

## Sex enhancers: challenges, threats and the need for targeted measures

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Humans have always aimed to use substances for improving their cognitive, physical and sexual performances: ancient civilizations resorted to hallucinogens in the attempt to get into contact with their gods; the widespread use of caffeine in its various forms (caffeinated and energy drinks, tablets, etc.) and the more recent development of glutamate activators (1,2).

Products promising to enhance sexual performance have been promoted for over a century, dating back to the patent medicines of the 1800s. Very often, such products came with overstated claims, backed up by little evidence of safety or effectiveness. In 1906, in an effort to shield consumers from such potentially harmful practices, the Pure Food and Drug Law was enacted in the United States, so that consumers could be made aware of untrustworthy drugs and treatments sold as sex-drive and performance boosters.

Currently available sexual enhancers do not present selective central action and they can potentially affect more neurotransmitters. Several studies have associated enhanced sex-drive with the dopamine agonists apomorphine, bromocriptine, and pergolide, or the dopamine precursor levodopa (3). Cabergoline, a dopamine agonist that normalizes serum prolactin by acting centrally, is expected to have a similar effect (4) and could be beneficial in cases of orgasmic dysfunction. Antidepressants bupropion (5) and nomifensine (6) have been shown to increase libido. A noradrenergic action mechanism has been hypothesized for the libido-enhancing effect of bupropion (7). Improved libido has also been reported in studies with the serotonergic agents trazodone, venlafaxine and fenfluramine, whereas no correlation between the improvement in libido and the changes in mood (8) with the use of trazodone has been reported. Venlafaxine and its metabolite O-esmethylenlafaxine are potent inhibitors of norepinephrine and serotonin reuptake but weak inhibitors of dopamine reuptake. More specific serotonergic agents, however, are generally considered to have an inhibitory neurotransmitting effect in the control of sexual drive (9).

A worrisome trend, however, has come to the fore in recent years: erectile dysfunction medications (EDMs),

illegally marketed, have grown increasingly as a sort of “sexual enhancement aid” without any medical prescription or supervision.

A higher incidence of hazardous sexual behaviors has been observed among EDMs users, as well as an increased risk for STIs, HIV infection, and high rates of concomitant use of illicit and extremely abuse liable drugs (10,11) such as crystal methamphetamine,  $\gamma$ -hydroxybutyrate (GHB),  $\gamma$ -butyrolactone (GBL), ketamine, mephedrone and other synthetic cathinones and cocaine. All of them are used to facilitate and enhance prolonged, often unprotected sexual sessions with multiple sexual partners (12,13).

“Chemsex” is a term that has been firstly used in the United Kingdom to characterize deliberate sex under the influence of psychoactive drugs, mostly among men who have sex with other men (MSM). Furthermore, those who engage in such conducts are exposed to a wide array of physical, psychological and social adverse effects: such as the tendency to lose sleep, even staying awake for days without eating. Hospitalization may ensue on account of prolonged drug use, overdosing, development of mental health issues such as paranoia, anxiety, depression, psychosis, disorientation and even neurological complications such as convulsions, stroke, coma. Possible overdosing on GHB/GBL or ketamine may turn out to be deadly for users, and even relatively small amounts can make an adult individual lose consciousness, thus becoming vulnerable to sexual assault and criminal acts (13), or carry out high-risk behaviors, such as driving under their influence (14-16). Motivations behind participating in chemsex have been widely debated (17). The most sought-after effects of drug use among homosexual males and women were the increase in sexual confidence, sexual desire and libido, intimacy and sexual connection, the artificial protraction of sexual sessions and the possibility of more reckless or extreme kind of sex. Besides, a desire exists for escapism as a key motivation behind use, whether it was to manage personal insecurities, HIV related stigma or the sense of guilt associated with having sex that was deemed inappropriate by the users themselves or by society at large (18). In that regard, a chemsex-related case of intoxication

involved gay men who consumed GHB that had been added with sildenafil for the specific purpose of enhancing sexual effects (19). GHB and its precursors gammabutyrolactone (GBL) and 1,4-butanediol act as powerful psychological disinhibitors and also as mild anaesthetics (21-23). GHB is not only a drug of abuse but also finds clinical applications in the treatment of alcohol abstinence and for narcolepsy with cataplexy (24). Moreover, in those who experience drinking issues, pain relieving drugs such as paracetamol might cause a more serious risk of hepatotoxicity, particularly if pre-existing conditions affecting the liver are present (25). Anecdotal reports and some small qualitative studies in the UK find that people engaging in chemsex report better sex, with these drugs reducing inhibitions and increasing pleasure. They facilitate sustained arousal and induce a feeling of instant rapport with sexual partners. Some users report using them to manage negative feelings, such as a lack of confidence and self-esteem, internalised homophobia, and stigma about their HIV status (26). The social side of the coin should not be overlooked: often, users suffer socially as chemsex takes up a large amount of their time, in both participation and recovery from the effects of drug use. The unfolding of that scenario is bound to negatively affect social interrelationships and connections, as well as the ability to find or maintain gainful employment. Chemsex is connected with risky sexual behaviour and poor adherence to HIV medication which facilitates the spread of HIV and other STI's. Research states that the majority of men who engage in chemsex do not pursue services intended to provide help for addicts. Users are under the misconception that they have their habit under control, becoming mistrustful of any official addiction recovery program. It is true, however, that most mainstream services are mostly focused on treating opiate and alcohol addictions and are often ill-equipped to even fully understand the chemsex phenomenon. Sexual health clinics, on the other hand, are arguably the most suitable venues to deal with sexual health issues, yet may lack the expertise to address substance abuse when the two aspects are intertwined. Hence, it appears essential to develop specialized clinics to grapple with the threats posed by chemsex and party substances, in order to better meet the needs of chemsex victims in their path to rehabilitation and recovery.

## References

1. Frati P, Kyriakou C, Del Rio A, et al. Smart drugs and synthetic androgens for cognitive and physical enhancement: revolving doors of cosmetic neurology. *Curr Neuropharmacol* 2015; 13:5-11
2. Carlier J, Giorgetti R, Vari MR, et al. Use of cognitive enhancers: methylphenidate and analogs. *Eur Rev Med Pharmacol Sci* 2019; 23:3-15
3. Simonsen U, Comerma-Steffensen S, Andersson KE. Modulation of Dopaminergic Pathways to Treat Erectile Dysfunction. *Basic Clin Pharmacol Toxicol*. 2016; 119 Suppl 3:63-74
4. Hollander AB, Pastuszak AW, Hsieh TC, et al. Cabergoline in the Treatment of Male Orgasmic Disorder-A Retrospective Pilot Analysis. *Sex Med* 2016; 4:28-33
5. Patel K, Allen S, Haque MN, et al. Bupropion: a systematic review and meta-analysis of effectiveness as an antidepressant. *Ther Adv Psychopharmacol* 2016; 6:99-144
6. Iovieno N, Dalton ED, Fava M, et al. Second-tier natural antidepressants: review and critique. *J Affect Disord*. 2011; 130:343-57
7. Safarinejad MR. The effects of the adjunctive bupropion on male sexual dysfunction induced by a selective serotonin reuptake inhibitor: a double-blind placebo-controlled and randomized study. *BJU Int* 2010; 106:840-847
8. Kandeel FR, Koussa VK, Swerdloff RS. Male sexual function and its disorders: physiology, pathophysiology, clinical investigation, and treatment. *Endocr Rev* 2001; 22:342-388
9. Higgins A, Nash M, Lynch AM. Antidepressant-associated sexual dysfunction: impact, effects, and treatment. *Drug Healthc Patient Saf* 2010; 2:141-150
10. Harte CB, Meston CM. Recreational use of erectile dysfunction medications in undergraduate men in the United States: characteristics and associated risk factors. *Arch Sex Behav* 2010; 40:597-606
11. Solimini R, Rotolo MC, Pellegrini M, et al. Adulteration Practices of Psychoactive Illicit Drugs: An Updated Review *Curr Pharm Biotechnol*. 2017; 18: 524-530
12. Zaami S, Giorgetti R, Pichini S, et al. Synthetic cathinones related fatalities: an update. *Eur Rev Med Pharmacol Sci* 2018; 22: 268-274
13. Karch SB, Busardò FP, Vaiano F, et al. Levamisole adulterated cocaine and pulmonary vasculitis: Presentation of two lethal cases and brief literature review. *Forensic Sci Int* 2016; 265: 96-102
14. Busardò FP, Vaiano F, Mannocchi G, et al. Twelve months monitoring of hair GHB decay following a single dose administration in a case of facilitated sexual assault. *Drug Test Anal* 2017; 9:953-956
15. Gentili S, Mortali C, Mastrobattista L, et al. Determination of different recreational drugs in sweat by headspace solid-phase microextraction gas chromatography mass spectrometry (HS-SPME GC/MS): Application to drugged drivers. *Pharm Biomed Anal* 2016; 129:282-287
16. Giorgetti R, Tagliabracci A, Schifano F, et al. When "Chems" Meet Sex: A Rising Phenomenon Called "ChemSex". *Curr Neuropharmacol* 2017; 15:762-770
17. Busardò FP, Kyriakou C, Marchei E, et al. Ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) for determination of GHB, precursors and metabolites in different specimens: Application to clinical and forensic cases. *J Pharm Biomed Anal*. 2017; 137:123-131
18. Deimel D, Stöver H, Höfelbarth S, et al. Drug use and health behaviour among German men who have sex with men: Results of a qualitative, multi-centre study. *Harm Reduct J* 2016; 13:36
19. Schmidt AJ, Bourne A, Weatherburn P, et al. Illicit drug use among gay and bisexual men in 44 cities: Findings from the European MSM Internet Survey (EMIS). *Int J Drug Policy* 2016; 38:4-12
20. Pichini S, Marchei E, Pacifici R, et al. Chemsex intoxication involving sildenafil as an adulterant of GHB. *Drug Test Anal*. 2017; 9:956-959
21. Marchei E, Tini A, Pirani F, et al. Is GHB-glucuronide useful as a biomarker for the exogenous use of GHB? *Eur Rev Med Pharmacol Sci* 2019; 23:2311-2313

22. Busardò FP, Pichini S, Zaami S, et al. Hair testing of GHB: an everlasting issue in forensic toxicology *Clin Chem Lab Med* 2018; 26; 56:198-208
23. Busardò FP, Gottardi M, Tini A, et al. Replacing GHB with GBL in Recreational Settings: A New Trend in Chemsex. *Curr Drug Metab.* 2018; 19: 1080-1085
24. Busardò FP, Kyriakou C, Napoletano S, et al. Clinical applications of sodium oxybate (GHB): from narcolepsy to alcohol withdrawal syndrome. *Eur Rev Med Pharmacol Sci* 2015; 19:4654-4663
25. Tittarelli R, Pellegrini M, Scarpellini MG, et al. Hepatotoxicity of paracetamol and related fatalities. *Eur Rev Med Pharmacol Sci* 2017; 21: 95-101
26. McCall H. What is chemsex and why does it matter? *BMJ* 2015; 351:h5790