

Fentanyl and xylazine crisis: Crafting coherent strategies for opioid overdose prevention

Lakshit Jain, Jasleen Kaur, Shahana Ayub, Danya Ansari, Rizwan Ahmed, Abdul Qadir Dada, Saeed Ahmed

Specialty type: Psychiatry

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Cheng J, China

Received: January 1, 2024

Revised: May 6, 2024

Accepted: June 4, 2024

Published online: June 19, 2024

Processing time: 170 Days and 11.4 Hours



Lakshit Jain, Department of Psychiatry, University of Connecticut, Farmington, CT 06032, United States

Jasleen Kaur, Addiction Services Division, Connecticut Valley Hospital, Middletown, CT 06457, United States

Shahana Ayub, Department of Psychiatry, Institute of Living, Hartford, CT 06102, United States

Danya Ansari, Department of Medicine, Islamabad Medical and Dental College, Islamabad 44000, Pakistan

Rizwan Ahmed, Department of Medicine, Liaquat College of Medicine and Dentistry, Karachi 75290, Pakistan

Abdul Qadir Dada, Department of Medicine, Trinity School of Medicine, Roswell, GA 30075, United States

Saeed Ahmed, Addiction Services and Dual Diagnosis Unit, Saint Francis Hospital and Medical Center, Hartford, CT 06105, United States

Corresponding author: Lakshit Jain, MD, Assistant Professor, Department of Psychiatry, University of Connecticut, 263 Farmington Avenue, Farmington, CT 06032, United States. lakshit.jain@ct.gov

Abstract

The United States is in the throes of a severe opioid overdose epidemic, primarily fueled by the pervasive use of fentanyl and the emerging threat of xylazine, a veterinary sedative often mixed with fentanyl. The high potency and long duration of fentanyl is compounded by the added risks from xylazine, heightening the lethal danger faced by opioid users. Measures such as enhanced surveillance, public awareness campaigns, and the distribution of fentanyl-xylazine test kits, and naloxone have been undertaken to mitigate this crisis. Fentanyl-related overdose deaths persist despite these efforts, partly due to inconsistent policies across states and resistance towards adopting harm reduction strategies. A multifaceted approach is imperative in effectively combating the opioid overdose epidemic. This approach should include expansion of treatment access, broadening the availability of medications for opioid use disorder, implementation of harm reduction strategies, and enactment of legislative reforms and

diminishing stigma associated with opioid use disorder.

Key Words: Fentanyl; Xylazine; Opioid overdose; Epidemic; Opioid use disorder; Buprenorphine; Medications for opioid use disorder

©The Author(s) 2024. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: This editorial addresses the escalating opioid overdose crisis in the United States, exacerbated by the use of fentanyl and the emerging threat of xylazine. Despite efforts like enhanced surveillance and distribution of test kits and naloxone, fentanyl-related deaths persist due to inconsistent state policies and resistance towards harm reduction strategies. The paper advocates for a multifaceted approach, including expanded treatment access, wider availability of medications for opioid use disorder, implementation of harm reduction strategies, legislative reforms, and reducing stigma associated with opioid use disorder.

Citation: Jain L, Kaur J, Ayub S, Ansari D, Ahmed R, Dada AQ, Ahmed S. Fentanyl and xylazine crisis: Crafting coherent strategies for opioid overdose prevention. *World J Psychiatry* 2024; 14(6): 760-766

URL: <https://www.wjgnet.com/2220-3206/full/v14/i6/760.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v14.i6.760>

INTRODUCTION

The deadly implications of fentanyl in the drug crisis: Fentanyl has recently emerged as a major risk factor and potentially leading cause of overdose deaths among people aged 18 to 45, with fatalities exceeding roughly 150 deaths per day in the United States alone[1,2]. This synthetic opioid, initially developed for medical purposes such as pain, anesthesia, and palliative care, is roughly 50 to 100 times more potent than heroin and morphine. Fentanyl has widely infiltrated the illicit drug market and is often mixed with other substances. It has been found to be augmented illicitly with heroin, cocaine, methamphetamine, and even counterfeit pills are manufactured that mimic prescription opioids such as oxycodone, alprazolam, or stimulants like amphetamines[2,3]. Illicit production of fentanyl occurs in countries like China, India and Mexico; but sometimes drug traffickers manufacture their own fentanyl in the United States with precursor chemicals sourced from China and Mexico[3]. Fentanyl has become a primary driver in increasing overdose deaths due to its deceptive appearance and significant potency[2,3]. Many users consume it unknowingly, significantly increasing the likelihood of rapid and fatal overdoses despite education efforts. In the contemporary discourse on public health, the escalating incidence of fatalities linked to fentanyl and other synthetic opioids is a subject of profound concern. In 2021, synthetic opioids were implicated in 88% of 80411 opioid overdose deaths, which constituted 75.4% of all drug overdose fatalities, highlighting the urgent need to address the growing crisis of opioid-related overdoses[1,2].

Fentanyl's unique pharmacological characteristics pose significant challenges when it comes to the management and treatment of opioid overdose. As a powerful synthetic opioid, fentanyl has a high affinity for opioid receptors, leading to its rapid and intense onset of effects. This rapid onset is mitigated by fentanyl's quick redistribution to other tissues leading to a short duration of action. This effect is due to differences in lipophilicity, with fentanyl being lipid soluble and other drugs such as morphine being more hydrophilic[4]. As a consequence, a higher dose of naloxone (10-fold higher) is required to reverse the effects of fentanyl as compared to morphine. Even low doses of fentanyl show decreased sensitivity to reversal by naloxone[5].

The pharmacological profile of fentanyl presents unique challenges in the treatment of opioid use disorder (OUD). Fentanyl's high potency and its user's quick development of high tolerance leads to severe cravings. These characteristics reduce response to low to moderate doses (8-16 mg) of life-saving medications such as buprenorphine[6]. A recent retrospective cohort study published in *JAMA* notably found that patients prescribed 24 mg of buprenorphine had a significantly lower risk of treatment discontinuation compared to those prescribed 16 mg (adjusted hazard ratio, 1.20; 95% confidence interval: 1.06-1.37)[6]. Patients prescribed 24 mg of buprenorphine were observed to have a better retention in treatment than patients prescribed 16 mg of buprenorphine. The current guidelines suggesting a daily maintenance target dose of 16 mg were established prior to the advent of fentanyl and appear to be insufficient in control of cravings and withdrawal associated with its use. Some studies from the past have indicated that the benefits of buprenorphine may increase with daily doses of up to 32 mg[6,7]. This highlights the urgent need for tailored treatment approaches in cases of fentanyl use, possibly requiring higher doses of buprenorphine or alternative treatments like methadone to manage the condition effectively.

WHY DO WE NEED RADICAL REFORMS

In the United States, individuals struggling with OUD often encounter obstacles in accessing treatment options. This issue

is largely due to the hesitation among lawmakers, public health agencies, and clinical providers to fully endorse ‘harm reduction’ as a viable approach to treatment. Despite evidence supporting the efficacy of harm reduction, there continues to be a struggle for acceptance and implementation. A collaborative study by NIDA (National Institutes of Health) and the Centers for Disease Control and Prevention’s National Center for Injury Prevention and Control found that in 2021 around 2.5 million adults in the United States suffered from OUD, but only 36% received substance use treatment, and just 22% received OUD-specific medications. This left an overwhelming 78% of adults with OUD without essential OUD treatment[8].

The gap in treatment is partly explained by systemic challenges such as the aforementioned decision makers (lawmakers, public health agencies, and clinical providers) often harboring internalized negative attitudes and beliefs toward people with OUD. These attitudes can affect the adoption of globally recognized effective treatment strategies[9]. Moreover, medications for OUDs (MOUDs) itself faces prejudice and stigma at a cultural level, adding further barriers to their its acceptance as a treatment option[10]. Compounding these issues is the operational model of many opioid treatment programs (OTPs) in the United States, which is often described as adhering to a “high threshold, low tolerance” approach[11]. This model is characterized by substantial initial barriers to treatment entry (‘high threshold’), making it challenging for patients with OUD to access necessary care. These programs also exhibit a ‘low tolerance’ for patient lapses or non-compliance, resulting in a propensity for swift removal of patients from treatment for minor transgressions. This model not only impedes the initiation of treatment but also jeopardizes the continuity and effectiveness of care for those with OUD who manage to overcome the initial hurdles[11]. This ‘high threshold, low tolerance’ attitude also extends to individuals who use illicit fentanyl, further complicating the treatment landscape and influencing decision-making processes. While there is advocacy from some decision-makers for increased access to safer alternatives and enhanced safety measures for people with OUD using fentanyl, many favor a more punitive approach, viewing legal action as a primary tool to combat the fentanyl crisis. The ‘high threshold, low tolerance’ model in many OTPs particularly affects individuals using fentanyl. For example, the stringent entry requirements often mean that individuals using fentanyl face considerable hurdles in accessing treatment such as extensive documentation, prerequisite counseling sessions, or detoxification requirements. Once in treatment, minor infractions such as missing appointments, relapsing, or positive drug tests can lead to dismissal from the program. This approach fails to acknowledge the chronic nature of OUD and the complex set of challenges faced by individuals in recovery. The lack of flexibility and understanding within these programs can result in individuals being ejected from treatment for relatively minor setbacks, which are often part of the recovery process.

Due to the widespread availability of fentanyl in the illicit drug supply, people are actively encouraged to test their opioids prior to consumption. The use of sterile injection supplies, naloxone, and fentanyl test strips is promoted as well [12-14]. Unfortunately, the potential benefits of each of these interventions are mitigated by significant barriers. The use of fentanyl testing strips remains a hurdle[15], with people facing challenges acquiring the test strips due to state laws banning their possession[12]. Apart from protection from overdose, injection drug users with a positive fentanyl test strip, are five times more likely to alter their drug use behavior[16].

Another set-back when combating the opioid crisis is limitations to needle and syringe programs in various parts of the United States, especially rural areas[17]. Although the number of programs has increased across the country, these programs face operational challenges and communities continue to struggle to deliver health and social services to drug users[18].

The North American Drug Checking Survey was conducted in 2022 to evaluate drug-checking services available for people who use drugs. This survey identified significant barriers to drug-checking services like poor staffing (50%), lack of funding (88%), and absence of technical expertise (38%). The survey also highlighted how drug-checking services are significantly impacted by local and state laws banning the possession and/or distribution of illicit drug samples, drug paraphernalia, or drug-checking equipment[19].

A study carried out in 2017 found a notable decline in opioid-related deaths following the passing of Naloxone Access and Good Samaritan laws[20]. Several barriers to naloxone distribution persist. These barriers include institutional rules, state regulations, stigma, cost, and lack of educational training. The presence of these barriers indicates that there is a crucial need for improvement in the use of naloxone for overdose prevention[21]. A recent review found that naloxone availability varies significantly among different pharmacies. The study evaluated around 11000 audited pharmacies and found that 37.2% did not have naloxone in stock and 48.1% did not have naloxone immediately accessible upon request. Despite a recent ruling that allowed naloxone to be dispensed without a prescription, 37.1% of pharmacies indicated they were not willing to do so[22]. Hence, radical reforms are required to curb the existing fentanyl epidemic. Despite significant willingness to use overdose prevention sites and/or supervised consumption sites among people who use opioids, several local governments are either reluctant to consider creating such sites or face significant challenges in creating these sites for people who use opioids[23,24].

DISCUSSION AND RECOMMENDATIONS

Recent statistics released by the Centers for Disease Control and Prevention’s National Center for Health Statistics reveal a concerning trend in drug overdose deaths in the United States. Over a 12-month period ending in May, the number of fatalities due to drug overdoses surpassed 112000 cases. This finding reflects an increase of approximately 2.7% from the previous year’s figure of 109261 deaths[2]. The data also highlights that the crisis disproportionately affects young individuals and communities of color, underlining the urgent need for targeted interventions and support in these populations. The continuously changing landscape of the opioid crisis is marked by the emergence of new and serious

threats. One such threat is the $\alpha 2$ adrenergic agonist animal tranquilizer xylazine[25]. Xylazine has been detected in increasing numbers of overdose deaths, and it is known to cause severe and long-lasting flesh wounds in its users[26-28]. In addition, the advent of nitazenes, a class of synthetic opioids, introduces a new level of risk to the crisis[29,30]. Nitazenes could potentially be more potent than fentanyl, already notorious for its own extreme potency[31-33]. The introduction of these substances into the drug market intensifies the complexity of the opioid crisis. This concern adds another layer of difficulty to the formidable task of curtailing opioid misuse and overdose incidents, underscoring the urgent need for comprehensive strategies and interventions. The pervasive use of fentanyl not only has severe health repercussions but also significant socio-economic impacts. These include increased healthcare expenditures due to the necessity for emergency overdose treatments, frequent hospitalizations, long-term addiction care and loss of lives, as well as broader societal costs such as diminished productivity and greater demands on the criminal justice system. Such challenges highlight the need for comprehensive public health strategies. Effective measures could include enhanced surveillance systems, the widespread availability of naloxone, and educational programs aimed at healthcare providers and the general public about the dangers of fentanyl and effective management practices. Implementing these initiatives can alleviate the direct economic impact and foster improvements in community health outcomes.

The mental health implications of drug use are substantial, with a notable rise in psychiatric disorders. The impact on mental health is further exacerbated when fentanyl is combined with other substances, such as stimulants or xylazine, compounding the severity of these effects. Addressing this aspect requires both preventive and therapeutic strategies, underscoring the importance of accessible mental health services and robust support systems. At an international level, addressing the spread of fentanyl transcends national boundaries and requires concerted global cooperation. Strengthening international partnerships, particularly with key countries in the fentanyl supply chain, is vital. Enhanced diplomatic efforts, such as those between the United States and China, which led to the recent reconvening of the United States-China counternarcotics commission[34], are critical steps towards mitigating the challenges posed by fentanyl production and trafficking. These collaborative efforts are essential for crafting effective strategies that can save lives and stabilize affected communities globally.

Given the increasing complexity and severity of the crisis, a multi-dimensional approach is vital. Public health strategies must evolve to address the changing nature of substance abuse. This includes consolidating harm reduction services by increasing access to naloxone, promoting needle exchange programs, offering MOUD, and providing testing strips for substances like fentanyl and xylazine. The implementation of mobile methadone clinics and the modernization of methadone treatment would also offer flexible and accessible care[35]. The opioid crisis has disproportionately impacted certain segments of the population, particularly marginalized groups such as African American individuals and other people of color[36-38]. These communities often face significant barriers to accessing healthcare services, including MOUDs. Mobile narcotic treatment programs operating through vans that travel to multiple locations are crucial in delivering methadone treatment to these underserved populations[39], mitigating barriers such as transportation access, long travel distances, and stigma.

The integration of digital health technologies such as mobile medical apps and telemedicine plays a crucial role in expanding reach and enhancing treatment plans. Technologies like wearable health monitors, artificial intelligence-powered analytics, and innovative approaches such as the Wheels and Waves VDOT program as well as smart drug dispensers contribute to improved treatment adherence and reduced misuse[40]. Virtual reality therapy offers a novel method for psychological support and relapse prevention. Integrating services with social determinants of health like housing and employment services and genetic testing are key to personalized treatment approaches.

As we continue to grapple with the opioid crisis, innovative approaches are being explored. These approaches include the implementation of safe consumption sites (SCS)[23,24]. These facilities offer a controlled environment where individuals can consume drugs under medical supervision with the aim of reducing overdoses and infectious disease transmission. These sites are not without controversy. Legal pushback and public criticism are commonly encountered in their implementation. Critics argue that saline infusion sonography (SIS) may enable drug use rather than deter it and could potentially lead to an increase in neighborhood crime. The legality of SIS under federal law is currently being contested which adds another layer of complexity to the issue. It is crucial to continue evaluating the effectiveness of SIS and other harm-reduction strategies. As the opioid crisis continues to evolve, so too must our approach to addressing it. It is necessary to center our approach on evidence-based practices and a commitment to improving public health.

Policy reforms and targeted programs are essential in the comprehensive fight against the opioid epidemic. Essential steps include expanding insurance coverage for addiction treatment, enforcing mental health parity laws, and developing programs targeting emerging threats such as xylazine and nitazenes. A comprehensive response also encompasses broadening the scope of services to support mental health and social needs, reinforcing harm reduction strategies such as needle and syringe programs, overdose education and naloxone distribution, SCS, and drug checking services[41-43]. These strategies offer practical ways to reduce the direct and indirect harm associated with substance use and are crucial in mitigating the immediate risks of drug use while providing long-term support for individuals battling addiction. Lastly, addressing the stigma associated with substance use disorders is vital. Efforts to reduce stigma such as nationwide anti-stigma campaigns and the promotion of person-centered language when discussing substance use can foster a supportive environment for those seeking help and enhance treatment outcomes[44]. Educational campaigns aimed at raising awareness about the dangers of potent new substances are crucial.

CONCLUSION

Addressing the fentanyl crisis is a complex and interconnected challenge that demands a comprehensive response.

Overcoming the stigma associated with addiction, expanding access to evidence-based treatment, and advocating for harm reduction initiatives are central to tackling this epidemic effectively. This multifaceted crisis also involves issues such as polydrug use, limited treatment accessibility, and criminal justice reform. A collaborative effort is essential and must involve healthcare providers, policymakers, communities, and individuals affected by fentanyl use. Other vital components of this response include public awareness, education, and comprehensive data collection. By addressing these challenges holistically and working together, we can make meaningful progress in reducing the harm caused by fentanyl and preventing further devastation to individuals and society.

FOOTNOTES

Author contributions: All authors made significant contributions to this paper; Ahmed S designed the overall concept and outline of the manuscript; Jain L, Kaur J, Ayub S, Ansari D, Ahmed R, and Dada AQ contributed to the discussion and design of the manuscript; and all authors contributed to the writing, editing of the manuscript, illustrations, and literature review.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country of origin: United States

ORCID number: Lakshit Jain 0000-0003-3080-9356; Jasleen Kaur 0009-0002-3007-7562; Danya Ansari 0009-0008-0666-2968; Rizwan Ahmed 0000-0002-4108-0444; Abdul Qadir Dada 0009-0002-5342-6614; Saeed Ahmed 0000-0002-9483-2355.

S-Editor: Wang JJ

L-Editor: A

P-Editor: Che XX

REFERENCES

- 1 **Centers for Disease Control and Prevention.** National Vital Statistics System. [cited 10 December 2023]. Available from: <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>
- 2 **Centers for Disease Control and Prevention.** Fentanyl Facts. [cited 10 December 2023]. Available from: <https://www.cdc.gov/stopoverdose/fentanyl/index.html#print>
- 3 **Drug Enforcement Administration.** Counterfeit Pills Fact Sheet. [cited 10 December 2023]. Available from: https://www.dea.gov/sites/default/files/2021-12/DEA-OPCK_FactSheet_December%202021.pdf
- 4 **Comer SD, Cahill CM.** Fentanyl: Receptor pharmacology, abuse potential, and implications for treatment. *Neurosci Biobehav Rev* 2019; **106**: 49-57 [PMID: 30528374 DOI: 10.1016/j.neubiorev.2018.12.005]
- 5 **Kelly E, Sutcliffe K, Cavallo D, Ramos-Gonzalez N, Alhosan N, Henderson G.** The anomalous pharmacology of fentanyl. *Br J Pharmacol* 2023; **180**: 797-812 [PMID: 34030211 DOI: 10.1111/bph.15573]
- 6 **Chambers LC, Hallowell BD, Zullo AR, Paiva TJ, Berk J, Gaither R, Hampson AJ, Beaudoin FL, Wightman RS.** Buprenorphine Dose and Time to Discontinuation Among Patients With Opioid Use Disorder in the Era of Fentanyl. *JAMA Netw Open* 2023; **6**: e2334540 [PMID: 37721749 DOI: 10.1001/jamanetworkopen.2023.34540]
- 7 **Fareed A, Vayalapalli S, Casarella J, Drexler K.** Effect of buprenorphine dose on treatment outcome. *J Addict Dis* 2012; **31**: 8-18 [PMID: 22356665 DOI: 10.1080/10550887.2011.642758]
- 8 **Jones CM, Han B, Baldwin GT, Einstein EB, Compton WM.** Use of Medication for Opioid Use Disorder Among Adults With Past-Year Opioid Use Disorder in the US, 2021. *JAMA Netw Open* 2023; **6**: e2327488 [PMID: 37548979 DOI: 10.1001/jamanetworkopen.2023.27488]
- 9 **Calcaterra SL, Bach P, Chadi A, Chadi N, Kimmel SD, Morford KL, Roy P, Samet JH.** Methadone Matters: What the United States Can Learn from the Global Effort to Treat Opioid Addiction. *J Gen Intern Med* 2019; **34**: 1039-1042 [PMID: 30729416 DOI: 10.1007/s11606-018-4801-3]
- 10 **Madden EF.** Intervention stigma: How medication-assisted treatment marginalizes patients and providers. *Soc Sci Med* 2019; **232**: 324-331 [PMID: 31125801 DOI: 10.1016/j.socscimed.2019.05.027]
- 11 **McElrath K, Joseph H.** Medication-Assisted Treatment (MAT) for Opioid Addiction: Introduction to the Special Issue. *Subst Use Misuse* 2018; **53**: 177-180 [PMID: 29220615 DOI: 10.1080/10826084.2017.1404106]
- 12 **Reed MK, Roth AM, Tabb LP, Groves AK, Lankenau SE.** "I probably got a minute": Perceptions of fentanyl test strip use among people who use stimulants. *Int J Drug Policy* 2021; **92**: 103147 [PMID: 33583679 DOI: 10.1016/j.drugpo.2021.103147]
- 13 **Peckham AM, Young EH.** Opportunities to Offer Harm Reduction to People who Inject Drugs During Infectious Disease Encounters: Narrative Review. *Open Forum Infect Dis* 2020; **7**: ofaa503 [PMID: 33241069 DOI: 10.1093/ofid/ofaa503]
- 14 **Fernandes RM, Cary M, Duarte G, Jesus G, Alarcão J, Torre C, Costa S, Costa J, Carneiro AV.** Effectiveness of needle and syringe programmes in people who inject drugs - An overview of systematic reviews. *BMC Public Health* 2017; **17**: 309 [PMID: 28399843 DOI: 10.1186/s12889-017-4210-2]
- 15 **Krieger MS, Goedel WC, Buxton JA, Lysyshyn M, Bernstein E, Sherman SG, Rich JD, Hadland SE, Green TC, Marshall BDL.** Use of rapid

- fentanyl test strips among young adults who use drugs. *Int J Drug Policy* 2018; **61**: 52-58 [PMID: 30344005 DOI: 10.1016/j.drugpo.2018.09.009]
- 16 **Peiper NC**, Clarke SD, Vincent LB, Ciccarone D, Kral AH, Zibbell JE. Fentanyl test strips as an opioid overdose prevention strategy: Findings from a syringe services program in the Southeastern United States. *Int J Drug Policy* 2019; **63**: 122-128 [PMID: 30292493 DOI: 10.1016/j.drugpo.2018.08.007]
- 17 **Lancaster KE**, Cooper HLF, Browning CR, Malvestutto CD, Bridges JFP, Young AM. Syringe Service Program Utilization, Barriers, and Preferences for Design in Rural Appalachia: Differences between Men and Women Who Inject Drugs. *Subst Use Misuse* 2020; **55**: 2268-2277 [PMID: 32748730 DOI: 10.1080/10826084.2020.1800741]
- 18 **Des Jarlais DC**, Feelemyer J, LaKosky P, Szymanowski K, Arasteh K. Expansion of Syringe Service Programs in the United States, 2015-2018. *Am J Public Health* 2020; **110**: 517-519 [PMID: 32078343 DOI: 10.2105/AJPH.2019.305515]
- 19 **Park JN**, Tardif J, Thompson E, Rosen JG, Lira JAS, Green TC. A survey of North American drug checking services operating in 2022. *Int J Drug Policy* 2023; **121**: 104206 [PMID: 37797571 DOI: 10.1016/j.drugpo.2023.104206]
- 20 **Rees DI**, Sabia JJ, Argys LM, Latshaw J, Dave D. With a Little Help from My Friends: The Effects of Naloxone Access and Good Samaritan Laws on Opioid-Related Deaths. *J Law Econ* 2017; **62**: 1-27
- 21 **Rudisill TM**, Ashraf AJ, Linn HI, Sayres S, Jeffries JE, Gurka KK. Facilitators, barriers, and lessons learnt from the first state-wide naloxone distribution conducted in West Virginia. *Inj Prev* 2021; **27**: 369-374 [PMID: 32873604 DOI: 10.1136/injuryprev-2020-043666]
- 22 **Lai RK**, Friedson KE, Reveles KR, Bhakta K, Gonzales G, Hill LG, Evoy KE. Naloxone accessibility without an outside prescription from U.S. community pharmacies: A systematic review. *J Am Pharm Assoc (2003)* 2022; **62**: 1725-1740 [PMID: 35989151 DOI: 10.1016/j.japh.2022.07.008]
- 23 **Ivsins A**, Warnock A, Small W, Strike C, Kerr T, Bardwell G. A scoping review of qualitative research on barriers and facilitators to the use of supervised consumption services. *Int J Drug Policy* 2023; **111**: 103910 [PMID: 36436364 DOI: 10.1016/j.drugpo.2022.103910]
- 24 **Schneider KE**, Urquhart GJ, Rouhani S, Allen ST, Morris M, Sherman SG. High willingness to use overdose prevention sites among suburban people who use drugs who do not inject. *Harm Reduct J* 2023; **20**: 138 [PMID: 37735447 DOI: 10.1186/s12954-023-00865-z]
- 25 **Kariisa M**, O'Donnell J, Kumar S, Mattson CL, Goldberger BA. Illicitly Manufactured Fentanyl-Involved Overdose Deaths with Detected Xylazine - United States, January 2019-June 2022. *MMWR Morb Mortal Wkly Rep* 2023; **72**: 721-727 [PMID: 37384558 DOI: 10.15585/mmwr.mm7226a4]
- 26 **Warp PV**, Hauschild M, Tookes HE, Ciraldo K, Serota DP, Cruz I. A Confirmed Case of Xylazine-Induced Skin Ulcers in a Person Who Injects Drugs in Miami, Florida, USA. *Res Sq* 2023 [PMID: 37547000 DOI: 10.21203/rs.3.rs-3194876/v1]
- 27 **Reyes JC**, Negrón JL, Colón HM, Padilla AM, Millán MY, Matos TD, Robles RR. The emerging of xylazine as a new drug of abuse and its health consequences among drug users in Puerto Rico. *J Urban Health* 2012; **89**: 519-526 [PMID: 22391983 DOI: 10.1007/s11524-011-9662-6]
- 28 **Rodríguez N**, Vargas Vidot J, Panelli J, Colón H, Ritchie B, Yamamura Y. GC-MS confirmation of xylazine (Rompun), a veterinary sedative, in exchanged needles. *Drug Alcohol Depend* 2008; **96**: 290-293 [PMID: 18472231 DOI: 10.1016/j.drugalcdep.2008.03.005]
- 29 **Guzman J**. Ohio AG warns of rise in 'Frankenstein opioids' more dangerous than fentanyl. [cited 10 December 2023]. Available from: https://thehill.com/changing-america/well-being/prevention-cures/3460077-ohio-ag-warns-of-rise-in-frankenstein-opioids-more-dangerous-than-fentanyl/?email=43d784631a7190909e3d88c515c669013bb55cda&email=5129da2a0d40efe90a5b313b3c319795&emailb=a027addf97201237c704bfbeba40852b1465a64231c2d642e855b91ebdf807a5b&utm_source=Sailthru&utm_medium=email&utm_campaign=04.22.22%20EM%20The%20Hill%20-%20Health%20Care&utm_term=Health%20Care
- 30 **Kernstine K**. Nitazenes, opioid 10x more powerful than fentanyl, found in Colorado. [cited 27 December 2023]. Available from: <https://www.newsnationnow.com/crime/nitazenes-colorado-opioid-fentanyl/>
- 31 **Center for Forensic Science Research and Education**. NPS Discovery New Drug Monograph, N-Desethyl Etonitazene. [cited 10 April 2024]. Available from: <https://www.cfsre.org/images/monographs/N-Desethyl-Etonitazene-New-Drug-Monograph-NPS-Discovery-113023.pdf>
- 32 **Amaducci A**, Aldy K, Campleman SL, Li S, Meyn A, Abston S, Culbreth RE, Krotulski A, Logan B, Wax P, Brent J, Manini AF; Toxicology Investigators Consortium Fentalog Study Group. Naloxone Use in Novel Potent Opioid and Fentanyl Overdoses in Emergency Department Patients. *JAMA Netw Open* 2023; **6**: e2331264 [PMID: 37642962 DOI: 10.1001/jamanetworkopen.2023.31264]
- 33 **Roberts A**, Korona-Bailey J, Mukhopadhyay S. Notes from the Field: Nitazene-Related Deaths - Tennessee, 2019-2021. *MMWR Morb Mortal Wkly Rep* 2022; **71**: 1196-1197 [PMID: 36107790 DOI: 10.15585/mmwr.mm7137a5]
- 34 **Felbab-Brown V**. China, Mexico, and America's fight against the fentanyl epidemic. [cited 12 April 2024]. Available from: <https://www.brookings.edu/articles/china-mexico-and-americas-fight-against-the-fentanyl-epidemic>
- 35 **Breve F**, Batastini L, LeQuang JAK, Marchando G. Mobile Narcotic Treatment Programs: On the Road Again? *Cureus* 2022; **14**: e23221 [PMID: 35449647 DOI: 10.7759/cureus.23221]
- 36 **Hoopsick RA**, Homish GG, Leonard KE. Differences in Opioid Overdose Mortality Rates Among Middle-Aged Adults by Race/Ethnicity and Sex, 1999-2018. *Public Health Rep* 2021; **136**: 192-200 [PMID: 33211981 DOI: 10.1177/0033354920968806]
- 37 **Lippold K**, Ali B. Racial/ethnic differences in opioid-involved overdose deaths across metropolitan and non-metropolitan areas in the United States, 1999-2017. *Drug Alcohol Depend* 2020; **212**: 108059 [PMID: 32447173 DOI: 10.1016/j.drugalcdep.2020.108059]
- 38 **Mason M**, Soliman R, Kim HS, Post LA. Disparities by Sex and Race and Ethnicity in Death Rates Due to Opioid Overdose Among Adults 55 Years or Older, 1999 to 2019. *JAMA Netw Open* 2022; **5**: e2142982 [PMID: 35015062 DOI: 10.1001/jamanetworkopen.2021.42982]
- 39 **Rigg KK**, Monnat SM, Chavez MN. Opioid-related mortality in rural America: Geographic heterogeneity and intervention strategies. *Int J Drug Policy* 2018; **57**: 119-129 [PMID: 29754032 DOI: 10.1016/j.drugpo.2018.04.011]
- 40 **Brooklyn JR**, Stothart M, Stunell M, Berman VM, Rylant D, Hanson M. Characterizing the Clinical use of a Novel Video-assisted Dosing Protocol With Secure Medication Dispensers to Reduce Barriers to Opioid Treatment. *J Addict Med* 2022; **16**: 310-316 [PMID: 34282084 DOI: 10.1097/ADM.0000000000000895]
- 41 **Walley AY**, Xuan Z, Hackman HH, Quinn E, Doe-Simkins M, Sorensen-Alawad A, Ruiz S, Ozonoff A. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ* 2013; **346**: f174 [PMID: 23372174 DOI: 10.1136/bmj.f174]
- 42 **Potier C**, Laprévotte V, Dubois-Arber F, Cottencin O, Rolland B. Supervised injection services: what has been demonstrated? A systematic literature review. *Drug Alcohol Depend* 2014; **145**: 48-68 [PMID: 25456324 DOI: 10.1016/j.drugalcdep.2014.10.012]
- 43 **Aspinall EJ**, Nambiar D, Goldberg DJ, Hickman M, Weir A, Van Velzen E, Palmateer N, Doyle JS, Hellard ME, Hutchinson SJ. Are needle and syringe programmes associated with a reduction in HIV transmission among people who inject drugs: a systematic review and meta-

analysis. *Int J Epidemiol* 2014; **43**: 235-248 [PMID: 24374889 DOI: 10.1093/ije/dyt243]

- 44 **Livingston JD**, Milne T, Fang ML, Amari E. The effectiveness of interventions for reducing stigma related to substance use disorders: a systematic review. *Addiction* 2012; **107**: 39-50 [PMID: 21815959 DOI: 10.1111/j.1360-0443.2011.03601.x]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: office@baishideng.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

