Mini review

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Potential impact of drug effects, availability, pharmacokinetics, and screening on estimates of drugs implicated in cases of assault

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Drug-facilitated sexual assault (DFSA) is a serious and troubling crime. It is important to know if and how different drugs might be used to facilitate assault in order to deter such crime. There are a number of ways in which drugs that are used for DFSA might not be detected by routine screens. The purpose of this analysis was to draw reasonable inferences regarding drugs with a high likelihood of being used for DFSA and not being detected by routine screens. National data from poison control centres, hospital emergency rooms, and law enforcement seizures were used to evaluate the relative magnitude of problems and illicit availability associated with different classes of drugs. General drug classes were examined to include additional drugs that might be used for DFSA on the basis of their amnesic effects, widespread availability, and pharmacokinetics (i.e. short half-life). The benzodiazepine-site ligands zolpidem and eszopiclone, 'club drugs' GHB and ketamine, muscle relaxants such as carisoprodol, and antihistamines such as diphenhydramine were identified as drugs that might be used for DFSA and remain undetected by routine screens. Future studies that are designed to examine the role of these drugs in DFSA cases could provide better estimates of their use for DFSA. A better understanding of what is being missed in DFSA cases might help prioritize the development of new assays, provide rationale for the availability of particular assays for routine testing, and inform practitioners and the general public of the potential DFSA risks of certain drugs.

Keywords: date-rape; sexual assault; zolpidem; GHB; carisoprodol

Introduction

Reports that say that something hasn't happened are always interesting to me, because as we know, there are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns – the ones we don't know we don't know.

- Donald Rumsfeld, Former US Secretary of Defense

Drug-facilitated assault refers to a criminal act such as violence, robbery, or sexual assault (i.e. rape) that is perpetrated against a victim while he or she is intoxicated. Drug-facilitated sexual assault (DFSA) is perhaps the most common type of drug-facilitated assault; however, the prevalence of DFSA is difficult to determine for a variety of reasons. In the USA, data from the Department of Justice Bureau of Justice Statistics estimate that 190 000 – 272 000 rapes and sexual assaults have occurred each year from 2004 to 2008.[1–5] National surveillance systems do not differentiate between sexual assaults in which an intoxicant was involved and those in which an intoxicant was not involved. However, a retrospective study of sexual assault cases in Canada from 1993 to 1999 reported that 12% of all sexual assault cases met criteria for suspected DFSA[6] and a prospective study of sexual assault admissions in Canada from 2005 to 2007 reported that 21% of sexual assault cases met criteria for suspected DFSA.[7] Taken together, these data suggest that DFSA affects a large number of individuals every year.

There are several factors that contribute to the difficulty of estimating the prevalence of DFSA, each of which likely results in an underestimation of the true prevalence. First, the submission of biological specimens for analysis is voluntary and might not occur for a number of reasons. Amnesia and confusion surrounding the circumstances of the DFSA might result in a failure to collect or submit biological specimens for testing. Social stigma, embarrassment, or lack of desire to endure an invasive examination might also decrease the likelihood that individuals will report a DFSA or submit specimens for forensic testing. The voluntary consumption of illicit drugs by a victim of DFSA might also result in the refusal to participate in forensic testing for fear of medical or legal consequences. Indeed, a recent study has shown that victims of DFSA are more likely to have consumed alcohol (odds ratio 4.00), over-the-counter medications (odds ratio 3.97), or illicit drugs (odds ratio 1.71) as compared to other victims of sexual assault.[9] Second, limitations of testing or the ability to detect drugs in biological matrices at the time of submission are also likely to result in an underestimate of the true prevalence of DFSA. A relative unavailability of routine laboratory tests with high specificity and sensitivity to detect a wide range of drugs that might be used for DFSA could limit the number of true positives that are detected. Drugs with shorter half-lives would also be expected to be detected at lower rates than those with

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longer half-lives, thereby resulting in an underestimation of the prevalence by which those specific drugs are used for DFSA.

Previous studies that have examined the types of drugs present in cases of DFSA have typically identified alcohol, cannabinoids, cocaine, and benzodiazepines as the most commonly detected drugs,[7,9–13] which is consistent with the relative rates of the voluntary (i.e. recreational) use of these drugs in the USA.[14] Other drugs and drug classes that are commonly detected, but at rates lower than those listed above include opioids, amphetamines, gamma-hydroxybutyrate (GHB), and barbiturates.[7,9–13] Thus, the drugs and drug classes listed above crudely represent 'what we know' about the use of drugs in cases of DFSA. The focus of this paper is not so much on what we think we know about the drugs that are used for DFSA (i.e. the 'known knowns'), but rather what we likely do not know with regard to drugs that are used for DFSA (i.e. the 'unknown unknowns'). This paper is not a review of analytical methods *per se*, but rather what we should be looking for and which analyses might be of greatest interest in cases of suspected DFSA. A better understanding of what we do not know or what we are likely missing in cases of DFSA (i.e. shifting 'unknown unknowns' to 'known unknowns') might help prioritize the development of new assays, provide rationale for the availability of particular assays for routine testing, and inform practitioners and the general public of the potential DFSA risks of certain drugs.

Methods

The starting point for this review was the published forensic studies of drugs involved in cases of suspected DFSA already described.[7,9–13] Drugs and drug classes were identified from those studies and eliminated or expanded for future consideration according to the rationale now described. First, alcohol has been identified as the drug most frequently used for DFSA and is therefore considered a 'known' drug involved in DFSA. Cannabis is the most commonly used recreational illicit drug in the USA and has a relatively long window of detection of 1–6 days after acute use,[15] which is likely to result in positive identifications of cannabis that are unrelated to sexual assault. Moreover, surreptitious administration of alcohol or cannabis to individuals who were otherwise not using the drug voluntarily was deemed to be possible, but unlikely and these two drugs were therefore not considered as likely 'unknowns'. Second, drugs that are frequently used voluntarily (i.e. recreationally) and have been detected in cases of suspected DFSA, but for which evidence of amnesic effects are lacking, were also excluded from further consideration. Although drugs used for DFSA may be used with the intent of producing global impairment or decreasing 'inhibitions', drugs that produce some level of amnesia or loss of memory for the details of the assault itself are more likely to go unreported or undetected. Therefore, cocaine, amphetamines, and opioids were excluded from further consideration as likely 'unknowns' due to their previous identification in the studies described earlier and their lack of amnesic effects.[16–18] Third, an important characteristic of 'unknown' drugs that might be used for DFSA and remain undetected is a relatively short half-life. Drugs with short half-lives might remain undetected even when analyses are performed soon after an assault. Data from one study reported that in 167 cases of suspected DFSA, the median time from assault to examination was 18 h.[6] Thus, even with rapid reporting to an emergency room or clinic after an assault, approximately 96% of a drug with a half-life of 3 h would be metabolized after 15 h (5 half-lives of the drug) and such a drug would be unlikely to be detected in the absence of drug metabolites that could be identified. On the basis of half-life, the barbiturate class of drugs was excluded from further consideration as likely 'unknowns' in light of the fact that most of the barbiturates have half-lives greater than 8–10 h (methohexital is an exception with a half-life of 3–5 h[19]). The remaining 'known drugs' that have been indentified from cases of suspected DFSA include the benzodiazepines and GHB. These drugs represent the more general class of sedative/hypnotic drugs and 'club drugs'; some of which are known to have amnesic effects,[20,21] short-half lives, and/or widespread commercial and illicit availability. On the basis of these characteristics, these general classes of drugs were expanded to include licit and illicit drugs that might be used in cases of DFSA (i.e. potential unknowns).

Data from 2004–2008 (the five most recent years as of this writing) from three independent national reporting services in the USA were used to estimate the relative prevalence of problems associated with specific drugs including: benzodiazepines and non-benzodiazepine ligands that bind to the benzodiazepine site (e.g. zolpidem); 'club drugs' such as GHB, ketamine, and phencyclidine (PCP); muscle relaxants such as carisoprodol, cyclobenzaprine, and metaxolone; and antihistamines such as diphenhydramine, hydroxyzine, and promethazine. Reports of drug exposures from calls to poison control centres were used as a measure of problems associated with those drugs that caused substantial concern (i.e. enough to contact the poison control centre). Data were taken from the American Association of Poison Control Centers' Annual Reports from the National Poison Data System database, which provides information on all of the poisonings reported to one of the approximately 60 poison control centres in a calendar year. Each report of a drug exposure to a poison control centre is coded as unintentional (e.g. medication error, environmental exposure), intentional (e.g. suspected suicide, drug abuse), adverse reaction, unknown, or other (malicious, contamination/tampering, or drug withdrawal). Drug exposures coded as 'other' are presented here because that category contains the type of exposure most relevant to DFSA – malicious intent; however, it should be noted that this category also contains exposures related to contamination/tampering and drug withdrawal because each of these types of exposure are not reported separately.

National estimates of drug-related visits to hospital emergency departments from the Drug Abuse Warning Network (DAWN) were used as a measure of problems associated with those drugs that resulted in a visit to the emergency room. DAWN is a public health surveillance system that monitors drug-related hospital emergency department visits and drug-related deaths in non-Federal hospitals operating 24-hour emergency departments. Data were taken from the annual DAWN reports. In each participating hospital, emergency department medical records are reviewed retrospectively to identify visits that involved recent drug use. Cases are coded as a drug-related visit if they include: drug abuse or misuse, suicide attempt, overmedication, adverse reaction, accidental ingestion, malicious poisoning, underage drinking, or patients seeking detoxification or drug abuse treatment. Thus, as with the poison control centre data, the DAWN data contain cases that are most relevant to DFSA – malicious poisoning; however, these data also contain a large number of other types of cases as well.

Drugs identified through the Drug Enforcement Administration (DEA) National Forensic Laboratory Information System (NFLIS) were used as a measure of the illicit use and availability of

prescription and illegal drugs. The NFLIS systematically collects results from drug chemistry analyses of drugs seized by law enforcement that are conducted by approximately 250–300 state and local forensic laboratories nationwide. Data were taken from each of the annual reports of the NFLIS from all NFLIS laboratories that reported six or more months of data (including data from labs not included in the national sample for all drugs except carisoprodol and PCP for which the national sample data were the only data available).

Results

What we (think we) know

Data from the annual reports of the American Association of Poison Control Centers 2004–2008 show that drug exposures coded as 'other', which include malicious intent, contamination/tampering, and drug withdrawal were greatest for benzodiazepines (286 exposures in 2008; reports do not differentiate between different benzodiazepines) followed by GHB (55 exposures in 2008, including GHB precursors and analogs). As shown in Figure 1A, considerably lower numbers of exposures coded as 'other' were reported in 2008 for diphenhydramine (18), PCP (5), carisoprodol (5), cyclobenzaprine (3), and ketamine (2).

Data from the annual DAWN reports 2004–2008 were similar to those from the poison control centres and showed that drug-related emergency department visits were greatest for alprazolam (39 063 visits in 2008) and PCP (37 266 visits in 2008), each of which had increased markedly in recent years (Figure 1B). Other benzodiazepines such as clonazepam, diazepam, and lorazepam ranked behind PCP and also exhibited increasing trends with 14 270, 8572, and 6040 visits, respectively, in 2008 (Figure 1B). Drugs that were related to fewer than 5000 emergency department visits in 2008 included (in order of prevalence): carisoprodol (4123), diphenhydramine (3152), zolpidem (2061), GHB (1441), cyclobenzaprine (1202), temazepam (755), and ketamine (344).

Data from the NFLIS reflecting the identity of drugs seized by law enforcement were also similar to data from the poison control centres and the DAWN data. Of these drugs of interest, alprazolam was by far the most common drug identified with 31 414 analyzed substances testing positive for alprazolam and an increasing trend of substances identified as alprazolam from 2004 to 2008 (Figure 1C). Other benzodiazepines, such as clonazepam and diazepam, ranked behind alprazolam and also exhibited increasing trends with 7771 and 6287 substances identified as clonazepam and diazepam, respectively, in 2008 (Figure 1C). Following the benzodiazepines, the national estimate for substances identified as PCP was 5968, which represents an approximately 50% increase from 2007 to 2008. The next most frequently identified substance was carisoprodol, which was identified in each of the years 2004–2008 as one of the top 25 most frequently identified drugs, has exhibited an increasing trend across those years, and was identified in 4291 of substances analyzed in 2008 (Figure 1C). Other drugs that were identified fewer than 2000 times in 2008 included (in order of prevalence): lorazepam (1846), ketamine (1338), temazepam (395), GHB (226), chlordiazepoxide (90), triazolam (52), midazolam (13), and flunitrazepam (6).

Thus, data from three independent national reporting services in the USA that report problems associated with drug exposure, problems requiring medical care, and drugs seized by law enforcement, respectively, indicate that benzodiazepines are likely to be of greatest concern, followed by PCP and carisoprodol, and potentially GHB and diphenhydramine, depending on the type of data (Figure 1). The following section will evaluate the likelihood that these classes of drugs would be used for DFSA and the possibility that the use of similar drugs might be occurring undetected.

What we do not know

Benzodiazepines and other positive $GABA_A$ receptor modulators

There are several factors that might increase the likelihood a drug will be used for DFSA: the drug has amnesic effects, it is widely available or easy to obtain, and it is unlikely to be detected due to a short half-life or a lack of routine screening for the drug or drug metabolite. All of the benzodiazepines and positive allosteric modulators of $GABA_A$ receptors that have been studied to date have been shown to have robust amnesic effects. Specifically, anterograde amnesia (i.e. loss of memory during the period of drug effect) has been demonstrated for alprazolam,[22–24] clonazepam,[25] diazepam,[26,27] lorazepam,[27–29] zolpidem,[30–32] zaleplon,[33] and zopiclone.[34] The relative availability of these drugs for illicit use also appears to be high as evidenced by the large number of substances seized by law enforcement that have been identified as alprazolam, clonazepam, or diazepam (Figure 1C).

The half-lives of most of the benzodiazepines are substantially long enough (i.e. greater than 10 h) such that most of these compounds should be identified when tests designed to detect these compounds or their metabolites are employed (Table 1). However, there are several positive $GABA_A$ receptor modulators that might represent 'unknowns' on the basis of their relatively short half-lives and lack of routine screening for them. As shown in Table 1, triazolam, midazolam, zolpidem, eszopiclone, and zaleplon each have half-lives from 1 to 6 h. In addition, the major metabolic pathways for triazolam and midazolam involve alpha-hydroxylation and not metabolism to oxazepam,[19] which might limit the likelihood of these drugs being detected by routine screens for benzodiazepines. It is also not clear to what extent analyses for newer sedative/hypnotics such as zolpidem, zopiclone, and zaleplon are included in routine forensic screens. Analytical procedures have been developed to detect zolpidem, zopiclone, and zaleplon in blood,[35–39] hair,[40,41] urine,[40–43] and saliva.[44] However, most of these procedures involve liquid or gas chromatography and mass spectrometry, which might limit their practical utility in certain settings.

The fact that zolpidem and zopiclone have not been widely identified as drugs used for DFSA in the USA might be a result of a combination of factors including their short half-lives and a failure to look for these drugs in routine screens. Data on the number of prescriptions filled for these drugs suggests that they are widely available. The branded version of immediate-release zolpidem (Ambien in the USA) was among the top 10 branded drugs prescribed 2004–2006 with an average of approximately 22 million prescriptions filled during each of those years (Table 2). Eszopiclone, marketed in the USA as Lunesta, has been among the top 60 brand name drugs prescribed 2006–2008 with an average of approximately 6 million prescriptions filled during each of those years (Table 2). The use of zolpidem for DFSA has been documented.[42–47] Thus, although data from the USA might suggest that zolpidem and eszopiclone are relative 'unknowns' with regard to their use in cases of DFSA, the experience of countries where these drugs have longer histories of use compared to that of the USA (e.g. France) suggest that there is value in routine screening for these drugs in cases of suspected DFSA.

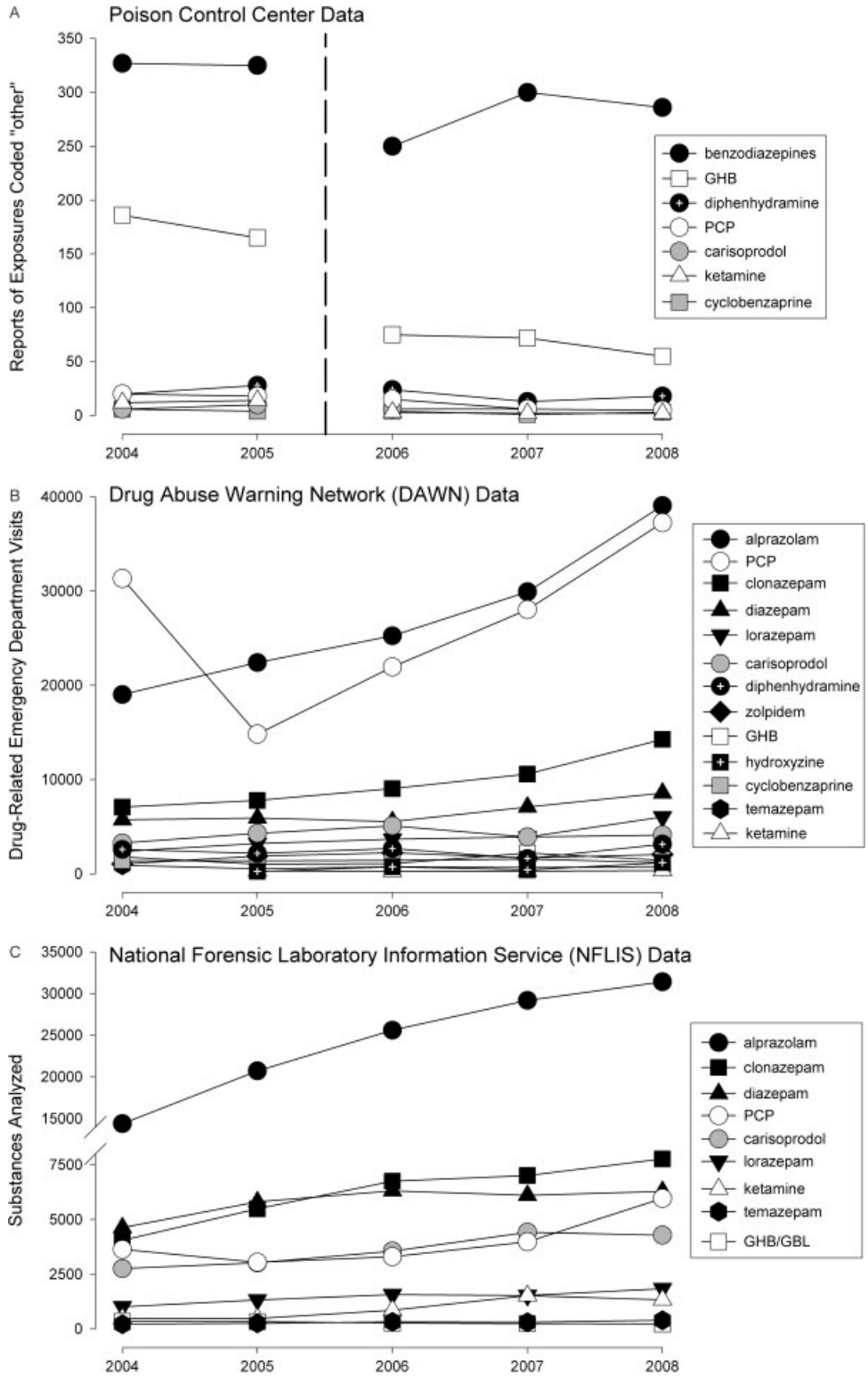

Figure 1. Estimates of the magnitude of the problems associated with different drugs 2004–2008. (A) Reports of drug exposures to poison control centres in the USA coded as 'other', which includes cases of malicious poisoning, contamination/tampering, and drug withdrawal. Data were taken from the American Association of Poison Control Centers' Annual Reports from the National Poison Data System database. The dashed line indicates that data prior to 2006 cannot be compared to data from 2006 and beyond due to a change in methodology. Filled symbols are benzodiazepines, open symbols are 'club drugs', filled-hatched symbols are antihistamines, and grey symbols are muscle relaxants. (B) Drug-related emergency department visits from the Drug Abuse Warning Network (DAWN). Data were taken from the annual DAWN reports. (C) The number of substances identified as each of the drugs shown from all of the substances seized by law enforcement and analyzed through the Drug Enforcement Administration (DEA) National Forensic Laboratory Information System (NFLIS). Data were taken from each of the annual reports of the NFLIS from all NFLIS laboratories that reported 6 or more months of data (including data from labs not included in the national sample for all drugs except carisoprodol and PCP for which the national sample data were the only data available). Note: different scales are used below and above the broken ordinate.

Table 1. Drugs identified as potential 'unknowns' for use in drug-facilitated sexual assault

Drug or drug class	Trade name	Half-life (hours)
Benzodiazepines		
alprazolam	Xanax	12[19]
clonazepam	Klonopin	23[19]
diazepam	Valium	43[19]
lorazepam	Ativan	14[19]
temazepam	Restoril	11[19]
chlordiazepoxide	Librium	10[19]
triazolam	Halcion	3[19]
midazolam	Versed	2[19]
flunitrazepam	Rohypnol	13.5[b]
Non-benzodiazepine sedative/hypnotics		
zolpidem	Ambien	2[19]
eszopiclone	Lunesta	6[c]
zaleplon	Sonata	1[19]
'Club drugs'		
GHB	Xyrem	0.5–1[d]
PCP	NA	21[e]
ketamine	Ketaset/Ketalar	3[f]
Muscle relaxants		
carisoprodol	Soma	2[59]
cyclobenzaprine	Flexeril (IR), Amrix (ER)	18[g]
metaxolone	Skelaxin	8–9[h]
Anithistamines		
diphenhydramine	Benadryl	8.5[i]
hydroxyzine	Atarax/Vistaril	20[j]
promethazine	Phenergan	12[k]

[b] Boxenbaum *et al*., *J Pharmacokinet Biopharm*, **1978**, 6, 283.
[c] Lunesta Package Insert. Available at: http://www.lunesta.com/PostedApprovedLabelingText.pdf?iid=LHC_fullPrescribing [31 July 2010].
[d] Xyrem Package Insert. Available at: http://www.xyrem.com/xyrem-pi.pdf [31 July 2010].
[e] Cook *et al*., *Clin Pharmacol Ther*, **1982**, 31, 625.
[f] Clements *et al*., *J Pharm Sci*, **1982**, 71, 539.
[g] Amrix Package Insert. Available at: http://www.amrix.com/pdf/PrescribingInformation.pdf [31 July 2010].
[h] Skelaxin Package Insert. Available at: http://www.skelaxin.com/pdf/Skelaxin_Web_PI.pdf [31 July 2010].
[i] Gengo *et al*., *Clin. Pharmacol. Ther*. **1989;** *45*, 15.
[j] Aterax Package Insert. Available at: http://home.intekom.com/pharm/ucb/aterax.html [31 July 2010].
[k] Taylor *et al*., *Br. J. Clin. Pharmacol*. **1983;** *15*, 287.

PCP, GHB, and ketamine

In addition to the benzodiazepine flunitrazepam, PCP, GHB, and ketamine are perhaps the drugs most commonly identified with DFSA (i.e. referred to as 'date-rape' drugs). PCP and ketamine are NMDA receptor antagonists that have been shown to have amnesic effects.[48,49] The half-life of PCP is relatively long (21 h) compared to the shorter half-lives of ketamine (3 h) and GHB (0.5–1 h), which likely contributes to a greater proportion of PCP exposures being detected by forensic analyses as compared to exposures to ketamine or GHB (i.e. PCP might be considered a 'known' drug for DFSA). The short half-lives of ketamine and GHB (Table 1) increase the likelihood that their use for DFSA might go undetected. However, methods have been developed that can detect levels of ketamine and norketamine (a ketamine metabolite) for up to 6 days and levels of the ketamine metabolite dehydronorketamine for up to 10 days after the administration of an oral dose of 50 mg ketamine.[50]

NFLIS data of substances seized by law enforcement suggest that the availability of PCP has been on average 5 times greater than that of ketamine and 15 times greater than that of GHB 2004–2008 (Figure 1C). In addition, the fact that estimated drug-related emergency department visits for PCP have been approximately 50–100 times greater than those for ketamine and 12–25 times greater than those for GHB suggest that individuals exposed to PCP tend to experience more serious problems than those exposed to ketamine or GHB.

GHB is an $GABA_B$ receptor agonist and GHB receptor ligand that has also been shown to have amnesic effects in humans, although to a lesser extent than those of a benzodiazepine or barbiturate.[20,21] GHB is marketed as a prescription medication in the USA as sodium oxybate (trade name: Xyrem®). However, unlike other prescription medications, the vast majority of problems related to abuse or DFSA associated with GHB are not thought to be due to diversion of the pharmaceutical product, but rather clandestine manufacture of illicit GHB from commercially available precursors or the use of the precursors (e.g. gamma-butyrolactone or GBL) themselves.[51] The availability of Xyrem for illicit use is likely to be very low as a result of the relatively narrow medical indication of the drug to treat the symptoms of narcolepsy, a rare sleep disorder, and as a result of the highly restricted distribution system for Xyrem. As a result, approximately 26 000 prescriptions were filled for Xyrem from market introduction in 2002 through March, 2008 as compared to the millions of prescriptions filled each year for the sedative/hypnotics and muscle relaxants listed in Table 2.[52]

GHB has gained notoriety as a drug that is frequently used for DFSA; however, current evidence from cases of suspected DFSA does not support the notion that illicit GHB is frequently used for this purpose.[7,11,12,53] The detection of GHB in biological matrices is complicated by a number of factors, including how to determine what the appropriate baseline 'cutoff' values are for different specimens from different populations given that GHB is an endogenous molecule,[54,55] how certain storage conditions might cause or accelerate the catabolism of other molecules to GHB resulting in higher levels of detectable GHB over time,[56–58] and how the short half-life of GHB (0.5–1 h) in the body might limit detection. The two former factors could increase the likelihood of false positives (i.e. an overestimation of GHB involvement) if endogenous GHB is mistaken for exogenous GHB or if storage conditions result in greater levels of GHB in sample over time, whereas the latter factor could increase the likelihood of false negatives (i.e. an underestimation of GHB involvement) if exogenous GHB (i.e. GHB administered for DFSA) is not detected in a submitted specimen due to extensive metabolism. For the reasons described above, in addition to the possible omission of testing for GHB in routine screens, it is possible that the involvement of GHB in cases of DFSA has been underestimated. Thus, there is good reason to begin or continue to look for GHB, as well as ketamine and PCP in cases of suspected DFSA.

Carisoprodol and other muscle relaxants

Carisoprodol (trade name: Soma®) was identified from the DAWN data and the NFLIS data as a drug of interest on the basis of being related to an average of approximately

Table 2. The number of prescriptions filled for Top 200 branded drugs 2004–2008

Drug and trade name	2004	2005	2006	2007	2008
Zolpidem					
Ambien	22,747,000	23,145,000	20,344,000	8,765,000	a
Ambien CR		b	6,279,000	7,696,000	7,214,000
Eszopiclone					
Lunesta	c	2,981,000	5,893,000	6,318,000	5,622,000
Zaleplon					
Sonata	1,441,000	d			
Metaxolone					
Skelaxin	4,304,000	3,880,000	3,743,000	3,695,000	3,218,000
Cyclobenzaprine					
Flexeril	1,845,000	1,951,000		e	

a – April 2007: generic zolpidem IR is approved by FDA
b – September 2005: Ambien CR® is approved by FDA
c – December 2004: Lunesta® is approved by FDA
d – April 2005: generic zaleplon is approved by FDA
e – February 2007: Amrix® (extended release cyclobenzaprine) is approved by FDA
f – All data from Verispan, VONA

4000 emergency department visits and substances seized each year from 2004 to 2008 (Figures 1B and 1C). Carisoprodol (N-isopropyl-meprobamate) is a prodrug that is metabolized to meprobamate in the liver. As such, the half-life of carisoprodol is relatively short at 2 h, although the half-life of meprobamate is approximately 10 h.[59] Carisoprodol is not currently a Federally Scheduled drug in the USA; however, meprobamate (trade name: Miltown) is a Schedule IV drug in the USA. There are few controlled studies of the effects of carisoprodol in human subjects; however, blinded, placebo-controlled studies of meprobamate show that meprobamate (and very likely, carisoprodol) produces anterograde amnesia.[28]

Another muscle relaxant that was reported in the poison control centre data and the DAWN data (albeit at low levels) was cyclobenzaprine (trade name: Flexeril® for immediate release and Amrix® for extended release; Figures 1A and 1B), which suggests that together with carisoprodol, muscle relaxants as a class might be of interest as potential 'unknowns' regarding their involvement in DFSA. The availability of muscle relaxants in the USA is likely to be widespread and facilitated by the fact that muscle relaxants such as carisoprodol, cyclobenzaprine, and metaxolone (trade name: Skelaxin®) are widely prescribed (Table 2) and are not currently scheduled by DEA. In 2004 and 2005 prior to the approval of Amrix (the extended release formulation of cyclobenzaprine), approximately 1.8 and 1.9 million prescriptions, respectively, were filled for Flexeril (Table 2). Prescriptions filled for Skelaxin averaged 3.7 million per year 2004–2008 (Table 2). The half-lives of these drugs range from 2 h for carisoprodol (10 h for meprobamate), to 8–9 h for metaxolone, and 18 h for cyclobenzaprine (Table 1). Thus, it is possible that the seemingly low rates of involvement of these drugs in cases of DFSA might simply be a result of our failure to regularly look for them in routine screens.[7,11,12] In recent years, there has been increasing concern regarding the recreational use and abuse of carisoprodol.[60,61] Thus, there might also be good reason to suspect and begin or continue to routinely screen for muscle relaxants such as carisoprodol, cyclobenzaprine, and metaxolone in cases of suspected DFSA.

Antihistamines

Diphenhydramine (trade names: Benadryl®, others) and hydroxyzine (trade names: Atarax®, Vistaril®) are antihistamines that were identified from the DAWN data as being related to 3152 and 1182 emergency department visits in 2008, respectively (Figure 1B). Diphenhydramine is widely available in many over-the-counter allergy and cough and cold products. At high doses (200–400 mg or 4–16 times the intended therapeutic dose), diphenhydramine has been shown to produce a number of effects that are similar to those of benzodiazepines including amnesia.[29] The half-lives of common antihistamines such as diphenhydramine, hydroxyzine, and promethazine (trade name: Phenergan®) are relatively long at 8.5, 20, and 12 h, respectively (Table 1). Thus, these drugs appear to have a reasonable window of detection. Given the ease with which diphenhydramine (and other antihistamines) may be legally purchased over the counter, the routine screening for antihistamines in cases of suspected DFSA might be warranted.

Discussion

The problem with experts is that they do not know what they do not know.

- Nassim Nicholas Taleb, *The Black Swan*

Drug-facilitated assault is a serious and troubling crime. It is important to know if and how different drugs might be used to facilitate crime so that effective regulations and controls may be enacted and enforced to deter such crime while maintaining any medical or therapeutic benefits that the same drugs might offer. The information that we have regarding drugs that are used for DFSA comes from specific analytical tests of voluntarily submitted biological specimens – the compounds and the frequency with which they are identified might be considered to be the 'known knowns' or the true positives. However, there are a number of ways in which drugs that are used for DFSA might not be detected. A sample might not be submitted for analysis; submitted after

the drug has been metabolized and eliminated from the body; or submitted, but not tested for the drug that was used. Moreover, the frequency of involvement of drugs with certain characteristics such as a short half-life or a propensity to induce amnesia is even more likely to be underestimated because those characteristics are likely to increase the difficulty of detection and the time between the assault and the submission of a specimen. Those types of drugs, therefore, represent the 'unknown unknowns' of drugs used for DFSA. The purpose of this review was to draw reasonable inferences regarding drugs that might be being used for DFSA on the basis of their effects, availability, and pharmacokinetics in an attempt to highlight some of these 'unknown unknowns' and re-characterize them as 'known unknowns'.

To examine the potential prevalence by which different drugs are likely to be used for DFSA and remain undetected (i.e. to identify the 'unknowns'), the 'knowns' were excluded from consideration. As such, drugs that are frequently consumed for recreational purposes and are already acknowledged to be used for DFSA (e.g. alcohol, some benzodiazepines) were considered to be drugs for which a relationship to DFSA is 'known'. Other drugs that are also known to be used for recreational purposes and lack robust anterograde amnesic effects (e.g. opioids, stimulants) or drugs that have relatively long half-lives and are typically included in routine drug screens (e.g. cannabis, barbiturates, PCP) were also excluded from consideration as 'unknowns'. Drugs and drug classes that were identified as likely 'unknowns' included the benzodiazepine-site ligands zolpidem and eszopiclone, 'club drugs' GHB and ketamine, muscle relaxants such as carisoprodol, and widely available antihistamines such as diphenhydramine.

Each of the drugs identified as a potential 'unknown' has been shown to be able to produce anterograde amnesic effects in controlled human studies. Many of the drugs such as zolpidem, eszopiclone, GHB, and ketamine also have relatively short half-lives, which might limit their detection in the absence of identifiable metabolites. Several of the drugs also appear to be widely available as evidenced by the large number of prescriptions filled (e.g. zolpidem, eszopiclone), NFLIS seizures (e.g. carisoprodol), or commercial availability without a prescription (diphenhydramine). Moreover, it is likely that these drugs are not included in the routine screens for drugs of abuse (e.g. the 'NIDA 5' panel includes cannabinoids, cocaine, amphetamines, opiates, and PCP, but none of the proposed 'unknowns'). Given that the characteristics of these drugs might lend them to being used for DFSA, but that comprehensive data on their use in cases of DFSA does not exist, they should be considered current 'known unknowns'.

Factors that further complicate our meta-knowledge (or what we think we know) about drugs used for DFSA include the ease by which a drug may be surreptitiously administered to an unsuspecting victim and the potential interactions between a drug of interest and commonly used recreational drugs such as alcohol or cannabis. Certain characteristics of a drug or product such as taste, potency, formulation, or solubility might facilitate or impede the surreptitious administration of a drug to a person's food or drink and influence the frequency with which a particular drug or product is used for DFSA. Another major limitation to our current knowledge is the enormous number of potential drug interactions that might occur between legal, prescription, and illegal drugs on measures of impairment, amnesia, and drug metabolism. Especially in light of the fact that alcohol and cannabis are frequently detected in cases of suspected DFSA, studies that carefully examine and identify relevant interactions between these and other drugs will also enrich our knowledge of the current 'unknowns'.[62,63]

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