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Criminal Poisoning: Drug-Facilitated Sexual Assault

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Sexual assault is defined as any undesired physical contact of a sexual nature perpetrated against another person. Sexual assault is much broader than the term rape, traditionally referred to as forced vaginal penetration of a woman by a male assailant [1]. In 2003 to 2004 an average of 204,370 sexual assaults were reported to law-enforcement agencies in the United States [2]. Because most sexual assaults are not reported, this national average is grossly underrepresented. The National Women's Study documented that 84% of women in their sample did not report their rapes to the police [3]. Among United States college students, approximately 25% of women reported experiencing completed or attempted rape [4]. In 2003, approximately 9% of high school students reported having been forced to have sexual intercourse [5]. Current estimates from available data indicate that 1 in 6 women will be the victim of a sexual assault at least once in her lifetime [6].

Drug-facilitated sexual assault (DFSA) is a complex and prevalent problem presenting to North American emergency departments (EDs) [7–10]. DFSA is defined as the use of a chemical agent to facilitate sexual assault. The reported prevalence of DFSA varies. The US Department of Justice estimates 44% of sexual assaults are perceived to occur under the influence of drugs or alcohol [2,11,12]. Often drugs and alcohol are used voluntarily by

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the victim and offender [11]. One multicenter study estimates 4.3% of the DFSAs examined were surreptitiously drugged victims and 35.4% of the DFSAs involved voluntarily use of illicit drugs [10]. Because of the absence of national scientific studies examining the prevalence of DFSAs in the United States, the exact number of alcohol and illicit drug–related sexual assaults is unknown. Yet an increasing number of independent testing programs are performing analyses on urine, blood, and hair samples collected from individuals who claim to have been sexually assaulted and believe that drugs were involved in the United Kingdom, France, and the United States [8,10,13,14]. These reports are attributable to an increased awareness of the problem and technological advances in rapid drug analyses.

Sexual assault victims and the emergency department

Identifying victims of DFSA and addressing specific medical and ultimately legal issues are essential roles of the emergency health care provider. When treating a victim of sexual assault, health care personnel have encountered numerous problems, such as not recognizing the urgency of medical attention, not treating the patient as a victim, and failing to document all available forensic evidence in a timely fashion. To help alleviate these problems, the Office for Victims of Crime (US Department of Justice) granted funding for implementing Sexual Assault Nurse Examiner (SANE) programs. A SANE is a registered nurse who works closely with medical staff and interacts with sexual assault crisis centers, law enforcement officers, prosecutors, judges, forensic laboratory staff, and child protective services workers to meet the multiple needs of victims and to hold offenders accountable for their crimes [15,16].

Physicians may encounter unique circumstances when treating DFSA victims because of potential delays when victims present for medical attention or not perceiving the patient as a sexual assault victim. The sedative-hypnotic and amnesic properties of the drugs used to facilitate a sexual assault can alter the victim's behavior, increase the victim's susceptibility to sexual assault, and diminish recollection of events surrounding the sexual assault. Often victims are reluctant to report incidents because of a sense of embarrassment, guilt, perceived responsibility, or acquaintance to their assaulter. Numerous reports have documented that the victims either do not seek medical attention or delay seeking medical treatment for 3 to 7 days after the assault [17–23]. Extended delays in collecting specimens from DFSAs may reduce the probability of detecting drugs potentially used to facilitate a sexual assault. Most of the drugs typically used in the facilitation of sexual assaults are rapidly absorbed and metabolized by the body, thereby rendering them difficult to detect in routine urine and blood drug screenings.

The most commonly reported symptoms from victims of DFSA are confusion, dizziness, drowsiness, impaired judgment, anterograde amnesia, lack of muscle control, loss of consciousness, reduced inhibitions, nausea,

Box 1. Common clinical effects reported by DFSA victims

Confusion
Dizziness
Anterograde amnesia
Impaired judgment
Reduced inhibitions
Drowsiness
Lack of muscle coordination
Loss of consciousness
Nausea
Vomiting
Hypotension
Bradycardia

hypotension, and bradycardia (Box 1). Victims of sexual assault may present to the ED with physical injuries resulting from the assault or clinical effects of the drugs. For example, a victim may present to the ED with one or a combination of the following: contusions, lacerations, broken bones, altered metal status, or intoxication [24]. The health care team treats the urgent injuries but may not inquire about the possibility of sexual assault. They may mistake the clinical effects of the drug used on the victim for self-induced substance abuse. Physicians should be aware that symptoms mimicking alcohol toxicity may point to the possibility of a DFSA. SANEs are trained in investigative interview techniques that may help a patient recall specific events leading up to injuries caused by DFSA. Physicians must recognize the need to provide prophylaxis against sexually transmitted disease, assess female patients for pregnancy risk, or provide follow-up care for medical and emotional needs. In addition, the emergency medical staff must be aware of the necessity of collecting sensitive forensic evidence if the victim decides to report the assault.

Forensic laboratory analyses

All reported sexual assault cases are tested for the abuser's DNA using a "rape kit." Care must be taken to ensure chain of custody. Semen, blood, urine, vaginal secretions, saliva, vaginal epithelial cells, hair, and other biologic evidence may be identified and genetically typed by a crime laboratory [23,25]. The information derived from the analysis can often help determine whether sexual contact occurred, provide information regarding the circumstances of the incident, and be compared with reference samples collected from patients and suspects. The most common form of DNA analysis used in crime labs for identification is called polymerase chain reaction (PCR). PCR allows the analysis of evidence samples of limited quality

and quantity by making millions of copies of very small amounts of DNA. Using an advanced form of PCR testing called short tandem repeats (STR), the laboratory is able to generate a DNA profile that can be compared with DNA from a suspect or a crime scene [25].

Sexual assault cases suspected of involving alcohol or drugs should have samples sent to the state Department of Forensics for toxicology testing. In addition to DNA testing, collection of urine and blood for forensic analysis at a state laboratory is typically performed to identify drugs used to facilitate sexual assault. Hair samples removed from the scalp may be requested for drug analysis when there is a significant delay in reporting a DFSA. Analysis of drugs present in hair can offer several advantages over urine and blood specimens in specific cases. The window of drug detection may be extended from days to weeks and even months because of the stability of the drug once it is deposited [26]. Analysis of sequential hair segments can provide a chronicle of drug use. Because the mechanisms by which drugs are deposited in hair are not well understood, prosecution of sexual abuse offenders based solely on results obtained from hair analysis is controversial [27]. Several factors are known to contribute to the deposition of drugs in hair: rate of hair growth, anatomic location of hair, thickness and color (melanin content) of hair, and environmental contamination. Drugs in hair are usually present in low concentrations (pg/mg to ng/mg); therefore, sensitive laboratory methods are required for detection [28–30].

Samples must be collected under strict chain-of-custody guidelines. A three-tier chain of testing may be used to analyze drugs used to facilitated sexual assault at many state forensic laboratories nationwide (Fig. 1). The first tier of testing quantitatively screens for ethanol from blood specimens using a gas chromatography with flame-ionization detection (GC-FID) or a gas chromatography linked to mass spectrometry detection (GC-MS). The second tier quantitates drugs of abuse, such as amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, lysergic acid diethylamide, opioids, γ-hydroxybutyrate (GHB), chloral hydrate, and dextromethorphan, using immunoassays and fluorescent polarization assays. Confirmation assays are performed using GC-MS or high-pressure liquid chromatography linked to tandem mass spectroscopy (HPLC-MS/MS) analyses. The third tier of testing, focusing on basic amine drugs (BAD), uses an extremely sensitive and specific means of screening (HPLC-MS/MS) for analysis of a broad array of 300 to 400 amine-containing compounds, such as tricyclic antidepressants and benzodiazepines, that may not be detected using tier two methodologies. In many states, victims perceived to be under the influence of alcohol and having a blood alcohol concentration greater than 0.08 are not typically analyzed beyond the level of first tier ethanol testing without specific medical documentation suspecting symptoms of additional drug exposure. Many DFS cases (other than alcohol) may therefore be undetected under the current screening protocols performed at some state forensic laboratories. Several published reports

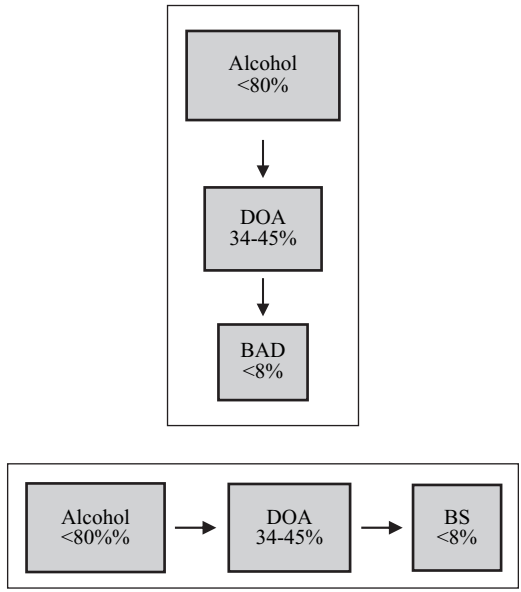

Fig. 1. Three-tier chain of testing for drug-facilitated sexual assault at state forensic laboratories. Recent publications indicate up to 80% of victims of sexual assaults are under the influence of alcohol; 34% to 45% of sexual assaults are under the influence of drugs of abuse; and less than 8% are under the influence of other basic amine drugs.

document 34% to 45% of victims of sexual assault are under the influence of drugs of abuse (DOA); 8% are under the influence of drugs not typically detected by standard DOA methods (eg, BAD) [7,8,10,21,31]. It is important for physicians and SANE teams to document suspicions of drugs in the patient's medical record, especially in cases of sexual assault. Documentation of these suspicions justifies drug-specific analyses by the state forensic laboratory. These analytic results are mandatory for the prosecution of sexual predators.

The Drug-Induced Rape Prevention and Punishment Act of 1996 (Public Law 104-305) modified 21 U.S.C. § 841 to provide penalties of up to 20 years' imprisonment and fines for people who intend to commit a crime of violence (including rape) by distributing a controlled substance to another individual without that individual's knowledge. This act provides specific definitions of controlled substances and crimes of violence that assist prosecutors in maximizing the penalties against sexual predators. Controlled substances are categorized as schedule I to V drugs by the US Drug Enforcement Administration (DEA) (Box 2). Extensive efforts have focused on documenting detection limits for common drugs used to facilitate sexual assault to aid in prosecution of sexual predators [10]. Without the extensive efforts of medical staff, forensic toxicologists, police, and judicial officials these penalties against sexual assault offenders cannot be implemented.

Box 2. Classification of scheduled drugs in the United States

Schedule I drugs

The substance has a high potential for abuse.
The substance has no currently accepted medical use in treatment in the United States.
There is a lack of accepted safety for use of the substance under medical supervision.
The drugs are not available by prescription and are deemed to have no medical use.

Schedule II drugs

The substance has a high potential for abuse.
The substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.
Abuse of the substances may lead to severe psychologic or physical dependence.
The drugs or other substances are only available by prescription, and distribution is carefully controlled and monitored by the DEA.

Schedule III drugs

The substance has less potential for abuse than the drugs or other substances in schedules I/II.
The substance has a currently accepted medical use in treatment in the United States.
Abuse of the substance may lead to moderate or low physical dependence or high psychologic dependence.
The drugs or other substances are available only by prescription, although control of wholesale distribution is somewhat less stringent than schedule II drugs.

Schedule IV drugs

The drug or other substance has a low potential for abuse relative to the drugs or other substances in schedule III.
The drug or other substance has a currently accepted medical use in treatment in the United States.
Abuse of the drug or other substance may lead to limited physical dependence or psychologic dependence relative to the drugs or other substances in schedule III.
The drugs are available only by prescription, although control of wholesale distribution is somewhat less stringent than schedule III drugs.

Schedule V drugs
The drug or other substance has a low potential for abuse relative to the drugs or other substances in schedule IV.
The drug or other substance has a currently accepted medical use in treatment in the United States.
Abuse of the drug or other substance may lead to limited physical dependence or psychologic dependence relative to the drugs or other substances in schedule IV.
Schedule V drugs are sometimes available without a prescription.

In addition to providing immediate, prophylactic, and follow-up medical care to the sexual assault victim, physicians need to implement resources necessary to maintain the integrity of physical evidence, document the victim's examination results/interpretation and interview history, and serve as an expert opinion during judicial proceedings. Integration of all these events is necessary to assist a victim of DFSA and support the prosecution of the sexual predator [11,32].

What drugs are used to facilitate sexual assault?

Most sexual assaults have been linked to the abuse of alcohol [7,9,31,33,34]. It is commonly accepted that there is a high degree of correlation between alcohol intoxication and the risk for being sexually assaulted [10]. In recent years, however, there has been increased attention in the literature to people using other drugs to render their victims unconscious or lower their level of resistance with the intent to sexually assault them [14,20,35,36]. In addition to alcohol, the drugs most often implicated in DFSAs are GHB, flunitrazepam, and ketamine, although others, including other benzodiazepines and sedative-hypnotics, are used also (Box 3). These drugs share similar characteristics for producing sedation, hypnosis, and anterograde amnesia. These effects often rapidly incapacitate victims and the effects can be intensified when they are willingly or involuntarily taken with alcohol. Because of the sedative and amnesic properties of these drugs, victims often have no memory of an assault, only an awareness or sense that they were violated.

Ethanol

The most common drug associated with DFSA is alcohol [7]. Because most sexual assault cases are not reported, the percent of alcohol-associated sexual assault cases varies greatly (30%–75%). Because of the prevalence of

Box 3. Drugs used to facilitate sexual assault

Ethanol
Chloral hydrate
Benzodiazepines
Nonbenzodiazepine sedative-hypnotics
GHB
Ketamine
Opioids
Dextromethorphan
Barbiturates
Anticholinergics
Antihistamines

alcohol consumption by college students, numerous institutions across the United States offer health information programs focused on increasing the awareness of alcohol-associated sexual assaults [37,38]. These programs heighten awareness that alcohol is a drug often used to facilitate sexual assault and they assist victims in finding medical and legal aid.

Clinical effects

The clinical effects of alcohol are dose and time dependent. Ethanol metabolism follows zero-order kinetics. Although the rate of metabolism varies from person to person, because of phenotypic differences in alcohol dehydrogenase and metabolic tolerance in chronic drinkers, the reported average rate of metabolism is found to be constant (about 15 mL/dL/h) [39,40]. The clinical effects of ethanol intoxication include impaired judgment, incoordination, behavioral changes, ataxia, cognitive slowing, memory impairment, nausea, vomiting, diplopia, and lethargy. Depending on a person's pre-existing tolerance, respiratory depression, coma, and death may occur at levels of 300 to 400 mg/dL. It takes little volume to intoxicate a person. For example, to achieve levels of intoxication of 200 mg/dL requires consumption of about 100 mL of absolute ethanol in a 70 kg adult. Many liquors contain 40% to 50% ethanol; therefore six to seven shots (30 mL per shot) of liquor in rapid succession may result in an ethanol level of 200 mg/dL [41]. Significantly lower concentrations of ethanol are required to incapacitate (or increase the susceptibility for sexual assault in) a smaller-framed victim or a person who voluntarily or unwillingly coingests drugs with sedative or psychotropic effects.

Laboratory monitoring

Analysis of ethanol levels from urine and blood specimens are commonly evaluated in many clinical laboratories, private laboratories, and state

laboratories. Blood alcohol is determined using enzymatic analyses. Blood alcohol and urine analysis confirmation is performed using a GC-FID or gas GC-MS [42,43]. Although most clinical laboratories set the limit of detection at 10 mg/dL, published reports document the limits of detection for ethanol using GC-FID and GC-MS as low as 1 and 0.02 mg/dL, respectively [40,42]. These sensitive detection assays may therefore extend the time (12–24 hours) required for submitting specimens from sexual assault cases and enhance the possibility of prosecuting a perpetrator for a DFSA crime. Back-tracking calculations (15 mg/dL/h and one half-life every 4 h) are often performed to estimate the blood alcohol level at a given time before the actual time the blood sample was taken. Caution must be used with this method of reverse extrapolation, because chronic alcohol abusers and heavy drinkers metabolize alcohol faster than social or naïve drinkers [40].

Choral hydrate "Mickey Finn"

Anecdotal reports of combining drugs and alcohol to assault victims date back to the early nineteenth and twentieth centuries. An infamous example is Mickey Finn, the proprietor of Chicago's Lone Star Saloon in the late nineteenth and early twentieth centuries. He was alleged to have drugged his customers with the addition of chloral hydrate to their ethanol-based beverages and subsequently robbed them.

Chloral hydrate is classified as a nonbarbiturate hypnotic. It is an inexpensive transparent crystalline compound that can be easily dissolved in beverages. It was first synthesized in 1832 and was one of the original depressants developed for the specific purpose of inducing sleep. At therapeutic single doses, chloral hydrate has a rapid onset (30 minutes), produces minimal side effects, and is useful in alleviating sleeplessness caused by pain or insomnia in a relatively short time. The abuse and misuse of this drug and subsequent introduction of newer sedatives (barbiturates and benzodiazepines) led to its decline for medicinal purposes.

Clinical effects

The diagnosis of chloral hydrate can be difficult to differentiate from alcohol, benzodiazepine, and barbiturate intoxication, because all share similar clinical effects. Although the exact mechanism of action of chloral hydrate has not been determined, it is a general central nervous system (CNS) depressant having sedative effects with minimal analgesic effects when administered independently. At low doses (<20 mg/kg) symptoms may include relaxation, dizziness, slurred speech, confusion, disorientation, euphoria, irritability, and hypersensitivity rash. At higher doses (>50 mg/kg) chloral hydrate can cause hypotension, hypothermia, hypoventilation, tachydysrhythmia, nausea, vomiting, diarrhea, headache, and amnesia [44]. The elimination half-life ($t_{1/2}$) of chloral hydrate is 4 to 12 hours

[44,45]. If coingested with alcohol, chloral hydrate metabolism may be seriously impaired. Because ethanol and chloral hydrate are both metabolized by CYP2E1 and alcohol dehydrogenase, coingestion may not only exacerbate their clinical effects but also prolong their duration of action [45,46].

Laboratory monitoring

Chloral hydrate is not detected on routine, commercially available drug screens. Quantification of chloral hydrate and its metabolites trichloroethanol (TCE), TCE-glucuronide, and trichloroacetic acid can be detected in less than 1 mL plasma using HPLC-MS/MS and capillary gas chromatography with electron-capture detection (GC/ECD) [47–49]. Limit of detection for chloral hydrate is 5 ng/mL and 10 ng/mL for its metabolites using GC/ECD [49].

Benzodiazepines

Benzodiazepines are a large class of drugs that bind to specific receptor sites on γ-aminobutyric acid (GABA)-mediated receptor synapses in the brain. Benzodiazepines are believed to increase GABA-mediated chloride conduction into the postsynaptic neuron, prolonging hyperpolarization of the cell and diminishing synaptic transmission, thereby producing its sedative properties. Drugs within this class vary in their affinity and efficacy at their receptor. This variation results in differences in the degree of clinical effects, time of onset, and rate of metabolism. Ultimately, with a faster rate of onset there tends to be greater abuse potential [50]. Although national statistics are not available to estimate the prevalence of benzodiazepines used to facilitate sexual assault, recent publications estimate approximately 8% of sexual assault cases are positive for benzodiazepines [7,8,10,28]. Flunitrazepam (Rohypnol) is the most frequently reported (4% of sexual assault cases) date rape drug belonging to the benzodiazepine class [7]. The high incidence of flunitrazepam in DFSA is partially attributable to the development and implementation of specific toxicologic tests in response to increased public awareness resulting in a testing bias [7,9,32,51,52]. Other benzodiazepines that have been reported in sexual assault victims are diazepam, triazolam, temazepam, tetrazepam, and clonazepam [13,19,28,53,54].

Flunitrazepam is a fast-acting sedative-hypnotic and is categorized as a schedule I drug in the United States. Because it is still licensed for use in Europe, Asia, and Latin America for sedation and treatment of insomnia, sexual predators can acquire this drug through illegal trafficking [55]. On the street, flunitrazepam is known as Roofies, Forget pill, Rubies, Ruffies, Rope, Roopies, Ropies, Rib, R-2, Roaches, Papas, Mexican Valium and Circles. Sexual assault predators use flunitrazepam because it can be easily dissolved into a beverage, it is relatively tasteless and odorless, it quickly incapacitates victims, and routine drug screens do not detect its presence.

Clinical effects

Flunitrazepam is more potent than diazepam owing to its slower dissociation from the GABA receptor [56–58]. It is rapidly absorbed and distributed into tissues on oral administration. The onset of its sedative, amnesic, hypnotic, and disinhibitory effects can occur within 20 to 30 minutes [56]. Although the effects of flunitrazepam occur rapidly when used alone, it is often coingested with alcohol, which amplifies its effects [59,60]. Initial symptoms may consist of dizziness, disorientation, lack of coordination, and slurred speech, which mimic alcohol intoxication. Other unique effects are anterograde amnesia as early as 15 minutes after oral administration [20]. Rapid alternation of hot and cold flashes may precipitously be followed by loss of consciousness. Large doses (>2 g) have produced aspiration, muscular hypotonia, hypotension, bradycardia, coma, and death [13,21,54,61]. The clinical diagnosis of flunitrazepam can be difficult to differentiate from alcohol intoxication.

Laboratory monitoring

Patients who have a complaint of sexual assault who seem intoxicated or have anterograde amnesia should be suspected of unknowingly ingesting a benzodiazepine. Commonly marketed drug screens turn positive for most benzodiazepines, but not all (ie, flunitrazepam; other benzodiazepines marketed outside the United States). Point of care testing is available for benzodiazepines in the ED, but clinical samples must be confirmed and documented under strict chain-of-custody procedures [62]. In addition to adhering to standard rape protocols, a urine or hair specimen should be analyzed for benzodiazepine and their metabolites by a state forensic laboratory using GC-MS or HPLC-MS/MS [30,61,63–65]. Flunitrazepam metabolites can be detected up to 60 hours in the urine using an automated immunoassay system (EMIT II), categorized as a general toxicologic screen that is available in many hospital laboratories. Flunitrazepam metabolites can be detected and as early as 7 days in hair samples (HPLC-MS/MS) [54].

Nonbenzodiazepine hypnotics

Zopiclone, eszopiclone, zolpidem, and zaleplon belong to a new generation of sedative-hypnotics that are structurally different from benzodiazepines (Fig. 2). Like benzodiazepines, these drugs modulate the $GABA_A$ receptor chloride channel by binding to the benzodiazepine (BZ) receptors, otherwise known as the omega (ω_1) receptors, in the brain [66] without binding to peripheral BZ receptors [67,68]. These drugs therefore have fewer muscle-relaxant properties [68]. The rapid-onset and amnesic properties of this class of drugs can result in disinhibition, passivity, and retrograde amnesia, making it a favored DFSA drug. These drugs require only a low dose

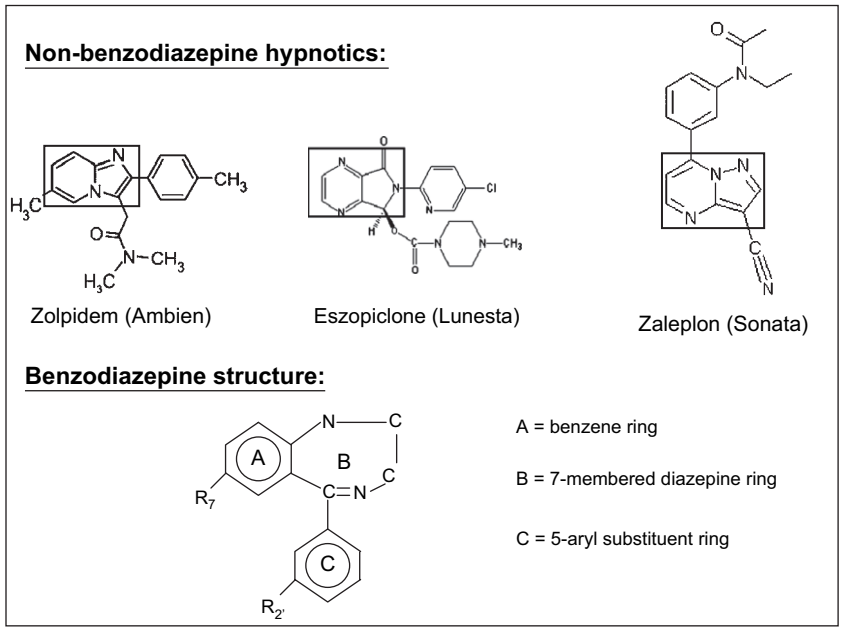

Fig. 2. Structural similarities between benzodiazepine and nonbenzodiazepine sedative-hypnotics. The nonbenzodiazepine hypnotics share a common pyrimidine ring (*boxed*) structure containing various chemical side groups. Members of the benzodiazepine class share common structural features: (*A*) benzene ring; (*B*) 7-membered diazepine ring; (*C*) 5-aryl substituent ring.

to cause an effect and are rapidly metabolized. Because of the amnesic properties of these drugs, victims are often confused following the event and may be delayed in reporting the sexual assault [7]. Commonly used drug screens do not test for these substances; therefore, suspected amnestic drug use must be documented to justify more elaborate drug testing by state agencies. All these characteristics make these drugs potential agents in DFSA.

Recognition of these new-generation sleep aids as potential agents used in facilitating sexual assault has only recently been reported in the United States, United Kingdom, and France [7,8,21,69,70]. Few published reports in the United States tested sexual assault victims for the presence of zolpidem, and unfortunately those that tested did not report its prevalence rate [61,71]. Because of the increased prevalence of short-acting nonbarbiturate use on college campuses and across the United States and minimal data estimating the prevalence of these drugs used in sexual assault, there is a strong demand for national systematic studies to estimate the prevalence of nonbarbiturate sleep aids in DFSA.

Most of the nonbenzodiazepine sleep aids are available through a prescription as a schedule IV drug and are readily available in North American social circles (ie, college campuses). These highly prescribed insomnia drugs are available in a tablet form that may be crushed and dissolved into

a beverage or food of an unsuspecting victim. All may produce additive CNS-depressant effects when coadministered with other psychotropic medications, such as anticonvulsants, antihistamines, ethanol, and other drugs that themselves produce CNS depression.

Clinical effects and drug characteristics

Zolpidem

Zolpidem is available as an immediate- or extended-release tablet. An average oral dose of 10 to 15 mg has a rapid onset of clinical symptoms between 10 and 30 minutes. Clinical effects peak at approximately 1.5 hours for immediate release, duration lasts for about 6 to 8 hours for both immediate- and extended-release preparations, and the $t_{1/2}$ is approximately 2.5 hours [72]. Clinical effects may include dizziness, psychomotor, confusion, nervousness, amnesia, and hallucinations. There is evidence of minimal respiratory depression when used as a single agent, but zolpidem may produce additive CNS-depressive effects and death when coadministered with other sedatives [73].

Zaleplon

Zaleplon is available as an immediate-release tablet or capsule. An average oral dose of 10 to 15 mg has a rapid onset of clinical symptoms of approximately 10 to 30 minutes. Although the $t_{1/2}$ for zaleplon is about 1 hour, the duration of clinical effects may persist for greater than 6 hours. This persistence may be because of the higher affinity of zaleplon for specific α_2 and α_3 subunits of the GABA receptor, unlike zolpidem or zopiclone [74]. Clinical effects may include somnolence, dizziness, psychomotor, confusion, nervousness, rebound amnesia, and hallucinations. Higher doses ($>$40–60 mg) may cause increased CNS effects and impaired motor skills [44].

Eszopiclone

The precise mechanism of action of eszopiclone is unknown, but its effect is believed to result from its interaction with GABA-receptor complexes at binding domains located close to or allosterically coupled to benzodiazepine receptors. An average dose of 2 to 3 mg has a rapid onset of clinical symptoms occurring in approximately 30 minutes. Both immediate and extended-release forms are available. Clinical effects may include dizziness, psychomotor dysfunction, confusion, nervousness, amnesia, and hallucinations. Nausea, vomiting, and anticholinergic effects have been reported in less than 10% of patients [75]. By itself, eszopiclone has not been reported to cause respiratory depression, but it may produce additive CNS-depressant effects when coadministered with other sedatives. The clinical effects of eszopiclone are longer in duration compared with zopiclone or zolpidem, with a $t_{1/2}$ of 6 hours [67].

Zopiclone

Zopiclone is not currently available in the United States. It is the racemic mixture of two stereoisomers; the active stereoisomer is eszopiclone. Clinical effects therefore are similar to eszopiclone.

Laboratory analysis

Because of the amnesic properties of these drugs, victims often may not report the sexual assault for several days. Sensitive analytic techniques are necessary to detect these drugs and their metabolites in urine or hair samples after a single dose. Unfortunately, the drug screens found in most hospital laboratories do not detect the new generation short-acting class of sleep aids called nonbenzodiazepine hypnotics. Although numerous private facilities are now capable of detecting nonbenzodiazepine drugs, most state forensic laboratories integrate these HPLC-MS/MS amine-detection tests into their repertoire of available toxicologic screens. Because testing of nonbenzodiazepine drugs is a third tier of testing in many state forensic laboratories, only cases containing documentation suspecting drugs other than alcohol or common drugs of abuse may be analyzed in this manner.

γ-hydroxybutyrate, 1,4-butanediol, and γ-butyrolactone

Since March 2000, GHB and the synthetic precursor compounds, 1,4-butanediol (1,4-BD) or γ-butyrolactone (GBL), have been schedule I agents in the United States. The availability of GHB has been restricted in numerous countries, such as Australia, Brunei, Canada, Finland, France, Italy, Japan, New Zealand, Norway, the United States, South Africa, Sweden, Switzerland, and the United Kingdom. GHB can be illegally purchased as an odorless and colorless liquid form or an off-white powder that easily dissolves in liquids. GHB is sold on the street under various names, including Liquid ecstasy, Liquid X, Liquid E, Gib, Natural sleep-500, Somatomax, Georgia home boy, Grievous bodily harm, Soap, Scoop, Easy lay, Salty water, G-riffick, Cherry menth, and Organic Quaalude.

Sexual assault perpetrators have used GHB as a fast and effective means of intoxication for their victims. Although national statistics are not available to estimate the prevalence of GHB used to facilitate sexual assault, recent publications estimate approximately 4% of alleged sexual assault cases in the United States are positive for GHB [7,9,21,76]. Numerous GHB-related DFSA cases have also been published in the United Kingdom and France [21,70,77,78]. Sexual assault cases report victims have either voluntarily or unwillingly ingested GHB on a date, at social parties, or in "rave" dance party settings.

GHB is a naturally occurring substance produced in the brain. GHB is reversibly metabolized to GABA through multiple endogenous enzymes (Fig. 3) [79–81]. Illicit consumption of GHB, or the synthetic GHB

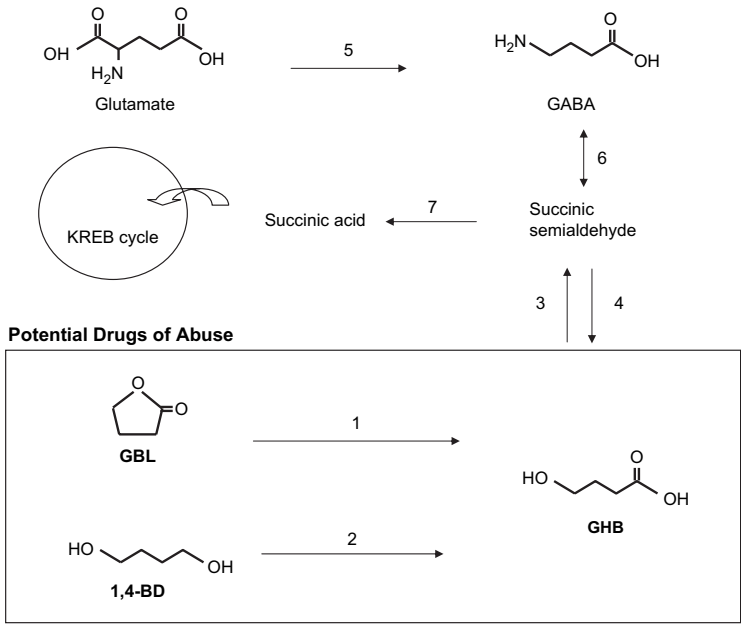

Fig. 3. GHB metabolism. In the brain, γ-hydroxybutyrate (GHB) is reversibly metabolized into γ-aminobutyric acid (GABA) using the endogenous enzyme GABA transaminase. Illicit consumption of 1,4-butanediol (1,4-BD) or γ-butyrolactone (GBL) may also be metabolized into GABA by way of multiple endogenous enzyme systems. The endogenous metabolic enzymes involved are (*1*) lactonase, or nonenzymatic ester hydrolysis; (*2*) alcohol dehydrogenase or aldehyde dehydrogenase; (*3*) GHB dehydrogenase; (*4*) succinic semialdehyde reductase or NADPH-dependent aldehyde reductase; (*5*) glutamic acid decarboxylase; (*6*) GABA transaminase; (*7*) succinic semialdehyde dehydrogenase. Potential drugs of abuse are boxed and in bold.

precursor compounds 1,4-BD or GBL, promotes GABA activity [81]. In addition to increased metabolism to GABA, GHB has direct effects on the CNS by binding GHB-specific receptors. Animal studies support the existence of distinct GHB receptors in the CNS, because GHB can still act as a neuromodulator even in the presence of the $GABA_B$-specific inhibitor baclofen and in $GABA_B$ receptor knockout mice [82–84]. GHB is suggested to increase dopamine levels in the substantia nigra, potentiate the endogenous opioid system, and mediate GABA transmission [81].

GHB, 1,4-BD, and GBL are frequently sold on the street and at rave dance parties in liquid form and are colorless and tasteless. These drugs can be easily masked in drinks and consumed by willing or unwilling victims of sexual assault.

Clinical effects

Onset of GHB effects occurs in approximately 15 to 30 minutes, depending on the dose (average 1–5 g) and chemical purity. Clinical effects are

augmented in the presence of coadministered drugs, such as alcohol and other sedative drugs [85]. The clinical effects are dose dependent and typically last 3 to 6 hours. Initial symptoms include drowsiness, disorientation, and dizziness. Low dose (<1 g) produces mild symptoms, such as CNS depression, amnesia, hypotonia, and reduced inhibitions (similar to alcohol). Larger doses, 1 to 2 g, cause increased somnolence, drowsiness, dizziness, bradycardia, and bradypnea. High doses (>2 g) often interfere with motor coordination and balance, induce significant respiratory depression and bradypnea, Cheyne-Stokes respiration, nausea, vomiting, diminished cardiac output, coma, and death [73,86,87].

Laboratory monitoring

GHB is metabolized quickly ($t_{1/2} \sim 30$ minutes) and is not detected on most routine urine and serum toxicology screens. Several state and private laboratories have the ability to perform analyses on blood, urine, and hair samples using GC-FID or GC-MS [30,76,88]. Testing sensitivity is not the primary issue with GHB; timely collection of sample collection is. Because of its rapid metabolism, plasma samples should be collected less than 6 to 8 hours after ingestion and urine samples collected in less than 10 to 12 hours. Urine and plasma may exhibit endogenous levels of GHB within 8 to 12 hours after ingestion (<1 mg/dL in urine, <4 mg/L in blood/plasma) [89]. Samples reaching endogenous levels make it difficult to legally prove GHB doping in sexual assault cases. Exogenous levels of GHB have been detected in hair samples at 7 days postintoxication [70]. The timely presentation of the patient for medical attention and physician recognition of GHB symptoms presented by sexually assaulted victims are essential for prosecution of sexual offenders.

Ketamine

Ketamine (ketamine hydrochloride) is an analgesic and general anesthetic that produces a rapid-acting dissociative effect. It was first synthesized in1962 as a medical anesthetic for humans and animals. Today ketamine is approved for use in emergency medicine, critical care, and veterinary medicine. The prosecution of a ketamine-facilitated sexual assault perpetrator in 1993 and the increase in its illicit use prompted the DEA to restrict ketamine as a schedule III drug in August 1999. Ketamine is outlawed in the United Kingdom and classified as a schedule I narcotic in Canada. Ketamine is available by prescription as a tablet or a parenteral solution. On the street, ketamine is sold under various names, including K, Ket, Special K, Super acid, Super C, Spesh, Vitamin K, Smack K, Kit-kat, Keller, Barry Keddle, HOSS, The Hoos, Hossalar, Kurdamin, Kiddie, Wonk, Regreta, and Tranq. Ketamine generally is sold illegally as either a colorless, odorless liquid or as a white or off-white powder. Liquid ketamine can be rapidly

injected intramuscularly. Either liquid or powder form can be easily disguised in a victim's beverage. Ketamine powder can even be sprinkled onto marijuana or tobacco and smoked.

Clinical effects

The onset of action after oral ingestion can be as little as 20 minutes [90]. Hallucinatory effects may be short-acting (<1 hour) but so intense that the victim may have trouble discerning reality [77]. Ketamine produces effects similar to phencyclidine and dextromethorphan. The onset of clinical effects is rapid and depends on route of administration. Anesthesia effects by way of intramuscular injection take as little 20 to 30 seconds, oral ingestion about 30 minutes, and nasal insufflation approximately 10 minutes [44,91,92]. The $t_{1/2}$ for ketamine is 2 to 3 hours [93]. Duration of anesthetic effects is dose dependent (usually <1 hour) and effects on the senses, judgment, and coordination can have a longer duration (~6–24 hours). Ketamine can cause delirium, amnesia, dissociative anesthesia hallucinations, hypersalivation, nystagmus, impaired motor function, hypertension, and potentially fatal respiratory problems. Effects on blood pressure and respiratory depression can be significantly enhanced when coingested with alcohol.

Laboratory monitoring

No immunoassays are available to detect ketamine at this time. Ketamine and its active metabolites norketamine and dehydronorketamine can be detected in urine samples using GC-MS or LC-MS analyses. The limit of detection is 1 ng/mL [94,95].

Barbiturates

Barbiturates can produce a wide range of CNS depression, ranging from mild sedation to general anesthesia. They are categorized based on their ultrashort-acting, short-acting, medium-acting, or long-acting duration of clinical effects (Table 1). Barbiturates are classified as schedule II to IV drugs based on their rapid time of onset and duration and their abuse potential. They can inhibit excitatory or enhance inhibitory synaptic transmission. Barbiturates inhibit excitatory synaptic transmission by reducing glutamate-induced depolarizations [96]. Barbiturates enhance the effectiveness of GABA transmission by directly activating chloride channels and depressing synaptic transmission at virtually all synapses. Barbiturates effect the duration, not frequency, of GABA channel opening, thereby hyperpolarizing and decreasing the firing rate of neurons [97].

The estimated prevalence of barbiturates used to facilitate sexual assault is only about 1%, because of limited availability in recent years [7]. The

Table 1
Characterization of barbiturates

Chemical name	Duration	DEA scheduled classification
Thiamylal	Ultrashort	Schedule III
Thiopental (“truth serum”)	Ultrashort	Schedule III
Methohexital	Ultrashort	Schedule IV
Amobarbital	Short	Schedule II
Aprobarbital	Short	Schedule II
Butabarbital	Short	Schedule II
Pentobarbital	Short	Schedule II
Secobarbital	Short	Schedule II
Butalbital	Medium	Schedule II
Cyclobarbital	Medium	Schedule III
Talbutal	Medium	Schedule II
Methylphenobarbital	Long	Schedule IV
Mephobarbital	Long	Schedule IV
Phenobarbital	Long	Schedule IV

ultrashort-acting barbiturate thiopental was recently reportedly used to facilitate a sexual assault in Italy [98]. The slang terms for these drugs are barbs, barbies, sleepers, blue bullets, nembies, pink ladies, and red devils.

Clinical effects

Onset of clinical symptoms varies (15–40 minutes) and the degree of symptoms is dose and drug dependent. Clinical effects may consist of CNS and respiratory depression, hypothermia, bullous skin lesions, aspiration pneumonia, nystagmus, dysarthria, ataxia, drowsiness hypothermia, renal failure, muscle necrosis, hypotension, hypoglycemia, coma, and death [44]. Coingestion with alcohol or other CNS depressants enhances toxic effects. Duration of effects depends on the dose and the specific drug itself.

Laboratory monitoring

Detection periods for barbiturates vary greatly depending on the specific barbiturate being used. Each barbiturate has a different half-life in the body. Ultrashort- and short-acting barbiturates (thiopental, secobarbital) may only be detected in the urine for 1 to 4 days, whereas longer-duration barbiturates (phenobarbital) can be detected for 2 to 3 weeks. Many larger hospital facilities can detect most barbiturates from urine samples with an extensive toxicology screen using competitive fluorescence polarization immunoassays [99]. Detection depends on the dose and half-life of the specific drug being tested. State forensic laboratories have extremely sensitive assays, such as HPLC-MS/MS and GC/MS-MS, capable of detecting very low concentrations of barbiturates from urine and hair samples that can greatly expand the window of detection [98].

Opioids

Several opioid drugs are included in the analysis for date-rape drugs. Although these drugs are highly regulated or only available by prescription, illicit use of these drugs is still common nationwide. Opiates are the naturally derived narcotics, such as heroin, morphine, and codeine. These are isolated from the poppy plant *Papaver somniferum*. Heroin is the only opiate currently listed as a schedule I drug, primarily owing to the rapid onset of action, clinical effects (euphoria and sedation), and its high abuse potential. Metabolism of codeine to morphine is required for its analgesic effects (Fig. 4). Opioids include the semisynthetic compounds, such as hydrocodone, hydromorphone, oxycodone, and fentanyl. These drugs all have potent analgesic and sedative properties but different pharmacokinetic properties. These drugs are available in powder or tablet forms having a slightly bitter taste. Either form can be hidden in a beverage, smoked, or inhaled. These drugs can easily be used to incapacitate a sexual assault victim.

Clinical effects

The major clinical effects of opioids are analgesia, sedation, pinpoint pupils (miosis), euphoria, and respiratory depression [44]. Pinpoint pupils may not always be seen in all and should not be solely relied on for the diagnosis. The onset of clinical symptoms varies with the drug and the method of administration. Onset of effects for oral ingestion of opioids varies, but most are within 30 to 60 minutes; inhalation or injection is more rapid (within 5 minutes). Duration of clinical effects depends on the specific opioid drug. Naloxone reversal of sedation may clue the health care team to the presence of opioids.

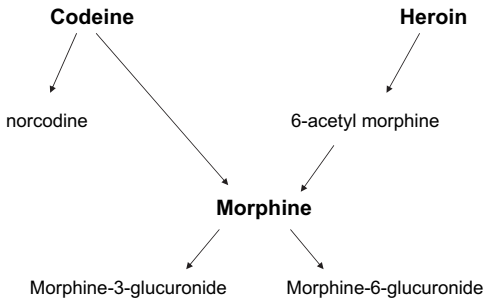

Fig. 4. The opiate metabolites detected by immunoassay and GC-MS. A small percentage of codeine is converted to active metabolites by CYP2D6 to norcodeine (~10%), morphine (~10%), and hydrocodone (<2%). Heroin is rapidly metabolized to 6-acetyl morphine and then hydrolyzed to morphine; both are active metabolites. Morphine is conjugated to inactive metabolite morphine-3-glucuronide and the potent metabolite morphine-6-glucuronide.

Laboratory monitoring

In the hospital setting commercial immunoassays are designed to detect naturally occurring opiates (morphine and codeine). Specific GC-MS analysis protocols are available for confirming natural, synthetic, and semisynthetic opioid compounds from urine specimens. In addition, specific immunoassays and GC-MS protocols are available for detection of methadone and propoxyphene. Documentation of suspected opioid-related clinical symptoms assists state laboratories in detecting and confirming a diverse array of opioid compounds potentially used to incapacitate a victim of sexual assault.

Over-the-counter medications

Several medications that may be used to facilitate sexual assault are legally available without a prescription. Although these medications are diverse in class, their clinical effects may be used to incapacitate a sexual assault victim. Sexual predators may use these drugs because their effects are exacerbated with alcohol and can easily be used to adulterate a victim's drink.

Dextromethorphan

Dextromethorphan is sold over the counter as an antitussive agent alone or in combination with other cough aids (pseudoephedrine, acetaminophen, chlorpheniramine). It is the *d*-isomer of the potent opiate analgesic 3-methoxy-N-methylmorphine (levorphanol). Although dextromethorphan is structurally related to opioids, it is devoid of analgesic or sedative effects at therapeutic doses. Dextromethorphan is metabolized by CYP2D6 to a more potent metabolite, dextrorphan [100,101]. Dextrorphan is a stronger noncompetitive antagonist than dextromethorphan for the N-methyl-D-aspartate glutamate receptor [102]. These properties promote its use in treatment of neuropathic and postoperative pain management [102–106].

Even though dextromethorphan has a strong safety profile at therapeutic concentrations, it is highly abused for its sedative, hallucinogenic, short-term memory loss, dissociative, and euphoric properties at high doses. Although no cases have been published using dextromethorphan in DFSA, large doses can impair a victim's sensory and motor skills making it a potential drug for use in DFSA. Dextromethorphan is widely available over the counter in liquid, tablet, and gel capsule formulations, or over the internet in a white power form [107]. Although liquid dextromethorphan has a bad taste, crystallized and powder forms can easily be disguised in drinks and consumed by an unknowing victim. Street names for dextromethorphan are Dex, DXM, Tuss, Robo, Skittles, Triple-C, and Syrup.

Despite the safety of dextromethorphan when used at the recommended dosage ($<$120 mg/day), higher doses can result in nausea, vomiting, seizure,

loss of consciousness, irregular heartbeat, and death [108,109]. Serotonin syndrome may develop in patients on other serotoninergic drugs because of additive inhibition of serotonin reuptake by dextromethorphan [110]. Patients who have genetic variations in CYP2D6 causing rapid metabolism of dextromethorphan may present with greater clinical effects [111–113].

Anticholinergics

Scopolamine and atropine are anticholinergic agents of the belladonna alkaloid family. Scopolamine is used for motion sickness and as an adjunct to anesthesia to produce sedation and amnesia. Scopolamine produces a higher degree of sedation than atropine because of the higher degree of penetration into the CNS. The high potency, rapid onset, and amnestic effects of scopolamine have lead to its being included on testing for DFSA cases [114].

The major clinical effects of scopolamine are classic anticholinergic symptoms, such as dilated pupils (mydriasis), dry mouth, hallucinations, and slurred speech. Other clinical effects are tachycardia, vomiting, confusion, and amnesia. Large doses can result in coma, seizures, and death. The onset of clinical symptoms is fast (within 15–30 minutes) and duration of effects may last up to 2 to 3 days.

Antihistamines

Antihistamines are typically used in the treatment of allergies or insomnia. First-generation antihistamines (diphenhydramine, chlorpheniramine) readily cross the blood-brain barrier, producing greater CNS effects than second-generation antihistamines (fexofenadine). First-generation antihistamines hit central and peripheral histamine (H_1 and H_2) receptors, but are still widely used because they are effective and inexpensive [115]. Few cases have documented the use of diphenhydramine in DFSA [32], yet the anticholinergic proprieties of antihistamines make this a class of drugs feasible for DFSA.

First-generation antihistamines can cause CNS depression and anticholinergic symptoms, such as sedation, hallucinations, confusion, agitation, and psychosis. Onset of action is 15 to 60 minutes and clinical symptoms typically last 4 to 6 hours [116]. Large doses can exacerbate these effects and can even result in cardiotoxicity, coma, and seizures [117]. Coingestion with alcohol or other sedative-hypnotic drugs may increase some or all of these clinical symptoms. Victims may have difficulty distinguishing events of a sexual assault because of the anticholinergic effects of the drugs. A victim may not present for hours or days after a sexual assault, therefore, because of the clinical effects of the drugs themselves.

Laboratory monitoring

Analysis of blood or urine antihistamine levels is not typically performed in the health care setting. Because these nonprescription drugs are

commonly used by the general public, interpretation of a positive test result is problematic. Dextromethorphan cross-reacts with most immunoassays for opioid compounds. Confirmation protocols for dextromethorphan are available using GC-MS. Most anticholinergics are detected using GC-MS. Urine specimens are sufficient for the highly specific GC-MS and HPLC-MS/MS analyses [47,118]. When a victim of sexual assault reports or presents with specific signs and symptoms, it is imperative that the medical staff document these findings and relay this information to the laboratory on collecting the necessary biologic samples. Without such documentation, state forensic laboratories may overlook the need to specifically analyze biologic specimens for these agents.

Summary

DFSA is a complex and ever-prevalent problem presenting to North American emergency departments. Emergency personnel should consider DFSA in patients who are amnestic to the specific details of the event following a reported sexual assault. The presence of ethanol or a positive routine drug screen in a sexual assault victim does not exclude the potential for another drug being present. In addition, a negative routine drug screen does not exclude all potential agents that are used in DFSA. It is imperative for emergency personnel to clearly document the history and the presenting signs and symptoms to assist laboratory personnel to hone in and detect the agent used in a DFSA.

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