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New recreational drugs – new challenges

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„ChemSex", or sexual contact under the influence of drugs, and associated complications has become a widely discussed topic and a problem area not only in metropolises. At least half of MSM report substance use with sex. [1]

Indications for minimizing risk

The influence of rationality and morals on both sex and drug usage is limited. Sex under the influence of mind-altering drugs – even if "just" alcohol – is not new. However, until a few years ago, this combination was self-limiting, since these agents reduced erectile function. With the availability of substances stimulating erectile function (e.g. PD5 inhibitors), the use of performance-enhancing amphetamines has increased. This combination comes with a significant risk. First, the intravenous use of these drugs ("slamming") is on the rise and with it the use of non-sterile utensils with potential for HIV/hepatitis C infection, abscesses, etc. Furthermore, this combination leads to an increased duration of sex (with changing partners) that can last for hours, even days. The extreme strain on the mucosa makes it vulnerable to infection. [1]

Methamphetamine ("Crystal Meth", "Ice", "Meth") is consumed by an estimated 25 million people and has higher addictive qualities than heroin and cocaine. It is taken orally, inhaled as a vapor, applied rectally or injected. Injection should be avoided since it is the quickest route to addiction and can cause severe health problems (e.g. abscesses, sepsis, cardiac inflammation). As with all drugs: the faster the entry into the central nervous system, the stronger the "kick" and the higher the potential for addiction.
Methamphetamine reduces fatigue, hunger and pain perception, increases performance and aggressiveness and results in a drastic release of dopamine. It in turn activates the brain's reward system to such a degree that sex under the influence of methamphetamine initially leads to an ultimate euphoric sensation. A depletion of dopamine follows rather quickly, leading to a depressed mood and the consumption of more drug. A vicious circle often commences with initial substance abuse, leads to further dopamine depletion and eventually psychoses, often combined with paranoia. Physical complications arise from not eating and sleeping for days under the influence of drug. [1, 4, 5]

Drug interactions with HIV medications
Crystal Meth is metabolized via liver enzymes, which may be inhibited by certain medications used in the field of HIV (e.g. boosting agents). A resulting increase in methamphetamine levels can lead to adverse events, such as a rise in body temperature, hypertension and convulsions, as well as a risk for myocardial infarction. [3, 4, 6]

Mephedrone ("meow-meow", "drone", "white magic") a cathinone derivative, has similar activity but not as long as a duration of action and is particularly prevalent in London. Wrapped in cigarette paper it can be swallowed ("bomb"), snorted, injected intravenously or applied rectally. The latter prevents the irritation of mucosa of the nose, veins and the esophagus. Mephedrone is highly irritating and can cause inflammation.
Like methamphetamine, mephedrone causes euphoria, stimulation and enhanced openness. At parties, these two agents are often combined along with GHB/GBL, and consumed several times for an ongoing duration of action. The adverse events are like those of amphetamine; tachycardia, agitation, anxiety, vomiting, migraines and sleeplessness

are often reported. There are cases of hallucinations and unconsciousness. Psychological dependence is often seen. [2, 3, 5]

Drug interactions with HIV medications
Mephedrone is also metabolized in the liver, and can increase adverse events (e.g. tachycardia) if combined with boosting agents in HIV-therapy. [8]

Gammabutyrolactone (GBL) and 1,4-butanediol (BD) are a prodrug, which both are rapidly (t1/2 around 1 min) converted in the body to its active form gammahydroxybutyrate (GHB), also used as a drug. Since it is a commonly used cleaner and solvent, it is easily accessed via the Internet. It is rapidly absorbed when taken orally. Maximal concentration is reached after 20–40 minutes. Duration of action is 1.5 to 3 hours. So to avoid overdosing it is not recommended to take a second dose within 2 hours after taking the first one. After 4 to 8 hours, it is completely eliminated from the body. GHB is likely converted to GABA (gamma-aminobutyric acid), an endogenous neurotransmitter and hence indirectly influences dopamine levels. The effect is similar to that of alcohol, but reached with fewer amounts. Larger amounts lead to sleep and possibly vomiting, since GHB irritates the gastric mucosa. Loss of consciousness together with vomiting bears the risk of aspiration. GHB/GBL should not be consumed together with alcohol due to an unpredictable additive effect. Also co-administration with hypnotics and ketamine must be avoided. Since it has a very narrow dosage window with 1.8 ml potentially leading to toxicity, it needs to be dosed with a calibrated pipette or syringe. Subsequent doses should be spaced at least by two hours. In order to avoid difficult abstinence phenomena, users tend to take GBL/GHB in defined time intervals. This should be limited to week-end usage. Longer use can result in such dangerous abstinence phenomena that require intensive care. [7, 2, 3, 4]

Drug interactions with HIV medications
Elimination pathways of GLB, BD, GHD are theoretically metabolized non-hepatically. Drug interaction via alcoholdeydrogenase were discussed. In a case report, GHB toxicity with HIV-medications manifested itself with convulsions, bradycardia, respiratory depression and coma. If GHB is used with HIV-therapy, it must be taken in a low dose. Because of pharmacodynamics effects ketamine, opioids and hypnotics should be avoided within 12 hours. [4, 7, 8]

Ketamine ("Special K", "Vitamin K")
is often used with more extreme sexual practices for its dissociative anesthetic effect, characterized by a detachment between the objective and subjective sense of pain. At sufficiently high doses, users may experience what is called the "K-hole", a state of extreme dissociation while fully conscious. It has the potential of causing panic. An accidental over-dose of ketamine can be fatal, since the user cannot call for help in a state of paralysis. Chronic use of ketamine damages the epithelial lining of the bladder ultimately leading to removal of the bladder ("ketamine-induced ulcerative cystitis").
Ketamine can be snorted, injected intramuscularly or applied rectally. [2]

Drug interactions with HIV medications
Ketamine is primarily metabolized in the liver. An increased risk for adverse reactions including respiratory depression or myocardial infarction exists if taken with boosted HIV-therapy. This is based on a study with clarithromycin, which has similar inhibiting effects on liver enzymes. A three- to four-fold increase in ketamine levels were reported, emphasizing the importance of consuming low ketamine doses. Efavirenz and nevirapine induce the metabolism of ketamine. This reduces the desired effect. [8]

Poppers use is particularly common among gay men and refers to the chemical class of inhaled alkyl nitrites (originally isoamyl nitrite, today mostly pentyl or isopropyl nitrite). Their relaxation effect on involuntary smooth muscles eases anal intercourse and intensifies orgasm. Their synergistic effect with PD5-blockers (Viagra®, etc.) can lead to serious hypotension. Users can lose consciousness, fall and become injured. Concurrent use is not recommended; however if used together, poppers should be administered when lying down to reduce the risk of injury. Also liquid poppers should not come into contact with skin or mucosa; moisture hydrolyzes it to alkyl alcohol and nitrous acid. [2]

Cocaine is commonly insufflated, inhaled or injected. It increases energy levels and self-confidence. It inhibits the reuptake of dopamine and therefore has highly addictive qualities. [3]

Drug interactions with HIV medications
Cocaine is metabolized, to an extent of ten percent by liver enzymes. Due to liver enzyme inducing properties of certain HIV medications eg. Efavirenz , the concurrent use can lead to increased levels of a hepatotoxic metabolite of cocaine. Therefore it is important to monitor liver function in cocaine users. Co-administration of certain antihypertensives is contraindicated due to the potential for severe hypotension or angina pectoris. [8]

MDMA (3,4-methylenedioxy-N-methylamphetamine) (Ecstasy, E)
is an indirect serotonin/norepinephrine agonist with hallucinogenic properties. It is taken in form of a capsule, a pill or a powder and often combined with aspirin, caffeine, ketamine, LSD or pseudoephedrine. Desired effects include increased euphoria and decreased inhibition. Contrary to ChemSex substances, MDMA increases empathy. The addictive potential is lessened by the fact that ecstasy is rarely consumed daily. [2, 3]

Drug interactions with HIV medications
All amphetamine derivatives are metabolized via liver enzymes, which in turn are inhibited by certain booster medications used in HIV medicine. This increases amphetamine levels and the risk for adverse events, such as hypertension and tachycardia. Fatal toxicity has been reported with highly dosed ecstasy and concurrent use of boosted HIV-therapy. Canadian pharmacists recommend a reduced amphetamine intake of one-quarter of its usual dose, when also taking boosted HIV-regimens. Further, co-administration with statines is contraindicated due to a risk for rhabdomyolysis. Toxic events, such as severe hypotension may be seen when combined with certain antihypertensives. [8, 9, 10, 11]

The sequence of substance use

Drug use at a typical "party" usually does not involve the administration of a single agent. On the contrary, most users become experts on how to counteract unwanted effects of one substance with the use of another. For example, the following may be used at a sex party:

Prior to sex: Viagra®, alcohol, tobacco, marijuana

During sex: methamphetamine, cocaine, ketamine, poppers

Post sex: Benzodiazepine, other sedative or hypnotic

The use of five to ten substances within the course of a „session" is not unusual. Adding at least three medications when on HIV-therapy, the number of agents taken reaches the double-digits, making it difficult to theoretically consider all drug interactions. Therefore, the primary message is to dose carefully, especially if the substance is unknown to the user (which is always the case in illicit drug use, since the precise composition is variable). [2]

Addressing ChemSex in a general medicine practice

Patients participating in ChemSex are mostly young, homosexual men without a history of psychiatric disorders and are seen by general practitioners, some specialized in HIV-care. In addition, most patients have not come to the realization that their recreational drug use may be problematic, even potentially addictive. Most users do not consider themselves addicted, and also do not meet the definition for addiction according to the traditional diagnostic criteria.

Yet, complications are increasing and drug use is becoming more of a clinical problem, since the risks associated with the various substances are not to be underestimated.

Case 1:

- Male, MSM, in a steady relationship, socially well integrated, diagnosed with HIV-infection in 2004, on Kaletra and Truvada since 2010, open relationship for five years, ChemSex has not been mentioned
- Patient presents at the doctor's office one Monday morning without an appointment, in notable psychiatric distress: nervous, agitated, anxious, appearing depressed, cognitive disorder
- Patient mentions sex party on the week-end and initial intravenous drug use, substance unknown. Subjectively he felt poorly, self-accusations, significant psychological strain with respect to cognitive disorders
- Patient received an acute intervention, treatment with lorazepam, booked follow-up appointment in four days; did not show for follow-up; eight weeks later, his partner informed that he had committed suicide.

Case 2:

- Young female, in a steady relationship, no prior medical history aside from a mild social phobia in teen-age years
- Initial use of MDMA "out of curiosity" in January 2015, followed by malaise, increasing anxiety, panic attacks
- Patient started a behavioral therapy without significant improvement, was then seen by a psychiatrist and treated with lorazepam and pregabalin, alternatively with duloxetine or excitalopram

Aside from organic risks (phlebitis, inflammation, etc.), drug use may be associated with numerous psychiatric manifestations (anxiety, panic disorder, depression, psychotic symptoms, even psychosis, personality change and sleep disorders). These have a significant impact on subjective psychological strain and pose a high risk of becoming chronic. Anxiety and panic attacks as well as sleep disorders have a high potential for conditioning, meaning they remain even without further drug use. Most users are not well informed; the risks are often trivialized. How should the health care profession deal with it in clinical routine? Ignore the subject, as long as it is not being addressed, since everyone is responsible for oneself? Address the subject routinely? Only act when complications arise?

Most consumers do not present as "usual drug users" due to the sporadic use of drugs and being mostly socially well integrated. They become noticeable only when negative symptoms arise. Usually the awareness (or the knowledge) of possible risks is minimal; additionally defense mechanisms are applied ("I am not a junkie", "I have everything under control", etc.). Hence, the first step is to initiate discussion and produce awareness.

The risk of a person becoming addicted can be estimated based on certain patterns of consumption and personality traits. This however requires time. Since users primarily seek care from their general practitioner and not an addiction specialist, this approach is not feasible. Addressing the topic in a direct and non-judgemental way is most appropriate. There is no need to worry about patients feeling wrongly accused. Most persons concerned are unable to address the subject themselves and often are thankful when being able to talk about it. Patients, who do not use substances, signal this quite clearly. [2]

Several clues may indicate substance use and its trivialization by users in clinical practice:

- Missed appointments
- More frequent presentation at the office without an appointment (eg. Monday mornings)
- More frequent sick leaves (especially after week-ends)
- Nose bleeds (damage to the mucosa due to snorting of substances)
- Increase in viral load
- Increase in STDs
- Request for sedatives
- Endocarditis
- Problems with relationships

Potential for drug interactions

1. **Drugs and HIV-protease inhibitors:** increase in drug concentrations/duration of action
2. **Amphetamine/opiates and MAO-inhibitors (moclobemide, selegiline, etc.):** impaired vision, hypertensive crisis, cerebral hemorrhage
3. **Cocaine or ecstasy and non-selective beta-blockers:** hypotensive shock, bradycardia, AV-block, angina pectoralis symptoms
4. **substances, which can increase body temperature (eg. interleukins/interferons, nevirapine, abacavir):** hyperthermic crisis (with rhabdomyolysis) especially in a party setting
5. **Ecstasy and statins:** both drug groups can cause rhabdomyolysis inhibitors of CYP3A4, eg. HIV protease inhibitors, can increase statin levels significantly

6. **Inhaled nitrites (poppers) and phosphodiesterase inhibitors, eg. Sildenafil:** hypotension, decrease in coronary perfusion with potential myocardial infarction

In conclusion, we suggest that when taking a general medical history, the use of recreational substances should be included. When young, agitated patients present with cardiovascular and/or psychiatric symptoms, undefined complications or sudden psychological changes, the use of psychotropic substances should be considered. If indicated, the patient may be advised to seek a specialist or an addiction help service. The goal may not always be abstinence, but risk reduction through education and information. Since the novel substances have different effects, new therapies must be considered. It is important to paint a up-dated picture of drug usage. Expert in this field is David Stuart, Dean-Street Clinic, London, UK.

Potential interactions between ART and recreational drugs [8, 9, 10, 11]

Substance	Interaction	Symptoms	Comment
Amphetamines			
Methamphetamine	metabolism via CYP2D6 can be inhibited by RTV and possibly Cobicistat, leading to increased levels of the substance	hypertension, hyperthermia, convulsions, arrhythmias, tachycardia	if on RTV or Cobi: start with¼ of the usual recreational substance dose, if use is unavoidable
MDMA (Ecstasy)			
Mephedrone			?
Cannabis (THC)	THC ↑ mit RTV, Cobi	hallucinations, paranoia, anxiety, panic	likely clinically irrelevant
Miscellaneous			
Ketamine	Ketamine ↑ mit RTV, Cobi	respiratory depression, hallucinations, loss of conciousness	caution with RTV and Cobi: use lower drug doses, inform user on signs of ketamine toxicity
Cocaine	metabolism via CYP3A4 can be inhibited by RTV and Cobicistat, leading to increased levels of the cocaine metabolism via CYP3A4 can be induced by Neveripine and Efavirenz with increased levels of hepatotoxic metabolite norcocaine	CNS: tremors, muscular spasms, paranoia CV: hyertonie GI: nausea, vomiting	clinically relevant esp. in patients with cholinesterase deficiency
GBL/GHB	possible increase in GHB levels with RTV or Cobicistat	case report: GHB toxicity (convulsion, bradychardia, loss of consciousness) with SQV/r	caution with RTV and Cobi: use lower drug doses, inform user on signs of GHB toxicity
LSD	elimination pathways unknown	hallucinations, agitation	caution with RTV and Cobi: use lower drug doses, inform user on signs of LSD toxicity
Poppers	no interaction	dizziness, hypotension, circulatory collapse	
Sildenafil, tardalafil, vardenafil	LPV/r: vardenafil ↑ 49-fach		reduced doses: sildenafil: 25 mg/48h tardalafil: 10 mg /24h vardenafil: no interaction with LPV/r
Benzodiazepines	increased benzodiazepine levels with RTV or Cobicistat due to inhibition of CYP	drowsiness, disorientation	contraindicated: alprazolam, midazolam, triazolam dose reduction required: diazepam, flunitrazepam alternatives: lorazepam, oxazepam, temazepam

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Kindly supported by gsk GlaxoSmithKline

References: 1. Daskalopoulou M, et al. Recreational drug use, polydrug use, and sexual behaviour in HIV-diagnosed men who have sex with men in the UK: results from the cross-sectional ASTRA study. Lancet HIV. 2014 Oct;1:e22-31. 2. Schwarze S, et al. Neue Drogen-neue Herausforderungen, ein Blick aus verschiedenen Perspektiven. INXFO Newsletter 11/2015. 3. Bracchi M, et al. Increasing use of party drugs in people living with hiv on antiretrovitals: a concern for patients safety. AIDS 2015;29:1585-92. 4. Stuart D. Recommendation of a request in the INXFO-Forum. Nov 2016. 5. Reisinger M, et al. Partydrogen unter einer antiretroviralen Therapie. Newsletter Meettheexperts, Wien 6/2014. 6. Reeves J, et al. GHB/GBL intoxication and withdrawal: a review and case presentation. Addictive Disorders & Their Treatment 2003:25-8. 7. Busardo FP, et al. GHB pharmacology and toxicology: acute itoxication, concentration in blood and urine in forensic cases and treatment of the withdrawal syndomes. Curr Neuropharmacol 2015;1347-70. 8. Antoniou T1, et al. Interactions between recreational drugs and antiretroviral agents. Ann Pharmacother. 2002;36:1598-613. 9. Hales G, et al. D. Possible fatal interaction between protease inhibitors and methamphetamine. Antivir Ther. 2000;5:19. 10. Mirken B. Danger: possibly fatal interactions between ritonavir and "ecstasy", some other psychoactive drugs. AIDS Treat News. 1997;265:5. 11. Henry JA, et al. Fatal interaction between ritonavir and MDMA. Lancet. 1998; 28;352:1751-2. 12. www.Checkyourdrugs.at

published by: InXFo GbR, Hirzstraße 17, 50937 Cologne
logistic-team: Patrick Braun, Leonie Meemken, Eva Wolf
technical support: Stefan Preis, Clinovate; **photo:** Gunther Willinger
CECL/HIVP/0004/17; date of publication: June 2017