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Unmasking Adulterants in Illicit Opioids: Toxcity Profiles, Review of Detection Methods, and Public Health Responses

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Abstract
The adulteration of opioids presents a significant public health and forensic challenge This study has been undertaken to investigate the fatal adulterants present in illicit opioids. To review different analytical techniques and public health responses for the emerging novel synthetic opioids (NSO). The paper also focuses on the research gaps in the current scenario in screening and analyzing of various synthetic analogs.

Keywords: adulterant, opioids, fentanyl, xylazine, Novel Synthetic Opioids (NSO).

Introduction

The past three decades paved the way for opioid crisis. The use of narcotic analgesics was instituted to relieve people from acute pain. However, a letter in 1980 of New England Journal was reviewed by healthcare professionals on opioid addiction delivered to patients and it was found that only 4 out of 11,882 patients administered opioid for pain were addicted to it. And soon the health care industry started to administer the drugs on any pain whether acute or terminal illness or chronic pain.[1] This boosted the increasing consumption of prescription opioids even though there was negligible difference in pain reduction between opioid and non-opioid medications[2], increasing the dependence on it and since refill prescriptions were not made available this opened the way for illegal sources to capture the increasing market of opioids and this involved many unregulated sources, counterfeit opioids, new psychoactive substances, diverted opioids adulterated drugs causing opioid epidemic. The crisis evolved in three phases: increased prescription opioid use (1990s-2010), shift to increase heroin use and supply (2010-2013), and rise of synthetic opioids (2013-present) (Maclean et al., 2020). Since this illicit drug (synthetic and counterfeit) made it to the market so early through clandestine labs it is was difficult for Drug Enforcement Administration (DEA) to catalog and outlaw them.[3]

An adulterant is defined as an impurity or additive that is considered to have an undesirable effect or to dilute the active material to reduce its therapeutic or monetary value.[4] Generally, adulterants in drugs implies to pharmacologically active ingredients, contaminants refer to by-products of manufacturing process, diluents are considered to be bulking agents. Commonly involved diluents like talc, sugar, chalk, which are now replaced with pharmacological valued substance like procaine/caffeine in cocaine, paracetamol in heroin,[5] which conveniently mask the effect of active ingredient and helps getting profit in dealer's pocket. (R. Shesser, 1991) reported the additives in heroin which corresponded to 9 volatile

compounds, 5 alkaloids, 13 inert additives and 33 pharmacologically active additives.[6] To further complicate the condition rapid emergence of variety of New Psychoactive substances (NPS) makes it difficult for screening due to lack of pharmacological and structural information. For example, very few studies considering carfentanil as Novel Synthetic Opioid has been reported.[7]

The following review paper focuses on the critical aspects of opioid adulteration which includes types of adulterants in focus, the health impact associated with increased toxicity of adulterants, detection, and toxicology screenings to identify adulterants, to review the law and policies aimed at shrinking the adulteration and to find any discrepancies involved in the literature for further improvement.

Overview of Drug Adulterants in Opioid

The paper by **Cunningham, Venuto, and Zelensky (1984)** explores heroin associated nephropathy (HAN) a kidney disease linked to intravenous heroin users. The study suggests that adulterants used to cut heroin might be key contributors to the disease. Analysing over 12000 samples of confiscated street heroin the researchers identified 11 adulterants commonly used to dilute heroin including quinine, mannitol, lactose, and procaine. Quinine, found almost exclusively in heroin samples, is particularly concerning due to its known nephrotoxic effect previously linked to kidney failure. [8]

A study by **Hamilton et al.,** discussed a heroin epidemic caused by heroin adulterated with Scopolamine in Eastern cities of the globe in 1995. Scopolamine, an anticholinergic agent, was added to heroin, leading to severe toxic effects in users. The affected patients often exhibited symptoms like respiratory depression, agitation, dilated pupils, dry skin, and other anticholinergic signs, especially after receiving naloxone to counter opioid effects. Using Gas Chromatography Mass spectrometry, the identification of scopolamine in heroin was confirmed. Wrapping it up the study drew attention to roles of poison centres in recognizing and responding to drug epidemics, allowing for timely communication with healthcare providers and law enforcement.[9]

The document by **Behrman** discusses common heroin adulteration which include a) fentanyl- Mixed with heroin to boost potency, though it significantly increases the risk of overdose due to severe central nervous system and respiratory depression. Various street names that denote these mixtures are “Tango& Cash” or “Drop Dead.” B) Clenbuterol- During 2005 many heroin users experienced unusual symptoms such as tachycardia (fast heart rate) and hypokalaemia (deficiency of potassium in bloodstreams) due to clenbuterol, a veterinary medication that can cause prolonged adverse effects. C) Diphenylamine & Acetaminophen – Popularly known as “Cheese Heroin” was a prevalent drug among young users in the West leading to affects like lethargy and disorientation. [10]

Cole (2010)[11] highlights adulterants in opioids and other illicit drugs that serves multiple purposes, such as increasing bulk, mimicking drug effects, or aiding drug delivery. Emphasising on the risk injectable opioids due to some additives pose significant health risks. For example, lead contamination from manufacturing processes, phenobarbital (barbiturate) added to facilitate smoking of heroin and fentanyl highly potent opioid associated with fatal overdose. The study also addressed bacterial contaminants, especially in injectable opioids, that can lead to infection like anthrax.

Xylazine considered to be a veterinary sedative has emerged as a hazardous adulterant in heroin and morphine. Aimed for animal sedation xylazine is prohibited for human use due to severe side effects like central nervous system depression, respiratory depression, bradycardia (slow heart rate) and hypotension. When mixed with opioids like heroin, xylazine enhances sedation and respiratory depression, which lead to fatal outcomes. The presence of it in street drugs may amplify the high but increases the risk of overdose

due to the combined depressant effects. Reports from **Puerto Rico**[12] indicate xylazine is frequently found in "speedball" mixtures (heroin and cocaine) and heroin samples, with users often unaware of its inclusion. Chronic use has led severe health issues such as physical deterioration and open skin ulcers. In several cases, xylazine was found alongside heroin metabolites, further underscoring its risk. Healthcare professionals and law enforcement are urged to be vigilant about xylazine's use as an adulterant. Increasing awareness and forensic monitoring can improve responses to xylazine related health risks among opioid users.

The paper by **Luong et al.,**[13] investigates the use of pyridinium chlorochromate (PCC), an adulterant in masking codeine and its primary metabolite, codeine-6-glucuronide (C6G) in urine drug tests. PCC, a common ingredient in commercial products for urine adulteration, was added to both codeine and C6G-positive urine samples to study its impact on these compounds. Using techniques like Liquid chromatography/mass spectrometry (LC/MS) and Nuclear Magneti c Resonance (NMR) researchers inferred that PCC effectively oxidizes codeine and C6G, transforming them into other opioid analogs, such as 6-O-methylcodeine, codeinone, and 14-hydroxycodeinone. This oxidation process significantly reduces the concentration of codeine and C6G in the urine, altering the typical codeine-to-C6G ratios generally used in drug testing. PCC can disrupt standard urine drug tests by chemically converting detectable opiates into undetected analogs, complicating the interpretation of results.

The interference of common adulterants like lemon juice, nitrogen-based fertilizers, and carbon copy paper on morphine urine screening was examined by **Zare et al.,**[14] The study found that adding these adulterants generally did not cause false negative at standard morphine levels (300ng/mL or higher). However, lemon juice and fertilizer could lead to false negative results at lower morphine concentration (150ng/mL), carbon copy had no significant interference in the sample screening. This highlights that adulterants might reduce test sensitivity in some cases, they do not consistently produce negative thresholds. More sensitive technique needs to be developed for countering potential adulteration.

(Jon B. Cole, 2017) [15] in his article discussed the adulteration of heroin with synthetic opioids, significantly on carfentanil. Carfentanil, a fentanyl analogue, is 10,000 times more potent that morphine and poses severe public health risks due to its presence in the illicit drug supply. The paper emphasizes on how carfentanil's appearance in the U.S. has complicated overdose treatment and increased fatalities, as even minimal exposure can result in life threatening conditions. Further discussion involves the low efficiency of standard opioid antidotes, such as naloxone, in treating carfentanil overdoses. Higher doses of naloxone may be needed to restore respiratory function, although there is a need for extended observation due to high risk of recurrent toxicity.

Severe public health risks are associated with lead-adulterated opium, especially in Iran where opium use is prevalent is mention in the article by **Alinejad et al.**[16] Lead, a toxic heavy metal, is sometimes added to opium to increase its weight and, thus, its profitability. This has led to widespread lead poisoning among opium users, displaying various symptoms like abdominal pain, constipation, anaemia, and neurological impairments. Hypertension, organ damage and death in severe cases is associated with chronic exposure. The review emphasizes on effective screening as the symptoms exhibited are like general poisoning symptoms and very non-specific.

The paper by **Daniel Ciccarone et al.**[17] investigates the impact of fentanyl-laced heroin on opioid users in Massachusetts. Inclusion of fentanyl, a synthetic opioid 30-50 times stronger than heroin, leading cause of overdose deaths. Through qualitative interviews, the study explores user's perceptions of different types of heroin on the market, including fentanyl-adulterated, pure fentanyl and fentanyl-heroin mixtures. The

study aims at the risk of fentanyl in drug supply, with users reporting difficulty in distinguishing between heroin and fentanyl products, which leads to unintentional overdoses.

In the book Neuropathology of Drug Addictions and Substance Misuse, Volume 1 authored by **Maryam Akhgari et al.**[18] pens down adulterant through their sources. Acetylcodeine is the notable impurity obtained as a by-product in manufacturing process of heroin. It is produced because of improper purification process of morphine and is responsible for the convulsant effect of heroin. The chapter also discusses the microbial contamination of the opioid sample due to in efficient manufacturing techniques, packaging, storage, and distribution. Especially IV users are affected through microbial contamination which results into soft -tissue infections.

Since the opioid crisis the drugs are predominantly been in the physical market as 'street drugs.' The popularization of illicit drugs has made it to the crypto market. Through the hidden web heroin is sold with a novel synthetic opioid ocfentanil, analog of fentanyl and much more potent. The paper by **P. Quintana et al.**,[19] reports the presence of ocfentanil in the samples collected from Spanish NGO (Energy Control) submitted by the hidden web users. GC/MS spectra revealed the presence of ocfentanil along with caffeine and paracetamol in heroin samples from the crypto market.

The last decade (2010-2020) market has seen significant rise in the New Psychoactive Substances. The wide spread availability of the NPS /NSO has spiked overdose deaths. Most of the fatalities reported are due to illicitly manufacture fentanyl and fentanyl analogs. [20] Of the reported fentanyl analogs, the Law enforcement of USA confiscated acetylfentanyl, butyrylfentanyl, and furanylfentanyl, in addition to non-fentanyl compounds such as U-47700, AH-7921, MT-45[21] . The data by NFLIS of US stated 52 -acetylfentanyl, 40 -butyrylfentanyl, 128-furanylfentanyl, and 46 U-47700 fatalities in the year 2013. All of these substances induce a classical opioid toxidrome.

Salmone and Palamar[22] in their article "Toxicosurveillance of novel opioids: just screening tests may not be enough" have mentioned the emergence of novel synthetic opioids such as fentanyl and its various analogues which are clandestinely synthesized for illegal market. Generally used as cutting agent in heroin fentanyl is considered to be a very potent drug and has been responsible for opioid overdose death in the West. However, the article focuses the need on screening methods for rapidly growing derivatives of fentanyl. The major drawback in developing assays is either the assays have poor sensitivity to fentanyl or fentanyl analogues appear without fentanyl in it in the market.

Skolnick et al.[23] examines the challenges and solution in addressing opioid overdose caused by synthetic opioids, particularly fentanyl and its analogs. These susbstances, increasing prevalent as adulterants in illicit drugs, lead to rapid respiratory depression and a heightened risk of death. Unlike traditional opium-based opioid, their potency and physicochemical properties require faster and more effective reversal agents. Naloxone, the standard antidote for opioid overdoses, is often insufficient in reversing synthetic opioid toxicity, particularly in community settings where intravenous administration is not viable. Simulation using a translational model revealed that higher doses or more potent formulations are essential for effective intervention. Intranasal nalmefene, a newer opioid receptor antagonist, demonstrates superiority over naloxone due to its rapid absorption and higher receptor affinity, significantly reducing the incidence of cardiac arrest in overdose scenarios.

Purpose and Sources of Adulteration

Through several studies it can be deduced that adulterants in the substance may be added in the production or at highest level of distribution chain. Some studies assessed that heroin was adulterated before

exportation or right after importation in the country of destination.[24] More recent studies bifurcate the concept of diluents and adulterants. Adulterants are considered as pharmacologically active substances to enhance or mimic the effect on the other hand diluents are pharmacologically inactive substance added to bulk the drug. Heroin is found to have more of adulterants than diluent. Caffeine -Paracetamol is the common adulterant mixture found in the production phase of heroin. Caffeine facilitates vaporization of heroin for easy administration whereas paracetamol masks well with the property of heroin giving a bitter taste similar to heroin.

When discussing adulterants a common perspective that emerges is to make the substance in use profitable to the producers. This can be achieved by adding cheaper quality products to increase the weight of the drug. For ex. Diluting with talc, chalk powder, sugar, lead to heroin in many manufacturing units. This will relatively cost less than adding adulterants like carfentanil, xylazine. Through marketing point of view the producers need to keep hold of their customers, provide a potent drug that enhances the effect and to attract more consumers it is required to adulterate the drug with active substances. Therefore, the market is always dynamic and offers many novel synthetic opioids.

Coomber[25] through is qualitative research on street drug dealers stated on what point adulteration/dilution takes place in the chain of distribution. It was found that almost 90% of the dealers were unaware of the consequences of cutting agents being added to the substance. Some of the dealers adulterated heroin based on their subjective perception like tasting or trying out for the strength of the drug. Thus, the variability in adulteration was never known due to hierarchical distribution of the drug. The ones who sold heroin responded adding a diluent as sugar, usually glucose. It was found that most desperate street dealers used to adulterate the substance with harmful additives.

According to **M. Morelato, et al.**[26] who studied the phase of when cutting of cocaine and heroin occur in the supply chain mentioned that in heroin adulterants found at distribution level accounted to 94% of heroin and at consumption level 99.8% of heroin. Considering the dilution at distribution level it was found in 13% of heroin and at consuming level 11% were diluted. A significant difference in the purity of heroin sample is observed between the heroin seized by customs and heroin seized at the street level.

The document by **Ross Coomber**[27] examines the common beliefs and myths surrounding the adulteration of heroin and other street drugs. It challenges the widespread notion that heroin is commonly mixed with highly dangerous substances such as brick dust, rat poison or ground glass, arguing that such claims lack substantial forensic evidence. Instead, the study highlights that the most common adulterants, like paracetamol, caffeine, and sugars, are relatively benign and often added to dilute the drug or enhance its effects. Coomber also explains that adulterants and diluents are typically chosen for their compatibility with the drug's intended use, such as improving bioavailability or mimicking its effects. The report also addresses misconception that dangerous adulterants are routinely used by dealers, emphasising that most drug distribution systems are commercially driven, with sellers having little incentive to harm their customers. Additionally, the paper identifies that heroin adulteration generally occurs at higher levels in the distribution chain, leading to limited adulteration at street levels in countries like the UK. High-purity heroin, rather than adulterants, is often implicated in overdose deaths. The author argues for more research into street drug composition and suggests potential harm-reduction strategies, such as testing services for users to ensure drug safety and purity.

Ross Coomber[28] examined practices of heroin adulteration and dilution in the U.S. It challenges conventional models that assume systematic cutting occurs at every stage of distribution. Data from the 1990s reveal a tenfold increase in heroin purity compared to previous decades, with street-level heroin

often being over 50% pure in major cities like New York and Boston. Contrary to popular belief, heroin is rarely adulterated with harmful substances, and much of the dilution occurs before importation, using benign agents such as sugars or caffeine, Coomber's findings indicate that adulteration is unsystematic and not prevalent at the street level. Some heroin samples contained no additives, and purity levels varied based on the drug's origin. For instance, Mexican heroin was less likely to cut, while southeast Asian and South American heroin often arrived already diluted. The study also highlights dealer's motivations, including fear of customer reprisal and ethical concerns about user safety, which limit dangerous adulteration.

Health and Safety Implications

The emergence of fentanyl has deepened concerns about the opioid crisis. The shift has created new distinctions in patterns of opioid use, which may be important for prevention and intervention. **Kelly et al.**[29] examined socio-demographic correlates as well as health and substance use characteristics of different groups of opioid users. They utilized the 2015-2019 National Survey on Drug Use and Health to examine distinctions between groups of individuals who misuse prescription opioids, use heroin but not fentanyl, misuse pharmaceutical fentanyl but not heroin, and use both heroin and fentanyl. Multinomial and logistic regression models were used to identify these distinctions. Findings few socio-demographic differences emerged between the prescription opioid group and pharmaceutical fentanyl misuse group. While those who misuse fentanyl have higher odds of using other drugs and experiencing certain mental health problems than those misusing prescription pills, both the heroin and fentanyl-heroin use groups reported considerably poorer health and substance use indicators relative to those who solely misuse fentanyl. It is also notable that both heroin use groups are more highly associated with cocaine and methamphetamine use than those misusing fentanyl alone. Originally this study highlights distinctions between pharmaceutical fentanyl users, heroin users, and users of both substances. Important differences between the fentanyl-only group and the group who consume both drugs may have implications for prevention, intervention, and clinical work amidst shifting patterns of opioid use.

Aims et al.[30] in their study sought to develop and assess an exploratory model of how demographic and psychosocial attributes, and drug use or acquisition behaviors interact to affect opioid-involved overdoses through exploratory and confirmatory factor analysis (EFA/CFA) to identify a factor structure for ten drug acquisition and use behaviors. Further it was evaluated alternative structural equation models incorporating the identified factors, adding demographic and psychosocial attributes as predictors of past-year opioid overdose. They used interview data collected for two studies recruiting opioid-misusing participants. The first investigated current attitudes toward drug-checking. The second was an RCT assessing a telehealth versus in-person medical appointment for opioid use disorder treatment referral. Demographics included gender, age, race/ethnicity, education, and socioeconomic status. Psychosocial measures were homelessness, psychological distress, and trauma. Self-reported drug-related risk behaviors included using alone, having a new supplier, using opioids with benzodiazepines/alcohol, and preferring fentanyl. The EFA/CFA revealed a two-factor structure with one factor reflecting drug acquisition and the second drug use behaviors. The selected model accounted for 13.1% of overdose probability variance. No demographic attributes were significant direct or indirect overdose predictors. Psychosocial attributes, particularly homelessness, increase the probability of an overdose through associations with risky drug acquisition and drug-using behaviors. To increase effectiveness, prevention efforts might address the interacting overdose risks that span multiple functional domains.

The article by **Manuel Cano et al.**[31]. investigates the increasing presence of xylazine in fatal overdoses and forensic drug submissions across the U.S. Using data from state reports, the National Forensic Laboratory Information System (NFLIS), and other sources, the study analyzes trends between 2019 and 2022 to understand xylazine's geographical reach and associated risks. Key findings reveal that xylazine-related overdose deaths have expanded to at least 43 states, with the highest mortality rates reported in Vermont and Connecticut in 2022. Forensic drug reports indicate a growing presence of xylazine, especially in northeastern states of Western countries, where it represents a significant percentage of analyzed drug samples. The study emphasizes the challenges of tracking xylazine due to inconsistent postmortem toxicology testing and reporting practices across states. Despite its designation as an emerging threat, comprehensive state-level data on xylazine-related deaths remain limited, highlighting the need for standardized testing and improved reporting systems. The authors recommend integrating xylazine-specific harm reduction strategies, including xylazine test strips and enhanced overdose response protocols, into existing public health initiatives. They also stress the importance of expanding research to better understand the unique risks posed by

Friedman and Shower [32] in their article examine the evolving overdose crisis, particularly the rise of polysubstance fentanyl-related deaths. Using national mortality data, the study tracks trends in fentanyl overdoses and co-involved substances, such as stimulants, across different states and demographic groups. The study finds that fentanyl-stimulant co-involvement in overdose deaths surged from 0.6% in 2010 to 32.3% in 2021, with stimulants becoming the most common co-involved drug class. The Northeast countries saw a shift from heroin-fentanyl overdoses to cocaine-fentanyl cases, while the West and much of the South and Midwest experienced an increase in methamphetamine-fentanyl deaths. Black and African American individuals in the West were disproportionately affected. The authors highlight the challenges posed by this "fourth wave" of the overdose crisis, where fentanyl's presence in the illicit drug supply has fueled polysubstance use. They emphasize the need for enhanced drug surveillance, harm reduction strategies, and targeted public health interventions to address the growing risks associated with stimulant-fentanyl combinations. This research provides critical insights into the changing dynamics of drug-related mortality, emphasizing the urgent need for policy and healthcare adaptations.

The article by **Cano M. et al.**[33] examines the relationship between drug seizures and overdose deaths in the United States. Using data from the National Forensic Laboratory Information System and the Centers for Disease Control and Prevention, the study analyzes trends from 2013 to 2021 across different states and demographic groups. The study finds that fentanyl and stimulant availability, as measured through law enforcement drug seizures, is strongly correlated with overdose mortality rates. Specifically, the proportion of fentanyl-related seizures emerges as the most significant predictor of overdose deaths. The analysis reveals regional variations in drug seizure trends, with fentanyl replacing heroin as the dominant opioid. The study highlights the limitations of relying solely on drug seizure data, as not all seizures are analyzed or reported consistently across states. Despite these challenges, the findings support the use of seizure composition measures as indicators of illicit drug availability and potential predictors of overdose trends. By identifying the strongest predictors of overdose deaths, the research suggests that public health responses should focus on fentanyl interventions, including harm reduction strategies and early warning systems. Overall, this study contributes valuable insights into the evolving landscape of drug-related mortality in the U.S., reinforcing the need for continuous monitoring and targeted prevention efforts.

The article by **Chhabra et al**.[34] investigates the prevalence of fentanyl analog exposure in patients with positive urine screens for fentanyl or opiates. Conducted in a large public healthcare system in Chicago,

the study uses high-performance liquid chromatography/tandem mass spectrometry (HPLC-MS/MS) to detect synthetic opioids in urine samples. The study analyzed 219 urine samples, revealing that 65.3% contained at least one fentanyl analog, with 26% testing positive for multiple analogs. The most frequently detected analogs included 4-ANPP, 2-furanylfentanyl, acryl fentanyl, butyrylfentanyl, cyclopropylfentanyl, and carfentanil. Interestingly, among samples screening positive for opiates but negative for fentanyl, 35.5% still contained fentanyl analogs, highlighting the limitations of standard immunoassay screenings. The findings underscore the widespread presence of fentanyl analogs in illicit opioid use, emphasizing the need for improved surveillance and harm reduction strategies. The study suggests expanding fentanyl and synthetic opioid testing in healthcare settings to enhance early detection and intervention efforts.

Detection and Analytical Technique

Griswold et al.,[35] explores the use of liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) to detect fentanyl and clandestine opioids in oral fluid and urine specimens following heroin overdoses. The study involved 30 adult participants with heroin overdose diagnosis requiring naloxone. Paired oral fluid and urine samples were collected and analyzed for fentanyl and other opioids. The study revealed high agreement (93.3%) between oral fluid and urine for fentanyl detection, suggesting oral fluid testing as a viable alternative for recent drug use surveillance. Additionally, it detected clandestine opioids like acetylfentanyl, U-47700. The methodology showed the utility of LC-QTOF-MS for broader opioid detection compared to traditional methods, offering advantages like non-targeted acquisition and retrospective data analysis. However, challenges included lower concentrations of drugs in oral fluid, limiting detection of norfentanyl. The findings highlight the potential for LC-QTOF-MS in clinical and forensic settings to enhance public health responses to opioid crisis. Further research is necessary to validate the approach and optimize detection thresholds.

The use of Direct Analysis in Real-Time Mass spectrometry (DART-MS) as a forensic tool for seized drug analysis has been validated. The paper by **Sisco et al.**[36] even emphasizes it potential to address challenges posed by the rise of novel psychoactive substances (NPS) and opioids. DART-MS offers rapid and sensitive qualitative analysis with minimal sample preparation, making it suitable for identifying opioids and related substances in forensic settings. The validation process examined aspects like accuracy, precision, reproducibility, sensitivity, and robustness, alongside environmental effects and real-world casework applications. Results showed that DART-MS could reliably identify controlled substances, including opioids such as heroin and fentanyl, but had limitations in differentiating isomers and handling mixtures with poor ionization efficiency for minor components. The work underscores DART-MS as a valuable tool for opioid detection, complementing existing methods like GC-MS. The study also provides a validation template and additional resources to facilitate adoption of DART-MS in forensic laboratories dealing with emerging drug challenges.

Sisco[37] further has narrowed down the detection of fentanyl analogues and other opioids using thermal desorption direct analysis in real time mass spectrometry (TD-DART-MS) and ion mobility spectrometry (IMS). Fentanyl and its analogues are highly potent synthetic opioids, posing severe health risks, especially to law enforcement and first responders. The study highlights the need for safe and efficient screening methods for these substances in field and laboratory settings. Both TD-DART-MS and IMS demonstrated high sensitivity for detecting trace amounts of fentanyl and related compounds, even in mixtures with heroin or in complex background matrices like fingerprints, dirt, and plasticizers. The

techniques achieved detection limits as low as nanograms and picograms per wipe. TD-DART-MS provided better discrimination between isomers compared to IMS, although IMS effectively detected fentanyl in challenging scenarios by optimizing alarm settings. The study concludes that TD-DART-MS and IMS are effective qualitative tools for the rapid screening of fentanyl and its analogues. Their deployment in forensic, and medical contexts could enhance safety, improved opioid detection.

Florea et al.[38] investigated the novel electrochemical methods for rapid detection of heroin and its adulterant in street samples. The identification technique involved square wave voltammetry (SWV) with unmodified graphite screen-printed electrodes, researchers identified heroin's unique electrochemical fingerprint at pH 7.0 and pH 12. Adjusting the pH to 12 improved detection accuracy, resolving interference from common adulterants such as caffeine, paracetamol and papaverine. A preconditioning step further enhanced the separation and detection of heroin in complex mixtures. Binary mixtures of heroin with other drugs like cocaine, MDMA etc. were also analyzed. Morphine and heroin, due to structural similarities, could not be distinguished. Additionally, paracetamol adulteration required detection adjustments at pH 5 for better discrimination. The method was validated using street samples from forensic cases, highlighting its potential for on-site drug screening. The dual-pH approach proved effective for detecting heroin and its adulterants, setting the stage for portable field-ready devices capable of screening multiple illicit drugs with high sensitivity and specificity.

The performance of a portable quadrupole-based gas chromatography-mass spectrometer (GC-MS) for analyzing seized drugs and adulterants was assessed by **Fiorentin et al.**[39] It compares the device (FLIR Griffin™ G510) with a traditional benchtop GC-MS system. Twenty-four substances, including drugs like heroin, cocaine, and methamphetamine, as well as common adulterants, were selected for validation due to their prevalence in drug samples globally. The portable GC-MS demonstrated high accuracy and sensitivity for most substances, with limits of detection ranging between 0.01 and 0.1 mg/mL. Some issues, such as occasional false negatives for substances like heroin and caffeine, were noted due to manual handling errors. The method showed no carryover or interference from common substances. The portable GC-MS achieved accuracy values exceeding 90% in most cases and was particularly effective for on-site screening of multiple substances simultaneously. Authentic seized drug samples were tested, and the portable device's results closely matched those of the benchtop GC-MS. The study concludes that the portable GC-MS is a reliable, field-ready screening tool for illicit drugs and adulterants, suitable for rapid forensic applications.

Public Health Responses and Policies

Fentanyl has accounted for over 65% of new psychoactive opioids (NPO)[40]. Over 5 decades in clinical settings fentanyl has been used as therapeutic tool, but fentanyl abuse has taken place in the market through illicit fentanyl formulations that are synthesized in clandestine laboratories following different chemical pathway, depending on the precursors available. Various fentanyl analog like Alfentanil, sufentanil, remifentanil, Carfentanil, Acetylfentanyl, Butyrfentanyl, Fluorofentanyl have been reported in a decade with much fatal effect. The following fentanyl analog has potency almost 100- 1000 times more than natural opioid (morphine and heroin). The NPSs (New Psychoactive substances) scene constantly evolves. Therefore, surveillance and monitoring programs are critical to keep up with the associated public health challenges. It is imperative to implement regional drug testing and forensic services where they do not exist. In addition, laboratories must modify their current methodologies or develop new forensic and toxicological analytic methods to detect the emerging drugs. This can be challenging as data about NPSs

emergence differ between regions and become rapidly outdated. The NPSs Discovery program and the Society of Forensics Toxicologist Designer Drugs Committee have established recommendations for NPSs detection, categorizing them into three tiers of analysis: Tier 1- strongly recommended (includes metonitazene, fluorofentanyl, brorphine, isotonitazene, and carfentanil); Tier 2- recommended, and Tier 3- consider testing. It is worth noting that substances in each tier constantly evolve[41]

Campbell in his article has thrown light on Naloxone technology. The proliferation of NPOs is a worldwide problem that requires multilateral approaches because these substances are available through the dark web, easy to conceal, and easy to deliver through regular or express mail services. Clinicians must consider that commonly available antidoping kits may not detect fentanyl analogs and other new synthetic opioids and stay alert to symptoms associated with opioid use, especially slow and shallow breathing, cyanosis, and miosis. In those cases, naloxone[42] is the drug of choice to counteract opioid intoxication. Due to the high potency of fentanyl and other synthetic opioids, it may be necessary to administer several naloxone doses (or several nasal spray administrations where Narcan is available), and more prolonged observation periods. Naloxone is an effective antidote without intrinsic activity that displaces opioid drugs from their receptors, effectively counteracting the life-threatening respiratory depression caused by heroin, fentanyl, and other NOPs1. Naloxone is internationally accepted to help opioid users recover from respiratory depression and has saved countless lives.

The article by **Daniulaityte et al.**[43], investigates the growing issue of counterfeit fentanyl pills in Arizona's illicit drug market. Utilizing qualitative interviews with 22 individuals who used opioids, the study reveals critical insights into the motivations, practices, and consequences associated with counterfeit fentanyl pill usage. The findings emphasize the proliferation of these pills, colloquially referred to as “blues” or “dirty oxys,” which have largely replaced heroin due to their increased availability and affordability. Additionally, the authors highlight the role of socioeconomic factors, including the COVID-19 pandemic, in shaping drug availability and usage patterns. Notably, the study identifies a shift in drug administration practices, with many participants opting to smoke fentanyl pills rather than injecting heroin, viewing this method as less stigmatized and potentially safer. However, the research also highlights the heightened risks of overdose and the significant challenges of quitting fentanyl due to its potency and severe withdrawal symptoms. The authors call for enhanced harm reduction strategies, such as expanding access to drug testing technologies and refining opioid use disorder treatment protocols. They underscore the importance of community-based approaches to address the unique risks posed by counterfeit fentanyl pills.

In the article by **Liu, McCall and Piper**[44] examines the distribution and adverse drug events (ADEs) of 11 commonly prescribed opioids. Using data from the FDA Adverse Event Reporting System (FAERS) and the DEA’s Automation of Reports and Consolidated Orders System (ARCOS), the study assesses trends from 2006 to 2021. The study finds that oxycodone, fentanyl and morphine accounted for over half of all reported ADEs with meperidine contributing less than 1%. Opioid distribution remained relatively stable over time, with methadone consistently making up the largest proportion. However, certain opioids. Such as meperidine, oxymorphone, and tapentadol, were disproportionately linked to ADEs when compared to their distribution. Notably, methadone was underrepresented in ADE reports despite its high distribution. The study highlights the importance of using both FAERS & ARCOS data to assess opioid safety post-marketing. It underscores the need for continuous monitoring, particularly for opioids with high ADE-to-distribution ratios. The findings suggest that policies should target high-risk-opioids while considering their medical necessity. By identifying opioids that are disproportionately associated with ADEs, it supports efforts to refine regulatory and clinical strategies to mitigate opioid related harms.

The article by **Saunders et al.**[45] analyzes geographic patterns of drug overdose deaths across U.S. counties. Using data from the National Vital Statistics System, the study maps overdose death rates involving any opioid, synthetic opioids, and psychostimulants over time. The findings highlight the evolving nature of the drug overdose crisis. Initially, synthetic opioid deaths were concentrated in the Northeast and Midwest, but by 2020, they had spread to the Mississippi River region and the western U.S. These shifts suggest an expanding and evolving drug crisis, influenced by changes in drug supply and regional drug use patterns. The authors emphasize the need for targeted public health interventions, including increased access to medications for opioid use disorder and naloxone distribution in high-risk areas. Overall, this study provides valuable insights into the geographic spread of overdose deaths, offering a data-driven approach to inform policy and public health efforts.

Research Gaps and Future Directions

The shift to Novel Synthetic opioids has disrupted the natural opioid market. It has such a huge and dynamic environment, before the research institutes could work on it and identify and put it in a prohibited category, analog for the same emerges in the market. It has now become difficult for the huge agencies like Drug Enforcement Administration (DEA) to keep up with the emerging trends. Even at many levels it is necessary to regulate the non-pharmaceutical synthetic opioid distribution. Test kits based on immunoassays are developed for detection of synthetic opioids but it becomes tedious every time to analyze different analogs. Even the detection kit has not been reaching at the ground level to investigate the cluttered market. The main gap that is associated in adulteration is the origin of it. Many papers reported its source during distribution or at times of production. But at the end it is difficult to get to a single source as the market is so wide spread that investigating each of the illicit production will provide no inference. All these issues could be controlled to an extent if certain measures are taken. Foremost being developing and maintaining surveillance programs for monitoring drug trends and rapid NPSs identification. Implementing drug checking services, syringe exchange programs, self-consumption services, and other harm reduction strategies for people with opioid use disorder. Diagnosing opioid poisoning/overdose is always a task because the cutting agents introduced always mimic general toxin signs and symptoms which misleads to the prognosis of the same. There is difficulty in categorizing the symptoms peculiar to these pharmacologically active additives which has always related in lethality. Therefore, it has now become vital to monitor the distribution and production of the opioid market and get them under a roof and organize it in the manner which makes it easy to reach to its source.

Conclusion

The adulteration of opioid presents a significant public health and forensic challenge, contributing to increased overdose risks, unpredictable toxicity, and complication of law enforcements efforts. This review has highlighted the diverse range of adulterants found in illicit opioid, including fentanyl analogs, synthetic depressants like xylazine, and various cutting agents, each posing unique health hazards. Advancements in forensic detection methods, including chromatography, mass spectrometry, and rapid field-testing kits, have improved the ability to identify these adulterants. However, limitations in accessibility, regulatory frameworks, and real-time surveillance hinder comprehensive monitoring. Addressing opioid adulteration requires a multidisciplinary approach, integrating analytical science, public health policies, and harm reduction strategies. Moving forward, increased investment in real-time drug surveillance, forensic research, and harm reduction initiatives such as drug-checking programs and

public education will be crucial in mitigating the impact of opioid adulteration. Strengthening collaborations between healthcare professionals, forensic scientists, and policymakers can help develop effective responses to this ongoing crisis. By enhancing detection capabilities and implementing targeted public health interventions, we can work toward reducing the dangers associated with adulterated.

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