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Characterizing fentanyl-related overdoses and implications for overdose response: Findings from a rapid ethnographic study in Vancouver, Canada

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Abstract

Background: North America is experiencing an opioid overdose epidemic, fuelled by the proliferation of fentanyl, related analogues, and fentanyl-adulterated opioids. British Columbia, Canada has similarly experienced a rapid increase in the proportion of opioid overdose deaths associated with fentanyl. This study builds off of research characterizing fentanyl exposure to further explore the presentation of fentanyl use and related overdoses among people who use drugs.

Methods: From December 2016 to April 2017, rapid ethnographic fieldwork was conducted in Vancouver, Canada to examine the implementation of low-threshold overdose prevention sites, where people use drugs under the supervision of staff and peers trained to respond to overdose. Data collection included 185 hours of ethnographic observation and in-depth interviews with 72 people who inject drugs, 44 of whom reported experiencing an overdose in the year prior to the interviews.

Results: While most participants had experienced previous opioid-related overdose, they characterized how fentanyl was markedly distinct in terms of: potency, and rapid onset. Ethnographic observations and participant narratives highlighted how fentanyl use and related overdoses had implications for frontline response, including: rapid onset, multiple concurrent overdoses, body and chest rigidity, and the need to administer larger doses of naloxone.

Conclusions: Participant narratives, and observational data documented distinct symptoms for fentanyl-attributed overdoses compared to other opioid related overdose events, which had

implications for response. Findings may serve to inform best practices in responding to fentanylrelated overdoses including; the provision of oxygen and effective doses of naloxone, and also considerations regarding overdose identification.

Keywords

Fentanyl; Overdose; Opioids; Qualitative; Ethnographic

1. INTRODUCTION

North America is experiencing an opioid overdose crisis (Dart et al., 2015), which has in part been driven by changes to the illicit opioid supply, involving the proliferation of illicitly-manufactured fentanyl, related analogues, and fentanyl-adulterated opioids (Gladden, 2016; Rudd et al., 2016; Suzuki and El-Haddad, 2017). Fentanyl, is a synthetic opioid, and is the main component of over twenty analogues and by volume approximately 80–100 times more potent than morphine (Burns et al., 2016) and 30–50 times more potent than heroin (Ciccarone, 2017). Because fentanyl can be produced reliably and transported in smaller volumes, it has been sold as counterfeit prescription medications, and it has replaced or is being combined with heroin in illicit drug markets (Fairbairn et al., 2017; Gladden, 2016). Fentanyl is highly and persistently lipophilic, leading to faster onset of effects, while also exiting the central nervous system rapidly, therefore it is rapid-acting, but short-lasting (Fairbairn et al., 2017). This in combination with high potency, increases risk of overdose, addiction, and withdrawal symptoms (Suzuki and El-Haddad, 2017). In 2016, synthetic opioids (other than methadone) became the leading cause of overdose death in the United States, contributing to 6.2 deaths per 100,000 persons and doubling from 2015 (Hedegaard, 2017). Illicitly manufactured fentanyl has been primarly responsible for this increase, in ten reporting states fentanyl was detected in 56.3% of the 5,152 overdoses between July-December 2016 (O'Donnell, 2017). In Canada, fentanyl and related analogues were present in 72% of the approximately 7000 overdose deaths occurring in 2016 and 2017 (Public Health Agency of Canada, 2018).

People who regularly inject heroin are often exposed to fentanyl (Carroll et al., 2017; Macmadu et al., 2017), with one study finding that weekly heroin use was associated with known or suspected fentanyl exposure in the previous year (Hayashi et al., 2018). Recent research suggests that the heroin supply is increasingly adulterated, resulting in significant changes with regards to how this drug is experienced by people who use drugs (PWUD) (Mars et al., 2018). Ciccarone et al. (2017) have identified new heroin typologies, including 'pure heroin' and fentanyl-adulterated heroin, based on the experiences PWUD and have characterized the latter as more potent and associated with increased overdose risks (Ciccarone et al., 2017). However, increasing variability in the evolving supply means that some individuals may be unable to discern fentanyl-adulteration (Amlani et al., 2015; Kenney et al., 2018). Research suggests that the fentanyl-adulteration does result in different intoxication effects in comparison heroin, including: intensity of onset, duration of action, increased overdose risk, and other embodied effects (Carroll et al., 2017; Ciccarone, 2017; Ciccarone et al., 2017; Macmadu et al., 2017; Mars et al., 2018; Miller et al., 2017;

Somerville, 2017). As a result, fentanyl-adulteration has implications for overdose response in terms of rapid progression, and atypical physical symptoms (Somerville, 2017).

Utilizing qualitative and ethnographic methodologies, this study contributes to a growing body of research focused on fentanyl-adulteration to examine how illicit fentanyl affects the experience and presentation of overdoses, and examines implications for overdose response in Vancouver, British Columbia (BC), Canada. As in other parts of North America, fentanyl and fentanyl-adulterated drugs have driven a rapid increase in overdoses in BC. In 2017, the province experienced 1399 opioid related overdoses, with fentanyl detected in approximately 83% of overdose deaths (Public Health Agency of Canada, 2018). Following the declaration of a public health emergency in BC in April 2016, overdose-focused interventions have been implemented or scaled-up across the province, including low-threshold supervised consumption facilities, termed Overdose Prevention Sites (OPS). OPS are low-threshold spaces in which people can inject and, in some cases, smoke drugs under the supervision of staff and volunteers trained to respond to overdoses. While central to the emerging overdose response in the province, OPS are also unique settings to undertake research to gain insights into the presentation of and response to fentanyl-related overdoses.

2. METHODS

Rapid ethnographic fieldwork was undertaken in Vancouver's Downtown Eastside neighbourhood between December 2016 and April 2017 to explore the overdose epidemic and the implementation of OPS. Rapid ethnography involves highly focused ethnographic fieldwork, including observation and interviews, harnessing researchers' familiarity with a specific context to gather data from participants within a rapid timeframe (Handwerker, 2001). This technique has often been employed to understand dynamics of public health emergencies (Johnson and Vindrola-Padros, 2017). This study harnessed the infrastructure and partnerships of our established program of qualitative and community-based research in the Downtown Eastside. Ethical approval was obtained from the Providence Health Care / University of British Columbia Research Ethics Board.

Data collection included approximately 185 hours of participant observation at five OPS, which also included unstructured conversations with PWUD accessing these sites, as well as site operators (peer workers and other staff members, volunteers). Ethnographic fieldwork included direct observation of injecting spaces within OPS, as well as the wider environment (e.g., entranceways, drop-in spaces). The ethnographers (JB, RM) attempted to remain unobtrusive when directly observing injecting spaces to limit impacts on OPS operations, and the majority of informal conversations with PWUD and site operators occurring in adjacent spaces. This approach allowed for nuanced and heterogeneous witnessing of the OPS environments, including direct observation of suspected fentanyl-related overdoses, and facilitated follow-up conversations about specific dynamics with PWUD.

Participants were also recruited for in-depth qualitative interviews directly from OPS both during ethnographic field work by a research team member and through outreach by two peer researchers (e.g., people with lived experience using drugs). All individuals who were accessing OPS and able to provide informed consent were eligible to participate. We also

sought to recruit a heterogenous sample of participants based on age, gender, and ethnicity, among other characteristics. Participants were interviewed on-site at an OPS or at a research office by one of six research team members with experience and training in qualitative interviewing. An interview guide was used which included questions and probes on a range of topics related to the overdose epidemic, including experiences and perceptions related to overdose and fentanyl use. Interviews were approximately 45–60 minutes in length, audio recorded and transcribed by externally-contracted transcriptionists, and participants each received a \$30 CAD honorarium after their interview.

In-depth interviews were conducted with seventy-two people who use drugs, 44 of whom reported experiencing an overdose in the last year prior to interview. The characteristics of the sub-sample of respondents who reported overdose in the last year are presented in Table 1. Research team members who participated in data collection engaged in the codevelopment of a comprehensive data code book in order to capture emergent themes and sub-themes. Data analysis focused on the experiences of individuals who had overdosed, all of whom had also responded to or witnessed suspected fentanyl overdoses. Interview transcripts were imported into NVivo, a qualitative data analysis software program, and analyzed using deductive and inductive approaches. Concepts of structural vulnerability were employed during analysis in order to better understand the larger socio-structural factors shaping participants experiences with fentanyl and overdose (Quesada et al., 2011). Relevant ethnographic data was triangulated with interview data, in order to further examine and contextualize specific experiences (e.g., overdose presentations).

3. RESULTS

3.1 Fentanyl Use Experiences and Fentanyl-related Overdose

3.1.1 Noticing differences in illicit opioids—Participants who had overdosed in the last year and who regularly injected opioids reported exposure to fentanyl-adulterated opioids, and commonly noted that the entirety of the illicit opioid supply was "contaminated". Participants contrasted their experiences of using fentanyl adulterated heroin with their previous experiences using illicit heroin and prescription opioids (e.g., hydromorphone, oxycodone). Characterizations of experiences using fentanyl-adulterated drugs emphasized the immediate recognition that something was "different" in comparison to illicit heroin or prescription opioids due to both overall, and fluctuations in, drug potency. In describing this experience 'Jennifer' explained:

As soon as I did it, I realized it. I felt this taste in my mouth and just a feeling I'd never felt before. It was almost like I knew something was gonna happen [i.e., an overdose] (White transgender woman, Age 47).

These experiences led participants to seek methods to discern fentanyl adulteration in illicit opioids, such as inspecting these drugs for atypical characteristics (e.g. color, odour and taste), and sharing this information through peer networks. As 'Nicole' described: "[If] it smells a bit vinegary or it smells like a certain way...If you smoke it and you get instant high like instead of like a gradual, then you know that it might have more fentanyl in it" (Indigenous woman, age 35). 'Paul' further explained:

I can tell by tasting it and feeling it, and if I smell it, because heroin and cocaine have certain smells to it and certain taste and your body reacts to it. Same as [fentanyl], start feeling nauseous and like throwing up, that one got fentanyl in it and my body don't like it. (Indigenous man, Age 55)

Some participants subsequently enacted behavioral overdose prevention strategies, in addition to accessing OPS, when using suspected fentanyl-adulterated opioids, such as injecting or smoking small amounts of opioids first to determine their potency, or cutting doses with stimulants in order to use less opioids (e.g. methamphetamines). As described by, 'Teresa': "I always, always do testers [injecting a small amount]. After I do my tester, then I'll mix the rest up according to how strong it is" (Indigenous woman, age 55). However, because such drug characteristics were inconsistent over time due to changes within the illicit drug supply, participants expressed that these measures were often insufficient in identifying and negating the effects of fentanyl-adulterated drugs.

3.1.2 Potency—Descriptions of fentanyl and fentanyl-adulterated opioids centered on their potency relative to heroin and other prescription opioids. While many participants who were regular or long-term heroin injectors reported high opioid tolerance, they recognized that fentanyl was significantly more potent than other opioids that they were accustomed to. Participants commonly described the potency of fentanyl and fentanyl-adulterated opioids as 'stronger' and 'more intense', directly linking these drugs to overdose deaths. The potency of fentanyl and fentanyl-adulterated opioids was further associated with a 'loss of control' directly linked to overdose events. 'Teresa', a 55-year-old Indigenous woman, noted: "I know that it's really strong and it's not something that I think I could be able to control, so I prefer not to get it". Other participants reported that fentanyl and fentanyl-adulterated opioids made them less able to control their drug use because the potency and rapid onset led to more pronounced withdrawal symptoms. 'Amy' explained:

Heroin, it comes on slow. It stays with you for hours and hours and hours, and then it comes down slow. So, we have lots of time to know that you're going to be sick, so you can get better. Fentanyl goes bam, stays with you for a little, but maybe an hour, maybe a tiny bit more, and then you are full on sick as a dog, like you haven't used at all. (White woman, age 47)

Despite concerns relating to a loss of control associated with overdose or the management of withdrawal symptoms, participants reported challenges in acquiring non-adulterated opioids through the illicit drug market and noted that fentanyl was 'put into everything'. Furthermore, the rapid acting, but short-lasting effects of fentanyl had implications for some participants in terms of increasing the frequency with which they needed to acquire and use drugs. Participants noted that, while stronger, fentanyl-adulterated products did not last as long as they needed, and as a result they needed to use more often.

3.1.3 Characterization of fentanyl-related overdoses—Among participants, the potency of fentanyl and fentanyl-adulterated opioids had direct implications for their overdose experiences. Similar to other participants, 'Brianna' described the uncharacteristically small amount of fentanyl used in comparison to heroin and prescription opioids when overdosing: "It was probably 'cause I only bought a 10 paper [0.1 gram] and I

usually do like 3 times a 10 paper; like 3 ten papers at a time" (Indigenous woman, Age 21). Further, participants reporting fentanyl-related overdoses described them as sudden and unexpected due to drug's immediate onset and potency. 'Brian' explained:

With heroin, you feel it coming on, you feel the intensity. You feel like you're going to puke, you know, because it keeps coming and you know I'm going to go down [overdose]. Fentanyl, you're sitting there waiting for something and, the next thing you know, there is an ambulance attendant there. It hits you like a Mac truck. You don't feel it, nothing. It's just boom, down. You get up and you swear that you didn't even do your shot, and you're looking for it. (White man, age 23)

This rapid loss of consciousness was commonly described by our participants and observed at the OPS and contrasted the more gradual overdose progression associated with heroin and prescription opioid overdoses.

3.2 Reponses to Fentanyl-related Overdoses and Associated Implications

- Responding to rapid and multiple overdoses—While all overdoses were successfully attended to during observation, participant accounts and observational data revealed that the rapid onset of fentanyl-related overdoses posed challenges for overdose response. As overdoses commonly occurred within 'moments' of injecting based on observations at OPS and participant accounts, there were specific challenges in anticipating, identifying, and responding to overdoses. Throughout our fieldwork, PWUD and OPS workers emphasized the need to be diligent when observing people injecting drugs and closely monitor them for signs of overdose (e.g., non-responsiveness, blue-gray lips, decreased respiration, and hypoxia in OPS with monitors). Because OPS workers had less time to respond to fentanyl-related overdoses due to their rapid onset, these workers regularly checked on people immediately after they injected and again every few minutes. Further, we observed OPS workers intervening when someone appeared severely intoxicated immediately after injecting (e.g., pinching their shoulders, checking oxygen levels) and, as necessary, quickly administering naloxone or oxygen. We observed that overdoses often occurred simultaneously among people injecting opioids in the OPS when they had purchased drugs from the same sources, when highly adulterated opioids were being sold in the neighborhood, and during peak periods of community drug use (e.g., following the disbursement of social assistance). As a result, overdoses occurred in rapid succession which placed considerable demands on OPS workers. In these situations, all OPS workers on site had to respond to multiple concurrent overdoses, with some OPS workers responding to one overdose and then moving on to assist with another overdose, in some cases non-OPS workers who were onsite also assisted in responding.
- **3.2.2 Body and Chest Rigidity**—Responses to fentanyl-related overdose by OPS staff were further complicated by unique overdose presentations that included chest and bodily rigidity, and posed challenges to the identification of and response to overdoses. This rigidity was reported by some participants in relation to fentanyl-related overdoses, as well as observed during our ethnographic fieldwork at OPS. As described by Brianna when recounting her sister's recent overdose experience, "She was like rigid when they like got to her." The associated body rigidity negatively impacted the ability of observers to identify

overdoses, as these fentanyl-related overdose presentations differed from heroin and prescription opioid-related overdose presentations that they had previously witnessed. Throughout our observational fieldwork it was observed that some individuals did not slouch when overdosing, as is typically observed with overdose events involving other opioids, but rather remained rigid and upright. As a result, participants overdosing in this manner needed to be closely monitored in order to correctly identify and appropriately respond to overdose onset. Moreover, while airway ventilation is an important component of overdose responses, jaw and chest wall rigidity sometimes compromised the ability of OPS workers to effectively provide rescue breathing and/or administer oxygen.

3.2.3 Implications for Naloxone Administration—During our fieldwork and during interviews with participants, we documented that multiple doses of naloxone were often required to reverse fentanyl-related overdoses, sometimes up to 4–6 ampoules (0.4 mg). Similar reports were provided by participants who had witnessed such overdose events. Front line providers at OPS and participants felt that this amount exceeded the 1–2 ampoules (0.4 mg) normally required for heroin-related overdoses. As noted by 'Michael' (Indigenous man, age 53) who responded to an overdose, "I had to hit him like three times with naloxone, three caps. And then the paramedics finally showed up, and they hit him again". Participants also reported confusion in the timing of naloxone administration and the amount administered. 'Michael' further explained:

I got that first shot into him. I got the second one ready. I was about almost ready to give him the second shot, because with fentanyl you've got to give them like five or six shots to bring them back. No, the paramedics and the fire department showed up and pushed me out of the way, prevented me from giving him that second shot. And they waited ten minutes before they gave him the first shot.

Given that people were regularly administering naloxone in the community, participants adapted to this need by regularly securing multiple naloxone kits, extra ampoules, carrying pre-loaded naloxone syringes, and distributing naloxone supplies to others in the community. As expressed by 'Amanda' (White woman, age 37):

I used to carry four or five [...] Because there was that many being used. While somebody would be running over, "I need a kit, I need a kit," you know, they'd take off with it and there goes one of my kits.

Participants were able to access these supplies and accompanying training from a variety of community organizations and health clinics in the area. Widespread training opportunities and naloxone distribution for frontline workers and for the public was perceived favourably by participants and readily accessed. At the same time, participants sometimes expressed concern that large doses of naloxone were administered too rapidly when individuals could have possibly been revived with stimulation (e.g. rubbing sternum, pinching shoulders) or oxygen. These concerns stemmed from the fact that naloxone administration could precipitate opioid withdrawal symptoms, which participants struggled to manage within the context of poverty and drug criminalization. Aaron (White man, age 38) explained:

From what I hear it puts you into instant acute withdrawal, like instantly. I don't want that. [...] No. I work hard to get my fix and unless I'm fucking blue in the

face and I'm not breathing at all, don't fucking think about touching me with naloxone.

This is further emphasized by other participants, who reported that after having undergone an overdose and subsequent reversal using naloxone, they needed to use drugs immediately after in order to alleviate painful withdrawal symptoms.

4. DISCUSSION AND CONCLUSION

4.1 Discussion

In summary, our findings demonstrate that fentanyl and fentanyl-adulterated drugs result in overdose presentations that pose unique implications for overdose response. Aligned with recent studies characterizing the experiences of PWUD and fentanyl use (Carroll et al., 2017; Ciccarone et al., 2017; Macmadu et al., 2017; Mars et al., 2018; Miller et al., 2017; Somerville, 2017) participants in this study similarly characterized fentanyl-related use and associated overdoses as distinct with regards to potency, and rapid onset (Somerville, 2017). Furthermore, while all overdoses witnessed as part of this study were successfully attended to, fentanyl-related overdoses posed particular considerations for frontline response, including identification of overdoses, muscle and chest wall rigidity, rescue breathing and the provision of oxygen, and the rapid administration of effective doses of naloxone.

In characterizing the presentation of fentanyl-related overdoses, our findings regarding overdose-related body and chest wall rigidity are supported by research indicating that the rapid intravenous administration of fentanyl can produce skeletal muscle rigidity that is not related to dose (Burns et al., 2016; Streisand et al., 1993). Findings regarding potency and rapid onset of overdoses in community settings are also further supported by research findings indicating that, when used intravenously, fentanyl can cause life-threatening respiratory depression within two minutes (Green and Gilbert, 2016). The present study extends on this research by demonstrating that atypical overdose characteristics, such as muscle rigidity and multiple concurrent overdoses, may contribute to increased overdose severity by impeding the ability of witnesses and responders to accurately identify and/or effectively respond to overdose events. These findings may have implications for further OPS operations planning (e.g. staffing models, physical space, etc.), and also indicate that responsive information sharing regarding overdose signs and symptoms should be supported in order to better equip PWUD and responders with the knowledge necessary to identify and quickly respond to fentanyl-related overdoses.

Central to the overdose crisis has been the implementation and scale-up of naloxone training and kit distribution in community settings, which has proven to be highly effective in reducing overdose-related mortality (Fairbairn et al., 2017; Irvine et al., 2018). While underscoring the need for the continued expansion of these programs, our findings further indicate that diligent observation of persons at risk of overdose, and the rapid administration of naloxone and provision of oxygen are integral components of overdose response. Further, the amount of naloxone contained in these kits might need to be increased to ensure that responders can successfully reverse fentanyl-related overdoses and respond to the simultaneous occurrence of multiple overdoses. In addition to our study, several case

investigations (Schumann et al., 2008; Tomassoni et al., 2017), and review article (Rzasa Lynn and Galinkin, 2018) have also reported higher than normal doses of naloxone as being necessary to reverse fentanyl-related overdoses. Collectively, this body of research demonstrates an urgent need for more comprehensive studies to determine optimal naloxone dosing and routes of administration (e.g., injectable, intranasal) for overdoses stemming from fentanyl, fentanyl-related analogues, and fentanyl-adulterated drugs. Additionally, as naloxone administration may precipitate opioid withdrawal, there is an urgent need to develop post-overdose support strategies to respond to the experiences of PWUD and implement these in community settings, particularly those most impacted by fentanyl-adulterated drugs.

Finally, although an extensive body of literature has demonstrated the effectiveness of supervised injection services in reducing drug-related risks and harms (Kennedy et al., 2017; McNeil and Small, 2014), including overdose mortality (Marshall et al., 2011), less attention has been paid to their potential role in drug surveillance and monitoring amidst the ongoing proliferation of fentanyl, fentanyl-related analogues, and fentanyl-adulterated drugs. These findings demonstrate that overdose prevention sites can facilitate the real-time identification of changes to illicit drug markets, accompanying changes in drug use behaviors and outcomes (e.g., overdose presentations), and inform the development of recommendations to optimize interventions to ensure responsiveness to the evolving overdose crisis (e.g., increased number of ampoules of naloxone in kits). As such, supervised injection services should be pursued to ensure the real-time surveillance and monitoring of illicit drug markets, implemented alongside complementary interventions (e.g., fentanyl drug-checking), and further linked to overdose warning systems to facilitate rapid information sharing to affected communities. This is the case even in settings that have yet to see the proliferation of fentanyl, fentanyl-related analogues, and fentanyl-adulterated drugs, as these interventions are uniquely positioned to serve as 'early warning systems'. However, in order to reduce the occurrence of overdoses from the outset, additional efforts will be necessary, including the expansion of evidence-based treatment (e.g., opioid agonist therapies) and measures to facilitate access to unadulterated drugs (e.g., legalization and regulation).

This study has several limitations, it relies on direct observation and self-reported data of suspected fentanyl-related overdoses, but triangulation with fentanyl drug-checking services and laboratory testing was not possible. However, recent reports have documented that the majority of people using illicit opioids in Vancouver have been exposed to fentanyl based on drug urine screening (Jones et al., 2018). This research was also undertaken in a setting with an evolving illicit drug supply, including drugs adulterated with fentanyl-related analogues (e.g., carfentanil) and it was not possible to determine whether specific adulterants produce distinct overdose presentations. Further, this study focused on the experiences of PWUD accessing OPS in Vancouver, BC and thus may not be generalizable beyond the population studied. Additional research focusing on the experiences and perspectives of OPS operators, and overdose first responders will be critical in more robustly characterizing overdose presentation, and optimizing response.

4.2 Conclusion

As illicit fentanyl has become a primary driver of North America's overdose crisis, it may be resulting in atypical overdose presentations that have implications for frontline overdose response. There is likely a need to implement and scale-up interventions (e.g., supervised injection services, evidence-based treatment) to prevent and respond to overdoses, while also adapting these interventions to address new challenges posed by fentanyl and an increasingly adulterated drug supply.

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Table 1:

Participant Characteristics

Participant characteristics	n (%) N=44
Age Mean Range	42 years 20–68 years
Gender Men Women Transgender, two-spirit, or non-binary	17 (39%) 25 (57%) 2 (4%)
Race White Indigenous Other	20 (46%) 21 (48%) 3 (7%)
Overdose in last 30 days (Prior to interview) Yes	15 (34%)
Overdose in last year (Prior to interview) 1 overdose 2 overdoses 3 or more overdoses	15 (34%) 10 (23%) 19 (43%)
Drug used during overdose ^a Cocaine Crystal Methamphetamine Heroin Fentanyl Other opioids Other	2 (5%) 1 (2%) 37 (84%) 15 (34%) 2 (5%) 1 (2%)
Overdose on fentanyl or fentanyl-adulterated drug Yes No Not sure	33 (75%) 9 (20.5%) 2 (4.5%)
Naloxone Administration Family Member or friend Peer Social Services Worker Paramedic Nurse Other (e.g. stranger)	9 (21%) 10 (23%) 9 (21%) 16 (36%) 3 (7%) 10 (23%)

^aParticipants could report more than one drug.

 $b_{\mbox{\footnotesize Participants}}$ could report multiple administrations of nalox one.