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Research Article

Opioid abuse, the escalating crisis, xylazine co-use, and the forensic toxicology challenges

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Abstract

Introduction: The opioid crisis represents a longstanding public health emergency, significantly worsened by the concurrent use of xylazine. This epidemic has led to a surge in opioid-related fatalities, marking it as a pressing health crisis with global implications. The combination of xylazine with fentanyl and its analogs significantly increases the risk of overdose deaths. This study aims to analyze the current situation by reviewing scientific and governmental publications on the topic.

Methods: Our analysis, established on data from PubMed, Google Scholar, and Scopus, highlights the pharmacological risks related to the combination of xylazine and synthetic opioids, such as fentanyl. It underlines the increased chances of fatal overdoses due to this combination.

Results: The research associates weaknesses in current forensic toxicology screenings that fail to effectively detect these dangerous compounds. The illegal synthesis of these substances is a key challenge in directing the emergency. The combination of xylazine with synthetic opioids shows a significant public health risk, worsening the already critical opioid crisis. There is a critical need for improved drug detection and analysis methods to combat this growing challenge.

Conclusion: Developing forensic toxicology screenings to precisely identify the presence of these substances is crucial for both the diagnosis and prevention of fatal overdoses. Our findings emphasize the requirement for immediate and concerted efforts to address the complexities of the opioid epidemic and highlight the potential consequences of public health strategies intended to mitigate this crisis.

Abbreviations

CDC: Centers for Disease Control and Prevention

Introduction

One of the most devastating public health issues of this century is the opioid crisis, characterized by a marked increase in overdose deaths due to synthetic opioids, particularly fentanyl and its analogs. The recent inclusion of xylazine, a non-opioid veterinary sedative, into the illicit drug market has further complicated the epidemic [1,2]. The mechanism of action of xylazine potentiates the effects of opioids, presenting unprecedented risks to users. This situation complicates treatment interventions and emphasizes the urgency for effective public health responses, representing a significant challenge faced by physicians. The pharmacological impact of the co-use of xylazine and fentanyl is related to their sedative, analgesic, and muscle relaxant properties. This combination has been increasingly detected in illicit drug supplies, significantly elevating the risk of respiratory depression, unconsciousness, and fatal overdoses. The pharmacological synergism between xylazine and fentanyl exacerbates central nervous system depression, posing severe health risks even at small doses. To better understand the impact of related deaths, it is necessary to be acquainted with the statistics reported by governmental entities. This will provide us with an insight into how crucial it is to further standardize the analysis conducted in the routine screening of forensic toxicology, as this details the risks faced

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by society [3,4]. Considering that information is currently available without barriers, this allows for the immediate dissemination of unsafe modalities in drug abuse. Our study addresses three important points: 1-The magnitude of the impact of the crisis on overdose deaths, specifically involving the combination of fentanyl and xylazine. 2-The limitations of the general drug screening process. 3-Alternatives that we can develop to mitigate these weaknesses within the analysis process and enhance its efficacy.

Materials and methods

This short communication utilized data from scientific publications and state health departments. We explored three databases; PubMed, Google Scholar, and Scopus, for pertinent literature published in the last 5 years. Our search approach involved two key groups of terms: "xylazine and fentanyl" as the drug of interest and various types of exposure (including "drug use," "fatal overdose," and "substance abuse"). The search began with PubMed, after which we adapted the search terms to fit the syntax database requirements. To refine our search results, we switched, tested, and adjusted the search terms throughout the process, as shown in Figure 1.

Results and discussion

The magnitude of the impact of the crisis on overdose deaths is well documented and updated by the Centers for Disease Control and Prevention (CDC), which has reported that more than 70,000 individuals have died due to fentanyl abuse, marking a significant increase from the statistics reported previously. This number more than doubled the death toll from three years earlier. Since 2019, fentanyl has been involved in over half of all drug overdose deaths, with this proportion increasing to nearly 70% by 2022 [4]. The trend of escalating fentanyl overdose deaths has consistently risen over the past decade. This shocking tendency shows the fatal potency of fentanyl, a synthetic opioid that is up to 50 times stronger than heroin and 100 times stronger than morphine. However, 2022 marked a year with one of the lowest year-over-year growth rates, at 4.3%, suggesting that efforts to control the crisis may be having an impact. The shift from the abuse of prescription opioids to the use of illicitly manufactured fentanyl has been identified as a major factor in the surge of overdose deaths [5-7]. The illicit synthesis of fentanyl and its adulteration with substances like xylazine has created a highly unpredictable and dangerous illicit drug market. These practices complicate the estimation of street drugs' potency and challenge existing treatment and harm reduction strategies. Traditional opioid antagonists, such as naloxone, are less effective when drugs are combined with xylazine, due to xylazine being an alpha-2 agonist with a mechanism of action distinct from opioids [8,9].

A recent analysis of samples from eight syringe service programs in Maryland conducted between 2021 and 2022, revealed that xylazine was present in approximately 80% of opioid-containing drug samples [7,10-12]. Similarly, in the state of Pennsylvania, xylazine was detected in more than 30% of opioid-related overdose deaths (involving heroin and/or fentanyl) in 2019. Broad-based studies across 20 states and Washington D.C. have shown an increase in the monthly percentage of deaths involving fentanyl with xylazine, from 3% in 2019 to more than 10% by 2022. This data underscores the escalating presence of xylazine in conjunction with opioid use [10-12].

Table 1 Presents an overview of opioid-related overdose fatalities spanning from 1990 to 2021. The data was compiled from credible sources, particularly the CDC's National Center for Health Statistics and their dedicated opioid data analysis resource page, providing an extensive temporal snapshot of the opioid crisis impact in terms of mortality. The data reveals trends in opioid overdose deaths. Sources for the data are as follows: the CDC's Data Briefs (https://www.cdc.gov/nchs/data/databriefs/db457-tables.pdf#5) and the CDC's opioid data analysis resource page (https://www.cdc.gov/opioids/data/analysis-resources.html)."

The challenges in forensic toxicology screening are a significant barrier in addressing the opioid crisis, and the limitation of present forensic toxicology screenings, which often fail to detect substances such as xylazine. The lack of standardized screening methods for these emerging drugs impedes accurate cause-of-death determinations and hinders epidemiological tracking of the crisis's evolution. Although the practice of forensic science is well regulated by various accrediting bodies, which entails having highly efficient and

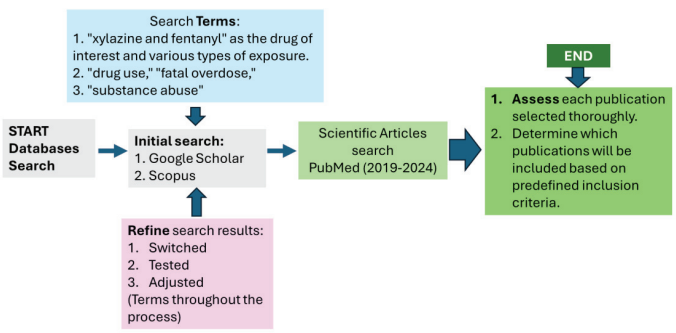

Figure 1: This schematic illustration presents a detailed diagram of the search process as outlined in the Materials and Methods section of the document. This visualization effectively conveys the step-by-step methodology employed to gather and analyze the data, providing a clear and comprehensive overview for readers to understand the procedural aspects of the study.

Table 1: Opioids Overdose Related Deaths Since 1990-2021.

Year	Deaths Reported
1990	8,000(10% of 2021)
2001	9,496
2010	21,089
2015	33,091
2017	47,600
2019	49,860
2020	68,630
2021	80,411

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competitive analytical standards, analytical challenges remain a concern that requires identifying tools to fulfill its organic functions in the face of new trends in illegal drug use and its consequences. The illicit synthesis of drugs encompasses many aspects that affect the conclusion of a case when determining the manner and cause of death. Most forensic toxicology laboratories use immunoassay in general or routine screenings, the advantage of which lies in the time and minimal sample preparation required, as well as the low cost of the equipment. Immunoassay tracking methods typically rely on identifying a drug family as part of a targeted reaction. This type of tracking is limited to what is commercially available. It is highly advisable that screenings are conducted using equipment such as gas chromatographs coupled with mass spectrometry and liquid chromatographs coupled with mass spectrometry, which, in addition to performing targeted analysis, can also carry out simultaneous screenings [13]. The disadvantage lies in the more extensive sample preparation required. However, this type of technology allows for the preliminary identification of the compound or substance with semi-quantification that can be corroborated in a second targeted analysis.

Strategies employed to maximize analysis with available resources include sample preparation techniques. One approach involves simplified sample preparation through dilution in the mobile phase, while another employs protein precipitation followed by direct analysis of the sample. Each method has its disadvantages, but the techniques can be successfully implemented in various settings to enhance routine screening analysis. These processes can be carried out using equipment or technology such as liquid chromatography coupled with mass spectrometry. Protein precipitation, followed by subsequent reconstitution or derivatization, serves as a useful tool for identifying the presence of drugs not routinely detected in general immunoassay screenings [14,15].

Data reported by the CDC have unequivocally demonstrated that the opioid crisis has worsened with the concurrent use of xylazine, affecting 80% of the addicted population, a conclusion drawn from the premise that this trend was identified in syringe analyses [16,17]. Furthermore, this trend is also being observed in deaths related to the use of these drugs. It is important to note that these figures do not represent the total number of cases that may have gone undetected by routine screenings [18-22]. Additionally, it must be emphasized that not all laboratories are equipped to identify xylazine and other novel substances that are being abused. The practice of polydrug abuse, where individuals use multiple substances simultaneously or sequentially, significantly exacerbates the challenges faced in public health and clinical settings, impacting various aspects of healthcare and forensic investigations [23-25]. This complexity arises not just in accurately determining the cause of death in overdose cases but also extends to the management of rehabilitation programs and the provision of care in emergency departments [26,27].

In forensic toxicology, polydrug abuse complicates the determination of the cause of death because multiple substances can synergistically enhance the toxic effects of each other, making it difficult to pinpoint the primary agent responsible for the fatality [28,29]. This necessitates sophisticated toxicological analyses and can lead to challenges in legal and medical interpretations of overdose deaths. From a clinical perspective, polydrug abuse presents unique challenges in emergency care. Patients presenting with overdoses involving multiple substances may require complex and immediate medical interventions [30,31]. Traditional treatment protocols, such as the administration of opioid antagonists like naloxone for opioid overdoses, may not be fully effective when other substances, such as xylazine or stimulants, are involved. This requires emergency room personnel to quickly adapt to changing situations, frequently with limited information about the exact mix of substances administered. Moreover, the rehabilitation and recovery process for individuals who abuse multiple drugs is significantly more difficult. Treatment programs must be modified to address the physical and psychological dependence on multiple substances, which can complicate withdrawal management and increase the risk of setbacks. This needs a multidisciplinary approach to treatment that involves medical, psychological, and social support services to address the myriad of polydrug abuse effects. In general, the polydrug abuse practice complicates the clinical management of overdoses and poses significant challenges for public health policies, rehabilitation strategies, and forensic investigations, highlighting the need for inclusive strategies to address the complicated impacts of substance abuse [32].

Several companies have responded to the urgent need for advanced toxicological analysis by developing sophisticated equipment capable of detecting a wide array of substances, including fentanyl, its analogs, and xylazine. These include Agilent Technologies, Thermo Fisher Scientific, Randox, Waters, PerkinElmer, Shimadzu, and others.

Conclusion

The opioid crisis, now exacerbated by the emergence of xylazine as a potent drug in concomitant use, requires a multidimensional response that includes public health, law enforcement, and scientific research. Developing and sharing advanced forensic toxicology screening methods are critical to addressing the challenges posed by the ever-evolving illicit drug market. With adequate financial resources, forensic toxicology laboratories could take advantage of technological advancements offered by industry leaders in analytical equipment. This would enhance their understanding of processes, improve detection capabilities, and ultimately increase their ability to report results accurately, effectively, and in a timely manner. Another alternative is to promote the validation of newly developed methods that are compatible with available instruments and technologies.

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