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Fatalities Associated with Fentanyl and Co-administered Cocaine or Opiates

ABSTRACT: Fatalities associated with fentanyl hydrochloride are increasingly seen in Massachusetts. Between September 2005 and November 2006, 5009 medicolegal investigations associated 107 deaths with licit or illicit fentanyl use, along with a co-detection of an opiate/opioid or cocaine/benzoylecognine, or both. Deaths associated with illicit fentanyl use occur in younger people (39.4 vs. 61.5 years) with higher fentanyl (17.1 ng/mL vs. 4.4 ng/mL) and lower morphine (76.9 ng/mL vs. 284.2 ng/mL) postmortem blood concentrations, and more frequent cocaine co-intoxication (65% vs. 3%), than deaths associated with licit fentanyl use. A wide range of postmortem blood concentrations of fentanyl was detected (trace–280 ng/mL), with a minimum concentration of 7 ng/mL of fentanyl strongly associated with illicit use of fentanyl in poly-drug cases. The most commonly detected opiates/opioids in illicit fentanyl users were: morphine (29%), oxycodone (14.5%), and methadone (14.5%). Ethanol, cannabinoids, diazepam, citalopram, and diphenhydramine were each detected in greater than 10% of the illicit fentanyl cases. Most fentanyl abusers died at their own home and their deaths were most often classified as accidental. Mapping of primary residences of decedents revealed conspicuous clustering of the illicit fentanyl use cases, as opposed to the random pattern in licit use cases. Fentanyl misuse is a public health problem in Massachusetts.

KEYWORDS: forensic science, forensic toxicology, fentanyl, opiates, cocaine, drug abuse, overdose, fatality, autopsy

Fentanyl hydrochloride is a synthetic narcotic analgesic and Schedule II controlled substance used medically in the treatment of severe and chronic pain, as well as an anesthetic agent (1). Fentanyl is estimated to be 30–50 times more potent than heroin and appeals to drug abusers, often as a substitute to heroin. Several forms of fentanyl are available for abuse: diverted prescription products, in particular the transdermal delivery system (Duragesic® patch), the transmucosal formulation (Actiq®) and clandestinely manufactured substances.

A contemporary wave of fentanyl-related deaths commenced in February 2006, with overdoses and deaths reported in several U.S. cities including Chicago, Detroit, St. Louis, Pittsburgh, Philadelphia, and Camden, New Jersey (2). Exposure was largely due to the use of illicit drugs contaminated with fentanyl, particularly heroin heralding street names such as "Drop Dead," "Flatline," and "Lethal Injection" (2). A clandestine laboratory in Mexico was targeted as the possible production source, after ultra-purified fentanyl hydrochloride was confiscated in raids made by the Drug Enforcement Agency's Southwest Laboratory in southern California (3). Another illegal laboratory producing mixtures of ecstasy-type tablets containing, in part, fentanyl was discovered in Azuza, California (4).

Fentanyl deaths in Massachusetts were recently reported in the media (5); however, to our knowledge, this study is the first scholarly documentation of the growing fentanyl abuse problem facing the Commonwealth.

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There is a small body of literature available on fentanyl-related fatalities. A study (6) of medical examiner cases in southwestern Virginia identified 23 cases of fentanyl-related fatalities over a 3-year period, with femoral postmortem blood concentrations ranging from 2 to 48 ng/mL (mean = 18 ng/mL). Nineteen of the 23 fatalities were due to fentanyl misuse or abuse. An older study (7) in Maryland described 30 medical examiner cases with blood fentanyl concentrations ranging from 2.2 to 100 ng/mL. Another older study (8) of 112 fentanyl-related fatalities predominantly in California found relatively low blood fentanyl concentrations at 3.0 ± 3.1 ng/mL. Isenschmid (9) reported 118 deaths in the Detroit metropolitan area associated with fentanyl and co-administered cocaine and/or heroin, with femoral blood fentanyl concentrations ranging from 3 to 190 ng/mL. Another recent report (10) documented 112 deaths related to fentanyl abuse in Ontario over a 2-year period. The study ide6ntified 54 cases of death due to illicit fentanyl use with a mean blood fentanyl concentration of 35 ng/mL (range 30–383 ng/mL).

The current study describes medicolegal autopsy cases in which toxicological analyses of a decedent's postmortem blood specimen identified fentanyl concomitant to morphine, other opioids and/or cocaine metabolites. The study's aim is to characterize the historical and toxicological findings in drug overdose fatalities due to fentanyl co-administration with cocaine and opiates/opioids, and then compare with data from fatalities associated with incidental, licit fentanyl use.

Methods

Case Selection

All forensic autopsy cases referred by the Commonwealth of Massachusetts Office of The Chief Medical Examiner for toxicological analyses to the University of Massachusetts Memorial Medical

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Center (UMass) Forensic Toxicology Laboratory between September 2005 and November 2006 which detected fentanyl and either the concomitant detection of an opiate (e.g., morphine and 6-acetylmorphine [6-AM]), an opioid (e.g., methadone) and cocaine or benzyoylecgonine were prospectively selected for this study.

Toxicological Analyses

Multiple specimen types per autopsy case were submitted for analyses and include: heart blood, femoral blood, urine, vitreous humor, and other tissues and fluids. Postmortem toxicological analyses were performed at the UMass Forensic Toxicology Laboratory for each case. The laboratory's analytical scheme includes: presumptive 6 drug/drug class blood analysis by enzyme-linked immunosorbent assay (ELISA) (Venture Labs, Redwood City, CA) for benzodiazepines, cocaine, fentanyl, methadone, opiates, and oxycodone; presumptive 10 drug/drug class urine screening by enzyme multiplied immunoassay technique (EMIT® II Plus; Dade-Behring, Deerfield, IL) for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, 3,4-methylenedioxy-N-methylamphetamine (MDMA), methadone, opiates, phencyclidine, and propoxyphene; an alkaline extractable drug screen in blood by gas chromatography/mass spectrometry (GC/MS); and volatile analyses for methanol, ethanol, acetone, and isopropanol by headspace dual column GC/flame ionization detection. Confirmation and quantitation for morphine was performed by GC/MS-selected-ion monitoring using a deuterated internal standard following solid-phase extraction and derivatization with BSTFA [N, o-Bis (Trimethylsilyl) trifluoroacetamide] +1% TCMS (trimethylchlorosilane). The limit of detection for this method was 20 ng/mL. Cocaine and benzoylecgonine were confirmed and quantitated by a similar method and the limit of detection for both compounds was 20 ng/mL. All cases with presumptive positive fentanyl results, as identified by the ELISA blood screen (cut-off calibrator of 2 ng/mL), were subsequently referred for quantitative analysis to a national forensic toxicology reference laboratory (NMS Labs, Willow Grove, PA). The analysis was conducted by LC/MS/MS with limits of detection for fentanyl and norfentanyl of 0.2 and 0.4 ng/mL, respectively. The preferred analytical algorithm is presumptive screening in heart blood and confirmatory quantitative analyses in a single blood source, generally peripheral blood when available.

Case History Review

In cooperation with The Office of the Chief Medical Examiner (Boston, MA), the postmortem records for all cases meeting inclusion criteria were reviewed. The following information was extracted, as available, for each decedent: age, gender, town of residence, race, cause of death, manner of death, and other noteworthy circumstances describing the means by which the decedent obtained and utilized fentanyl, and if fentanyl was deemed to be contributory to death. Cases were categorized as to whether the use of fentanyl was apparently "licit," "illicit," or "indeterminate." "Licit" is defined as medically relevant fentanyl use as prescribed and monitored by a physician. "Illicit" is defined as fentanyl that is used without the knowledge of a physician, for the purposes of intoxication, illegally obtained, or used in a way that was inconsistent with its intended purpose whether prescribed or not (i.e., misused). The designation of cases to the "illicit" category was executed conservatively by design to assure inclusion of cases with unequivocal, objective evidence of "illicit" use. Cases which included doubt as to the intent of the use of fentanyl were categorized as "indeterminate." The "indeterminate" category includes cases that cannot be clearly separated into illicit or licit categories based on confounding factors or lack of available information.

Statistical Analyses

All descriptive and comparative statistics were performed with Microsoft® Excel 2000 (Microsoft Corporation, Redmond, WA). Comparative statistics consist of an unpaired, two-tailed Student's *t*-test. Significance is $p < 0.05$.

Results

The Commonwealth of Massachusetts Office of The Chief Medical Examiner investigated 5009 deaths between September 2005 and November 2006. Likewise, the UMass Forensic Toxicology Laboratory completed toxicological examinations for 4996 of these cases during the same time period. One hundred and seven cases (2.1%) included the detection of fentanyl with either an opiate/opioid or cocaine/benzoylecgonine. A male to female ratio of 2.2 is noted in Table 1 with a total of 74 males (69.2%) and 33

TABLE 1—*Characteristics of fatalities associated with illicit, licit, and indeterminate fentanyl use with co-administered cocaine and/or opiates.*

Usage Category	Illicit	Licit	Indeterminate
Total, *n*	55	26	26
Males, *n* (%)	37 (67)	19 (73)	18 (69)
Females, *n* (%)	18 (33)	7 (27)	8 (31)
Male:Female	2.1	2.7	2.3
Age in years (range)	39.4 (20–60)	61.5 (27–95)	39.9 (0.75–61)
[Fentanyl] in all blood sources, mean (range), (95% confidence interval)*	17.1 (0.44–57) [13.5–20.8]	4.4 (trace–17) [2.5–6.3]	30.1 (0.25–280) [4.7–55.6]
[Fentanyl] in femoral blood, *n* **mean** (range)*	19 **17.5** (1.5–54)	10 **6.32** (0.7–17)	7 **50.7** (2.7–280)
[Fentanyl] in heart blood, *n* **mean** (range)*	23 **18.3** (1.2–57)	14 **2.9** (0.5–5.8)	16 **24.5** (0.26–150)
Male [fentanyl] in all blood sources, mean (range)*	16.1 (1.2–54)	5.2 (trace–17)	19.6 (0.26–150)
Female [fentanyl] in all blood sources, mean (range)*	19.4 (0.44–57)	2.2 (0.5–5)	57.3 (0.48–280)
[Norfentanyl] in all blood sources, *n* **mean** (range)*	36 **6.25** (0.54–29)	11 **3.8** (0.58–16)	16 **8.57** (0.54–39)
Cocaine metabolite† positive cases, *n* (%)	36 (65)	3 (12)	17 (65)
Opiate/opioid‡ positive cases, *n* (%)	30 (55)	21 (81)	16 (62)
Cocaine metabolite† and opiate/opioid‡ positive cases, *n* (%)	14 (25)	1 (4)	7 (27)
[Morphine] in all blood sources, mean (range)†,§	76.9 (<20–251)	284.2 (23–>1000)	128.4 (<20–300)

*All concentrations are in ng/mL.
†Cocaine metabolite refers to cocaine, cocaethylene, and benzoylecgonine all of which indicate cocaine use.
‡Opiate/opioid refers to substances other than fentanyl.
§The morphine limits of quantitation are <20 ng/mL and >1000 ng/mL.

TABLE 2—*Co-administered substances identified in fatalities associated with illicit, licit, and indeterminate fentanyl use.*

	Illicit (n = 55)		Licit (n = 26)		Indeterminate (n = 26)	
	(n)	%	(n)	%	(n)	%
Opiates/opioids						
Morphine	16	29.1	17	65.4	8	30.8
Oxycodone	8	14.5	2	7.7	4	15.4
Methadone	8	14.5	2	7.7	2	7.7
Hydrocodone	2	3.6	0	0.0	2	7.7
Meperidine	2	3.6	0	0.0	0	0.0
Tramadol	2	3.6	0	0.0	0	0.0
6-Acetylmorphine	1	1.8	0	0.0	0	0.0
Propoxyphene	1	1.8	0	0.0	0	0.0
Hydromorphone	0	0.0	1	3.8	1	3.8
Codeine	0	0.0	0	0.0	0	0.0
Stimulants						
Cocaine and metabolites	36	65.5	3	11.5	17	65.4
Dextromethorphan	1	1.8	0	0.0	1	3.8
Amphetamine	0	0.0	0	0.0	1	3.8
Ephedrine	0	0.0	0	0.0	1	3.8
Intoxicants						
Ethanol	7	12.7	2	7.7	3	11.5
Delta-9-tetracannabinol	6	10.9	1	3.8	4	15.4
Benzodiazepines*						
Diazepam	8	14.5	0	0.0	3	11.5
Alprazolam	5	9.1	1	3.8	2	7.7
Clonazepam	3	5.5	0	0.0	0	0.0
Chlordiazepoxide	2	3.6	0	0.0	0	0.0
Psychotropic Agents*						
Citalopram	11	20	1	3.8	2	7.7
Amitryptiline	5	9.1	2	7.7	3	11.5
Mirtazapine	5	9.1	1	3.8	2	7.7
Doxepin	4	7.3	0	0.0	0	0.0
Paroxetine	2	3.6	1	3.8	2	7.7
Trazodone	2	3.6	0	0.0	1	3.8
Olanzapine	1	1.8	1	3.8	0	0.0
Venlafaxine	1	1.8	0	0.0	0	0.0
Risperidone	1	1.8	0	0.0	0	0.0
Meprobamate	1	1.8	0	0.0	0	0.0
Other*						
Diphenhydramine	5	9.1	1	3.8	1	3.8
Lidocaine	1	1.8	8	30.8	3	11.5
Atracurium metabolites	1	1.8	2	7.7	0	0.0
Promethazine	1	1.8	0	0.0	2	7.7
Gabapentin	1	1.8	0	0.0	1	3.8
Doxylamine	1	1.8	0	0.0	0	0.0
Carbamazepine	1	1.8	0	0.0	0	0.0
Dicyclomine	1	1.8	0	0.0	0	0.0

*Includes all substances that were identified in individuals with illicit fentanyl use, but not all substances identified in the licit or indeterminate categories.

females (30.8%). Quantitative analyses were performed in femoral blood for 36 cases and in heart blood for 33 cases. The source of blood was unspecified in the remaining 18 cases. The concomitant detection of cocaine is noted in 56 cases (52.3%), with three additional cases demonstrating positive cocaine/cocaine metabolite results in urine by EMIT® II Plus only. Opiates and opioids were identified in 67 (62.6%) of the fentanyl cases (Table 2). Racial identification was available in 78 cases with 96.2% (n = 75) of the decedents Caucasian (which may include Hispanic ethnicity). The remaining three decedents were of African-Caribbean descent.

Illicit Fentanyl Use

From Table 1, illicit fentanyl use was identified in 55 cases (51.4%) with a male to female ratio of 2.1 and an average age of

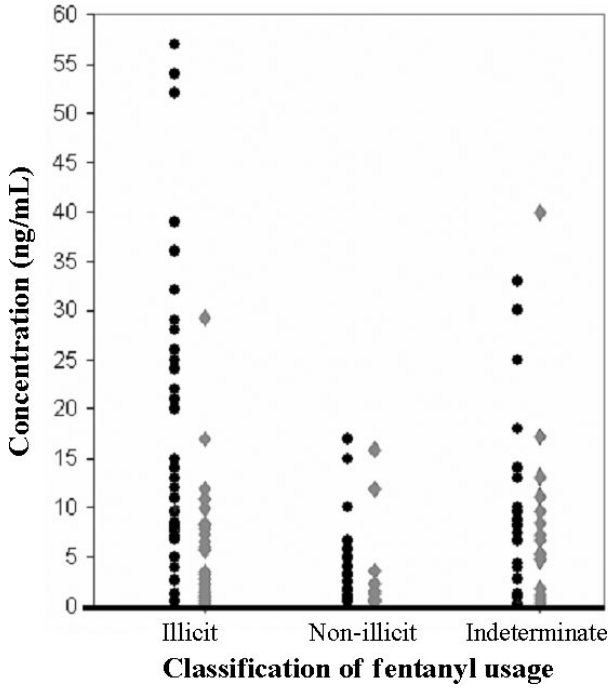

FIG. 1—*Fentanyl and norfentanyl concentrations (ng/mL) in illicit, licit, and indeterminate fentanyl-associated fatalities. Fentanyl concentrations are indicated by (●). Norfentanyl concentrations are indicated by (◆). Each marking indicates a single case. (Note: Fentanyl concentrations of 280, 93, and 150 ng/mL are omitted from the "indeterminate" category in order to present the rest of the data on a similar scale.) Postmortem blood concentrations of fentanyl greater than 7 ng/mL tend to be associated with illicit use of fentanyl, whereas 95% of licit-use cases have blood concentrations less than 7 ng/mL.*

39.4 years. The average fentanyl concentration in all blood specimens was 17.1 ng/mL (95% confidence interval [CI] = 13.5–20.8 ng/mL), with no difference (p = 0.3994) found between men and women. In comparing the mean fentanyl concentration from cases where heart blood (n = 23) was used for quantitation versus cases where femoral blood (n = 19) was used, no detectable difference was found (p = 0.8579). Norfentanyl was identified in 36 cases (65.5%) and had an average concentration of 6.25 ng/mL (Fig. 1).

Cocaine metabolites were present in 36 (65.5%) and opiates/opioids in 30 (54.5%) of these cases (Fig. 2). The most common co-detected opiates/opioids were morphine (29.1%), methadone (14.6%), and oxycodone (14.6%). 6-AM was present in one case (Table 2).

In 38 (69.1%) illicit use cases, acute intoxication with fentanyl, either alone (n = 4) or in combination with other drugs (n = 34), was specifically recorded by a Massachusetts medical examiner as a cause of death. The concentrations of fentanyl in the four cases where fentanyl was exclusively considered the cause of death were 8.6, 13, 36, and 28 ng/mL, with only the latter case having a significant level (benzoylecgonine concentration in heart blood of 710 ng/mL) of co-administered drugs present. In 25 cases (45.5%), cocaine was mentioned alone (n = 2) or in combination with other drugs (including fentanyl in 20 cases) as a cause of death.

The manner of death was accidental for the majority (78.2%) of cases (see Table 3). The home residences of the decedents who illicitly co-administered fentanyl with either cocaine or opiates/opioids tended to cluster in certain geographical regions within Massachusetts (Fig. 3). In 34 cases (61.2%), the decedents were discovered at their home by significant others, including

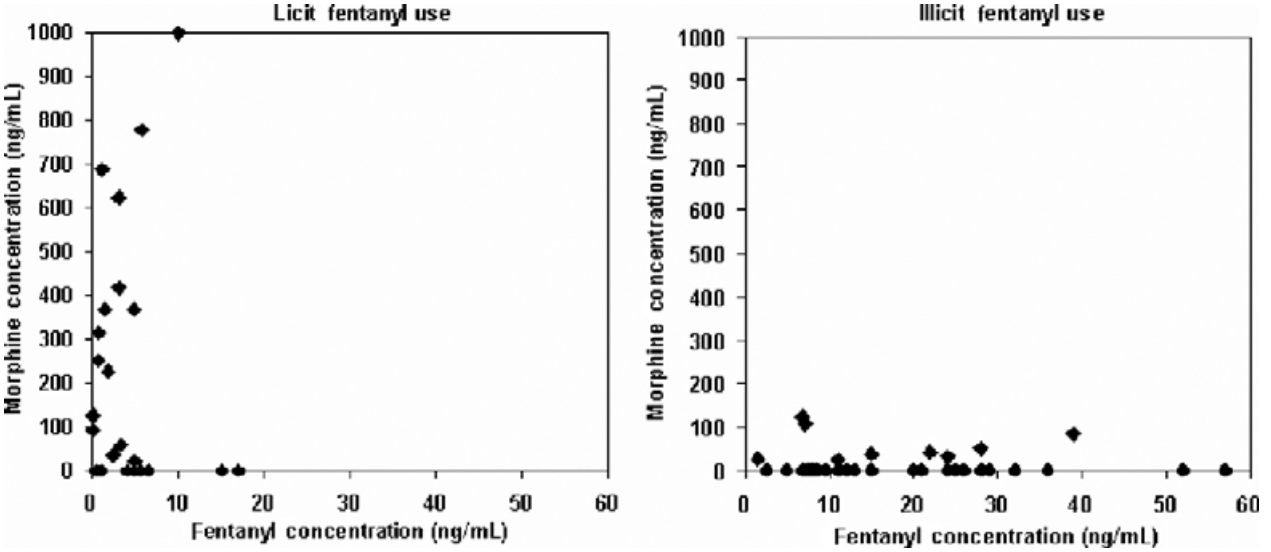

FIG. 2—*Fentanyl concentration versus morphine concentration in cases of licit and illicit fentanyl use. Decedents who used fentanyl licitly have a comparatively higher blood concentration of morphine and lower blood concentration of fentanyl when compared with illicit fentanyl users.*

TABLE 3—*Place of death, manner of death, and identification of drug paraphernalia at the scene of fentanyl-associated fatalities.*

	Illicit (n = 55)		Licit (n = 26)		Indeterminate (n = 26)	
	n	%	*n*	%	*n*	%
Place of death						
Primary residence	34	61.8	4	15.4	3	11.5
Home of acquaintance	6	10.9	0	0	0	0
Hospital or institution	7	12.7	22	84.6	7	26.9
Commercial property	6	10.9	0	0	0	0
Manner of death*						
Accident	43	78.2	16	61.5	3	11.5
Undetermined	2	3.6	0	0	1	3.8
Natural	1[†]	1.8	8	30.8	2	7.7
Suicide	0	0	1	3.8	2	7.7
Homicide	0	0	1	3.8	1	3.8
Drug paraphernalia at death scene	20	36.4	0	0	0	0

*The manner of death is determined by a Massachusetts medical examiner.

[†]The cause of death was ''chronic substance abuse.''

Only cases with available data are represented on this chart, so percentages will not add up to 100%.

parents in 10 cases, romantic partners in nine cases, offspring in two cases, siblings in three cases, and a friend, a neighbor, and a spouse in one case each. In six cases (10.9%), the decedent died at a friend's house. In six other cases, decedents were found in commercial properties including two cemeteries, bathrooms at a gas station, and an office building, a unit within a storage facility, and in a truck in a parking lot. Five people died in a hospital and two at a residential facility. Evidence of drugs or drug paraphernalia was identified in 20 cases (36.4%), with definitive evidence of acute intravenous drug abuse (e.g., syringes/needles/tourniquets at scene) in seven cases and acute fentanyl administration in seven cases. Identifiable methods of fentanyl administration included: oral ingestion (n = 4) either by licking or chewing the contents of prescription fentanyl patches, smoking patch contents (n = 1), skin application of patch (n = 1), and identification of a tube containing fentanyl for unclear use found in a decedent's mouth (n = 1). Drug paraphernalia was identified in one instance in relation to a death at a friend's house, with the majority of paraphernalia identified either when the decedent died at home (n = 13) or on commercial property (n = 4).

Licit Fentanyl Use

Licit fentanyl use was identified in 26 cases with a male to female ratio of 2.7 and an average age of 61.5 years (Table 1). In contrast to illicit users of fentanyl, women (average = 80.8 years) who used fentanyl for licit purposes were significantly older than men (average = 55.4 years) who also licitly used fentanyl (p = 0.0005). The average fentanyl concentration for all blood collection sites was 4.40 ng/mL (95% CI = 2.5–6.3 ng/mL) with no statistical difference (p = 0.1483) found between men and women. There was no difference detected between the mean fentanyl concentration obtained from cases in which heart (n = 14) versus femoral (n = 10) blood was analyzed (p = 0.0718). Norfentanyl was identified in 11 cases (42.3%) with an average concentration of 3.84 ng/mL (Fig. 1).

Cocaine metabolites were present in three (11.5%) and opiates/opioids were present in 21 (80.8%) of these cases (Table 1). From Table 2, the most common co-detected opiate/opioid was morphine (65.4%). Methadone and oxycodone were present in two cases each.

Licit fentanyl use cases had a significantly higher average decedent age (p = <0.0001), lower fentanyl concentrations (p = <0.0001), and greater average morphine concentrations (284.2 ng/mL vs. 76.9 ng/mL; p = 0.0020) than illicit cases (see Fig. 2).

The causes of death varied, but essentially encompassed acute fatal traumatic injury in 12 cases and critical or iatrogenic medical problems (including metastatic cancer, therapy- or surgery-associated deterioration, sepsis due to various cause, etc.) in 13 cases. Eight of these were considered a natural manner of death. From Table 3, the most prevalent manner of death was accidental. Fentanyl was physician prescribed and apparently appropriately used in all cases. In two cases, including one of the cocaine metabolite (benzoylecgonine only, 506 ng/mL) positive cases and another

FIG. 3—*Geographic distribution of fatalities associated with illicit, licit, and indeterminate fentanyl use co-administered with cocaine and/or opiates. There is marked clustering of illicit fentanyl use cases (◆) The licit fentanyl use cases (■) have a random, "shot-gun" pattern, with limited clustering. The indeterminate fentanyl use cases (●) tend to co-segregate with the illicit use cases.*

with high methadone levels (1315 ng/mL in heart blood) and benzodiazepine immunoreactivity, fentanyl patches appeared to be licitly used as prescribed for severe back pain. These cases were associated with 5.6 and 1 ng/mL heart blood fentanyl concentrations, respectively. Drug use was however considered contributory to death in only in the latter case, apparently due to the high methadone level. The other two cases that were positive for cocaine metabolites included a gunshot wound victim with bowel perforation and a motor vehicle accident victim who driving under the influence of cocaine and ethanol. Both decedents were brought immediately to the hospital where they were treated with fentanyl and succumbed quickly, accounting for the postmortem detectability of cocaine metabolites. In most cases of licit fentanyl use, decedents died in a hospital. The places of geographical residence for licit fentanyl users portray a random "shot-gun" pattern, with very little clustering when compared with the illicit or indeterminate fentanyl users (Fig. 3).

Indeterminate Fentanyl Use

In order to maintain the integrity of the "illicit" category, fentanyl cases were liberally deemed "indeterminate" with regard to the appropriateness of use, and 26 cases (24.3%) were categorized as such. The male to female ratio for indeterminate users is 2.3 with an average age of 39.9 years (Table 1). The average fentanyl concentration in all blood specimens was 30.1 ng/mL (95% CI = 4.7–55.6) with no significant difference ($p = 0.1738$) identified between men and women ($p = 0.1738$) or anatomical source ($p = 0.3938$). Norfentanyl was identified in 16 cases (61.5%) and had an average concentration of 8.57 ng/mL (Fig. 1).

Cocaine metabolites were present in 17 (65.4%) and opiates/opioids were present in 16 (61.5%) of these cases (Table 1). From Table 2, the most common co-detected opiates/opioids were morphine (30.8%) and oxycodone (15.4%).

Indeterminate cases were not significantly different from illicit cases in terms of decedent age ($p = 0.8463$), fentanyl concentrations ($p = 0.1410$), and morphine concentrations ($p = 0.2138$). Indeterminate cases trended toward significantly greater fentanyl concentrations ($p = 0.0517$) and significantly lower morphine concentrations ($p = 0.0609$), but did have significantly lower decedent age ($p < 0.0001$) when compared with licit cases (Table 1). While inconclusive, it is tempting to speculate that the indeterminate group parallels more closely to the illicit group, particularly in view of the high prevalence of cocaine co-administration in this group.

Of the 26 indeterminate cases, ultimate disposition is known in only nine cases (see Table 3). The cause of death was traumatic injury in four cases, and myocardial infarction, sepsis due to chronic drug abuse, and overmedication with fentanyl by hospital staff in a patient with terminal metastatic cancer in one case each. In two cases, the cause of death was acute intoxication with multiple substances including fentanyl and cocaine, however as fentanyl had been prescribed, it was unclear as to whether or not the drug was being abused. The concentration of fentanyl in both of these cases was very high (25 and 30 ng/mL). The primary geographical residences for indeterminate fentanyl users tended to cluster in the same regions as illicit users (Fig. 3).

Discussion

Opiate and opioid abuse is a major health problem in the United States, with an incidence of 2.4 million new addictions reported in 2004 alone (11). Unintentional opiate analgesic poisoning deaths in particular have been on the rise, increasing 129.2% from 1999 to 2002, with an absolute number of 5528 reported cases, based on *International Classification of Diseases, Ninth Edition* death certificate coding (12). Fentanyl and its synthetic analogs as recreational drugs have drifted in and out of vogue since the 1970s, with both prescription product diversion and clandestine laboratory production responsible for reports of misuse and abuse (6–8,10,13–18). Co-administration of opiates and cocaine has been a long recognized drug abuse pattern (19) and is particularly prevalent in this study cohort, with 65% of illicit fentanyl users also positive for cocaine or cocaine metabolites.

Our study characterizes the historical and toxicological findings in fatalities in Massachusetts associated with fentanyl used together with either cocaine or opiates/opioids from September 2005 and November 2006. Illicit and indeterminate fentanyl-associated deaths show marked geographic residential clustering in Massachusetts, compared with the random dispersion seen in licit use. We show that illicit fentanyl use occurred in younger people with higher

fentanyl and lower morphine postmortem blood concentrations, and more frequent cocaine co-intoxication, than fentanyl deaths associated with licit use. Like other studies, we also identified a wide range of blood concentrations (trace detected to 280 ng/mL) in postmortem samples with detectable fentanyl. This may reflect variable opioid tolerances of drug users, the dose and route of administration of use, and finally, co-intoxication with other central nervous system depressant drugs such as ethanol and benzodiazepines or cases of poly-drug toxicity. However, we have also shown that cases with licit fentanyl use have postmortem blood concentrations with a fairly narrow 95% CI of 2.5–6.3 ng/mL, and these values may reflect the high end of the therapeutic concentration of fentanyl. Only eight of the 55 illicit use cases had fentanyl concentrations below 6.3 ng/mL. The recommended antemortem therapeutic serum concentration of fentanyl is 1–2 ng/mL for analgesia and 10–20 ng/mL for surgical anesthesia and severe respiratory depression. Cases where fentanyl was deemed by a medical examiner as the exclusive cause of death had a minimum fentanyl concentration of 8.6 ng/mL, although this value is limited by the fact that it was not a single-agent fentanyl death. With acknowledgment that our study does not attempt to prove causation in regards to cause of death, our work cautiously associates a postmortem blood fentanyl concentration of ~7 ng/mL or greater with fatality in illicit use poly-drug cases.

One important issue to consider is that screening for fentanyl in medicolegal autopsy cases is not the norm in many toxicology laboratories. Martin et al. (10) acknowledge that their lab did not routinely test for fentanyl; therefore, in cases in which fentanyl was not initially suspected the drug may have eluded detection. We minimize this possibility by using an ELISA technique for fentanyl (cut-off 2 ng/mL) during initial screening of blood for drugs of abuse on each medical examiner case submitted for toxicological analyses. This strategy has enabled the identification of many more fentanyl positive cases than a case-history directed analysis would have allowed.

A note about the drug paraphernalia is also warranted. Presence of drug paraphernalia seems particularly indicative of the category of fentanyl use, and was exclusively identified on the scene of illicit users. Interestingly, drug paraphernalia was only rarely found when decedents died at the residence of an acquaintance versus in their own home or on commercial property, perhaps suggesting staging of the death scene. Special attention is warranted for properly documenting and securing drug paraphernalia which is found at a death scene. Likewise, the presence of fentanyl transdermal patches on or about the body also becomes an important item of physical evidence.

Our work has its limitations. Due to our data archiving system and collection methods, we do not know the number of deaths associated with fentanyl use, which do not include co-administered morphine and/or cocaine, but may be present in the pool of cases from which we retrieved our sample population. Also since 6-AM is relatively short-lived in blood, we do not know the number of deaths, in which morphine was detected, that actually are associated with heroin use. We identified just one case in which 6-AM was detected in blood. It seems prudent to include analysis of a second matrix (e.g., urine or vitreous humor) when attempting to detect this diagnostic chemical fingerprint for heroin.

Conclusion

This study suggests fatal fentanyl co-administration with opiates/opioids and/or cocaine to be prevalent in the Commonwealth of Massachusetts. A postmortem blood concentration exceeding 7 ng/mL is often associated with illicit fentanyl use regardless of poly-drug intoxication in our experience. Toxicologists and medical examiners must be alert to the possibility of fentanyl abuse as contributory to death; particularly as many laboratories do not employ a reliable means to detect fentanyl in routine postmortem toxicology screening procedures. In generalizing our experience, laboratories not routinely screening for the drug are quite likely overlooking possible fentanyl-related causes of death.

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