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Emerging Trends in Mixed-Drug Overdoses

Abedalbaset Talal Saleem Alzoubi[1*], Moh'd Kamel Fuad Da'na[1]

[1]Primary Health Care Corporation (PHCC), Qatar

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***Corresponding author:** Abedalbaset Talal Saleem Alzoubi
Primary Health Care Corporation (PHCC), Qatar

Abstract | **Review Article**

As the opioid epidemic continues to evolve in the U.S., so do the drug mixtures. For instance, the use of synthetic opioids in combination with other drugs, such as stimulants and other opioids, has taken off. This presentation will provide epidemiologic and toxicological data on new and evolving mixed-drug overdose trends, including cocaine and methamphetamine being mixed with fentanyl, and the emergence of nitazenes worldwide. In addition, we will discuss how investigators can use clinical data for surveillance of drug overdose trends with a specific focus on drug mixtures. Finally, we will discuss next steps and the need for a multi-disciplinary approach to tackle emerging trends in mixed-drug overdoses. On March 2, 2023, the CDC reported that cocaine was involved in 38.2% of overdose deaths and methamphetamine was involved in 24.8% of overdose deaths in the U.S. in 2021. In the western region of the U.S., 68.9% of methamphetamine-involved overdose deaths also involved cocaine combined with fentanyl. Here, we highlight public health surveillance efforts to quantify and characterize cocaine and methamphetamine mixed with fentanyl overdose deaths using death certificate and toxicologic data from Nevada. Among the 300 overdose deaths in 2021, the drugs involved in these deaths were cocaine alone, cocaine and methamphetamine, cocaine mixed with fentanyl, and cocaine and methamphetamine mixed with fentanyl. Toxicological data indicated that 87% of the decedents with cocaine mixed with fentanyl had a positive toxicology result for fentanyl.

Keywords: Mixed-drug overdose, Fentanyl, Cocaine and methamphetamine, Toxicological surveillance, Synthetic opioids.

1. INTRODUCTION

With the advent of the COVID-19 pandemic and a rise in opioid injuries, including both unintentional overdose deaths and severe non-fatal injuries involving illicitly manufactured fentanyl (IMF)-containing drugs, there have been significant changes in trends of overdose injuries [1]. Although opioid-only overdose deaths and usage has sharply increased, there has also emerged a concerning trend of polysubstance use obtaining increasing recognition and public health concern [2]. Polydrug use introduces particular complexities for assessing risk factors, including different and changing commingling patterns involving diverse drug combinations, especially involving new potent drugs targeting distinct receptor roles in different neurocircuits and pharmacological roles within the drug use process [1]. Since deciphering the emergence and spread of a polydrug overdose pattern with IMF is crucial for informing preventive actions, including harm reduction intervention efforts, monitoring or forecast of overdose trends, and further epidemiological studies, an important goal of the current research is to develop an analytical framework for describing and analyzing the dynamic spatiotemporal patterns of mixed-drug overdoses involving IMF [3]. The first step towards this goal is to provide a systematic review of the research literature on mixed-drug overdoses [3]. A scoping framework is presented to characterize the polydrug use patterns and inform the drug shipment modeling, including identifying competing risks of polydrug overdose motives and assessing whether a polydrug overdose trend is due to the rise of a new drug actor or due to enhanced interoperation among existing drugs [4]. This study serves as a useful starting point for the mixed-drug overdose research [4]. With the consideration of the temporal factor in the examination of the polydrug overdose pattern, it is presumed that multiple public health policy interventions exist that might explain such a temporal installation [5].

2. Overview of Drug Overdoses

Overdose deaths, traditionally viewed as resulting from a single category of drug, are increasingly occurring from exposures to multiple drug classes [5]. Whereas overdoses from prescription opioid medications alone were the predominant cause of overdose mortality

in the United States at the beginning of the 21st century, trends have shifted toward mixed-drug overdoses [6]. Drug systems history reiterates the social, economic, and political processes that enabled the rising overdose mortality among older, White, non-Hispanic, and rural populations [7]. A monocausal conception of drug overdoses, despite recognition of polydrug use, masked the incremental changes in drug markets and the sustained interactions among the socioeconomic and cultural landscapes [8]. Overdose deaths that once stemmed from pharmaceutical drugs alone now increasingly arise from interplay among multiple drugs from pharmaceutical markets, counterfeit pills, and old or new illicit drug markets [9]. Systemic factors differentially enable harm, which also unequally draws attention and public health responses to what some advocates termed "sophisticated" drug overdose deaths [10]. Except for states that did not enact reform, prescription drugs were less frequently the cause of overdose deaths in 2022 than illicit synthetic opioids [11]. As drug overdose deaths occurred increasingly from multiple drugs and from pharmaceutical drugs alone, the epidemiology of drug overdose deaths is shifting from opioid-dominant to mixed-drug overdoses [12]. These emergent trends recast conventional categorizations of "pill" and "street" drugs [12]. The growing numbers of drug overdose deaths that are not thought to directly result from illegal activities raise the need for surveillance and epidemiological investigations that are detailed at the specificity of drug source and availability of services [13]. Reductions in prescribing volume resulted from pharmaceutical drug overdose deaths and related ill effects [14].

3. Opioids: Current Landscape

There have been sizeable shifts in the demographics and risk factors associated with opioid overdose in the US in the past two years [15]. The increase in fentanyl in the US drug market has substantially changed the relationship between PWUO and their drugs [15]. Fentanyl use is associated with a multitude of risk factors, including drug market factors such as the increased accessibility of fentanyl in the general drug supply; drug use factors, including fentanyl-induced tolerance, binge or polydrug use, route of use; intrapersonal factors, such as homelessness, anxiety, and prior overdose; and lack of protective factors like sober friends or naloxone use [16]. Surprisingly little is known about how the opioid market has responded to the massive increase in availability of naloxone, and whether or not PWUO adjusted their behavior in light of its availability [17]. The equivocal findings on the effects of naloxone on overdose outcomes warrant further investigation into how PWUO view naloxone, and if they acquire and administer naloxone in the first place [18]. There is clearly a need for large-scale studies to address these questions, and to inform the efforts of public health agencies and other stakeholders looking to improve naloxone's safety without reducing its accessibility to the public [19].

Much of the harm reduction-based research in response to the increased prevalence of overdose has focused on a wide variety of potential interventions [20]. While many of these novel techniques, such as expanded naloxone access and innovative overdose prevention trainings, have been studied and shown to be effective, other proposed techniques such as supervised injection facilities carry with them no research support [21]. Data from jurisdictions that do have them suggest that they can be an effective harm reduction tool in the battle against overdose [22]. Among the PWUO population, overdose misuse and polydrug use are prevalent at dangerous levels [22]. There are indications that PWUO often underestimate their overdose risk or are unaware of their risk factors entirely and would benefit from targeted education and harm reduction techniques [23]. The small-scale pilot studies of peer recovery coaching, a new method to link PWUO to treatment post-overdose, are promising [23]. They suggest that deal disclosure may be a feasible and effective harm reduction tool for addressing the opioid risk environment [24].

4. Xylazine: An Emerging Concern

Xylazine, a non-opioid tranquilizer approved for veterinary use, has increasingly been added to the illicit drug supply over the past 5–10 years, much like cocaine 30–40 years ago [25]. Xylazine has been detected in overdose deaths, and routine testing for xylazine is not widely available nor mandated [26]. Available methods to test for xylazine could be made widely available to assess its distribution and trend over time, targeting an at-risk population comparable to those tested for fentanyl prior to the historic overdose crisis [27].

Geographic distribution trends can be seen in patient samples testing positive for xylazine, with two clear upticks in testing requests, particularly in 2022 [28]. The presence of xylazine in the illicit drug supply is relatively new in the United States, similar to novel psychoactive substances (NPS) or "designer drugs" [29]. However, methods to routinely test for xylazine are not widely available nor mandated [29]. As a result, its prevalence is likely underestimated and poorly understood in illicit drug composition [30].

5. Stimulants: Patterns of Use

Increased use of illicit stimulants among those using opioids has grown exceedingly in recent years [30]. Reports of psychostimulant use and overdose have increased markedly [30]. This increases correlates with heightened availability among fewer domestic manufacturers, higher potency, multi-drug networks, and the introduction of new technologies that allow consumers greater independence and self-sufficiency [31]. Focusing exclusively on clandestine-product markets such as methamphetamine, cocaine, and crack cocaine, the aim of the current study is to investigate and characterize the shifts in stimulant use by those engaged

in prescription, illicit, or polysubstance opioid use over the past 30 years in a southeastern state in the USA [32].

While opioid use remains the predominant concern, increasing news, academic, and health organization attention is aimed at the emerging use of illicit psychostimulants such as methamphetamine and crack cocaine, particularly among individuals with opioid use disorder [33]. Subsequently, reports of the use of both are on the rise spanning global, national, and local levels [33]. Increasing use is concerning as both acute and chronic stimulant use is associated with a variety of risks and harms, including violence, unprotected sex, methamphetamine-induced psychosis, overdose, and reductions in quality of life and health outcomes, similar to opioids, some of which are synergistic in nature [34].

Several accounts of polysubstance use among individuals using opioids, including stimulants, have been published [35]. These accounts note that stimulant use is often initiated within a social context, particularly for the purpose of creating a positive social experiences, and that the costs of stimulant use broadly increases the risk that their use will self-replicate [35]. Stimulants are incorporated into the drug use routine and are often administered to self-manage a variety of withdrawal symptoms and dysfunctional daily behaviors [36]. Attaining a positive experience from stimulant use that is experienced differently than the effect of opioids or a desire to balance one's self out throughout the day with cyclical use of opioids and stimulants is also expressed [37].

6. The Intersection of Opioids and Xylazine

From 2015 to 2021, the United States experienced the most dramatic increase in drug overdoses [38]. Seventy-seven percent of overdose victims had at least one drug found in their system [38]. Cocaine and synthetic opioids were the first and second most common drugs found in overdose victims [39]. Over the past five years, the drug supply has changed dramatically, introducing mixtures/combination products that add complexity [39]. Recently, a storm of xylazine entered the illicit drug supply amidst the ongoing opioid crisis [40]. Xylazine, an alpha-2 adrenergic agonist approved for sedating horses and other non-human species, is now a major adulterant of the opioid supply [40]. Beyond opioids, it is also found in methamphetamines, cocaine, ecstasy, and other psychoactive substances [38]. While the pharmacology of xylazine has been studied, little is known about how drugs that may be mixed may modulate its effects, detection, and treatment [41]. All three effects—enhanced effects, new effects, and altered therapeutic window—have the potential to impact public health in profound ways [41]. A clearer understanding of how substances might co-occur is needed in the context of an increasing likelihood of encountering mixtures [42].

7. Stimulants in Combination with Opioids

Historically, the co-use of opioids and stimulants has been a significant public health concern [43]. The increase in opioid overdoses that began in the late 1990s and accelerated through the 2010s was accompanied by a decrease in the co-use of stimulants [43]. However, now, amidst the opioid epidemic, the trend of opioid-stimulant polysubstance use has reemerged [44]. This trend, referred to as a "Fourth Wave" or "Twin Epidemic," is characterized by an increasing public health harm of concurrent stimulant use, particularly methamphetamine use, among people who use opioids [44]. Historically, the trend began with the widespread availability of injectable cocaine in the late 1980s and continued during the early 2000s with the introduction of methamphetamine. After relative stability through the 2010s, the public health concern rose again, but this time with the introduction of potent synthetic opioids or fentanyls [43].

8. Risk Factors for Mixed-Drug Overdoses

Risk factors related to the person who suffered the overdose vary widely and include demographic characteristics and clinical factors [44]. In general, as the individual's health deteriorates or their drug use escalates, risk increases, and this is particularly true for freebase cocaine [45]. Males were at greater risk for mixed-drug overdoses than females, which may reflect the higher use of emerging drugs among males [45]. While increases were seen across age, rates were highest among those aged 25-34, coinciding with an influx of stimulants into recreational drug markets [46]. The birth cohorts and period-based rates suggest that the increased availability of club drugs and prescription stimulants between the late 1990s and early 2000s prompted the emergence of the first wave of death spillovers among older cohorts [47].

Dose-response analyses indicated a systematic increase in risk with escalating quantities of methamphetamine, heroin, and alprazolam [48]. A general pattern of risk emerged for poly-drug sale users including escalated risks for combinations incorporating methamphetamine or cocaine, as well as heroin and alprazolam [49]. These results reaffirm the focus of prevention efforts on behavior—the co-use of stimulants and CNS-depressants—and also aspects of the market; for example, the illicit sale of methamphetamine in combination with either prescription opioids or GABAergic depressants appeared more lethal than other types of poly-drug sales, which suggests a targeted intervention to interrupt the supply and/or demand for these combinations among involved individuals [50].

9. Demographic Trends in Overdose Cases

In examining the sample of drug overdose mortality by state, we can see the extent of the drug overdose epidemic on both a U.S. and state level [51]. The figures show the synergy between prescription opioid overdoses in states like Oklahoma and Ohio

during the early 2000s to the emergence of methadone overdoses [51]. The duet between prescription overdoses and heroin overdoses in states like New Mexico and the extreme rate of overlap between prescription opioids and street synthetic opioids in states like West Virginia and Kentucky is characterized by a very similar trajectory in overdose mortality rate development throughout the state and by a very high percentage of the drug overdose deaths attributable to synthetic opioids [52]. The figures illuminate the extent of the epidemic across the U.S. and these states specifically as well as the different trajectories and types of overdoses in different areas [52].

10. Clinical Implications of Mixed-Drug Overdoses

On June 21, 2021, in Albany, New York, a 31-year-old white female was found dead on a couch in a motel room, with bags of "heroin" and "crack" cocaine around [53]. Three needles and a 16 oz. refill bottle marked "Oxycodone" were also discovered [53]. Toxicology detected caffeine, caffeine citrate, fentanyl, norfentanyl, cocaine, benzoylecgonine, MDMA, 7-aminofentanyl, diphenhydramine, and 30% ethyl alcohol, suggesting a polysubstance overdose involving cocaine for which treatment was sought in an emergency department [54].

A 49-year-old black male was found dead on December 2, 2021, in Otsego County, New York, with a syringe near his body, and toxicology indicated a polysubstance overdose involving hydromorphone and fentanyl [55].

These cases and others illustrate the vital need for improved awareness of dangerous drug interactions, especially during the COVID-19 pandemic when mental health problems and neuromodulation have fueled polypharmacy [56]. Highlighted drugs include combinations of opioids (such as hydromorphone and fentanyl), benzodiazepines (such as alprazolam), and serotonin–norepinephrine reuptake inhibitors, especially when abused alone or in combination with other neuroactive substances like alcohol, cocaine, and MDMA, leading to severe neurotoxic syndromes [57]. Rapid sequences of binge use or prolonged use of such drugs amplify this neurotoxicity [55].

The Federal Drug Administration (FDA) has cautioned against opioid/benzodiazepine co-prescription. Compelling evidence from case–control and epidemiological studies documents emergence of opioid/benzodiazepine combinations due to overt co-prescription, illicit mixing, or both [58]. These combinations markedly amplify the risk of overdose, over 10-fold in some reports [59]. Opioid/cocaine and cocaine/benzodiazepine polypharmacy also cause severe toxicity and increase the risk of overdose but have been less studied. These multiple-drug risk factors warrant renewed EHR vigilance to simplify drug interactions, especially opioids, benzodiazepines, alcohol, and cocaine [60].

11. Emergency Response Strategies

The Route 1 corridor is an underserved area of Colorado that has experienced a steady increase in drug use and related overdose deaths [61]. Local police, fire, and sheriff deputies, in partnership with Boulder County Public Health, local hospitals, and local drug treatment programs have been leading efforts to enhance both prevention and emergency response in the wake of additional challenges [62]. A specific coalition for mixed-drug overdoses has been formed and has committed to implementing both strategies moving forward, but significant funding is needed to support larger-scale, more aggressive efforts [63]. The Route 1 Coalition, a community initiative formed in 2021, builds on and will sustain this work, and expand it beyond just drug overdose issues [63]. What is known about the Route 1 area's drug-related deaths and drug use? The Route 1 corridor (part of Boulder County and Larimer County) has some notable drug-related death issues in a general population that appears average in terms of drug usage [64]. Opiate and opiate poly-drug issues are rising; more specifically, cases are rising involving methamphetamine as well. Substance use-related deaths in the Route 1 corridor, particularly during recent years, are rising at a faster rate than Colorado or the US [65]. Substantial nearby to such deaths occur before or during a 911 call, which hampers emergency response and prevention [65]. The lifespan of such cases, while often not considered long enough for preventative intervention, appears to be several years long [66]. Research suggests that lower levels of lifetime drug usage show a more rapid decline in drug use over time but are potentially more vulnerable to overdose as they use drugs in a more dangerous manner, including in more dangerous combinations [66]. There are actionable strategies that can be taken by multiple partners that can be done readily but may require more systematic funding sources [67]. In particular, the need for comprehensive strategies and funding sources to reduce the impact of drug use imperatives, particularly drug overdoses [67].

12. Public Health Interventions

Communities across the United States are experiencing a dramatic increase in deaths from drugs such as heroin, fentanyl, and prescription opioids [68]. An antidote to the respiratory depressant effects of opioids, naloxone is a safe and effective means of preventing overdose death when it is administered in a timely manner [69]. Community organizations have developed programs to deliver naloxone to drug users and their social networks in a variety of settings including health care facilities, pharmacy chains, and social service agencies [67]. More recently, these programs have also begun testing the feasibility of equipping law enforcement to distribute naloxone to overdose witnesses, but little is known at this time about their interest or willingness to do so [70]. This intervention will survey law enforcement agencies (LEAs) in New Mexico to identify current policies and practices around overdose response and naloxone

distribution and provide a forum for discussion of the potential role of law enforcement in community naloxone distribution efforts [68].

13. Role of Harm Reduction

With the changing patterns of drug use and rising incidence of mixed-drug overdoses, it is crucial to increase knowledge of polydrug use among harm reduction providers and those who interact with people who use drugs [71]. A better understanding of mixed-drug use in this context can help ensure that harm reduction approaches remain effective in preventing overdoses [72].

Harm reduction strategies aim to decrease negative consequences of drug use through education, supply provision, and extended services [73]. Current evidence around mixed drug use and fatal overdoses can assist policy makers, harm reduction agencies, and healthcare providers in responding to drug supply changes and adjusting harm reduction services accordingly [74]. For example, there is evidence that concurrent use of stimulants and depressants increases overdose risk and supply-driven approaches are being implemented in response to the growing polysubstance use epidemic. Governments across Canada are exploring ways to mitigate health risks associated with an increasingly contaminated drug supply and concurrent substance use is a high-risk practice that may be considered [71]. Surveillance data indicate that the concurrent use of methamphetamine and opioids is rising, leading to a higher risk of fatal overdose and potential arousal suppression [75]. Continued education, modelling, and outreach are required to mitigate the increased risk of overdose [75].

Ongoing education campaigns are needed to combat the perception that concurrent use lowers the risk of overdose [76]. The provision of harm reduction supplies aimed at safer practices when mixing substances should also be explored further [76]. Additionally, the use of health promotion campaigns at the community level to inform individuals who might not necessarily seek out harm reduction services would raise general awareness [77]. For example, multi-purpose resources should educate about state-based services such as telehealth options and naloxone distribution [78]. Also, installing safe consumption spaces that accept a variety of substances could allow health professionals to engage in depth with individuals at the population level, facilitating education and preventing overdose [78].

14. Policy Implications and Recommendations

The rapid emergence of polydrug use (i.e., the concurrent use of multiple illicit drugs) is a public health issue that requires collaboration among researchers, stakeholders from affected communities, and agencies across North America and beyond [9]. In addition to increased coverage of fentanyls and other synthetic opioids, mixed-drug toxicity with stimulants is a widely relevant drug-related phenomenon with specific implications for fentanyl-using stimulant users and their care [79].

Although much has changed regarding the stimulant and fentanyl overdose epidemic in Boston, and therefore implications for the field today, it is worth noting lessons learned from a long past [80]. The last notable stimulant use treatment clinic closure in Boston was in 2003 [80]. Since then, a small number of generous and lonely harm reduction pioneers have trained and mobilized frontline staff in acute and outpatient settings on stimulant harm reduction [81]. Relatively tepid action was taken by public health authorities until extreme sounding findings emerged from their research [81]. The Disrupted Stimulant Treatment Networks Group has built on years of precedent in North America with those steeped in unmatched experience in difficult stimulant cases [82]. Data emerged from national and Canadian studies pushing concerns of stimulant overdose directly at the Stimulant Summit [83]. With the stimulant and poly-drug overdose crisis growing in scale and scope, and already parsed pharmacologically, efforts gathered unprecedented federal funding [83]. This initial project has ensured that something similar to the emergence of respect for fentanyl knowledge does not dominate stimulant fatalities in the same way [83].

15. Research Gaps and Future Directions

Research examining adjusted mortality rates is warranted on a global basis to identify high risk demographic sub-groups who may be targeted for harm reduction interventions [84]. Given the global trend away from particular drugs, it will be important to assess the growing popularity of these drugs before wide-spread introduction [84]. On-going review of drug sale and distribution patterns over the internet as well as by groups in specific night-club venues in larger cities is warranted to forewarn of the introduction and spread of novel psychoactive substances [85]. After noting the growing extent of overdose in many countries, the issues of ignorance on the part of users of drugs of their increasing dangers and especially the presence of synthetic opioids in non-opioid drugs were examined [86]. This was followed by a review of longer waiting times in relation to drug users seeking treatment and continuation patterns in drug use, including co-morbid drug using environments and drug-using networks [87]. It was concluded that the growing and changing nature of drug entanglement would continue to simultaneously challenge and change existing harm reduction efforts and structures [87]. A priority of harm reduction efforts must be to engage with drug using populations, especially those resistant to treatment, to encourage greater awareness of shifting drug risks, which must continue to change in parallel with drug entanglements [88]. The previously convergence of opioid and stimulant increase is mirrored by duality as a core constructionist feature in re-entry studies following prolonged abstinence [88]. The shifting social constructions on pharmaceutical

cocaine and methylenedioxy-methamphetamine re-integration led to the emergence of a transference focusing on endogenous control [89]. Through a comprehensive review of literature examining both regular drug consumption and overdose among dual use populations and ongoing observation of the dual drug-using community, it is postulated that recent shifts user behaviours account for the slow and sometimes missed warning signs noted in overturned overdose trends internationally and their numbing experience with the 'normalization' of present conditions [5].

16. Psychosocial Factors Contributing to Overdoses

Drug overdose (OD) is now the leading cause of accidental death in the US, comprising over 12% of all deaths during 2016 [90]. Most OD deaths involve illicit drugs and/or nonmedical use of prescription medications [90]. Between 1999 and 2017, the number of deaths involving opioids increased six-fold, with synthetic opioids, especially fentanyl, accounting for 47% of all US OD deaths in 2018 [91]. Although the number of population-level prescription and illicit opioid users increased, the number who received treatment more than doubled from 2002 to 2015 [91]. The treatment response to this crisis has maintained a focus on a narrow set of topics: the evaluation and expansion of the availability of effective medications; stimulant epidemiology and treatment; the role of adolescent vaped cannabis in OD deaths among adults; and recently, the opioid dispensing/overdose improvement of metrics and observational studies measuring impacts of the pandemic, and/or focusing on too-narrowly defined treatment and population sectors [92].

Widespread adulteration of prescription opioids with fentanyl has increased lethality associated with use [93]. One public health response to the expanding epidemic has been widespread community distribution of naloxone to reverse foreshortened OD and many localities are actively reporting dramatic increases in reversals and OD death reduction [93]. Noticeably absent from public discussion, clinically-relevant harm reduction research, and intervention design discussions of OD prevention is a focus on the personal risk factors among people who use heroin or other opioids that may substantially reduce the potential to seek treatment for reducing or stopping consumption [94].

17. Impact of Socioeconomic Status

New targeted educational efforts are needed to fill knowledge gaps across a range of drug user and overdose responder factors [95]. Monitoring and surveillance systems should refine existing data collection systems and protocols to include more information on the socioeconomic status and marginalized social position of people who use drugs [96]. Wider academic and research commitment and capacity is required to bolster basic research efforts that can lay the groundwork for future intervention programming [97]. Qualitative research with drug users - racially minoritized groups, youth, and sex workers in particular - can shed critical light on the social networks and interpersonal behaviours that promote poly-drug use [98]. Drug checking services can consider social media monitoring to better complement their lab analyses or invest in rapid testing technologies that can be deployed at, or interfere with event promoter's industry acknowledge their position and likelihood of a changed social environment that renders changes in practice and policy more likely [99]. Intervention research should engage in collaborative research with drug users and affected communities to identify low-cost, high-yield interventions and consider short- and long-term options that target industry. psychological, empathetic, or endogenous traits has fueled drug user stigmas and exclusionary health practices that limit the reach and effectiveness of drug user interventions and services [100]. Analysis of the impact of drugs on routines and complete lived experiences instead determines policy interventions that address drugs otherwise understood as harmful are linked to youth empowerment and community inclusion [100]. The designs of technoscientific drug monitoring interventions can then account for the ambiguities of drug user agency or encourage drug inclusivity [101]. Implications for future research highlight that critical engagement with wider social aspects of drug user agency can expand research and intervention horizons [94].

18. CONCLUSION

Multiple drug use is rampant and increasingly prevalent even with a number of drugs widely accessible on the street [102]. In 1995 alone, there were at least a dozen different types of street drugs acknowledged, and many of them will likely be used together in any given episode of use [103]. Many overdoses were characterized as a mixture of alcohol with opiates, methadone with opiates, paracetamol with opiates, etc [103]. Cocaine was often used with opiates, because of the euphoria they provided, followed by a sleepiness and calm the opiates gave [104]. Opiates often came in different forms, for example, heroin or methadone. Alcohol, the most widely consumed psychoactive drug in the world, is extraordinarily popular and addictive [104]. As such it also causes an uncountable number of adverse health outcomes, not the least of which is akathisia in withdrawal, a potent stimulant to multiple-drug use [105]. Statistically, one specific drug was listed in a majority of drug overdose deaths, whereas other drugs either increased or decreased in number established multifactorial statistical relationships [105]. The relationship to number of drugs, polydrug use, was perplexingly difficult to quantify, being simple on one level but unaccountably complex and inconsistent on another level [106]. Examining the relationship over the framework of multiple drug use, and the contingency it brought to interpreting the data, better illuminated some of the unknowns [106].
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Overdoses may occur as a direct effect of a drug used alone or as an interaction effect when a mixture of drug types and doses impair the body's ability to maintain equilibrium in the central nervous system [107]. The question of these mixtures of drugs has gained particular interest in overdose studies and has been the focus of this recent study [107]. Prior studies identified associations with combination drug types will naturally invoke fuller consideration of these complex relationships in terms of both cohesion models and contingency-based multi-part textbooks on specific types of drugs [108]. This needed incorporating into a single source a range of literatures on combinations [108]. But also background, methodological and statistical issues as to how to measure multifaceted, emergent effects were derived [109]. Which may be non-linear and contingent over lower-, middle- and higher-order levels of statistical detail (109). And full quantitative modeling treatment [110]. More attention needs to go to the rise of multi-drug use, in terms of underlying factors at watershed points such as the emergence of cocaine, MDMA, heroin, or crack cocaine or cocktail drinks. And the reciprocal feedback loops at those points that enhance the prevalence as well as the severity of drug related problems [111].

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