REVIEW ARTICLE

Knock-Out Drugs: Their Prevalence, Modes of Action, and Means of Detection

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SUMMARY

Background: Knock-out drugs are used to facilitate the commission of a crime, generally either robbery or sexual assault. Although media reports on the use of knock-out drugs have become more frequent, there are no robust epidemiological data on the incidence of drug-facilitated robbery or sexual assault, presumably because many crimes of these types do not enter into official statistics.

Methods: The authors describe the modes of action and toxicological means of detection of the substances most frequently used as knock-out drugs on the basis of a selective literature research on the terms "drug-facilitated sexual assaults" (DFSA) and "drug-facilitated crimes" (DFC).

Results: The most frequently used drug in cases of sexual assault is still alcohol (ca. 40% to 60%), followed by illegal drugs (cannabis, cocaine). The presence of involuntarily consumed medications and drugs of abuse is demonstrated by routine toxicological analysis only in relatively few cases (ca. 2%). The substances most commonly found are benzodiazepines, followed by other hypnotics. In Europe, the illegal substance gamma-hydroxybutyric acid (GHB, "Liquid Ecstasy"), often mentioned as a "date-rape drug," is only rarely detected with sufficient medicolegal certainty. This may be due to its rapid elimination (it is detectable in blood for up to 8 hours, in urine for up to 12 hours) as well as its physiological occurrence in the body. If the toxicological analysis of blood and urine is negative in a case of suspected DFSA, then the analysis of a hair sample about four weeks after the assault can detect the presence of drugs consumed at that time. If the victim has long hair, it may be possible to detect knock-out drugs taken more than four weeks earlier. In Europe, convictions for drug-facilitated crimes are comparatively rare, mainly because of the difficulty of demonstrating conclusive evidence.

Conclusions: A careful medical history and physical examination and the careful taking of biological samples for toxicological analysis form the basis for the detection of drug-facilitated crimes.

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Press reports of the use of knock-out drugs to facilitate crimes have become more common in recent years, beginning in the USA, but now more commonly in Europe as well. Some years ago, the best-known cases in Germany involved robbery and other crimes against property: the public is familiar with reports of alcohol-intoxicated customers in St. Pauli (the Hamburg nightlife district), or in a traditional Munich establishment, being sedated with Noludar (methylprylone) for this purpose. Today, however, most of the crimes committed in association with knock-out drugs are of a sexual nature, occurring in the setting of the disco and rave scene (1–5). Three illustrative cases are presented in the Internet supplement (see *case illustrations*).

It is often difficult to prove that knock-out drugs have been administered because the victims can no longer remember the incident after a shorter or longer period of unconsciousness or antegrade amnesia, because they attempt to reconstruct the events at the time of the incident from their acquaintances' spontaneous or elicited recollections, and because they delay in reporting the incident to a doctor or to the police. The long temporal interval that results between the incident and the obtaining of blood and urine specimens often makes the administered substances impossible to detect by chemical toxicological analysis.

A further hindrance to laboratory detection is the fact that knock-out drugs are usually given in the smallest possible dose that will sedate the victim; also, knowledgeable criminals often choose to use substances that are rapidly eliminated, so that they will not be detected. In order not to arouse the victim's suspicion, the administered substance is ideally odorless, colorless, and tasteless, so that it can be added to a drink (for example) without being noticed.

Yet another difficulty is that persons who suspect that they have been given a knock-out drug against their will were often markedly intoxicated with alcohol at the time of the event (in the group of persons whom we have studied, the percentage of such cases is higher than 40%). Often, the presumed blood alcohol concentration calculated from the victim's own report of the amount of alcohol consumed already suffices to explain amnesia for the time of the event with a total loss of experiential continuity.

Volatile substances such as chloroform, ether, and halothane were formerly used more commonly to facilitate crime (6).

TABLE 1

Detailed information on all sedating medications (including GHB) that were detected in the studied cases, including information on involuntary consumption

Substance class	Substances	Number of cases	Involuntary consumption
Benzodiazepines	Diazepam Temazepam Lorazepam Total	44 24 5 84	3 6 1 12
Other hypnotic agents	Zopiclon GHB etc. (>10 µg/mL in urine) Total	6 2 8	1 2 3
Antihistamines	Diphenhydramine Total	6 14	2 2
Opioid analgesics	Total	103	0
Antidepressants	Total	7	1
Antiparkinsonian medications	Procyclidine	2	0
Antiemetics	Promethazine	4	0
Antipsychotics	Thioridazine	3	0
Barbiturates	Phenobarbital	1	0
Illegal drugs	Ecstasy	NA	3
	Total (% of cases)	**226 (22%)**	**21 (2%)**

Modified from (10)
GHB, gamma-hydroxybutyric acid

The spectrum of administered substances has become much wider in recent years. The commonly mentioned substance gamma-hydroxybutyric acid (GHB), also known as Liquid Ecstasy, can only be analytically detected in a very narrow temporal window (8 hours in the blood, 12 hours in urine).

The term "drug-facilitated sexual assault" (DFSA) has now become the standard international designation of this type of crime.

Criminals use drugs to facilitate sexual assault with the intention of producing the following effects:

- sedation and the induction of sleep
- alteration of the victim's behavior
- antegrade amnesia
- the creation of a helpless state that the criminal can deliberately exploit.

On the other hand, in the context of sex crimes, drugs are sometimes also given with the intention of increasing sexual desire and lowering behavioral inhibitions (amphetamines, cocaine).

On the basis of a selective literature search using the terms "drug-facilitated sexual assaults" (DFSA) and "drug-facilitated crimes" (DFC), the authors here present the mechanisms of action and windows of detectability of the substances most commonly used as knock-out drugs, so that medical colleagues involved in such cases will be better able to obtain adequate samples for chemical toxicological analyses.

Epidemiology

According to reports mainly originating in the USA, the incidence of drug-facilitated sexual assault seems to have risen markedly in recent years, although precise epidemiological data are lacking because of the naturally large number of cases that are not made known to the authorities. Many drugs of the types used for such crimes are taken voluntarily, and the covert administration of a drug can only rarely be proved (7, 8). GHB or flunitrazepam was detectable in only 3% of cases in an American study (8).

The Munich department of forensic medicine registered a total of 92 cases from 1995 to 1998 in which the administration of a knock-out drug was suspected (3). The crimes that were committed thereafter consisted mainly of robbery (47.8%), ranking well ahead of sex crimes (rape, 13%), homicide (5.4%), and other offenses.

The Bonn department of forensic medicine registered a tenfold increase in the number of investigations of possible intoxicating substances in sex crimes from 1997 to 2006, currently reaching 40 to 50 cases per year (5). Chemical toxicological studies are generally carried out both in victims and in criminal suspects.

In the United Kingdom, from 2000 to 2002, involuntarily consumed medications could be demonstrated in only 21 of 1014 cases (2%) (9, 10). Legal proceedings ensued in only half of all cases in which involuntarily consumed substances were detected, or 1% of the total, and even in these cases a conviction was not always the result. Criminal prosecution often had to be terminated

because no suspect was identified, the suspect could not be apprehended, or there was insufficient evidence to convict (*e-box*).

In this study, as in our own experience, benzodiazepines were the most commonly used type of substance (n = 12), followed by other hypnotic agents (zopiclone, GHB >10 mg/mL in urine, n = 3), antihistamines (diphenhydramine, n = 2), sedating antidepressants (n = 1), and other illegal drugs (Ecstasy, n = 3) *(table 1)*.

Subjective symptoms

Victims of the administration of knock-out drugs often describe the following symptoms, depending on the pharmacodynamics of the substances used (11):

- a nauseating, bitter taste in a previously unremarkable drink
- confusion
- dizziness
- light-headedness
- sleepiness
- impaired consciousness
- unconsciousness
- memory disturbance
- a feeling of not being in charge of one's own actions
- slow heart rate, abnormally low muscle tone
- loss of muscular control
- nausea
- lack of behavioral inhibition.

All of these symptoms should be asked about when the medical history is taken *(box 1)*.

Amnesia is mainly present when GHB and benzodiazepines have been used; in particular, 1,4-benzodiazepines like flunitrazepam are more likely to cause amnesia than 1,5-benzodiazepines like clobazam (12). Amnesia can also be present where there has not been any loss of consciousness. Midazolam can lead to the generation of fantasies of a sexual nature.

During physical examination, special attention should be paid to injuries, particularly injuries of an apparently sexual nature such as bruises on the medial surface of the thighs or scratches on the breasts, as well as apparently trivial injuries. Furthermore, specimens should be obtained for molecular-biological and toxicological analysis *(box 2)*.

Commonly used groups of agents

Here, we can give no more than a brief outline of the agents and groups of agents that are most commonly in question as potential knock-out drugs; further information is found in Musshoff and Madea (13). An extended list of potential knock-out drugs is also found in the *e-table*.

Benzodiazepines

Substances belonging to this large group are used therapeutically as tranquilizers, anticonvulsants, hypnotics, and sedatives.

All benzodiazepine medications are subject to regulation under the German Law on Narcotics (Betäubungsmittelgesetz, BtMG), where they are listed

BOX 1

Clinical history-taking in suspected cases*

- Voluntary intake of alcohol, medications, illegal drugs? If yes: time and dose?
- Did the drink taste unusual?
- Consumption of food or drink offered by someone else?
- Who served the drink?
- Was the drink out of sight before it was consumed?
- Sudden change of mental state?
- Twilight state ("as if swathed in cotton")?
- Feelings of loss of will, inability to move?
- Speech disturbances, muzziness?
- Psychovegetative abnormalities?
- Amnesia?
- Possible aftereffects - nausea, vomiting, dizziness, symptoms referable to the heart, muscle weakness?
- Temporal interval before reporting to police, seeking medical attention, giving blood and urine specimens?

*based on (11) and (14)

BOX 2

Medical procedure and the obtaining of samples when the administration of knock-out drugs is suspected

- Physical examination, including internal gynecological examination
- Detailed and meticulous documentation of injuries, including minor ones
- Securing of possible DNA samples/swabs
- Securing of specimens for toxicological analysis (bodily fluids should always be stored at cool temperatures; if serum and urine are to be stored for longer times, they should be frozen)
  - Blood specimen: 10 mL (citrate-free)
  - Urine specimen: ca. 100 mL
  - When the obtaining of a hair specimen is indicated, a lock of hair about the thickness of a pencil should be taken and marked at the scalp end with a string; if hair from the head is not available, pubic hair can be taken instead. Hair specimens should be taken about 4 weeks after the incident if the findings in blood and urine are negative and should be stored under dry and dark conditions at room temperature.

in Appendix III (narcotic drugs approved for sale with a physician's prescription). For each type of benzodiazepine, however, the law specifies a threshold quantity below which the specifications for the prescribing of narcotics do not apply.

Benzodiazepines can cause amnesia when taken in combination with alcohol or opioids. Flunitrazepam, in particular, has the reputation of being a "date-rape" drug. Above all in the 1990's, colorless and tasteless flunitrazepam tablets, as they then were, were often thus misused by being added to drinks, Often, tablets were dissolved in water beforehand for this purpose. As a result, the manufacturer changed the composition of the tablet in 1999 so that it has a bluish color, discolors drinks to which it is added, precipitates in solution, and tastes slightly bitter. Tablets of the older type are still available in some countries, however, and they are still often sold by generic drug manufacturers and other companies.

Other hypnotic agents

Zopiclone, zolpidem, and zaleplone are members of the latest generation of non-benzodiazepine hypnotic agents. They have anxiolytic, sleep-promoting, and muscle-relaxing effects. They are suitable for use as knock-out drugs especially because of the rapid onset of their effect (within 10 to 30 minutes), but also because they induce amnesia and can only be detected for a short time (short half-life).

Gamma-hydroxybutyric acid, 1,4-butanediol, and butyro-1,4-lactone

In medicine, gamma-hydroxybutyric acid is now only rarely used as an intravenous anesthetic agent. It has also been approved for the symptomatic treatment of narcolepsy (14).

Especially since the late 1990's, GHB has come into more common use as a party drug ("Liquid Ecstasy," "Liquid E," "Liquid X," "Fantasy"). It is available on the black market as a hygroscopic solid or as a colorless or colored liquid (aqueous solution of GHB salts).

At low doses (ca. 0.5 to 1.5 g), the stimulating effect of the drug dominates: it has an anxiolytic, mildly euphoric, and socially potentiating effect, although, like alcohol, it can impair motor control *(table 2)*. When taken in higher doses (up to 2.5 g), it leads at first, like alcohol, to a heightening of mood and drive, sometimes also of sexual desire. At still higher doses, it is heavily sleep-inducing. Overdoses can cause a sudden, deep sleep from which the affected person can hardly be aroused. GHB overdoses, i.e., doses that cause undesired, narcotized sleep, are relatively unproblematic, as long as other drugs have not been taken at the same time.

It is dangerous to combine GHB with alcohol, respiratory depressant drugs, or benzodiazepines. Nausea and vomiting may occur, and this, in combination with the narcotic effect of the drug, can lead to death by aspiration of vomitus and suffocation. Moreover, life-threatening respiratory depression and cardiac arrhythmias may arise. Because GHB shares its sleep-inducing property with a number of other substances, the correct diagnosis of GHB intoxication is often missed by emergency medical personnel and other persons trying to help. A benzodiazepine or opioid overdose is usually suspected at first, but neither flumazenil nor naloxone is an effective antidote to GHB. The possible reversibility of the effects of GHB with physostigmine is currently a matter of debate (14).

Butyro-1,4-lactone, also called gamma-butyrolactone (GBL), is a colorless liquid with a faint intrinsic odor. It is widely used as an industrial solvent and as a paint remover, graffiti remover, nail-polish remover, and cleaning agent. It is also used as a reagent for the manufacture of pharmaceuticals and agricultural chemicals. Unlike GHB, it has not yet been classified as an illegal narcotic agent, even though it is used as a knock-out drug. It is hydrolyzed to GHB in the body through the action of 1,4-lactonase. The plasma half-life of GBL is less than 60 seconds because of its rapid metabolism to GHB; thus, 5 minutes after GBL is consumed, only about 3% of the original amount is still present in the body.

1,4-butandiol (BDO) is used in industry as an emollient and is also an important intermediate product in the synthesis of other substances, including GBL. BDO, too, is metabolized in the body to GHB through the action of an alcohol dehydrogenase and an aldehyde dehydrogenase. It can thus be used as an alternative recreational or knock-out drug. Its effect begins about 5 to 20 minutes after it is taken by mouth and lasts about 2 to 3 hours. Doses above 4 mL have a sleep-promoting effect, like GHB. Again like GHB, BDO in very high doses can cause coma and death.

Ketamine

Ketamine is sold as a generic drug in Germany. It requires a prescription, but is not subject to the provisions of the Law on Narcotics. It is used for general anesthesia in anesthesiology as well as for analgesia and the treatment of otherwise intractable status asthmaticus, and furthermore as a hypnotic agent. It is used as a drug of intoxication and a party drug because of its dissociating, consciousness-altering effect. Its use as a knock-out drug has also been described.

Anticholinergic drugs

Scopolamine, hyoscine, and atropine from the belladonna family are the more important members of this class. Scopolamine is mildly calming at a low dose, with an inhibitory effect on the vomiting center in the brain; at higher doses, it has a blunting effect, producing apathy.

Antihistamines

Some first-generation H_1 antihistamines, in particular, have an antagonistic effect on

- muscarinic receptors (e.g., diphenhydramine),
- dopamine receptors (e.g., promethazine),
- serotonin receptors (e.g., promethazine).

Most of these agents also readily enter the central nervous system and are thus used, for example, as antiemetics (in sea-sickness) and as sleep-promoting medications. First-generation H_1 antihistamines are suitable for use as knock-out drugs because of their anticholinergic effects and, not least, because of their ready availability. The use of diphenhydramine and doxylamine for this purpose has been described.

Muscle relaxants and volatile substances

Many other substances, such as the muscle relaxants carisoprodol and cyclobenzaprine, have been used as knock-out drugs because of their sedating effects. The same is true of volatile substances including ether, chloroform, and laughing gas (nitrous oxide). Because these agents are rapidly eliminated or breathed off, however, they are detectable in the body for no more than a very short time.

Specimens must be secured in airtight, closed containers to prevent any further loss of the substance in question before the specimen can be analyzed. Special tests are necessary to detect these substances, e.g., head space gas chromatography or solid-phase microextraction.

Today, volatile substances are used in the party scene as "poppers"—these generally include amyl nitrite, butyl nitrite, isobutyl nitrite, and combinations of these three substances. They have a pronounced vasodilating effect. Five to 15 seconds after they are inhaled, mental effects set in, including an intensification of perception, which may persist for about 10 minutes (depending on the dose). Because of their short-lived effect, "poppers" are relatively unsuitable as knock-our drugs; they are taken for (also short-lived) sexual stimulation, as an aphrodisiac.

TABLE 2

Consequences of inappropriate use of gamma-hydroxybutyric acid

Dose (oral)	Effect
1.0–2.0 g	Relaxation, anxiolysis, euphoria, sedation
2.5–3.0 g	Nausea, vomiting, myoclonus, bradycardia, amnesia
3.0–4.0 g	Unconsciousness
>4.0 g	Respiratory depression, coma

GHB, gamma-hydroxybutyric acid
*according to (25)

The main remaining types of knock-out drugs are barbiturates (subject to the provisions of the Narcotics Prescription Order, Betäubungsmittelverschreibungsverordnung [BtMVV]), the antihypertensive agent clonidine, the atypical neuroleptic agent clozapine, and chloral hydrate.

Stimulants such as cocaine, amphetamine, and ecstasy are also being more commonly used in cases of drug-facilitated sexual assault. They can elevate the victim's sexual desire and lower behavioral inhibitions; on the other hand, criminals may wait till a phase of exhaustion after the actual intoxication sets in, characterized by pronounced tiredness with long, deep phases of sleep.

Chemical toxicological analysis

Most of the substances discussed above can be detected in the blood for several (up to 24) hours, and in the urine (including metabolites) for a few days. A special feature of GHB is that it is very rapidly resorbed, reaching its peak plasma concentration in 20 to 45 minutes. Its half-life is circa 30 minutes. It can be detected in the blood for 8 hours and in urine for up to 12 hours (15, 16).

Because of the brief time available for the detection of these substances in the blood and urine, the frequent long delays between the incident and its reporting to the police or a physician, and the fact that a low dose of a knock-out substance often suffices to impair consciousness in a person who has already consumed alcohol and other drugs, both blood and urine must often be obtained for chemical toxicological analysis, depending on the particulars of the case. The material should always be stored at a low temperature, because bacterial activity might otherwise raise the concentration of the substance in question, especially in the case of GHB.

For screening tests, 100 mL of urine should be obtained as soon as possible, no later than 2 to 4 days after the incident. At least 10 mL of (citrate-free) blood should also be obtained as soon as possible, optimally no more than 24 hours after the incident.

If a longer time has elapsed between the incident and the medical examination, or if the chemical-toxicological studies of blood and urine are negative despite a well-grounded suspicion that knock-out

drugs were administered, then the analysis of a hair sample can be considered. The sample should be obtained about 4 weeks after the incident. Hair grows an average of 1 cm per month; thus, the demonstration that a substance is present in a proximal hair segment but not more distally implies that it was ingested at a time near the incident. Many potential knock-out drugs can later be detected in hair samples even if they were only consumed once (17–19). The detection of GHB, however, is problematic, because the analysis must be capable of distinguishing the normal, endogenous concentration of this substance from the perhaps no more than slightly elevated concentration in a neighboring segment, resulting from exogenous administration (20, 21).

It must be pointed out that conventional testing laboratories are generally unable to cover the entire spectrum of required analyses, or to perform them with the necessary sensitivity (22–24). Thus, only specialized laboratories should be involved; the laboratory can also give helpful advice in individual cases. This is particularly true with respect to hair analyses after the consumption of a single dose of a foreign substance.

Judicial consequences

The possible judicial consequences of the use of a knock-out drug in Germany come under the following headings in the German criminal code (Strafgesetzbuch, StGB):

- § 179 StGB (sexual abuse of persons unable to defend themselves),
- § 177 StGB (sexual assault, rape),
- § 224 StGB (battery with physical endangerment),
- § 250 StGB (aggravated robbery).

According to § 177 Para. 3 StGB, the carrying on one's person of a tool or instrument for the prevention or overcoming of another person's resistance by means of violence or the threat of violence is an aggravating circumstance. The Federal Court (Bundesgerichtshof) has expressed the view that the use of knock-out drugs with the aim of preventing the anticipated resistance of a robbery victim constitutes the classic case of "carrying on one's person." Accordingly, cases of aggravated robbery committed with the aid of knock-out drugs can be assumed to be punishable by imprisonment for no less than three years. The same analogously holds in the case of sexual assault (§ 177 Para. 3).

Key messages

- Even in the absence of robust epidemiological data on the frequency of drug-associated sex crimes, the number of investigations for such crimes, e.g., in forensic laboratories, has risen markedly in recent years.
- Proof of the administration of knock-out drugs is often difficult because the victim can no longer recall the event after a shorter or longer phase of unconsciousness or antegrade amnesia and is therefore delayed in seeking a doctor or informing the police.
- The most commonly detected substance in sex crimes is still alcohol (ca. 40% to 60% of all cases), followed by illegal drugs (cannabis, cocaine). Routine tests only rarely detect involuntarily consumed medications and drugs (in ca. 2% of cases); the ones most commonly found are benzodiazepines and other hypnotics.
- When the administration of knock-out drugs is suspected, a 100 mL urine sample should be obtained as soon as possible for screening, and at least 10 mL of (citrate-free) blood should also be obtained as soon as possible, optimally within 24 hours.
- If a longer time has elapsed between the incident and the victim's coming to medical attention, or if the chemical-toxicological studies of blood and urine are negative despite a well-grounded suspicion that knock-out drugs were administered, then the analysis of a hair sample can be considered. The sample should be obtained about 4 weeks after the incident.
- Meticulous medical history-taking, physical examination, and obtaining of specimens are prerequisites for the successful detection of cases of this type.

Conflict of interest statement
The authors declare that they have no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.

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REFERENCES

1. Bechtel LK, Holstege CP: Criminal poisoning: drug-faciliated sexual assault. Emerg Med Clin N Am 2007; 25: 499–525.
2. Bratzke H, Klug E: Medikamentöse Betäubung mit krimineller Anschlusstat. Arch Kriminol 1988; 181: 33–40.
3. Christmann J: Zum Vorkommen von K.-o.-Fällen im Untersuchungsgut des Rechtsmedizinischen Institutes der Universität München in den Jahren 1995–1998. Diss Med München 2003.
4. Grossin C, Sibille I, Lorin de la Grandmaison G, Banasr A, Brion F, Durigon M: Analysis of 418 cases of sexual assault. Forensic Sci Int 2003; 125–30.
5. Madea B, Plieger S, Musshoff F: Begutachtung in Fällen von drogenassoziierten Sexualdelikten. In: Pragst F, Aderjan R, (eds.) GTFCh-Symposium 2007. Bad Vilbel: GTFCh 2008; 116–24.
6. Madea B, Musshoff F: Homicidal poisoning with halothane. Int J Leg Med 1999; 113: 47–9.
7. ElSohly MA, Salmone SJ: Prevalence of drugs used in cases of alleged sexual assault. J Anal Toxicol 1999; 23: 141–6.
8. Slaughter L: Involvement of drugs in sexual assault. J Reprod Med 2000; 45: 425–30.
9. Scott-Ham M, Burton FC: A study of blood and urine alcohol concentrations in cases of alleged drug-facilitated sexual assault in the United Kingdom over a 3-year period. J Clin Forensic Med 2005; 13: 107–11.
10. Scott-Ham M, Burton FC: Toxicological findings in cases of alleged drug-facilitated sexual assault in the United Kingdom over a 3-year period. J Clin Forensic Med 2005; 12: 175–86.
11. Luck B, Afflerbach L, Graß H: Sexualisierte Gewalt: Wie der Verdacht auf „K.-o.-Tropfen“ bewiesen werden kann. Dtsch Arztebl 2008: 105: A-318.
12. Goullé J-P, Anger J-P: Drug-facilitated robbery or sexual assault: problems associated with amnesia. Ther Drug Monit 2004; 26: 206–10.
13. Musshoff F, Madea B: K.-o.-Mittel. CME Weiterbildung Zertifizierte Fortbildung. Rechtsmedizin 2008; 18: 205–24.
14. Andresen H, Stimpfl T, Sprys N, Schnitgerhans T, Müller A: Liquid Ecstasy—A Significant Drug Problem. Dtsch Arztebl Int 2008; 105: 599–603.
15. Elliot SP: Gamma hydroxybutyric acid (GHB) concentrations in humans and factors affecting endogenous production. Forensic Sci Int 2003; 133: 9–16.

16. Erdmann F, Zandt D, Auch J, Schütz H, Weiler G, Verhoff MA: Untersuchungen zum Grenzwert zwischen endogener und exogener Gamma-Hydroxybuttersäure (GHB/liquid ecstasy). Arch Kriminol 2006; 217: 129–36.
17. Kintz P: Bioanalytical procedures for detection of chemical agents in hair in the case of drug-facilitated crimes. Anal Bioanal Chem 2007; 388: 1467–74.
18. Madea B, Musshoff F: Haaranalytik—Technik und Interpretation in Medizin und Recht. Köln: Deutscher Ärzteverlag 2004.
19. Musshoff F, Madea B: Analytical pitfalls in hair testing. Anal Bioanal Chem 2007; 388: 1475–94.
20. Goullé J-P, Chèze M, Pépin G: Determination of endogenous levels of GHB in human hair. Are there possibilities for the identification of GHB administration through hair analysis in cases of drug-facilitated sexual assault? J Anal Toxicol 2003; 27: 574–80.
21. Kintz P, Cirimele V, Jamey C, Ludes B: Testing for GHB in hair by GC/MS/MS after a single exposure. Application to document sexual assault. J Forensic Sci 2003; 48: 195–200.
22. LeBeau M, Andollo W, Hearn WL, Baset R, Cone E, Finkle B, Fraser D et al.: Recommendations for toxicological investigations of drug-faciliated sexual assaults. J Forensic Sci 1999; 44: 227–30.
23. Negrusz A, Gaensslen RE: Analytical developments in toxicological investigation of drug-faciliated sexual assault. Anal Bioanal Chem 2003; 376: 1192–7.
24. Papadodima SA, Athanaselis SA, Spiliopoulou C: Toxicological investigation of drug-facilitated sexual assault. Int J Clin Pract 2007; 61: 259–64.
25. Stein M: Stellungnahme zur nicht geringen Menge von Gamma-Hydroxybuttersäure. Toxichem & Krimtech 2003; 70: 87–92.

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Case Illustrations

Case 1

A 40-year-old bar owner fell into conversation before closing time with his last remaining customers, two women aged 23 and 25, who told him they had missed the last bus home. He invited both of them to stay in his apartment overnight. They accompanied him there, buying two bottles of champagne in a gas station along the way. Once at his apartment, the three drank champagne together. The bar owner had no recollection of what happened after that. When he woke up naked in bed the next morning, he found that the two women had disappeared, and all objects of value had been removed from the apartment.

Out of embarrassment, he waited till evening to report the incident to the police, whereupon blood and urine samples were taken. He was unable to give any more than a vague description of the two women. A chemical toxicological analysis indicated that he had consumed flunitrazepam: the 7-aminoflunitrazepam level in his blood was 50 ng/mL, and a urine test was positive (not quantified).

Video surveillance pictures from the gas station enabled the police to identify the two women. On questioning, they admitted having prepared a small bottle at home in which they dissolved 5 tablets of Rohypnol in water, and then having mixed an unknown quantity of this liquid with the bar owner's champagne in his apartment. They stated that he had had sexual intercourse with one of them after taking the drink, but he himself could not remember whether this had been the case. The women stated that he had fallen into a deep sleep afterward, and they had exploited his condition by searching the apartment and removing valuables from it.

Case 2

A young man pretending to be carrying out a study of "alco-pops" (carbonated alcoholic beverages) and clothing on behalf of a consumer protection organization told potential volunteers that they would receive a monetary reward for participating. A 30-year-old woman was induced in this way to try out several drinks. She later said that one of these, an orange-colored mixed drink, had tasted very bitter.

While undressing in order to try out various pieces of clothing, as required for the "study," she was secretly filmed by the suspect. After consuming a further orange-colored drink, she suddenly felt strange and lost consciousness, and she could not remember anything that happened afterward. She was later found in a deep sleep, wearing yet another set of clothes, in the suspect's grandmother's living room. She was at first unarousable and incapable of walking. This could not be explained by alcohol consumption alone, as she stated that she could ordinarily tolerate the amount of alcohol that she had consumed.

No chemical toxicological studies were performed to detect knock-out drugs in this case, because the police learned of this incident only later, during a separate investigation.

Case 3

A 21-year-old man was accused of putting diphenhydramine in a 23-year-old woman's beer in a bar in order to render her incapable of resisting his advances. She later stated that she had suddenly felt strange, her memory had become vague, and she had no longer felt capable of acting according to her own will. She had then engaged in a sexual act with the suspect in a lavatory.

The next day, the victim complained of nausea, palpitations, and tachycardia. Chemical toxicological analyses of blood and urine samples taken 39 hours after the incident were negative. Her calculated presumed blood alcohol concentration at the time of the incident, based on the amount of alcohol she said she had drunk, did not explain the condition she reported having been in at the time. A hair specimen was obtained 8 weeks after the incident: diphenhydramine was found in the proximal 3 cm of hair, in a concentration of 1.0 pg/mg. This finding can be summarized as follows: the alleged incident was within the time period during which the hair specimen had grown.

The concentration of diphenhydramine detected in the victim's hair is not consistent with regular, intensive consumption of diphenhydramine sleeping pills but rather with their occasional, or even single, use or administration. It should also be considered whether the patient was taking any other medications that might explain the finding.

REVIEW ARTICLE

Knock-Out Drugs: Their Prevalence, Modes of Action, and Means of Detection

Burkhard Madea, Frank Mußhoff

E-BOX

Criminal proceedings

- In 21 of 1014 cases (2%), medications or illegal drugs were found to have been consumed involuntarily
- Judicial proceedings ensued in only half of these cases
  – A conviction was not obtained in all cases
- No further judicial measures were taken because
  – no suspect could be identified
  – the suspect could not be apprehended
  – the evidence was insufficient

modified from (10)

REVIEW ARTICLE

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E-TABLE

Agents that can be used as knock-out drugs (an incomplete list)

Antidepressants/ Neuroleptic drugs	Benzodiazepines	Opioids	Other
Amisulpride	2-hydroxyethylflurazepam	6-acetylmorphine	1,4-butanediol
Amitriptyline	3-hydroxybromazepam	Alfentanil	Alcohol
Benperidol	7-aminoclonazepam	Buprenorphine	Amphetamines
Citalopram	7-aminoflunitrazepam	Codeine	Atropine
Clozapine	Alprazolam	Dihydrocodeine	Cannabinoids
Chlorpromazine	Bromazepam	EDDP (methadone metabolite)	Carisoprolol
Chlorprothixene	Chlordiazepoxide	Fentanyl	Chloral hydrate
Clomipramine	Clobazam	Heroin	Clonidine
Clotiapine	Clonazepam	Hydromorphone	Cocaine
Desipramine	Clorazepate	Methadone	Gamma-butyrolactone
Dibenzepin	Clotiazepam	Morphine	Gamma-hydroxybutyric acid
Dothiepin	Desalkylflurazepam	Nortilidine	H_1-antihistamines
Doxepin	Desmethylflunitrazepam	Oxycodone	Hyoscine
Fluoxetine	Diazepam	Oxymorphone	Ketamine
Flupirtine	Estazolam	Pentazocine	Meprobamate
Fluvoxamine	Flunitrazepam	Pethidine	Pentobarbital
Haloperidol	Flurazepam	Phenazocine	Phenobarbital
Hydroxyzine	Ketazolam	Pipamperone	Propofol
Imipramine	Loprazolam	Piritamide	Scopolamine
Levomepromazine	Lorazepam	Propoxyphene	Thiopental
Maprotiline	Lormetazepam	Remifentanil	Volatile anesthetic agents
Mirtazapine	Medazepam	Sufentanil	
Melperone	Midazolam	Tilidine	
Moclobemide	Nitrazepam	Tramadol	
Nordoxepine	Norclobazam		

E-Table (continued)

Antidepressants/ Neuroleptic drugs	Benzodiazepines	Opioids	Other
Nortriptyline	Nordazepam		
Olanzapine	Oxazepam		
Opipramol	Prazepam		
Paroxetine	Temazepam		
Perazine	Tetrazepam		
Promazine	Triazolam		
Promethazine			
Prothipendyl			
Quetiapine			
Reboxetine			
Risperidone			
Sertraline			
Sulpiride			
Thioridazine			
Tiapride			
Trazodone			
Trimipramine			
Venlafaxine			
Zaleplone			
Ziprasidone			
Zolpidem			
Zopiclone			
Zotepine			
Zuclopenthixol			