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Tramadol in seized drugs containing non-pharmaceutical fentanyl: Crime lab data from Ohio, USA

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Abstract

Introduction: Non-pharmaceutical fentanyl and related drugs (NPF) have contributed to increases in drug-related overdose mortality in the U.S. More data are needed to track the shifting composition of fentanyl-containing drug mixtures. The key aims of the study are to characterize the crime lab data from Montgomery County, Ohio on the increased cases of seized drugs containing mixtures of NPF and tramadol.

Methods: Crime lab data on seized drugs in Montgomery County, Ohio (2015 - 2020) were analyzed to extract information on cases that tested positive for NPF and tramadol. Descriptive statistics are provided to characterize NPF/tramadol mixtures in terms of the quantity, weight, form of the drug seized (powder, tablet, capsule, residue), and the types of fentanyl analogs and other drugs identified.

Results: In December 2017, the first case of NPF/tramadol mixture was identified in the amount of 0.2 g. Sub-sequently, cases containing NPF/tramadol increased significantly to 149 cases in 2018, 102 in 2019, and 134 in 2020. The total yearly amounts of seized NPF/tramadol mixtures increased to 373.27 g in 2018, 2,601.82 g in 2019, and 13,487.62 g in 2020. The majority (72.6%) of the cases were in powder form. There were 15 other drugs identified along with fentanyl with tramadol mixtures, including heroin (38.8%), 5.7% cocaine (5.7%), and methamphetamine (4.9%).

Conclusions: The addition of tramadol to NPF may be viewed as a harm mitigation strategy but contributes to the overall unpredictability of the illicit drug supply. According to Ohio legal statutes, identification of schedule IV drugs such as tramadol with fentanyl (schedule II) may

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Lance Ruhter: Writing – review & editing. **Matthew Juhascik:** Conceptualization, Data curation, Writing – review & editing. **Jennifer Watson:** Data curation, Writing – review & editing. **Kaylin Sweeney:** Writing – review & editing. **Raminta Daniulaityte:** Conceptualization, Supervision, Methodology, Writing – review & editing.

Supplementary materials

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provide a reduction in drug-related charges from a felony to a misdemeanor. More research is needed to characterize potential sources of tramadol in NPF-containing drugs.

Keywords

Tramadol; Fentanyl; Non-pharmaceutical fentanyl; Fentanyl analogs; Heroin; Crime lab data

Introduction

U.S. drug overdose mortality continued to rise in 2020, spiking to an unprecedented 91,799 drug-related overdose fatalities, over 30% increase from 2019 (Hedegaard et al., 2021). These increases are primarily driven by non-pharmaceutical fentanyl and related compounds (NPF) (Ciccarone, 2019; Hedegaard et al., 2021). Fentanyl is estimated to be approximately 30–50 times more potent than heroin, and about 50–100 times more potent than morphine (Ciccarone et al., 2017; Suzuki and El-Haddad, 2017). Changing composition of street drugs has profound impacts on overdose and other health-related risks, and there is a need for timely epidemiological monitoring to inform public health and harm reduction measures to help mitigate health-related risks (Pardo et al., 2019). Prior research has suggested that crime lab data on seized drugs have the potential to be used for improved early drug warning systems and near real-time assessment of shifting trends in illicit drug markets and local risk environments (Rosenblum et al., 2020). Prior studies have used crime lab data to characterize changing availability of heroin and NPF-containing drugs (Rosenblum et al., 2020; Zibbell et al., 2019) as well as trends in seized drug cases testing positive for both NPF and illicit stimulants (Park et al., 2021). In the context of the continuing increase in NPF-related mortality in the US, along with the growing availability of counterfeit drugs that mimic legitimate pharmaceutical drugs but may contain fentanyl and/or other drugs (Daniulaityte et al., 2022b; PSM, 2020), more research is needed to characterize the highly unpredictable illicit opioid supply in the U.S.

Tramadol, a first-of-its-class dual-action analgesic with the combined pharmacology of an opioid agonist and an uptake inhibitor of serotonin and norepinephrine, was originally synthesized in 1962 (World Health Organization, 2018). Considered a weak opioid, tramadol gained approval from the FDA as an unscheduled drug in 1995 but was later changed to a Schedule IV drug in 2014 (Miotto et al., 2017). Prior research conducted in the U.S. has shown that tramadol has significantly lower misuse potential than most other opioids (Cicero et al., 1999, 2005; Reines et al., 2020), although there are disparities in the bioavailability of tramadol's primary analgesic metabolite, O-desmethyltramadol (M1) based on CYP2DG phenotypes and drug interactions (Miotto et al., 2017; World Health Organization, 2018). Information about tramadol's presence in illicit drug supply has important implications for harm reduction and overdose prevention efforts. Prior research has noted that administration of naloxone in cases of tramadol-involved overdose, while working to reverse opioid-related respiratory depression, may increase the risk of seizures (Lagard et al., 2018).

The National Forensic Laboratory Information System (NFLIS) report indicates that tramadol drug cases submitted to state and local forensic laboratories increased nearly 400% between 2010 and 2019, whereas US tramadol prescriptions consistently declined, from 44.2

million in 2014 to 33.6 million in 2019. Furthermore, about 50% of all tramadol-containing cases in 2019 contained at least one other drug, with fentanyl present in 85% of those drug mixtures (Drug Enforcement Administration, 2020). However, standard data recording procedures used in the NFLIS database do not distinguish between seizures of a drug product consisting of a mix of two or more substances (i.e. NPF mixed with tramadol) and seizures of more than one drug product each consisting of a different substance (i.e. one container of NPF and a second container of tramadol); both cases would be recorded the same way and look indistinguishable in NFLIS data, whereas data from regional crime labs often do. In this study, we aim to characterize the occurrence of tramadol-positive cases in seized drugs testing positive for fentanyl and/or fentanyl analogs to help characterize changes in the illicit supply of non-pharmaceutical fentanyl and other illicit opioids in the U.S.

Our study uses data on drugs seized in Montgomery County, Ohio, which has experienced among the highest rates of NPF-related overdose mortality in the state and across the country (Centers for Disease Control and Prevention, 2020; Daniulaityte et al., 2019b; Kiang et al., 2019; Ohio Department of Health, 2020). Focusing on Ohio is important because NFLIS data also indicate that in 2019 Ohio had the highest number of tramadol reports across all 50 states (Drug Enforcement Administration, 2020). Overall, there is a limited understanding of intersections between tramadol and NPF-type drugs in the U.S., and our data will help fill this gap.

Methods

Data on seized drugs were obtained from the Montgomery County Coroner's Office/Miami Valley Regional Crime Lab (MVRCL). MVRCL drug chemistry section uses analytical instrumentation for the analysis of seized drugs submitted by law enforcement agencies in the region. This analysis is performed to determine if material taken from a suspect and/or location contains a controlled substance and thus whether charges should be filed against the suspect. The analysis consists of an indicator test and a confirmation test. The confirmation of a controlled substance is done using gas chromatography-mass spectrometry (GC–MS), Fourier transform infrared spectroscopy (FT-IR), gas chromatography-infrared spectroscopy (GC-IR), or a combination of these techniques.

This study used MVRCL data on seized drugs from Montgomery County, Ohio, and covers the time period from 2015 through 2020. Because no mixtures of NPF with tramadol were identified in 2015–2016, analysis of NPF/tramadol cases focuses on 4 years between 2017 and 2020. Data processing and analyses were conducted using IBM SPSS (version 27). Key drug variables/categories of interest were: tramadol, NPF, and heroin. NPF category included all cases that tested positive for fentanyl and/or fentanyl analog or other novel synthetic opioids. MVRCL data set does not differentiate between pharmaceutical versus non-pharmaceutical (illicitly produced) tramadol. Specific fentanyl analogs and other novel synthetic opioids that were identified in seized drugs during the specified time period by the MVRCL include carfentanil, acetyl fentanyl, furanyl fentanyl, acryl fentanyl, valerylfentanyl, fluoroisobutrylfentanyl, methoxyacetylfentanyl, crotonylfentanyl, cyclopropylfentanyl, U-47700, N-methyl norfentanyl, benzylfentanyl,

fluorofentanyl, butrylfentanyl, difluoro U-47700, ethyl U-47700, parafluoro furanyl fentanyl, 4-fluoroisobutrylfentanyl, and ANPP.

The MVRCL dataset includes free text entries to describe seized drug cases/products (e.g., “one plastic bag containing tan powder”; “nine gel capsules each containing tan chunky material”; “one cardboard slide box containing 8 white tablets marked "AN627"). These descriptions were classified and sorted to extract qualitative information on the form of the drug and create the following categories: 1) powder form, 2) capsule (capsule is a common way of packaging powder form drugs such as heroin for street-level sales and distribution), 3) residue, 4) syringe, 5) tablet.

To contextualize data on NPF/tramadol mixtures in comparison to other opioid presence in NPF-containing drugs, we also present data on NPF mixtures with heroin. There were no cases that tested positive for NPF and other commonly used pharmaceutical opioids such as oxycodone or hydrocodone.

First, yearly counts of tramadol only and tramadol with NPF cases were graphed for 2015–2020. Next, descriptive statistics were provided to characterize cases of NPF/tramadol mixtures for 2017–2020 in terms of the following characteristics: 1) a total number of cases identified each year, 2) weight (in grams) of seized NPF with tramadol cases, including total weight, mean weight per case, and frequencies in six distinct weight categories each year (the weights reported in the paper are total weight and not the weight of the active pharmaceutical ingredient); 3) other drugs identified in NPF with tramadol mixtures; 4) the form of the drugs seized (e.g., powder, capsule, residue, syringe, tablet).

Pearson chi-squared statistic was used to assess differences over time (e.g., comparing 2017 vs. 2018, 2018 vs. 2019, and 2019 vs. 2020) in the numbers of seized drugs testing positive for NPF/tramadol, and other drug combinations/characteristics. Fisher’s exact test was used when more than 20% of cells had an expected frequency of less than 5. A Kruskal-Wallis test was performed to assess the differences in median case weights (seizures with tramadol and NPF) over time.

Results

In 2015–2016, all tramadol positive drug submissions were tramadol-only cases (no NPF or other drug identified) (Fig. 1). In December 2017, the first mixture case of NPF with tramadol was identified (Fig. 1), containing 0.2 gs in a capsule form (Table 1). In the following three years, yearly counts of cases positive for NPF in combination with tramadol increased to 131 in 2018, 92 in 2019, and 124 in 2020 (Fig. 1). Tramadol in combination with NPF comprised 80.7% of all tramadol positive cases (data not shown in the table). Among all NPF positive cases, the prevalence of NPF with tramadol mixtures increased from 0.1% in 2017 to 8.7% in 2018 ($p<0.001$), declined slightly to 6.7% in 2018 ($p<0.05$), and increased to 13.2% in 2020 ($p<0.001$) (Table 1). For comparative purposes, Table 1 shows NPF mixtures with heroin, which increased from 23.% in 2017 to 30.7% in 2018 ($p<0.001$), but declined to 18.5% in 2020 ($p<0.001$). There were no NPF mixtures identified with oxycodone or hydrocodone during the analyzed time period.

The majority (over 60%) of all NPF/tramadol mixtures had less than 1 gram in weight (Table 1). However, drug cases containing larger amounts increased over time. For example, drug submissions weighing between 10 and 100 gs increased from 8 (6.1%) in 2018 to 15 (12.1%) in 2020. In 2020, there were two large seizures of NPF/tramadol mixtures, each in the amount of 6500 gs. Overall, the total weight of seized NPF/tramadol mixtures increased from 373.3 gs in 2018 to 13,487 gs in 2020 (Table 1). Since the data were skewed because of two large cases in 2020, we conducted a non-parametric Kruskal-Wallis test to assess the difference in median case weight for 2018, 2019, and 2020, and the differences were not statistically significant ($p = 0.797$).

NPF/tramadol mixtures were most commonly available in powder form, comprising 71.8% of the 348 drug submissions involving NPF/tramadol mixtures (Table 1) and 98.6% of the total weight seized (not shown in the table). The capsule drug form followed in prevalence, occurring in 69 (19.8%) of NPF/tramadol drug submission (Table 1) and 0.4% of total weight (of note, the capsule is a common way to package powder-form drugs for street-level sales). Over time, the prevalence of cases in powder-form increased from 63.4% in 2018 to 83.1% in 2020 ($p<0.01$), while cases in capsule form declined from 30.5% in 2018 to 11.3% in 2020 ($p<0.001$). It is important to note that only 2.9% of all NPF/tramadol cases were in tablet form.

Drug submissions that contained only fentanyl with tramadol (without other fentanyl analogs or other drugs) mixtures were the most commonly identified (180, 51.7%) (Table 1) with a total weight of 14,285.49 gs. However, their prevalence declined from 61.1% in 2018 to 43.5% in 2019 ($p<0.01$). Close to half of all NPF/tramadol mixtures, contained other drugs (besides fentanyl and tramadol), with a total of 15 other drugs identified. Heroin was the most commonly identified drug in NPF/tramadol mixtures (38.2%) (Table 1), with a total weight of 2126.9 gs. The presence of other drugs in NPF/tramadol mixtures increased over time. In 2018, heroin was the only other drug identified in fentanyl/tramadol mixtures, while between 2019 and 2020, increasing numbers of fentanyl/tramadol mixtures also contained other drugs, including cocaine (5.7%), methamphetamine (4.9%), and the fentanyl analog acetyl fentanyl (5.5%) (Table 1). In addition, a few instances of designer benzodiazepines (e.g., one case of etizolam, one case of flualprazolam) and three instances of 3-HO-PCE (designer phencyclidine analog) were identified in NPF/tramadol mixtures.

Discussion

Our data indicate an increased presence of NPF/tramadol mixtures in Montgomery County, Ohio. Nearly all NPF/tramadol cases were in powder (71.8%) or capsule (19.8%) form, and only 2.9% were in tablet form. Although our data are limited to one county in Ohio, they are consistent with prior NFLIS findings of increasing seized drug cases with co-occurring fentanyl and tramadol drug submissions (Drug Enforcement Administration, 2020). It is not clear if tramadol present in NPF/tramadol mixtures is linked to diversion from medical sources. Global data suggest increased trafficking of counterfeit, illicitly produced tramadol products in several regions in Asia, Africa, and Middle East (World Health Organization, 2018). Although there is limited information on illicitly produced, non-pharmaceutical tramadol presence in the U.S., given the increasing presence of illicitly produced synthetic

opioids (Pardo et al., 2019), it is possible that tramadol present in NPF/tramadol mixtures is sourced through illicit production. Overall, more research is needed to identify potential sources of tramadol in non-pharmaceutical fentanyl supply.

Qualitative data derived from our ongoing research with individuals who use NPF and other drugs in Montgomery County (Daniulaityte et al., 2019a, 2022a; Silverstein et al., 2021, 2019) also indicate the high unpredictability of NPF-type drugs that dominate local illicit opioid supply and are typically available in powder form. In the future, we will include questions to probe for a more detailed understanding of community knowledge and experiences with NPF/tramadol mixtures (e.g., cases when testing positive for tramadol but using NPF).

The reasons for the increased presence of fentanyl/tramadol mixtures are not clear but could be related to a few potential factors. First, according to Ohio law, the addition of tramadol to fentanyl could reduce drug-related sentencing from felony to misdemeanor. The Ohio Revised Code 2925.11 section (Legislative Service Commission, 2021) states that when fentanyl or a fentanyl-related compound is found combined with any schedule III, schedule IV, or Schedule V controlled substance that is not a fentanyl-related compound, the offender is not guilty of possession of a fentanyl-related compound and cannot be charged with possession of a fentanyl-related compound. They may only be charged with possession of the other controlled substance. This can reduce the legal system's ability to prosecute a case as a felony rather than a misdemeanor.

Second, the addition of tramadol to fentanyl-containing compounds might serve as a harm mitigation strategy. Prior studies have shown that some individuals who sell illicit drugs engage in a range of strategies to reduce overdose risks in their client population (Carroll et al., 2020; Kolla and Strike, 2020). The addition of weak-opioid tramadol could reduce the potency of fentanyl-containing drug mixtures and may be viewed as a strategy to mitigate overdose-related risks (Wang et al., 2013). On the other hand, use of tramadol for adulteration of street drugs may be motivated by attempts to increase profits, overcome production shortages or create drug mixtures with more desirable psychoactive properties (Browne et al., 2021). In addition, an increased presence of fentanyl/tramadol mixtures contributes to the unpredictability of illicit drug markets since persons who use drugs may find it more difficult to determine their dosing regimens when unknowingly exposed to less or more potent fentanyl drugs or mixtures (e.g., fentanyl alone versus fentanyl/tramadol mixtures versus fentanyl mixture with potent fentanyl analogs such as carfentanil or other drugs) (Daniulaityte et al., 2019a, 2022a). Increased tramadol exposures through the use of fentanyl/tramadol mixtures may pose additional risks of serotonin syndrome, especially in individuals who use other drugs such as antidepressants (Hassamal et al., 2018; Nakhaee et al., 2021). Persons who use illicit drugs often suffer from a number of comorbid mental health conditions and the use of antidepressant medication is common (e.g., over 20% of all unintentional overdose mortality cases in Montgomery County in 2020 tested positive for antidepressants) (Public Health Dayton and Montgomery County, 2021).

Information on the identification of tramadol in overdose mortality cases in the U.S. is limited since tramadol-positive cases are typically grouped under the broader pharmaceutical

opioid category (Mattson et al., 2018) or included in the synthetic opioid category along with fentanyl (Hedegaard et al., 2021). Our findings underscore the need for greater specificity in reporting opioid and other drug-related trends.

More research is needed to characterize the availability of fentanyl/tramadol mixtures in other states and in the context of local state laws regarding sentencing for fentanyl-containing mixtures. Additionally, some crime laboratory-seized drug sections may only issue a report containing the drug they detected with the highest schedule. This can lead to nationwide underreporting of drug combinations in which a Schedule I or II drug is detected (e.g., fentanyl), but the presence of tramadol (Schedule IV) is not reported. It is also important to reiterate that our data on NPF/tramadol weights offer insight into the quantity of products seized but not the total quantity of active ingredients in seized samples. Our data are also limited because they do not provide information on the concentrations of NPF, tramadol, and other drugs in analyzed drug submissions. In addition, it has been noted that data on seized drugs have inherent biases in characterization of drug supply since they are tied to differential community policing practices (Park et al., 2021). Overall, our findings emphasize the need for increased access to comprehensive harm reduction services, including strategically deployed community-based drug checking services and technologies (Pardo et al., 2019).

These findings have important practical implications for clinicians working with individuals who use illicit opioids and for epidemiologists tracking toxicology data to characterize opioid overdose-related trends. Given our data, clinicians should consider that tramadol-positive cases may indicate inadvertent exposures through the use of NPF-type drugs that also contained tramadol. In the analyses of overdose mortality data, tramadol-positive cases (that also contain NPF), if grouped along with other pharmaceutical opioids, could add to the overestimation of pharmaceutical opioid-related overdose mortality. Overall, our findings highlight the extreme unpredictability of illicit drug supply and suggest an urgent need for early drug warning systems to identify shifting trends in illicit drug supply, along with improved community access to advanced drug checking technologies and other harm reduction tools (Tupper et al., 2018; Wallace et al., 2020).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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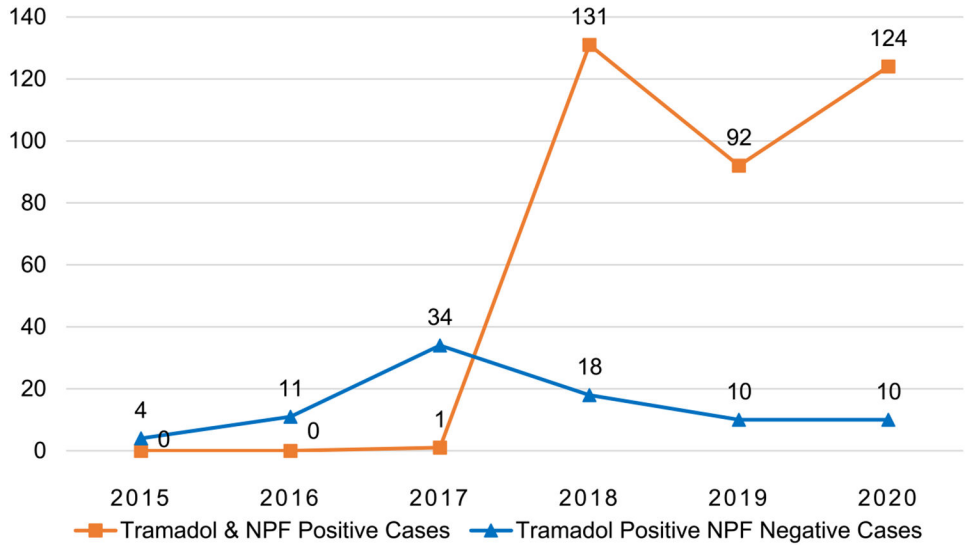

Fig. 1.

Numbers of seized drug cases testing positive for tramadol only and for tramadol in combination with fentanyl (NPF), Montgomery County, Ohio, 2015–2020.

Table 1

Characteristics of fentanyl, tramadol and other opioid mixtures seized in Montgomery County, Ohio, 2017- 2020.

Characteristics	2017 n (%)	2018 n (%)	2019 n (%)	2020 n (%)	All Years n (%)
NPF (fentanyl and/or analogs, novel synthetic opioids)[1]	1786 (100%)	1503 (100%)	1380 (100%)	945 (100%)	5614 (100%)
NPF and heroin	424 (23.7%)	461 (30.7%) ***	480 (34.8%) *	175 (18.5%) ***	1540 (27.4%)
NPF and tramadol	1 (0.1%)	131 (8.7%) ***	92 (6.7%) *	124 (13.1%) ***	348 (6.2%)
Weight of seized drugs containing NPF and tramadol mixtures in grams (n = 348)					
< 1 g	1 (100.0%)	86 (65.6%)	59 (64.1%)	78 (62.9%)	224 (64.4%)
1–9.99 g		30 (22.9%)	15 (16.3%)	25 (20.2%)	70 (20.1%)
10–99.99 g		8 (6.1%)	9 (9.8%)	15 (12.1%)	32 (9.2%)
100–999.99 g		1 (0.8%)	5 (5.4%)		6 (1.7%)
>1000 g				2 (1.6%)	2 (0.6%)
Unmeasured amount		6 (4.6%)	4 (4.3%)	4 (3.2%)	14 (4.0%)
Total weight (g)	0.2	373.3	2601.8	13,487.6	16,462.9
Average weight/case (g)	0.2	2.8	28.3	108.8	47.3
Other drugs in NPF and tramadol mixtures (n = 348)					
Fentanyl and tramadol only (no other drugs)	1 (100%)	80 (61.1%)	40 (43.5%) **	59 (47.6%) ^	180 (51.7%)
Heroin		51 (38.9)	47 (51.1%)	35 (28.2%)	133 (38.2%)
Cocaine			8 (8.7%)	12 (9.7%)	20 (5.7%)
Acetylfentanyl			4 (4.3%)	15 (12.1%)	19 (5.5%)
Methamphetamine				17 (13.7%)	17 (4.9%)
Valerylfentanyl			5 (5.4%)		5 (1.4%)
Ketamine			1 (1.1%)	4 (3.2%)	5 (1.4%)
3-HO-PCE				3 (2.4%)	3 (0.9%)
Pentobarbital			1 (1.1%)	1 (0.8%)	2 (0.6%)
Diclazepam				2 (1.6%)	2 (0.6%)
Fluorofentanyl				2 (1.6%)	2 (0.6%)
Etizolam			1 (1.1%)		1 (0.3%)
Flualprazolam			1 (1.1%)		1 (0.3%)
Metonitazene				1 (0.8%)	1 (0.3%)
Morphine				1 (0.8%)	1 (0.3%)

Characteristics	2017 n (%)	2018 n (%)	2019 n (%)	2020 n (%)	All Years n (%)
THC				1 (0.8%)	1 (0.3%)
Form of NPF/tramadol mixtures (n = 348)					
Powder		83 (63.4%)	64 (69.6%) *	103 (83.1%) ^^	250 (71.8%)
Capsules	1 (100.0%)	40 (30.5%)	14 (15.2%) **	14 (11.3%) ^^^	69 (19.8%)
Residue only		3 (2.3%)	3 (3.3%)	3 (2.4%)	9 (2.6%)
Syringes		4 (3.1%)	3 (3.3%)	3 (2.4%)	10 (2.9%)
Tablets		1 (0.8%)	8 (8.7%)	1 (0.8%)	10 (2.9%)

1 List of fentanyl analogs/other novel synthetic opioids: carfentanil, acetylfentanyl, furanylfentanyl, acrylfentanyl, valerylfentanyl, fluoroisobutrylfentanyl, methoxyacetylfentanyl, crotonylfentanyl, cyclopropylfentanyl, U-47700, N-methyl norfentanyl, benzylfentanyl, fluorofentany, butrylfentanyl, difluoro U-47700, ethyl U-47700, para-fluoro furanyl fentanyl, 4-fluoroisobutrylfentanyl, and ANPP.

* Indicates statistically significant difference compared to the prior year at p-value <0.05.

** Indicates statistically significant difference compared to the prior year at p-value <0.01.

*** Indicates statistically significant difference compared to the prior year at p-value <0.001.

^ Indicates statistically significant difference between 2020 and 2018 at p<0.05.

^^ Indicates statistically significant difference between 2020 and 2018 at p<0.01.

^^^ Indicates statistically significant difference between 2020 and 2018 at p<0.001.

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