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*Editorial*

# New Choking Epidemic Trends in Psychoactive Drugs: The Zombifying Combination of Fentanyl and Xylazine Cause Overdoses and Little Hope in Rehabilitation

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The world of drugs of abuse is a complex clinical and forensic topic since their misuse can lead to devastating consequences. Therefore, understanding the lessons embedded can contribute to a more comprehensive approach to prevention, treatment, education, and public health initiatives. The impact is not only related to health concerns, with stigma, discrimination, and the legal implications being other issues to pay attention [1,2].

After several years of working with drugs of abuse, I must confess that I was not expecting big surprises regarding new signs and symptoms of exposure. But I was completely wrong. Firstly, it was krokodil, a synthetic homemade drug that emerged in Russia around 2012. The drug is outstanding the most fruitful imagination since it is one of the most recent harrowing chapters in the world of substance abuse [3,4]. Known for its catastrophic effects on both physical and mental health, it earned it the moniker "the flesh-eating drug." Injecting the drug leads to severe tissue damage, causing skin and muscle to rot away and drastically shorten the life expectancy. Users often develop gangrenous sores and ulcerations, exposing bones and internal organs [3,4]. The corrosive nature of krokodil is attributed to the ingredients used in preparation and to the impurities left in the final product [5]. Governments and health organizations worldwide have responded to the krokodil crisis with a combination of law enforcement efforts, public awareness campaigns, and addiction treatment programs. However, the elusive nature of the drug's production and the challenges of reaching marginalized populations make effective intervention a daunting task. And since its appearance, krokodil was, for me, on the top of the most tragic drugs of abuse inventions. Fortunately, the number of abusers was never very high and did not gain until now much popularity among abusers.

After visiting North America at the beginning of 2024 for a scientific congress, I was badly impressed with the number of fentanyl abusers in the streets, mostly homeless, smoking or injecting, some of them still exhibiting needles hanging out of their arms and abscesses in the legs. Besides North America, in several other parts of the world, heroin supply has been substituted by fentanyl, a synthetic opioid that is more profitable for the cartels that sell it [6]. The same has been happening in the medical field, with fentanyl being increasingly prescribed in comparison to hydromorphone and oxycodone throughout North America [7]. This wave was aggravated by the COVID-19 pandemic since overdoses and deaths sharply rose to unprecedented levels compared to pre-pandemic levels [8]. Fentanyl is estimated to be 50 to 100 times more potent than morphine and about 50 times more potent than heroin [9]. This extreme potency increases the risk of overdose, especially when individuals are unaware that the substance they are consuming contains fentanyl. Such reality is so important that the drug has become an important cause of death in some

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countries and even a topic of debate in political campaign trail [10–12]. Indeed, the fentanyl presence in both prescription medications and illicit street drugs has complicated efforts to control the crisis, necessitating comprehensive strategies that address both the medical and illicit aspects of opioid use.

Among the toxic effects I easily recognized, the bent spines of almost 90 degrees and the risk of amputations due to abscesses were for me choking. Walking by the streets, very close to stores of expensive brands, it was easy to see residents with contorted spines, trousers falling, possessing needles and glass pipes for drug administration, performing repetitive movements, and using walkers or wheelchairs most probably due to the disturbing wounds and gangrenous limbs. After thousands of observations of drug abusers, including the preparation of an atlas [13], these were, for me, new signs of exposure. However, the scientific literature is very limited in understanding of the adverse effects of synthetic opioids such as fentanyl, although the thousands of consumers arriving the clinical settings. While opioid overdoses typically feature pinpoint pupils, respiratory depression leading to "foam-cone" [14,15], and unconsciousness, other signs such as muscle rigidity, particularly stiff posturing, chest wall and jaw rigidity, dyskinesia, low or irregular heart rate, confusion, or delirium, anisocoria or unequal pupils have been recently reported in case of atypical overdose presentations [16]. Muscle rigidity was the most common atypical presentation in overdose cases, followed by dyskinesia. Muscle rigidity ranged from jaw clenching to decorticate posturing with arms held in towards the body, legs held out straight, clenched fists, and overall stiffness. The "fentanyl death pose" is a phrase that has been used in media to refer to the stiffening of the body when someone overdoses on fentanyl. Dyskinesia reflected a spectrum of involuntary muscle movements ranging from myoclonic jerks and twitches to more severe cases of chorea, including uncontrollable flailing of limbs and rolling around on the floor. In the absence of other typical opioid overdose characteristics, those atypical signs and symptoms may delay in recognizing opioid overdoses. A review of coroner reports of fentanyl-related deaths led researchers to hypothesize that acute chest wall rigidity was a significant and previously unreported factor leading to increased mortality among illicit opioid users [17]. Although this finding is largely unreported in association with illicit drug use, fentanyl-induced chest muscle rigidity and consequently respiratory problems is a well-known complication in anesthesia practice [17–19]. The chest wall rigidity (also known as "wooden chest syndrome") has been more frequently observed with synthetic lipid-soluble compounds such as fentanyl, acetylfentanyl, alfentanil, and sufentanil, and less frequent with other opioids [17,18]. But why abusers hang upside down in a zombie-like trance position, almost touching their toes, often with their trousers falling (Figure 1)? And why it is not more comfortable for them to sit or lie down? Well, this needs to be scientific clarified. A possible explanation might be related to the rigidity and stiffness of the body, namely of the of backs, predisposing to a more comfortable position in that posture. Also, since fentanyl decreases normal breathing rate and blood pressure, abusers hang upside down to keep their blood pressure up to avoid fainting and dying. Because nearly 90% of "street" opioid samples contained xylazine, its presence may be also the main responsible of these effects [20] as discussed following. Finally, opioid abuse may lead to vertebral osteomyelitis (i.e., the most common form of vertebral infection) and consequently moderate to severe pain in the back, legs and arms, fever, muscle spasm, difficulty in walking properly, and exaggerated forward convex rounding of the spinal thoracic and sacral regions (i.e., kyphosis) [21]. Hematogenous spread of *Staphylococcus aureus* is the most frequent etiological microorganism, and this reality should monitored as a cconsequence of opioid crises [21].

**Figure 1.** The zombie-like trance position, contorted backs almost touching their toes, often with their trousers falling most probably as consequence of fentanyl or xylazine alone or combined.

Indeed, new dangers are spiking with the non-addictive drug xylazine often referred to as "tranq" when used alone or as "tranq dope" when used as an adulterant to cut fentanyl [22,23]. Xylazine is also called the "zombie drug" due to its heavy sedative effect and associated-severely infected skin ulcers [24]. This is an $\alpha_2$-adrenergic receptor agonist used as a non-opioid sedative, analgesic, muscle relaxant and general anesthetic in veterinary medicine [25]. Although, not approved for human use, is increasingly being found in the united States illegal drug supply and linked to overdose deaths especially when combined with fentanyl [26]. Indeed, both fentanyl and xylazine produced dose-dependent increases in lethality when administered alone [27]. In humans, xylazine may cause hypotension, central nervous system depression, respiratory depression, and bradycardia [25,28]. Since xylazine is not an opioid, naloxone will not reverse its breathing effects. Nevertheless, as fentanyl is a common combination, naloxone can reverse its effects and will not cause harm if opioids are not involved in an overdose. Moreover, abscesses, necrosis and skin ulceration are frequently reported after xylazine injection, probably due to its partial $\alpha_1$-adrenergic agonist activity that causes direct vasoconstriction of peripheral blood vessels and decreased skin perfusion [29]. Although not fully understood, xylazine may prolongs and enhances opioids euphoric effects and delay the time to withdrawal [30]. Interestingly, *postmortem* fentanyl concentrations were greater in cases with xylazine detected than those without xylazine detected, suggesting that exposure to xylazine results in toleration of higher opioid doses prior to succumbing to death [31]. The lethargic trance-like state and sometimes blackout, predispose abusers to robbery or assault [28].

In conclusion the world of psychoactive substances is changing posing clinical and forensic issues. Understanding the risks and consequences of substance abuse is essential for individuals, communities, and policymakers in developing effective strategies to mitigate these impacts. Continued advancements in neuroscience may lead to a deeper understanding of the neurological mechanisms underlying addiction. The precision medicine, which involves tailoring treatment strategies to individuals based on their genetic makeup, lifestyle, and environment, may be applied to addiction treatment, allowing for more personalized and effective interventions that consider an individual's unique vulnerabilities and response to drugs. The integration of digital technologies in addiction treatment is likely to expand to support, monitor the progress, and deliver interventions to individuals struggling with substance abuse. Finally, future perspectives on Psychoactives should also involve mind changes in policy and legislation recognizing addiction as a health issue privileging harm reduction and treatment over punitive measures. This reality offers to our Psychoactives journal a privileged scientific stage to address these challenges, particularly in the field of new trends of substance abuse, such as fentanyl and xylazine. As Editor-in-Chief I encourage scientists and scholars to submit their cutting-edge research to our journal for the dissemination of impactful clinical and forensic discoveries that will shape

the future of Psychoactive substances, without forgetting strategies aiming prevention and education.

Compliance with Ethical Standards: Images were burred to avoid identification of individuals.

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## References

1. Farrugia, A.; Pienaar, K.; Fraser, S.; Edwards, M.; Madden, A. Basic care as exceptional care: Addiction stigma and consumer accounts of quality healthcare in Australia. *Health Sociol. Rev.* **2021**, *30*, 95–110. [CrossRef]
2. Zwick, J.; Appleseth, H.; Arndt, S. Stigma: How it affects the substance use disorder patient. *Subst. Abuse Treat. Prev. Policy* **2020**, *15*, 50. [CrossRef]
3. Alves, E.A.; Grund, J.P.; Afonso, C.M.; Netto, A.D.; Carvalho, F.; Dinis-Oliveira, R.J. The harmful chemistry behind krokodil (desomorphine) synthesis and mechanisms of toxicity. *Forensic Sci. Int.* **2015**, *249*, 207–213. [CrossRef]
4. Nogueira, D.; Caldas, I.M.; Dinis-Oliveira, R.J. Bisphosphonates and osteonecrosis of the jaws: Clinical and forensic aspects. *Arch. Oral. Biol.* **2023**, *155*, 105792. [CrossRef] [PubMed]
5. Soares, J.X.; Alves, E.A.; Silva, A.M.N.; de Figueiredo, N.G.; Neves, J.F.; Cravo, S.M.; Rangel, M.; Netto, A.D.P.; Carvalho, F.; Dinis-Oliveira, R.J.; et al. Street-Like Synthesis of Krokodil Results in the Formation of an Enlarged Cluster of Known and New Morphinans. *Chem. Res. Toxicol.* **2017**, *30*, 1609–1621. [CrossRef] [PubMed]
6. Gladden, R.M.; Martinez, P.; Seth, P. Fentanyl Law Enforcement Submissions and Increases in Synthetic Opioid-Involved Overdose Deaths—27 States, 2013–2014. *MMWR Morb. Mortal. Wkly Rep.* **2016**, *65*, 837–843. [CrossRef] [PubMed]
7. Fischer, B.; Pang, M.; Jones, W. The opioid mortality epidemic in North America: Do we understand the supply side dynamics of this unprecedented crisis? *Subst. Abuse Treat. Prev. Policy* **2020**, *15*, 14. [CrossRef] [PubMed]
8. Xu, J.J.; Seamans, M.J.; Friedman, J.R. Drug overdose mortality rates by educational attainment and sex for adults aged 25–64 in the United States before and during the COVID-19 pandemic, 2015–2021. *Drug Alcohol Depend.* **2024**, *255*, 111014. [CrossRef] [PubMed]
9. Ventura, L.; Carvalho, F.; Dinis-Oliveira, R.J. Opioids in the Frame of New Psychoactive Substances Network: A Complex Pharmacological and Toxicological Issue. *Curr. Mol. Pharmacol.* **2018**, *11*, 97–108. [CrossRef] [PubMed]
10. D'Orsogna, M.R.; Böttcher, L.; Chou, T. Fentanyl-driven acceleration of racial, gender and geographical disparities in drug overdose deaths in the United States. *PLoS Glob. Public. Health* **2023**, *3*, e0000769. [CrossRef]
11. Belzak, L.; Halverson, J. The opioid crisis in Canada: A national perspective. *Health Promot. Chronic Dis. Prev. Can.* **2018**, *38*, 224–233. [CrossRef]
12. Nguyen, H.V.; Mital, S.; Bugden, S.; McGinty, E.E. British Columbia's Safer Opioid Supply Policy and Opioid Outcomes. *JAMA Intern. Med.* **2024**, *184*, 256–264. [CrossRef]
13. Dinis-Oliveira, R.J. One image is worth more than a thousand words: Producing an atlas of medical signs for teaching clinical and forensic toxicology. *Forensic Sci. Res.* **2022**, *7*, 815–822. [CrossRef]
14. Dinis-Oliveira, R.J.; Carvalho, F.; Moreira, R.; Duarte, J.A.; Proenca, J.B.; Santos, A.; Magalhaes, T. Clinical and forensic signs related to opioids abuse. *Curr. Drug Abuse Rev.* **2012**, *5*, 273–290. [CrossRef]
15. Dinis-Oliveira, R.J.; Santos, A.; Magalhães, T. "Foam Cone" exuding from the mouth and nostrils following heroin overdose. *Toxicol. Mech. Methods* **2012**, *22*, 159–160. [CrossRef] [PubMed]
16. Kinshella, M.W.; Gauthier, T.; Lysyshyn, M. Rigidity, dyskinesia and other atypical overdose presentations observed at a supervised injection site, Vancouver, Canada. *Harm Reduct. J.* **2018**, *15*, 64. [CrossRef] [PubMed]
17. Burns, G.; DeRienz, R.T.; Baker, D.D.; Casavant, M.; Spiller, H.A. Could chest wall rigidity be a factor in rapid death from illicit fentanyl abuse? *Clin. Toxicol.* **2016**, *54*, 420–423. [CrossRef] [PubMed]
18. Çoruh, B.; Tonelli, M.R.; Park, D.R. Fentanyl-induced chest wall rigidity. *Chest* **2013**, *143*, 1145–1146. [CrossRef] [PubMed]
19. Buxton, J.A.; Gauthier, T.; Kinshella, M.W.; Godwin, J. A 52-year-old man with fentanyl-induced muscle rigidity. *CMAJ* **2018**, *190*, E539–E541. [CrossRef] [PubMed]
20. Johnson, J.; Pizzicato, L.; Johnson, C.; Viner, K. Increasing presence of xylazine in heroin and/or fentanyl deaths, Philadelphia, Pennsylvania, 2010–2019. *Inj. Prev.* **2021**, *27*, 395–398. [CrossRef] [PubMed]
21. Yuschak, E.; Chase, S.; Haq, F.; Vandever, C. Demographics and Length of Stay for Osteomyelitis in Opioid Drug Users: A Unique Population with High Healthcare Costs. *Cureus* **2019**, *11*, e4339. [CrossRef]

22. Kariisa, M.; O'Donnell, J.; Kumar, S.; Mattson, C.L.; Goldberger, B.A. Illicitly Manufactured Fentanyl-Involved Overdose Deaths with Detected Xylazine—United States, January 2019–June 2022. *MMWR Morb. Mortal Wkly Rep.* **2023**, *72*, 721–727. [CrossRef]
23. Bradford, W.; Figgatt, M.; Scott, K.S.; Marshall, S.; Eaton, E.F.; Dye, D.W. Xylazine co-occurrence with illicit fentanyl is a growing threat in the Deep South: A retrospective study of decedent data. *Harm Reduct. J.* **2024**, *21*, 46. [CrossRef]
24. Bowles, J.M.; Copulsky, E.C.; Reed, M.K. Media framing xylazine as a "zombie drug" is amplifying stigma onto people who use drugs. *Int. J. Drug Policy* **2024**, *125*, 104338. [CrossRef]
25. Ruiz-Colón, K.; Chavez-Arias, C.; Díaz-Alcalá, J.E.; Martínez, M.A. Xylazine intoxication in humans and its importance as an emerging adulterant in abused drugs: A comprehensive review of the literature. *Forensic Sci. Int.* **2014**, *240*, 1–8. [CrossRef]
26. Gipson, C.D.; Strickland, J.C. Integrating public health and translational basic science to address challenges of xylazine adulteration of fentanyl. *Neuropsychopharmacology* **2024**, *49*, 319–320. [CrossRef]
27. Smith, M.A.; Biancorosso, S.L.; Camp, J.D.; Hailu, S.H.; Johansen, A.N.; Morris, M.H.; Carlson, H.N. "Tranq-Dope" Overdose and Mortality: Lethality Induced by Fentanyl and Xylazine. *bioRxiv* **2023**. [CrossRef] [PubMed]
28. Zagorski, C.M.; Hosey, R.A.; Moraff, C.; Ferguson, A.; Figgatt, M.; Aronowitz, S.; Stahl, N.E.; Hill, L.G.; McElligott, Z.; Dasgupta, N. Reducing the harms of xylazine: Clinical approaches, research deficits, and public health context. *Harm Reduct. J.* **2023**, *20*, 141. [CrossRef] [PubMed]
29. Malayala, S.V.; Papudesi, B.N.; Bobb, R.; Wimbush, A. Xylazine-Induced Skin Ulcers in a Person Who Injects Drugs in Philadelphia, Pennsylvania, USA. *Cureus* **2022**, *14*, e28160. [CrossRef] [PubMed]
30. Friedman, J.; Montero, F.; Bourgois, P.; Wahbi, R.; Dye, D.; Goodman-Meza, D.; Shover, C. Xylazine spreads across the US: A growing component of the increasingly synthetic and polysubstance overdose crisis. *Drug Alcohol. Depend.* **2022**, *233*, 109380. [CrossRef] [PubMed]
31. Hays, H.L.; Spiller, H.A.; DeRienz, R.T.; Rine, N.I.; Guo, H.T.; Seidenfeld, M.; Michaels, N.L.; Smith, G.A. Evaluation of the relationship of xylazine and fentanyl blood concentrations among fentanyl-associated fatalities. *Clin Toxicol* **2024**, *62*, 26–31. [CrossRef] [PubMed]