alleged DFSA cases in this study, 93.6 % of complainants reported voluntary consumption of psychoactive substances before the incident. The number of cases that did not report voluntary consumption
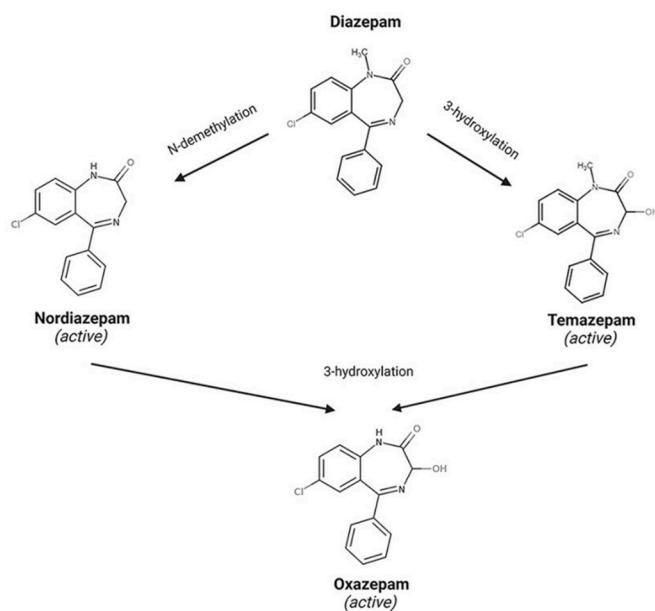

Fig. 3. Primary metabolic transformation pathways of the 1,4-benzodiazepine diazepam and chemical structures of its major metabolites. Image used under the Creative Commons Attribution – Non-Commercial License (CC BY NC 4.0) [35].
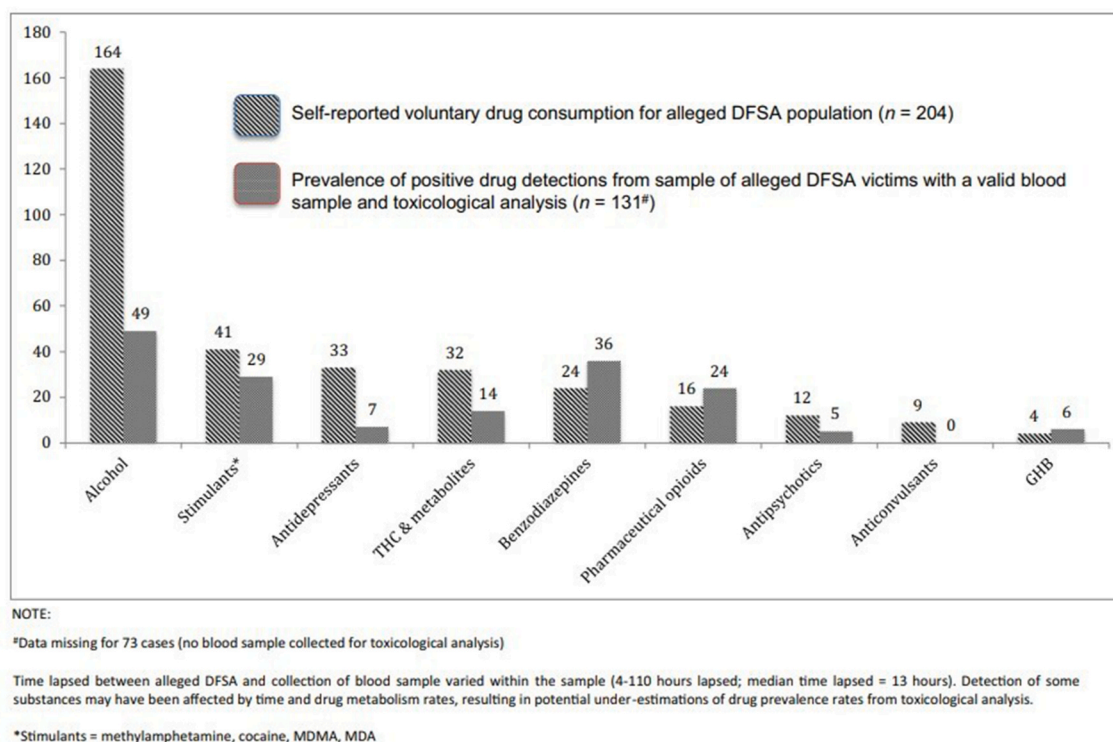
Fig. 4. Self-reported substances voluntarily taken compared to substances detected in blood samples. Image used with permission from Springer Nature Customer Service Centre (SNCSC) [11].

but produced a positive toxicology result was 7 % [11]. Combined consumption of alcohol, illicit drugs and some form of prescription medication was reported in 6.9 % of cases [11]. In this context illicit drug use includes abuse of prescription medication and was reported by over a quarter of complainants (27 %) [11]. A further 24 % reported prescribed use of medication known to have psychoactive properties [11].

The median delay from incident to sample collection was 6–17 h and this could be compromising the sensitivity of the analysis, particularly for shorter acting drugs [11]. This reiterates the importance of timely sample collection [11]. Medications such as benzodiazepines also have active metabolites which in such cases could result in multi-substance detection despite only one substance being consumed (i.e. Diazepam has metabolites temazepam and oxazepam) [11]. In such cases, quantification of results would be required to determine whether these compounds are a result of ingestion versus metabolism. No voluntary use of any substance was reported by 11 complainants, but psychoactive substances were detected in 4 of these individuals [11].

Limitations of this study include the fact that there were no means to verify the self-reporting of complainants as to their actual drug and alcohol use [11]. Many of the drugs also have a short half-life and given the typical delay in reporting of DFSA incidences and the popularity of GHB as a party drug, figures most likely underestimate the true prevalence of these drugs [11]. The data used were only collected from those that were reported to police and should only be considered as representative of "suspected DFSA" as not all investigations provided evidence that DFSA occurred [11]. The study also failed to capture the "dark figure" of sexual assault which is the numerous incidences that are not reported [11]. Also in Victoria, testing for GHB does not occur as routine toxicological analysis unless it is specifically requested (when the circumstances suggest GHB), this may also be contributing to underestimation of the prevalence of GHB in DFSA [11].

In 2009, a small study was conducted of 101 patients who presented to the emergency department of Sir Charles Gairdner Hospital (SCGH) and Joondalup Health Campus (JHC) in Western Australia, with

suspected drink spiking [20]. The final case numbers were 97 patients and of these, 9 cases were determined to be plausible drink spiking cases [20]. A summary of substances involved for all 97 cases is presented in Table 4.

There were limited results reported for substances found in all cases and only 4 cases had drugs detected, reported on. These substances included GHB, opiates, benzodiazepines, amphetamines, cannabinoids and ethanol [20]. The lack of comprehensive analytical results makes it impossible to gain a full understanding of the prevalence of substances in this study.

The National investigation into drink spiking that was released in 2004 was based on data collected over a 12-month period (July 1, 2002 to June 30, 2003). The investigation looked into estimating the rates of drink spiking over the year to try and determine its prevalence. The report did not focus on the prevalence of different substances in drink spiking; however, it did summarise the substances reported in 55 cases from police data [28]. The results are summarised below.

- 5 cases had benzodiazepines detected
- 6 cases had opiates detected
- 2 cases had amphetamines detected
- 5 Other
- 10 None
- 27 Unknown

Table 4
Summary of drugs detected and prevalence reported in a prospective study of 97 suspected drink spiking cases [20].

Substance	Self-reported	Detected
Alcohol	87	74
Amphetamines	0	10
Total illicit drugs	N/A	27

8. Implications of this review on the criminal justice system

The implications of these data to the criminal justice system are important. It is evident that criminal justice agents have challenges associated with prosecuting sexual assault cases. Reasons may include juror misconceptions formed by societal constructs such as social media, religious/cultural beliefs, and family dynamics [2,3]. Victims also struggle to report for a variety of reasons, including, feeling as though they could deal with it themselves, and not feeling like it was a serious enough offence, and by the time that they do decide to, physical evidence may be lost [16,58].

The challenges are exacerbated in cases of drug facilitated sexual assault. The deleterious effects of substances used in DFSA and specifically their psychoactive and cognitive altering effects may cloud the victims' recollection of events.

The difficulty associated with the pharmacological interpretation of analytical toxicology results is evident in the preceding discussion. To conclude that a victim has been drugged to facilitate a sexual assault is not straight forward, requiring an experienced pharmacologist to evaluate an array of toxicological and physiological data. The dissemination and communication of these results to non-scientific stakeholders in the criminal justice system in an understandable manner is also challenging. That stakeholders are relying on these results for resolution of DFSA cases is significant. More broadly, the unknowns of DFSA permeate across the criminal justice system and can include initial reporting issues and police investigative issues, through to expert testimony, lawyer summations and juror decision making. It is reasonable to expect that decisions on whether to proceed with an investigation and ultimately seek prosecution will be aided by the pharmacological conclusions, especially since they are based on objective deductions. This strong evidence base may also serve to dispel any preconceived notions or myths that lawyers, jurors and other criminal justice stakeholders may have with drug-facilitated sexual assaults. Such changes may empower victims to come forward and report these assaults in a more timely manner.

9. Conclusion

The literature reviewed in this article has shown that there is a large variety of substances that are shown to be present in DFSA. The symptoms experienced by drink spiking agents can be affected by any medications or illicit substances that a spiking victim may have voluntarily ingested. One common factor that all studies agree on is that it is crucial that early responders try to obtain an accurate medication history and substance consumption history to provide better context to the incident.

There is a lack of data on the prevalence of different substances involved in DFSA nationwide. The most recent data comes from Victoria and is now 10 years old. Drug trends can change quickly with new designer substances being discovered often and an update on the current environment is important.

This review has not considered genetic anomalies that may account for different metabolism of drugs and how this can affect how an individual may experience effects from a substance. It is important to understand that these substances may also have effects on prescription medications, potentially causing higher adverse effects and toxicity potential.

CRediT authorship contribution statement

Marie Lynam: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **David Keatley:** Writing – review & editing, Supervision, Methodology. **Garth Maker:** Writing – review & editing, Supervision, Methodology. **John Coumbaros:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

APPENDIX 1

Table A
CYP450 enzyme substrates and their inducers and inhibitors [38].

CYP enzyme	Substrates	Inducers	Inhibitors
CYP1A2	Agomelatine, amitriptyline, clozapine, duloxetine, erlotinib, fluvoxamine, imipramine, lidocaine, olanzapine, ondansetron, paracetamol, pirfenidone, propranolol, rasagiline, theophylline, warfarin (R-isomer), zolmitriptan	Omeprazole, phenobarbitol, phenytoin, rifampicin, ritonavir, tobacco smoking	Cannabidiol, ciprofloxacin, combined oral contraceptives, fluvoxamine, peginterferon alfa-2a, verapamil
CYP2B6	Bupropion, clopidogrel, cyclophosphamide, efavirenz, methadone, velpatasvir	Carbamazepine, efavirenz, phenobarbital, phenytoin, rifampicin, ritonavir	Clopidogrel, voriconazole
CYP2C8	Enzalutamide, ozanimod, paclitaxel, pioglitazone, velpatasvir	Rifampicin	Clopidogrel, gemfibrozil, trimethoprim
CYP2C9	Amitriptyline, celecoxib, cyclophosphamide, fluoxetine, glibenclamide, gliclazide, glimepride, glipizide, ibuprofen, phenytoin, rosuvastatin, siponimod, tamoxifen, voriconazole, warfarin (S-isomer)	Carbamazepine, enzalutamide, rifampicin, ritonavir, St John's wort	Amiodarone, efavirenz, fluconazole, fluoxetine, fluvoxamine, miconazole, ritonavir, voriconazole
CYP2C19	Amitriptyline, cannabidiol, citalopram, clopidogrel, cyclophosphamide, diazepam, escitalopram, esomeprazole, imipramine, lansoprazole, omeprazole, pantoprazole, phenobarbital, phenytoin, propranolol, vorionazole, warfarin (R-isomer)	Efavirenz, enzalutamide, rifampicin, ritonavir, St John's wort	Clarithromycin, efavirenz, esomeprazole, fluconazole, fluoxetine, fluvoxamine, ketoconazole, omeprazole, oxcarbazepine, topiramate, voriconazole

Table A (*continued*)

CYP enzyme	Substrates	Inducers	Inhibitors
CYP2D6	Amitriptyline, aripiprazole, atomoxetine, brexpiprazole, carvedilol, chlorpromazine, clozapine, codeine, dapoxetine, dextromethorphan, donepezil, duloxetine, flecainide, fluoxetine, fluvoxamine, galantamine, haloperidol, imipramine, lidocaine, metoclopramide, metoprolol, nebivolol, nortriptyline, olanzapine, ondansetron, oxycodone, paroxetine, perhexiline, propranolol, risperidone, tamoxifen, tolterodine, tramadol, venlafaxine, vortioxetine		Abiraterone, amiodarone, bupropion, celecoxib, cobicistat, duloxetine, fluoxetine, methadone, mirabegron, paroxetine, terbinafine
CYP3A4/ 5	Abiraterone, acalabrutinib, alprazolam, amiodarone, amitriptyline, apixaban, aripiprazole, atorvastatin, avanafil, betamethasone, brexpiprazole, buspirone, budesonide, cannabidiol, carbamazepine, ciclosporin, clarithromycin, clopidogrel, cobicistat, cocaine, codeine, colchicine, cyclophosphamide, dapoxetine, dasatinib, dexamethasone, diazepam, diltiazem, disopyramide, domperidone, donepezil, eletriptan, elvitegravir, enzalutamide, eplerenone, erythromycin, esomeprazole, ethinylestradiol, etonogestrel, etoricoxib, everolimus, felodipine, fentanyl, fluticasone, galantamine, guanfacine, haloperidol, hydrocortisone, ibrutinib, imatinib, imipramine, itraconazole, ivabradine, ketoconazole, lemborexant, lercanidipine, levonorgestrel, lidocaine, lopinavir, lurasidone, macitentan, methylprednisolone, midazolam, mirabegron, mirtazapine, nifedipine, nirmatrelvir, norethisterone, omeprazole, ondansetron, osimertinib, oxycodone, paclitaxel, palbociclib, perampanel, pazopanib, propranolol, quetiapine, quinine, reboxetine, risperidone, ritonavir, rivaroxaban, salmeterol, sildenafil, silodosin, simvastatin, siponimod, sirolimus, solifenacin, sunitinib, suvorexant, tacrolimus, tadalafil, tamoxifen, tiagabine, ticagrelor, tofacitinib, tramadol, triamcinolone, ulipristal, upadacitinib, vardenafil, velpatasvir, venetoclax, venlafaxine, verapamil, voriconazole, warfarin (R-isomer), ziprasidone, zolpidem	Armodafinil, carbamazepine, corticosteroids, efavirenz, enzalutamide, modafinil, phenobarbital, phenytoin, rifampicin, ritonavir, St John's wort	Amiodarone, atazanavir, ciclosporin, clarithromycin, cobicistat, diltiazem, erythromycin, fluconazole, fluvoxamine, grapefruit juice, itraconazole, ketoconazole, lopinavir, miconazole, palbociclib, ritonavir, ticagrelor, verapamil, voriconazole

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