HHS Public Access

Author manuscript

*Int J Drug Policy*. Author manuscript; available in PMC 2021 October 15.

Published in final edited form as:

*Int J Drug Policy*. ; 79: 102751. doi:10.1016/j.drugpo.2020.102751.

# Opioid overdose reversals using naloxone in New York City by people who use opioids: Implications for public health and overdose harm reduction approaches from a qualitative study

**Stephen Parkin**[a,†], **Joanne Neale**[a,b], **Caral Brown**[a], **Aimee N. C. Campbell**[c], **Felipe Castillo**[c], **Jermaine D. Jones**[c], **John Strang**[a,d,*], **Sandra D. Comer**[c,*]

[a]National Addiction Centre, King's College London, 4 Windsor Walk, Denmark Hill, SE5 8BB, United Kingdom

[b]Centre for Social Research in Health, University of New South Wales, Sydney, NSW 2052, Australia

[c]Division on Substance Use Disorders, Columbia University Medical Center and New York State Psychiatric Institute, 1051 Riverside Drive, Unit 20, New York, NY 10032, United States

[d]South London and Maudsley NHS Foundation Trust, Maudsley Hospital, London, SE5 8AZ

## Abstract

**Background—**Adverse reactions to naloxone, such as withdrawal symptoms and aggression, are widely recognised in the literature by pharmaceutical manufacturers and clinical practitioners as standard reactions of individuals who are physically dependent upon opioid drugs following the reversal of potentially fatal opioid overdose. This paper seeks to provide a differentiated view on reactions to naloxone that may have important implications for public health and harm reduction approaches.

**Methods—**Analyses from a qualitative investigation embedded within a 5-year Randomized Controlled Trial (RCT) examined the risks and benefits of Overdose Education and Naloxone Distribution (OEND) training models (brief or extended training) in various populations of people who use opioids in New York City. The qualitative experiences (obtained through semi-structured interviews) of 46 people who use opioids and who were each involved in the delivery of naloxone,

† Corresponding author (stephen.parkin@kcl.ac.uk).
* Co-last authors

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

**Stephen Parkin:** Conceptualization, Methodology, Data Curation, Formal Analysis, Writing – original draft
**Joanne Neale:** Conceptualization (of study), Methodology, Formal Analysis, Data Curation Writing – review and editing, Supervision
**Caral Brown:** Software, Writing – review and editing
**Aimee N. C. Campbell:** Writing – review and editing
**Felipe Castillo:** Writing – review and editing
**Jermaine D. Jones:** Conceptualization (of study), Data Collection – Interviewer, Writing – review and editing
**John Strang:** Conceptualization (of study), Formal Analysis, Writing – review and editing, Supervision
**Sandra D. Comer:** Conceptualization (of study), Writing – review and editing

S.P., C.B., A.N.C.C., F.C., and J.D.J. have no disclosures of interest to report.

during 56 separate overdose events that occurred throughout 2016–2018, were studied. Situational analysis and inductive content analysis of interview data focused upon overdose reversals in an attempt to provide understandings of the various adverse effects associated with naloxone from their perspective. These analyses were supplemented by data sessions within the research team during which the findings obtained from situational analysis and inductive content analysis were reviewed and complemented by deductive (clinical) appraisals of the various physical and psychological effects associated with the overdose reversals.

**Results—**People who use opioids recognise three distinct and interconnected outcomes that may follow a successful opioid overdose reversal after intramuscular or intranasal administration of naloxone. These outcomes are here termed, i) 'rage' (describing a wide range of angry, hostile and/or aggressive outbursts), ii) 'withdrawal symptoms,' and iii) 'not rage, not withdrawal' (i.e., a wide range of short-lived, 'harmless' conditions (such as temporary amnesia, mild emotional outbursts, or physical discomfort) that do not include rage or withdrawal symptoms).

**Conclusion—**Physical and psychological reactions to naloxone should not be understood exclusively as a consequence of acute, opioid-related, withdrawal symptoms. The three distinct and interconnected reversal outcomes identified in this study are considered from a harm reduction policy perspective and are further framed by concepts associated with 'mediated toxicity' (i.e. harm triggered by medicine). The overall conclusion is that harm reduction training programmes that are aligned to the policy and practice of take home naloxone may be strengthened by including awareness and training in how to best respond to 'rage' associated with overdose reversal following naloxone administration by people who use opioids and other laypersons.

### Keywords

take home naloxone; opioid overdose reversal; naloxone effects; opioid withdrawal symptoms; rage; mediated toxicity; harm reduction

## Introduction

The public health and harm reduction impact of the opioid antagonist naloxone in reversing overdoses in out-of-hospital emergencies is undisputed (EMCDDA 2016). In the last decade, naloxone availability in community settings has expanded internationally, partially in response to the 'triple wave epidemic' (prescription opioid analgesics, heroin, and illicitly manufactured fentanyl) and the exponential growth in international overdose crises and opioid-related mortality (Ciccarone 2019, Collins et al 2019). This global expansion of community-centred naloxone programmes also coincides with a World Health Organization (WHO, 2014) recommendation that: 'people likely to witness an opioid overdose should have access to naloxone and be instructed in its administration to enable them to use it for the emergency management of suspected opioid overdose' (WHO, 2014, 12).

Harm reduction initiatives are increasingly incorporating 'take-home naloxone' (THN) (Strang et al 1996, 2019, Williams et al 2014) and provide people who use drugs, their significant others, and/or their peer networks with the necessary training and knowledge for administering the naloxone in response to suspected opioid overdose events. The various successes attached to THN have been well-documented (Clark et al 2014, Dettmer et al

2001, Giglio et al 2015, Klebacher et al 2017, McDonald and Strang 2016, Minozzi et al 2015). However, layperson participation in THN initiatives are not without risk as there is the expectation that THN participants will enact *clinical* knowledge of overdose during emergencies and possibly encounter adverse reactions experienced by the naloxone recipient post-reversal. These adverse reactions typically relate to various physiological, psychological, and psychosocial outcomes associated with opioid withdrawal symptoms. These risks and expectations are perhaps further evident when one considers the way in which these known and established reactions to naloxone have been shaped through the discourse of science and medicine.

For example, focusing on the pharmacology of naloxone, Wermeling (2015) provides summaries of naloxone safety profiles obtained from package inserts provided by pharmaceutical companies in the US, with particular focus upon a product by Hospira. The insert refers to assorted ‘adverse effects after naloxone in reversal of opioid depression’ and ‘opioid acute withdrawal syndrome symptoms’ where the latter provides a comprehensive summary of physiological conditions and psychiatric responses associated with naloxone. Similarly, Adapt Pharma (2017) documents assorted ‘adverse reactions’ in a prescribing information leaflet for Narcan® Nasal Spray (a trade name for naloxone). These reactions are listed, somewhat generically, as symptoms of ‘severe opioid withdrawal’ and include aches, nausea, vomiting, anxiety and shivering. In addition, prescribing information further stresses that ‘abrupt reversal’ of an opioid overdose may result in ‘aggressive behavior’ (Adapt Pharma 2017, 7). A wide range of adverse reactions associated with the pharmacokinetics of naloxone are therefore recognised and described by pharmaceutical companies, and typically reported in terms of acute withdrawal symptoms in which aggressive behaviour may result from ‘abrupt’ reversals (i.e. too much naloxone and/or provided too quickly).

Authors writing for medical journals also often describe reactions to naloxone in terms of acute opioid withdrawal symptoms. Accordingly, episodes of ‘aggressive’, ‘violent’ and ‘combative’ behaviour following naloxone administration are regarded as correlates of opioid withdrawal (Belz et al 2006, Gaddis and Watson 1992, Osterwalder 1996) and adverse events are typically explained by the naloxone technology (dose and delivery systems) involved in the opioid reversal when conducted (almost exclusively) by emergency medical teams (EMT). From this position, intravenous (IV) delivery of higher doses of naloxone have been associated with ‘rude awakenings’ (Horowitz 1998), the precipitation of acute withdrawal symptoms and angry/violent patients. Alternative guidance from this field suggest that ‘slower awakenings,’ or gradual reversal from an opioid overdose, brought about by other naloxone technology (intramuscular (IM) or subcutaneous (SQ) injections), may minimise the rapid onset of withdrawal symptoms and diminish intense responses (Buajordet et al 2004, Horowitz 1998, Wanger et al 1998). For example, Wermeling (2015) states that intranasal (IN) naloxone produces a ‘milder reversal’ (due to slower absorption rates in which withdrawal effects are less severe and potential aggression is reduced), and also provides the pharmacokinetic data to support this assertion.

Related to the above, Buajordet and colleagues’ (2004) observational study of paramedics’ use of injectable naloxone during the late 1990s sought to determine the frequency and

characterisation of adverse events in out-of-hospital settings in Oslo, Norway. This work perhaps represents the first known attempt to classify the range of adverse effects of injected naloxone in a quantitative format. For example, out of 1192 overdose reversals, they report that 33% were characterised by 'withdrawal symptoms' (which included episodes of 'aggression'); 32% were characterised by 'confusion and restlessness' (and explained as an associated aspect of the withdrawal effect *or* as a consequence of polydrug use) and 25% were characterised by 'headaches / seizures' (explained as possible outcomes of hypoxia). Similarly, Avetiana and colleagues' (2018) survey of community-based organisations' distribution of naloxone (USA) provides a more recent categorical summary of observed events associated with nasal spray formulations of THN. More specifically, they note that the most frequently observed effects after reversal were 'withdrawal symptoms', 'nausea, vomiting or gagging/retching', and 'irritability or anger'. Additionally, 'confusion' was observed in only a single case from 261 opioid overdose reversals involving naloxone nasal spray. These similarities and differences in the assorted construction of outcomes within these two studies is made more remarkable as heroin was documented as the primary opioid involved in over 90% of overdose events in each study.

Further perspectives are situated within the *Social Sciences*, in which accounts of naloxone reactions are further constructed by assorted social theories, research methods, data sources, and epistemological perspectives. For example, Neale's (1999) ethnographic study of overdose and resuscitations within emergency settings in Scotland identified a wide range of negative perceptions about naloxone held by people who use drugs. This 'negative image' was premised upon a shared belief (amongst people who use drugs) that naloxone induced acute withdrawal symptoms and also explained aggression directed towards medical staff. For some, naloxone was also regarded as a form of punishment used to deter continued use of heroin (Neale and Strang 2015). However, the range of negative views of naloxone were also found, in part, to be socially constructed by the respondent group, who typically had varying degrees of knowledge and experience of naloxone. Nevertheless, subsequent re-analysis of the same ethnographic data (Neale and Strang 2015) identified naloxone-related 'over-antagonism' (over use of naloxone) as an example of iatrogenic harm (i.e. harm caused by medicine and/or medical intervention), due to the need to counter withdrawal symptoms (perceived to have been precipitated by naloxone) with further episodes of opiate use. Related to this debate is Faulkner-Gurstein's (2017) sociological critique of harm reduction policy and practice in North America and who further contributes to the discourse of naloxone in stating, 'a high dose of naloxone strips the body of opiates, which is *the functional equivalent of throwing a dependent user into sudden and violent withdrawal*' (p22, emphasis added).

Farrugia et al (2019) present sociological work from Australia that focuses upon violence arising from naloxone administration. The authors remark that such aggression 'tends to receive a passing mention rather than close attention' (2019, p1) by social scientists. Their analysis of post-reversal conflict provides a demonstration of Bruno Latour's theoretical concept of 'affordance' (involving the relationship between technology and humankind) in which they conclude that '*withdrawal and associated conflict* … can be greatly mediated by local relations and forces, such as careful titration, assurances, communication and care' (ibid, p8, emphasis added). In short, they appear to *maintain* the various views noted above

that violence or aggression by naloxone recipients are correlates of opioid withdrawal symptoms despite adding that conflict is an outcome that may be mitigated through the communication skills of the naloxone administrator.

Accordingly, and as with other medicines (e.g. Clarke and Montini 1993), scientific understandings of naloxone (including its various technologies and associated reactions) are informed from multiple positions within the arenas of addiction science, substance use research and associated policy and practice. As such, these heterogeneous positions have established multiple meanings associated with naloxone, and are perspectives that typically prioritise the 'situated knowledges' (Clarke and Montini 1993, Haraway 1991) of the relevant disciplines and backgrounds within the field.

The current article seeks to examine the situated knowledges and the social constructions of naloxone outcome from an arena largely understated in the literature to date; namely, from the perspectives of people who use opioids who have experience of using naloxone technology during their management of overdose events. In addition, this article focuses upon their recollections of any adverse effects that followed their administration of naloxone. This approach therefore seeks to unpack the lived experiences of overdose management from a qualitative perspective and in a way that cannot necessarily be achieved by using quantitative measures (similar to those described above). This approach to the study of naloxone provides a new contribution to understandings of overdose management and associated harm reduction approaches to the international opioid crisis.

## The Study

This qualitative study was part of a 5-year randomised trial (National Institute of Health [NIH]/National Institute on Drug Abuse [NIDA] Grant R01DA035207), conducted in New York City (NYC), which examined the risks and benefits of different Overdose Education and Naloxone Distribution (OEND) training models (brief or extended training) in various populations of people who use opioids (for more details on the larger trial see e.g., Jones et al., 2017). Brief overdose prevention training is common practice in NYC, and addresses overdose risk factors, how to recognise an opioid overdose and how to use naloxone (duration of training ~20 min). Extended training within this study comprised the aforementioned brief training plus a 2-hour session that reinforced basic training topic areas and additional components designed to increase knowledge, skills, attention, self-efficacy, optimism, and altruism (i.e., providing aid to others) (Glanz et al, 2008). Individuals, aged 21 to 65 years, who had met DSM-IV-TR[1] (American Psychiatric Association 2000) criteria for opioid use disorder within the past 6 months (regardless of current treatment status, and who were in otherwise good health) were eligible for the study. Major exclusion criteria were active psychiatric disorder that might interfere with participation, and training in overdose prevention, cardiopulmonary resuscitation, or Basic Cardiac Life Support within the past 2 years. The purpose of the latter criterion was to ensure that only people without specific prior (medical) knowledge relevant to overdose management were enrolled.

[1]The Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) is a clinical tool used for psychiatric diagnoses, published by the American Psychiatric Association.

Between September 2014 and October 2019, a total of 403 participants were enrolled, and 228 completed overdose prevention training and received THN, and participated in periodic assessments over 12 months (1, 3, 6, and 12 months following training). All participants had the option of receiving intramuscular (IM) or intranasal (IN) naloxone with their overdose response kits. All naloxone rescue kits, regardless of formulation, included two doses of naloxone plus a pair of latex gloves, a face shield for rescue breathing, alcohol prep pads, and an instructional handout. For their initial rescue kit, which participants received after training, 77.7% chose IN naloxone, and 22.3% chose IM naloxone. Over the course of the 1-year follow-up, 90 participants received a second kit because they had either used the naloxone in an overdose reversal or damaged or lost their initial kit. Eleven participants changed their initial choice of type of naloxone; four switched from IM to IN naloxone, and seven from IN to IM naloxone.

The timing of this trial provided the unique opportunity to consider three different types of naloxone kits (with different doses) for the training of participants in responding to opioid overdoses. At the beginning of the study, from September 2014 to August 2017, participants who chose IN naloxone were provided with multi-step naloxone, assembled by combining a pre-filled luer-lock syringe with a nasal atomizer that administers a dose concentration of 2 mg/2 ml, where 1 ml is administered to each nostril. In November 2015, the U.S. Food and Drug Administration (FDA) approved a nasal spray formulation delivered in an atomizer that no longer required assembly (Narcan® nasal spray), providing a potential time-saving advantage over the multi-step device (Kerensky and Walley, 2017). Following the recommendation from the Director of NIDA, Nora Volkow (NIDA, 2015), the trial switched from providing multistep IN naloxone to providing single-step IN devices in August 2017. The single-step nasal spray administers a dose concentration of 4 mg/0.1 ml into one nostril. All participants who had received the multi-step device were invited back to the study site to exchange the IN naloxone device for the new single-step device; devices were replaced at follow-up assessments as well. IM naloxone was provided in the same formulation throughout the study with a dose concentration of 0.4 mg/1 ml.

## Methods of Qualitative Research

The overall objective of the qualitative component of the study was to collect and analyse first-hand accounts of overdose events occurring post-training to better understand and potentially improve the effectiveness of current overdose prevention programs in NYC. All study procedures received human subjects approval from the Institutional Review Board (#6723). Criteria for inclusion within the qualitative component were 1) enrolment in the larger trial, and 2) having witnessed an opioid overdose and direct or indirect participation in an opioid reversal using naloxone.

The goals of the qualitative component of the study were to: (1) describe the circumstances surrounding opioid overdose events and the experiences of people present at such events who had received training and been provided with naloxone within the trial; (2) explore actual responses to opioid overdose events by both the overdose victim and the naloxone administrator; (3) assess the impact of the overdose event on subsequent drug-taking behaviours; (4) assess individuals' feelings about both the overdose training and naloxone

received after an actual overdose occurring; and (5) compare responses to the opioid overdose event by the naloxone device and formulation used.

Participation in the qualitative components of the study was optional and did not affect involvement in the larger trial. Participants were compensated $40 (US) for each single interview. In order to maximise recall, the time between the overdose event and the interview was restricted to less than 3 months. All interviews were conducted at the (removed for review) by three team members who had been trained in qualitative methods. Interviews were semi-structured, audio-recorded, lasted 20–65 minutes and followed a topic guide that covered: ‘demographic and psychosocial information’, ‘substance use and treatment’, ‘pre-trial overdoses (experienced and witnessed)’, the ‘last overdose witnessed’ (since joining the trial) and ‘views on overdose training’ (see also Neale et al., 2018). Interviews were transcribed verbatim for analysis.

## Qualitative Data Analysis

Qualitative data analysis for this work took place at the National Addiction Centre (King’s College London) and focused upon ‘last overdose witnessed after study enrolment’. This involved analysis of 56 overdose events that were successfully reversed by 46 participants (henceforth, people who use opioids) using one of the three formulations of naloxone described above. Analysis excluded reversals that were unsuccessful or those that were initiated by people who use opioids but completed by EMT.

The transcribed interview data relating to the 56 overdose events were managed using software specifically designed for qualitative data analysis (MaxQDA Version 2018). All analysis prioritised accounts of the actual overdose event, including their attempts at reversal and their witnessing of any perceived positive or negative outcome. Analysis also prioritised their responses to the specific question regarding ‘what happened after naloxone was administered’ in which they described reversal outcomes from their own perspective and as they understood what had happened. Similarly, analysis also prioritised any data within the interview that was directly connected to outcome of the intervention. These aspects of the ‘last overdose event’ therefore formed the ‘units of analyses’ (Graneheim and Lundman 2004) rather than the topics of wider discussion attached to the semi-structured interview schedule (see above).

The 56 overdose events were subject to elements of situational analysis (Clarke 2005) combined with the principles and processes of inductive content analysis (Slo and Kyngäs 2008). Situational analysis (SA) aims to provide a micro-analysis of particular events (here, overdose intervention) that considers the interrelationship between environment, actors and technology as part of a ‘situation-centred approach’ that unpacks the ‘complexities of situatedness’ (Clarke 2005). Content analysis (CA) may be applied to quantitative or qualitative data in either an inductive or deductive approach (Pandey 2019, Slo et al 2014). CA is concerned with the systematic description and quantification of a given phenomenon (Downe-Wambolt 1992) in which data concerning specific events/issues may be condensed to formulate broad-based conceptualisations for more general understandings of a phenomenon (Slo et al 2014). When CA is performed inductively, analysis aims to increase

existing knowledge of a topic that may be incomplete, fragmented or under-developed. (Conversely, deductive CA is driven by an *a priori* theoretical awareness of a given subject). In the present study, inductive content analysis of interview data focused upon people who use opioids recall of the overdosed person's responses to naloxone (upon recovery from overdose) in an attempt to uncover situated knowledges of overdose reversals from the perspective of the former. CA therefore complemented SA, as both approaches focused upon the aforementioned units of analysis that concerned the various social and action processes performed and articulated during an emergency *situation* by people who use opioids.

The above analytical approach was also supplemented by regular qualitative 'data sessions' (Knoblauch 2005) attended in person by the London-based research team (removed for review) and via Skype with the wider multidisciplinary team based in NYC (removed for review). All data sessions typically involved reflective and interrogative discussions of the coding, indexing and interpretation of qualitative data from several perspectives (academic, applied, clinical, non-clinical, sociology, pharmacology). The *clinical* components of these data *s*essions reviewed the findings obtained from inductive content analysis with more deductive appraisals of the various effects associated with naloxone and overdose reversal. That is, the relevant researchers' clinical knowledge of naloxone and pharmacokinetic effects upon opioids further informed the findings obtained from situational analysis of participants' experiences. This had the effect of producing a blended analysis of the 56 overdose events within the qualitative dataset.

## Findings

Analysis identified several patterns of reversal outcome relating to the 56 overdose events as described by 46 people who use opioids who administered naloxone at the time of the relevant event. These experiential qualities - *as described by people who use opioids* – were initially inductively labelled (1) 'rage', (2) 'dopesick / sick', and (3) 'assorted physiological and psychological effects', in order to reflect how people who use opioids understood the overdose reversal they had observed (see Table 1). In addition, in cases whereby multiple physiological effects were observed (for example, memory loss with withdrawal symptoms, confusion with nausea), then inductive labelling prioritised the type of outcome first reported by people who use opioids after the overdosed person regained consciousness. If the outcome effect included aspects of violence/aggression - either with or without assorted physiological effects - then inductive analysis prioritised this as 'rage', as this response was typically the most dominant when reported. This categorisation sought to identify situated knowledges of 'adverse reactions' that have become associated with opioid overdose reversals (see Introduction).

The above analysis of outcome also incorporated clinical knowledge associated with opioid overdose and the pharmacokinetics of naloxone as held by some of the research team. This more deductive approach (recognising physical symptoms associated with naloxone / withdrawal symptoms / opioid dependence etc.) subsequently noted a range of outcomes *within* each label. In short, 'withdrawal symptoms' and 'rage' were each noted to include a hierarchical range of outcomes from a more clinical perspective (see Table 1). However, the 'assorted physiological and psychological effects' described by people who use opioids were

considered by the team to be clinically ‘normative’ in that these effects would be ‘expected’ - or considered ‘unremarkable’ - following the reversal of an opioid overdose with antagonist medication. In addition, these particular outcomes could not be summarised with a suitable *in vivo* (obtained from interview) or clinical term to label the wide range of outcomes reported in this category. For these reasons, the category ‘not rage, not withdrawal’ was established to fully encapsulate what the various physiological and psychological outcomes *did not* include. This category therefore reflects the blended analysis described above as it does not prioritise clinical knowledge but maintains experiences of overdose reversal in summarising what people who use opioids *did not* observe. For these reasons, the label ‘not rage, not withdrawal’ replaced ‘assorted physiological and psychological effects’ and should not be erroneously regarded as a term that reflects any ‘underanalysis’ of the relevant data (as it is also a label that is consistent with the processes of situational analysis). Each of these three reversal outcomes are reported below.

### (i) Rage

The most reported reversal outcome described by people who use opioids is here labelled as ‘rage’ and concerns the manifestation of negative emotional reactions that followed overdose resuscitation. This term derives from the *in vivo* expression used by Participant 31 (see below) and is used throughout to describe a wide range of angry, hostile and/or aggressive outbursts by the overdosed person following their return to consciousness. 23/56 (41%) of all overdose reversals were labelled as ‘rage’ events. However, situational and deductive analyses also noted variation in the intensity and severity of rage within each of the 23 relevant events. As such, the ‘rage’ category has been hierarchically divided into ‘low level rage’ (×8) and ‘high level rage’ (×15) in order to best capture the range of responses reported by participants during these particular overdose reversals. Cases of ‘low level rage’ involved a reversal outcome characterised by the overdosed person articulating an obvious negative psychological state of mind. This was typified by a mixture of complaints, arguments, protests, and grievances. Low level rage also involved a reluctance to assist (friends, responders and/or emergency services) in post-reversal aftercare and a physical resistance to comply with emergency services or other responders (e.g. by running away, refusing assistance, rejecting hospital treatment). Low level rage may be noted in the following account that typifies this label.

> Interviewer: Did he have any side effects from the (naloxone)?
>
> Respondent: … He woke up (and) when snapped out of it he scared us, but he was coherent, he talked, but you could still see that he was kinda groggy, but he was aware, you know? Like sometimes when you come (back), you a little groggy. I think it was like that, but he was like ‘nah, get away from me.’ … He was more upset about the high, he’s like ‘no, you fucked my high up, leave me alone, leave me alone.’ He was a little combative, he was like ‘oh, just leave me alone.’ He wasn’t hitting or being aggressive. … He wanted to leave. … I mentioned the ambulance, that’s when he got a little combative. He’s like, ‘yo, what the fuck y’all doing?’ The guy said ‘yo, shut the fuck up. This guy just saved your life. You was OD’ing’. He said ‘no I wasn’t.’ He said, ‘nigga, tell me what happened.’ ‘No, leave

> me alone'. I said 'yo, call the ambulance, come on, let's go.' He's like 'the ambulance?' Then he left. (Participant 35, male, one dose using IN 2mg kit)

However, 'high level rage' appears to have been a much more intimidating experience for those involved. In cases of high level rage, the various outbursts associated with low level rage (above) become more acute, approaching hostility and aggression as may be noted in the following account. (A further noteworthy feature within this remark is the participant's reference to having been 'pre-warned' by others about 'rage' as a potential reaction to naloxone administration).

> Respondent: Listen, my friends already told me that when people come out of it … they might be angry. But I didn't realize how vehement they would be. I thought they'd be like 'fuck you.' It's not like that, like a simple 'fuck you.' I mean they come after you with rage. … I wasn't expecting that. I was expecting to be yelled at, but the rage level? No. No, I wasn't expecting that. The level of rage, I was not expecting. I was not expecting the level of rage. That really shocked me, because I'm like 'I just saved your life. Why are you so mad at me? I saved your life'. I don't know. It is what it is. Next question. (Participant 31, female, two doses using IN 2mg kit)

The 15 cases of high level rage also represent the most intensely negative outcomes attached to an otherwise successful overdose reversal. In the most acute of these cases, participants described extreme outbursts that included verbal abuse, intimidation, threats of violence and being spat upon. Such responses were typically directed towards the naloxone administrator (i.e. the study participant) but were also aimed at those within the wider environment. In the following account, Participant 51 describes the threat of violence from the naloxone recipient (i.e. a younger female) following successful resuscitation:

> Interviewer: You give her the dose in the one nostril?
>
> Respondent: She came out of it in a minute. I give it a minute. She came out and she (is) looking around like that. 'Who the fuck are you?' like that. … She came out of it and she pulls herself up. She just raised herself off her stomach. She is still on the ground and asked me who the fuck am I. Her girlfriend said, 'oh, he was trying to stick (something in your) nose like that. 'You better back the fuck up or get your wig split.' That's what she is telling me. (Get) back. I better back up before I get my wig split. (Participant 51, male, one dose using IN 4mg)

The following extract demonstrates the way in which 'rage' may escalate in a situation with different medical teams responding to the emergency.

> Respondent: … he became alert when (the paramedics) got there. … But he didn't wake up completely, cause he was trying (to) get away and he couldn't even walk. Looked like he was very drunk cause he couldn't walk straight. He was staggering, holding onto stuff. But still, pulling away from them trying to grab his shirt. He was taking his shirt off trying to get away from them. So I was like, 'don't get scared now', you know? 'You need help, you're gonna die'. So I convinced him to go with (the paramedics).
>
> Interviewer: So they got him strapped in then they gave him …?

Respondent: Narcan. And then he went nuts.

Interviewer: What happened?

Respondent: He got very violent. Started spitting - he was strapped, but he was spitting and kicking, and you know, then now they weren't nice no more.

Interviewer: Were they able to get him into the…?

Respondent: Oh yeah, what happened was first, he *was* gonna go with the regular ambulance, with the guys - the blue uniforms. But he started spitting and kicking and cursing, and now guys with a different ambulance with green uniforms came. So to me that was obvious. 'You're not going to the hospital now, pal, you're going to the psych ward'. (Participant 29, male, naloxone dose/kit unknown)

A further feature of participants' accounts of rage were those experiences that mostly affected naloxone administrators who identified as female. For example, some women's previous experiences (and/or the expectation) of rage from men who had overdosed was noted to have a negative impact upon actual and potential behaviour relating to overdose intervention. This may be noted in the following extract, in which Participant 01 describes her reluctance to administer naloxone to a male stranger during the emergency. Moreover, her deliberate attempt *to avoid* a rageful response from a male stranger resulted in a 'co-produced' naloxone intervention with her husband.

Interviewer: Did you (recognise it was an overdose) …

Respondent: Yeah. He pulled him off the toilet. He was like over the toilet. So he pulled him off the toilet. And he was breathing, so he wasn't dead. So I put the Narcan together, and I said, 'just hit him off, see if he comes through, and call an ambulance'.

Interviewer: So your husband actually delivered the naloxone?

Respondent: Yeah. So he did it. I mean, I was right there.

Interviewer: How come he did it instead of you? Did you make a decision?

Respondent: Because I didn't know if he was going to get aggressive or whatever. Yeah, like I didn't know the guy. (Participant 01, female, one dose using IN 2mg)

The *avoidance* of male aggression is also apparent in the following account by Participant 11 who describes her apprehension at any *future* intervention involving men who may have overdosed.

Interviewer: On a scale of 0–10, how confident do you think you would be to give it again?

Respondent: Confident to give it, but apprehensive.

Interviewer: So, you feel confident in giving it, but what about -

Respondent: The reaction.

Interviewer: How apprehensive would you be to give it again?

> Respondent: Like a 6. I think if my husband is there I think I wouldn't be, but if I'm by myself, yes. And if it's a man, yeah.
>
> Interviewer: You feel you would be more likely (to intervene) if you saw a female overdosing?
>
> Respondent: Definitely, but I don't know if it's because I have domestic violence issues and the way that he reacted, I don't know. He was just so … I couldn't believe how aggressive he was. I don't know if that's normal or what, but it freaked me out a little bit. (Participant 11, female, one dose using IN 2mg)

### (ii) Withdrawal symptoms

A second reversal outcome described by people who use opioids is here termed 'withdrawal symptoms'. This term derives from the common 'street' slang terms ('dopesick' and 'sick') that many participants used throughout their interviews to describe the rapid precipitation of opioid withdrawal symptoms. That is, these particular *in vivo* expressions summarise how people who use opioids perceived the outcome effect in 11/56 (20%) cases of overdose reversal. In each of these 11 cases, people who use opioids were able to recognise and describe one or more symptoms associated with opioid withdrawal. Analysis of these accounts established the label 'withdrawal symptoms', which appropriately reflects the terms used by the relevant interview respondents.

Deductive (clinical) analysis of these participant accounts further refined this outcome to consist of either 'minor' or 'major' withdrawal symptoms experienced by the overdosed persons. As such, 9/11 overdose reversals were labelled 'minor withdrawal symptoms' as these cases typically involved early onset symptoms such as muscle aches, lacrimation, sweating, shaking/trembling and anxiety. Conversely, 2/11 overdose reversals were labelled 'major withdrawal symptoms' as they included some of the aforementioned 'minor' symptoms as well as more acute symptoms of opioid-related withdrawal (e.g., painful muscle cramps, excessive sweating, temporary vision loss, nausea and/or vomiting).

The following interview extracts provide examples of 'minor' and 'major' withdrawal symptoms. The former may be noted in the following account:

> Respondent: … this was a heroin case and (naloxone) worked on the second (dose). He was very scared and shaking and I stayed with him for about …. two hours; and then we had … a senior counsellor come in and stay with him another additional two or three hours. …. We gave him a cup of coffee and we were talking to him. But remember, he was very shaken up; he was trembling for about a half an hour. For about a good 30 minutes he was trembling and scared.
>
> Interviewer: Did he have any other symptoms other than the trembling?
>
> Respondent: No. No vomiting; nothing like that. He was sweating. Perspiration and sweating. I had asked him what he had done and where he got the dope. (Participant 26, male, two doses of naloxone using IN 2mg kit)

In contrast, the following dialogue illustrates 'major withdrawal symptoms'.

Interviewer: … So you've given him the second (naloxone) dose; you said he comes out of it right away and he starts complaining about his sweating and stomach sort of immediately?

Respondent: He was nauseous, yes.

Interviewer: Did he actually vomit?

Respondent: Yes he did. … Twice

Interviewer: So he vomited twice; okay, did he feel like it got better after he vomited or was he still complaining of being nauseated?

Respondent: He didn't say anything after he threw up if he felt better. He didn't say it and I didn't even ask 'how do you feel?' I was more concerned of him just keep talking to me so he wouldn't slip back into it.

… Interviewer: So (there was an) unusual amount of sweat, any other thing you noticed after you gave him the (naloxone)?

Respondent: The sweating and his stomach issue that was the main things that stood out to me. (Participant 18, male, two doses of naloxone using IM kit)

### (iii) Not rage, not withdrawal

The label 'not rage, not withdrawal' derives from a blended analysis (situational, content, inductive and deductive [clinical]) of accounts by people who use opioids of assorted physiological and psychological effects observed following their use of naloxone during an opioid overdose event. A total of 22/56 (39%) overdose reversals formed this category in which the assorted effects included short-lived, 'harmless' conditions such as (temporary) amnesia, mild emotional outbursts, 'non traumatic' physical discomfort, reduced ability to communicate effectively and confusion. As there were no cases of withdrawal symptoms or rage within this category, the negative label 'not rage, not withdrawal' adequately reflects the situated knowledges of people who use opioids with these particular outcomes.

The most widely reported feature in 16/22 in cases of 'not rage, not withdrawal' was various descriptions of 'confusion'. More accurately, 'confusion' featured *exclusively* in 11 events and was an aspect of multiple physiological/psychological outcomes in a further 5 events. Accordingly, 'confusion' represents a specific outcome to feature in almost one third of all reversals described in this study (namely 16/56, 29%).

The term 'confusion' is also an expression used by several respondents to describe the reversal outcome that naloxone produced upon recovery of the overdosed person. In this regard, 'confusion' was typically described as involving some form of temporary 'disorientation' or 'short-lived (temporary) amnesia'. These features are noted in the following interview extracts. In the first illustration, the participant makes a clear distinction between confusion and 'getting mad' (i.e. 'rage'):

Respondent: So, I hit him. I gave him a shot. And I think it took about a minute; and he just came out of it. And came out of it confused.

Interviewer: What did he say, do you remember?

> Respondent: Like, ‘what we doing here?’ He didn’t remember nothing. He was like confused. Then he started - he remembered - and basically like started laughing …. and that was strange for me because normally people (…), they get mad at me. (…) Mad that you took them out of their high, and they claim … ‘I was just enjoying my high. I wasn’t going to die’; you know, that type of attitude. This guy, it was like he wasn’t mad at anything. (Participant 10, male, one dose of naloxone using IM kit)

In the next example, however, the participant recounts the explanatory conversation that took place following an overdose reversal characterised by confusion:

> Respondent: (After one dose of naloxone) And then, all of a sudden, he just like …
> Interviewer: Eyes wide open?
>
> Respondent: ‘What’s going on?’ He didn’t even realize what’s going on. It was like he just was sleeping; and he just woke up. ‘What’s going on? What happened?’ ‘Calm down first of all; calm down man. You just OD’d.’ ‘What? Oh my God; no; don’t tell me that.’ They panic you know, and they start talking. I’m like, ‘listen man. I’m not trying to hear all that shit man. The ambulance is going to come over here. He’s going to talk to you whatever. All I’m going to tell them is this and this guy OD’d. I gave him a shot of naloxone and you know right now he’s sitting up.’ I went and got a towel, you know, he started sweating.
>
> Interviewer: What else? Was he complaining of any other symptoms afterwards?
>
> Respondent: Nothing, he was just sitting there like he couldn’t believe … what just happened. (Participant 41, male, one dose of naloxone using IN 4mg kit)

Overdose reversals characterised by ‘confusion’ were typically non-problematic (to all parties involved) as the effects were short-lived with the overdosed person gradually returning to full cognisance. This was regardless of the type of naloxone kit used (whether IM, IN 2mg, or IN 4mg) and/or regardless of the number of doses provided (i.e. single or multiple doses).

In addition to ‘confusion’, this category also includes several physiological and psychological effects experienced simultaneously by the overdosed person upon reversal. For example, physiological responses (including chest/nasal pain, flatulence, gasping and sweating) were observed in 7/22 events, emotional responses (including remorse, shock, paranoia and hilarity) in 5/22, short-lived (temporary) amnesia in 5/22, poor communication ability in 4/22, gratitude in 3/22, and intentional acts (e.g. involving running away from the scene) in 2/22. A descriptive summary of these assorted (clinically benign) outcomes can be found in Table 2.

Overall, descriptions of outcomes labelled ‘not rage, not withdrawal’ were different from other naloxone outcomes that were previously ‘known’ to to those interviewed. These other ‘known’ outcomes were typically associated with ‘being sick’ and/or ‘getting mad. For these reasons, several people who use opioids were confident and adamant in describing these outcomes as *not* associated with opioid withdrawal symptoms.

**Take Home Naloxone (THN) dosage administered by people who use opioids—**As noted above, three different types of THN were involved in this study, in which each kit comprised a different formula that ranged from 0.4 – 4 mg of naloxone via injection or intra-nasal spray. Despite this variation in technology and formulae, each of the three kits were associated with the outcomes here labelled 'rage', 'withdrawal symptoms' and 'not rage, not withdrawal symptoms'. Additionally, these outcomes were also noted in overdoses that involved people who use opioids administering *single* or *multiple* doses of naloxone to achieve a successful reversal. Table 3 presents a summary of the range of kits, doses and outcomes attached to the 56 overdoses, in which it may be noted that 28 overdoses were reversed with a single dose and 28 reversed with multiple doses. Following reversal of 56 overdoses, 23 'rage' events emerged from 14 single doses and 9 multiple doses; 11 'withdrawal symptoms' from 1 single dose and 10 multiple doses and 22 'not rage and not withdrawal symptoms' events involved 13 single doses and 9 multiple doses of naloxone.

**Post reversal drug seeking/use—**Analysis of the range of outcomes and dosages administered also identified accounts of potential/actual drug seeking and drug use that took place after the reversal of an overdose by the persons concerned. These post-reversal behaviours were associated with each of the three reversal categories but were also noted to escalate in cases involving 'withdrawal symptoms' and 'rage'. More specifically, in cases of 'not rage, not withdrawal' two participants reported potential drug-seeking (×1) and continued drug use (×1). In the latter case, Participant 50 stated that the person concerned went on to overdose a second time in a different location. Similarly, of the 11 cases that experienced 'withdrawal symptoms', 3 involved subsequent drug-seeking (×1) or continued drug use (×2). With regard to the two cases of continued drug use, Participants 19 and 25 not only reversed the relevant overdoses, but also *facilitated* access to drugs for use by the recovered persons concerned. In both cases, substances were provided *to relieve withdrawal symptoms* as part of a negotiated arrangement between friends. This may be noted in the following interview extract in which Participant 19 empathises with the physical suffering of his friend's withdrawal symptoms.

> Respondent: Honestly, I forgot to tell you this part. I went to the hospital and I rolled him a bag because he was in (inaudible) withdrawal.
>
> Interviewer: When did you do that?
>
> Respondent: About two hours later. He called me and begged me, like 'bro, you have no idea, these people not going to get me methadone until tomorrow, I'm fucking dying. I'm going to leap'. And I know the feeling (….), I know that desperation like you'll fucking rob the doctor's computer if you have to, like not even think of the consequences. I know that was a devil's mistake, I don't know what it was, but the bags that I had found, I kept them. … And then I brought him one. He kind of relaxed and then he was able to go through whatever he was going to go through. (Participant 19, male, two doses using IN 2mg in addition to one dose IN 2mg provided by persons unknown)

With regard to 6/23 accounts of 'rage', drug-seeking behaviour (×3) or continued drug use (×3) occurred most often in this category. Three of these six events were associated with

'low level rage' (1 × continued drug use, 2 × drug seeking) and three with 'high level rage' (2 × continued drug use, 1 × drug seeking). In the case of 'low level rage' with continued drug use, the naloxone administrator also facilitated access to further drugs as a method of *conflict resolution* and on condition they were consumed in a location removed from the overdose scene:

> Respondent: (Following the reversal of two overdoses in the respondent's vehicle and in an attempt to resolve a drug-related argument between so-called 'get high buddies') … And they're like, just bring us back to the spot. Just bring us back to the spot. (i.e. return to the drug seller to buy more heroin).
>
> Interviewer: So you took them back to the place where you…
>
> Respondent: I took them back to the spot. I got, you know, they gave me the money. I got them some - I got something for them again. And then I was like, 'you're not doing it in my car. When I drop you off, then I'll give you your shit.' (Participant 13, male, two doses using IN 2mg)

In total, 11% (6/56) of people recovered by naloxone subsequently consumed more drugs following an opioid overdose reversal. Half of these cases (3/56) were facilitated by the naloxone provider as an empathetic response to the outcome effect of naloxone (i.e. to decrease withdrawal symptoms or to avoid an escalation in rage). However, drug-related behaviours following naloxone occurred most often in reversals characterised by 'rage' (namely, 3 × seeking/ 3 × reuse).

## Discussion

This study indicates that response patterns to the reversal of opioid overdose are neither constant nor predictable. Even though the study participants were all people who actively use drugs, there were major differences in the experiences of response to overdose reversal. In addition, this study suggests that the adverse effects associated with overdose reversal outcomes should not be understood solely in terms of presence or absence of 'opioid withdrawal symptoms' (e.g. Belz et al 2006, Gaddis and Watson 1992, Horowitz 1998, Osterwalder 1996, Wanger et al 1998). Analysis of accounts of naloxone outcomes observed by people who use opioids during their experience of overdose reversal identified three types of interconnected outcome (here termed 'rage', 'withdrawal symptoms' and 'not rage, not withdrawal'). From the perspective of people who use opioids, each of these outcomes was observed as a separate, recognisable and distinguishable effect that could be described by particular qualities not typically regarded as 'acute withdrawal symptoms', such as 'confusion,' 'feeling sick,' or being 'mad as hell'. These outcomes reflect the way in which given populations may construct a shared understanding of naloxone that is premised upon 'situated knowledges' obtained from direct experience (cf: Clarke and Montini 1993).

When considered from an applied position, the various physiological and psychological outcomes here termed 'not rage, not withdrawal' perhaps reflect the optimal responses one may clinically/socially expect from reversal of a near-fatal incident involving opioid overdose. That is, whilst temporary memory lapse, confusion and minor emotional outbursts are possibly remarkable at an individual level, these effects may actually best represent a

'successful reversal' as such short-term conditions might be considered 'non-serious' and 'unremarkable' from a clinical perspective. Namely, they represent a satisfactory harm reduction outcome to emerge from a clinical emergency involving opioid overdose that would not necessarily impede or inhibit the reversal at a future similar emergency situation.

Indeed, this claim is made further evident if contrasted with reversals characterised by 'withdrawal symptoms' or 'rage'. In these cases, reversals are characterised by more sub-optimal clinical/social outcomes, in which subsequent behaviours (such as running away, avoiding paramedics, becoming abusive, seeking out and/or reusing further drugs) may serve to problematise the pharmacokinetic interaction of naloxone upon opioids as well as possibly place individuals in a high-risk drug-using situation. In short, these outcomes may diminish attempts at harm reduction.

This contention also has relevance to a recent editorial regarding current understandings of drug/medicine-related toxicity (Strang et al 2017) in which the authors propose that the concept of toxicity should be expanded beyond generic adverse events/outcomes associated with licit/illicit drugs to include 'mediated-toxicity'. Mediated-toxicity refers to the harms produced via 'intermediate behaviour or reputational damage that are triggered by a medication' (ibid, pp592–4)[2]. These extended concepts of toxicity, in relation to naloxone and the findings presented above, have implications for harm reduction as a form of public health intervention. These implications are discussed below as examples of behavioural and reputational mediated toxicity (Strang et al 2017).

## Behavioural related toxicity

Although all overdose events involved in this analysis were 'successful' reversals (in that possible fatalities were prevented and those who overdosed were believed to have made full recoveries), iatrogenic harm was also evident throughout these events. That is, post-reversal, drug-related behaviours by those who overdosed were noted in 11/56 events (20%) and although observed in reversals characterised by 'not rage, not withdrawal', 'withdrawal symptoms' and 'rage', they were most noted in the latter category.

These aspects of harm have been described elsewhere as illustrations of 'over-antagonism' (Neale and Strang 2015) and are outcomes that may be considered as an example of 'behaviourally mediated toxicity' (Strang et al 2017, 592–4). For these reasons, the overall implication for harm reduction policymakers / practitioners is that those involved in the distribution and actual provision of naloxone should regard the range of reversal outcomes (including adverse events) as simply more than 'non-serious' reactions associated with acute withdrawals symptoms.

For example, as the experience of naloxone administration in this study suggests, if and when naloxone recipients subsequently seek out/use opioids after overdose reversal, then the initial harm reduction intervention may be diminished. Accordingly, within the arena of applied harm reduction, it is perhaps more important to manage post-reversal behaviours

[2]Examples of mediated toxicity cited include liver damage in paracetamol overdose and allergic reactions to penicillin as harm in both cases is 'attributable directly to the medication' (Strang et al 2017, 592)

(especially ‘rage’) instead of focusing upon assumptions of withdrawal symptoms. This may take the form of scaling-up of how naloxone administrators may best take care of an overdosed person post-reversal within a harm reduction framework. This would, for example, include avoiding facilitating access to drugs (see above) and also providing calming reassurance as post-resuscitative aftercare when possible (cf. Farruggia et al 2019). Similarly, harm reduction training programmes in THN may emphasise how to best react and respond to the more negative (social and physiological) components of ‘withdrawal symptoms’ and ‘rage’ in a way that is empathetic and supportive to all parties involved in the overdose event (responder, peers, bystanders, emergency response teams etc.). In short, such training components should aim to enable the lay responder (people who use opioids or otherwise) to follow the same objective as EMTs attending a crisis *to the extent possible in a given setting*; namely, to re-establish consciousness and a safe breathing pattern. In addition, it is important to avoid an unnecessarily high naloxone dose, when the excess naloxone may cause ‘over-antagonism’ (Neale and Strang 2015) and precipitate the sudden onset of opioid withdrawal and, sometimes, further opioid-seeking to counter the effect. Amongst the harm reduction community, there was early emergence of a consensus that best practice would involve training in incremental dose increase, and this was applied from early adaptation of provision of take-home naloxone by pioneering groups such as Chicago Recovery Alliance in the USA (Campbell, 2020, p.165) and Fixpunkt in Europe (Dettmer et al, 2001) and as described in ‘patient information sheets’ (provided with medication), with the guidance to administer the first dose and then to wait for a specified period of time between doses (e.g. 2 or 3 minutes) to observe reactions and then make a decision as to whether a further dose is required. This incremental dosing protocol would aim to ‘antagonise the respiratory-depressant actions without eliciting a full withdrawal syndrome’ (Brunton and Parker 2008, 365) and are actions that have been successfully embedded within overdose response training in other locations (Dettmer et al., 2001; Madah-Amiri et al., 2019).

### Reputational related toxicity

A second form of iatrogenic harm identified in this study relates to ‘reputational related toxicity’ (Strang et al 2017, 592–4). This aspect of harm concerns the way in which people who use opioids perceive naloxone as a substance that they wish to avoid, due to the negative physical outcome it is assumed it will produce (see Cozzolino et al 2019, Faulkner Gurstein 2017, Neale and Strang 2015).

Such negative perceptions of naloxone were noted amongst those who had *received* naloxone in this study. However, similar perceptions were noted within the experiences of naloxone *administrators.* For example, the various hostile encounters experienced by naloxone administrators during the accounts of ‘rage’ contributes to the reputational harm associated with naloxone as a direct result of being verbally abused, insulted, or physically intimidated following its use. Female respondents who administered naloxone to male overdose victims, and who described tactics to avoid a rage response within male overdose reversals, also exemplify a form of reputational harm associated with naloxone reversals. However, these gender-related findings were marginal and limited within the wider dataset, and so definitive conclusions about the ‘gender-exclusivity’ of this matter cannot be drawn.

Nevertheless, future research may wish to consider any similar avoidance tactics implemented by men upon men [or men upon women] during an overdose episode.

Reputational-related toxicity amongst those who *administer* naloxone in overdose emergencies is counter-productive to harm reduction intervention. If avoidance of a 'rage' response results in a reluctance (or hesitation) to assist in an overdose emergency, then carriage of naloxone is less likely to produce benefit. Additionally, the production of reputational-related toxicity is possibly the antithesis of the 'social logic' (Faulker Gurstein 2017) attached to the design and delivery of THN programmes. That is, the latter are often dependent upon the way in which naloxone may be distributed and delivered in community settings by networks of people who use drugs, laypersons and their significant others (intimate partners, family members etc.). The social logic of such schemes therefore depends upon trust and recognition of the product (naloxone) and the perception that it is 'safe technology' to use without fear of retaliation. Accordingly, fear, reluctance and apprehension to deliver naloxone as a result of a potential rage response is counterproductive to the social logic underlying THN. Further research that seeks to understand and explain the conditions under which (specifically) 'rage' occurs and seeks to establish appropriate harm reduction responses that mitigate this particular reaction are needed. An identification of best responses to avoid, or diminish, 'rage' may also serve to increase the likelihood that an administrator may intervene in future overdose emergencies and simultaneously seek to minimise the reputational-related toxicity associated with naloxone. While fears of inducing 'rage' may be one reason that bystanders would avoid using naloxone, failure to reverse an overdose after using naloxone might be even more impactful as a deterrent to its use.

The presence of fentanyl and its analogs in the street drug supply is an emerging factor that may require its own special consideration, especially if reversal of fentanyl overdose proves to require different interventions (or different naloxone doses). Some of the challenges described as features of fentanyl overdose may relate to the severe overdose event that might occur if major errors of judgement of opioid dose occur (since such small quantities of fentanyl and its analogs produce major opioid effect) while other challenges may relate to different pharmacological properties of fentanyl itself such as chest wall rigidity (Gill et al, 2019), although the emergency medical understanding is still emerging. Reports are also emerging about the need for very high doses of naloxone to reverse overdoses related to fentanyl and its analogs (Bardsley, 2019; Moe et al., 2020; Somerville et al., 2017). Such considerations may also affect the reputational-related toxicity associated with naloxone. For example, it remains unclear whether there will be change in official advice, or in evolving practice within harm reduction organisations (perhaps including amongst people who use opioids), with regard to how naloxone should be used over a period when rates of overdose deaths due to fentanyl and its analogs continue to increase e.g. in North America (Ciccarone, 2019), despite the availability of naloxone.

Finally, the impact of reputational-related toxicity is made further significant due to the geographical context of this study (NYC). In that North American setting, Good Samaritan Laws provide varying degrees of immunity from criminal and civil prosecution to encourage people to carry naloxone and prevent hesitation in assisting others during emergency events. More specifically, in New York State, Good Samaritan provisions protect from charges and

prosecution for possession of controlled substances (anything under 8 ounces), alcohol (where underage drinking is involved), cannabis (any quantity), and drug paraphernalia, and for sharing drugs. In short, legislation seeks to prevent hesitation in assisting others during emergency events and prevents prosecution if a person dies during bystander assistance/intervention. However, if a negative reputation of naloxone (held by administrators and recipients) maintains this avoidance of assistance, then not only do individuals continue to suffer as a consequence, but the legal framework that seeks to facilitate harm reduction intervention may become problematised at societal, collective and individual levels.

## Acknowledgments

FUNDING DISCLOSURE

This study was supported by the National Institute on Drug Abuse Grant R01DA035207 to Dr. Sandra Comer.

DECLARATIONS OF INTEREST

In the last 3 years, J.N. has received, through her University, research funding from Mundipharma Research Ltd and Camurus AB. J.S. is a researcher and clinician who has advocated for wider pre-provision of take-home naloxone, using several types of naloxone. He has also worked with pharmaceutical companies to seek to identify new or improved treatments (including forms of naloxone) from whom he and his employer (King's College London) have received honoraria, travel costs and/or consultancy payments. This includes work with, during past 3 years, Martindale, Indivior, MundiPharma, Braeburn/Camurus and trial medication supply from iGen and from Camurus. His employer (King's College London) has registered intellectual property on a novel buccal naloxone formulation and he has also been named in a patent registration by a Pharma company regarding a concentrated nasal naloxone spray. For a fuller account, see J.S.'s web-page at http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx. Within the past three years, S.D.C. has received research funding from Alkermes, Braeburn Pharmaceuticals, Cerecor Inc., Corbus, Go Medical, Intra-cellular Therapies,and Lyndra. In addition, Dr. Comer has also consulted for: Alkermes, Charleston Labs, Clinilabs, Collegium, Daiichi Sankyo, Depomed, Egalet, Endo, Epiodyne, Inspirion Delivery Sciences, Janssen, KemPharm, Mallinckrodt, Nektar, Neurolixis, Newron, Opiant, Otsuka, Pfizer, and Sun Pharma. She also has received honoraria from the World Health Organization. S.D.C. has received compensation (in the form of partial salary support) from studies supported by Alkermes, Braeburn Pharmaceuticals, Cerecor Inc., Endo Pharmaceuticals, Indivior PLC/Reckitt-Benckiser Pharmaceuticals, Johnson & Johnson Pharmaceutical Research & Development, MediciNova, Omeros, and Schering-Plough Corporation. In addition, S.D.C has received compensation from Grunenthal GmbH to conduct a meta-analysis of drug-induced subjective responses and she served as a consultant to the following companies: Analgesic Solutions, AstraZeneca, BioDelivery Sciences International, Cephalon, Clinilabs, Daiichi Sankyo, Egalet, Endo, Inflexxion, Innovative Science Solutions, Janssen, KemPharm, King, Lightlake (now Opiant), Mallinckrodt, Neuromed, Pfizer, and Salix.

Acknowledgements here (post peer review)

## References

Adapt Pharma Inc. (2017). Highlights of prescribing information Narcan® (naloxone hydrochloride) nasal spray. Radnor, PA 19087 USA

American Psychiatric Association (1994). The Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition). American Psychiatric Association

Avetiana GK, Fiutyb P, Mazellac S, Koppab D, Heyeb V, and Hebbard P (2018). Use of naloxone nasal spray 4mg in the community setting: a survey of use by community organizations. Current Medical Research and Opinion. 34, 4, pp 573–576 10.1080/03007995.2017.1334637 [PubMed: 28535115]

Bardsley R (2019). Higher naloxone dosing may be required for opioid overdose. Am J Health-Syst Pharm; 76:1835–1837 [PubMed: 31665765]

Belz D, Lieb J, Rea T, Eisenberg M (2006) Naloxone use in a tiered-response emergency medical services system. Prehospital Emergency Care 10, 468–471 [PubMed: 16997776]

Berling I, Mostafa A, Grice JE, Roberts MS, Isbister GK (2017). Warfarin poisoning with delayed rebound toxicity. Journal of Emergency Medicine, 52, 2, pp194–196 [PubMed: 27838137]

Brunton L and Parker K (2008). Goodman and Gilman's Manual of Pharmacology and Therapeutics, McGraw Hill Medical, New York.

Buajordet I, Næss A, Jacobsen D, Brørs O (2004) Adverse events after naloxone treatment of episodes of suspected acute opioid overdose. European Journal of Emergency Medicine, 11, 19–23 [PubMed: 15167188]

Ciccarone D, (2019). The triple wave epidemic: Supply and demand drivers of the US opioid overdose crisis. International Journal of Drug Policy, 71, 183–188 [PubMed: 30718120]

Clark AK, Wilder CM and Winstanley EL, (2014). A systematic review of community opioid overdose prevention and naloxone distribution programs. Journal of Addiction Medicine 8 (3), pp. 153–63. [PubMed: 24874759]

Clarke A and Montini T, (1993). The many faces of RU486: Tales of situated knowledges and technological contestations. Science, Technology and Human Values, 18, 1, 42–78

Collins AB, Boyd J, Mayer S, Fowler A, Kennedy MC, Bluthenthal RN, Kerr T and McNeil R (2019). Policing space in the overdose crisis: A rapid ethnographic study of the impact of law enforcement practices on the effectiveness of overdose prevention sites. International Journal of Drug Policy, 10.1016/j.drugpo.2019.08.002

Cozzolino E, D'Egidio PF, De Facci R, Leonardi C, Nava F, Stella L, Maremmani I (2019) Improving response capacities in opioid overdose management. Heroin Addiction and Related Clinical Problems, 21, 1, 5–14

Dettmer K, Saunders B and Strang J, (2001). Take home naloxone and the prevention of deaths from opiate overdose: two pilot schemes. BMJ Vol 322 (7291), pp. 895–96. [PubMed: 11302902]

Downe-Wamboldt B (1992). Content analysis: Method, applications and issues. Health Care for Women International, 13, 313–321. [PubMed: 1399871]

Elo S, and Kyngäs H (2008). The qualitative content analysis process. Journal of Advanced Nursing, 62, 107–115. [PubMed: 18352969]

Elo S, Kääriäinen M, Kanste O, Pölkki T, Utriainen K, and Kyngäs H (2014). Qualitative Content Analysis: A Focus on Trustworthiness. SAGE Open, January-March 2014: 1–10 DOI: 10.1177/2158244014522633

EMCDDA (2016). Preventing opioid overdose deaths with take-home naloxone. Publications Office of the European Union, Luxembourg.

Farrugia A, Neale J, Dwyer R, Fomiatti R, Fraser S, Strang J, and Dietze P (2019). Conflict and communication: managing the multiple affordances of take-home naloxone administration events in Australia, Addiction Research and Theory. https://www.tandfonline.com/doi/pdf/10.1080/16066359.2019.1571193?needAccess=true

Faulkner-Gurstein R (2017). The Social Logic of Naloxone: Peer administration, harm reduction, and the transformation of social policy. Social Science and Medicine, 180, pp 20–27 [PubMed: 28315595]

Gaddis GM, and Watson WA, (1992). Naloxone-associated patient violence: an overlooked toxicity? Annals of Pharmacotherapy, 26,196–198. [PubMed: 1554930]

Giglio RE, Li G and DiMaggio CJ (2015). Effectiveness of bystander naloxone administration and overdose education programs: a meta-analysis. Injury Epidemiology 2, 1,10. [PubMed: 27747742]

Gill H, Kelly E, and Henderson G(2019). How the complex pharmacology of the fentanyls contributes to their lethality. Addiction, 114, 1524–1525 [PubMed: 30883941]

Greene J, Deveau B, Dol J and Butler M (2019). Incidence of mortality due to rebound toxicity after 'treat and release' practices in prehospital opioid overdose care: a systematic review. Emergency Medical Journal, 26, 4, 219–224.

Graneheim UH and Lundman B (2004). Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. Nurse Education Today, 24, 2, pp105–112. [PubMed: 14769454]

Haraway D (1991). Situated knowledges: The science question in feminism and the privilege of partial perspective In Simians, Cyborgs and Women: The Reinvention of Nature. London, Routledge and Kegan Paul, pp 183–201.

Horowitz Z (1998). Commentary. Subcutaneous naloxone. A less rude awakening? Academic Emergency Medicine, 5, 4, 283–285. [PubMed: 9562188]

Jones JD, Campbell A, Metz VE, and Comer SD (2017). No evidence of compensatory drug use risk behavior among heroin users after receiving take-home naloxone. Addictive Behaviours, 71, 104–106.

Glanz K, Rimer BK and Viswanath K, (eds). (Jossey-Bass Public Health) (2008). Health behavior and health education: theory, research and practice (4th ed). J. Wiley and Sons Ltd, San Francisco, CA.

Kerensky T, and Walley AY (2017). Opioid overdose prevention and naloxone rescue kits: what we know and what we don't know. Addiction Science and Clinical Practice, 12(1), 4. [PubMed: 28061909]

Klebacher R, Harris MI, Ariyaprakai N, Tagore A, Robbins V, Dudley LS, Bauter R, Koneru S, Hill RD, Wasserman E, Shanes A, and Merlin MA, (2017) Incidence of Naloxone Redosing in the Age of the New Opioid Epidemic, Prehospital Emergency Care, 21, 6, 682–687 [PubMed: 28686547]

Knoblauch H (2005). Focused Ethnography. Forum Qualitative Sozialforschung / Forum: Qualitative Social Research, 6 (3), Art.44 http://www.qualitative-research.net/index.php/fqs/article/view/20/43 Accessed 09/09/2019

Kolinsky D, Keim SM, Kohn BG, Schwarz ES, and Yealy DM (2017). Is a prehospital treat and release protocol for opioid overdose safe? The Journal for Emergency Medicine, 52, 1, 52–58.

McDonald R and Strang J (2016), Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. Addiction 111 (7), pp. 1177–87. [PubMed: 27028542]

Madah-Amiri D, Gjersing L, & Clausen T (2019). Naloxone distribution and possession following a large-scale naloxone programme. Addiction,114, 92–100. [PubMed: 30129078]

Moe J, Godwin J, Purssell R, O'Sullivan F, Hau JP, Purssell E, Curran J, Doyle-Waters MM, Brasher PMA, Buxton JA, and Hohl CM, (2020). Naloxone dosing in the era of ultra-potent opioid overdoses: a systematic review. CJEM – JCMU, 1–9.

Minozzi S, Amato L and Davoli M (2015), Preventing fatal overdoses : a systematic review of the effectiveness of take-home naloxone. EMCDDA Papers pp. 1–37.

National Institute on Drug Abuse, NIDA (2015). FDA approves naloxone nasal spray to reverse opioid overdose.https://www.drugabuse.gov/news-events/news-releases/2015/11/fda-approves-naloxone-nasal-spray-to-reverse-opioid-overdose Accessed 22 December 2019

Neale J (1999). Experiences of illicit drug overdose: an ethnographic study of emergency hospital attendances. Contemporary Drug Problems, 26, 505–30.

Neale J, and Strang J (2015). Naloxone—does over-antagonism matter? Evidence of iatrogenic harm after emergency treatment of heroin/opioid overdose. Addiction. 110, 10, 1644–1652 [PubMed: 26119038]

Neale J, Brown C, Campbell AN, Jones JD, Metz VE, Strang J, & Comer SD (2019). How competent are people who use opioids at responding to overdoses? Qualitative analyses of actions and decisions taken during overdose emergencies. Addiction, 114(4), 708–718. [PubMed: 30476356]

Somerville Nicholas J., N.J., O'Donnell J, Gladden RM, Zibbell JE, Green TC, Younkin M, Ruiz S, Babakhanlou-Chase H, Chan M, Callis BP, Kuramoto-Crawford J Nields HM, and Walley AY, (2017). Characteristics of Fentanyl Overdose — Massachusetts, 2014–2016. Morbidity and Mortality Weekly Report, 66, 14, 382–386. [PubMed: 28406883]

Osterwalder J (1996). Naloxone - for intoxications with intravenous heroin and heroin mixtures – harmless of hazardous? A prospective clinical study. Clinical Toxicology, 34, 409–416. [PubMed: 8699555]

Pandey J (2019) Deductive Approach to Content Analysis In Gupta M, Shaheen M, and Reddy KP (eds) Qualitative Techniques for Workplace Data Analysis, IGI Global, pp 145–169.

Strang J, Darke S, Hall W, Farrell M, and Alu R (1996). Heroin overdose: the case for take-home naloxone. BMJ, 312, p1435.

Strang J, McDonald R, Campbell G, Degenhardt L, Nielsen S, Ritter A, Dale O (2019). Take-Home Naloxone for the Emergency Interim Management of Opioid Overdose: The Public Health Application of an Emergency Medicine. Drugs, 79, 1395–1418. [PubMed: 31352603]

Strang J, Neale J, McDonald R, and Kalk N (2017). Toxicity: exploring and expanding the concept. Addiction, 113, pp. 592–594. [PubMed: 29205614]

Wanger K, Brough L, MacMillan I, Goulding J, MacPhail I, and Christenson J (1998). Intravenous vs. subcutaneous naloxone for out-of-hospital management of presumed opioid overdose. Academic Emergency Medicine; 5, 4, 293–9. [PubMed: 9562190]

Watson WA, Steele MT, Muelleman RL, and Rush MD (1998).Opioid toxicity recurrence after an initial response to naloxone. Clinical Toxicology, 36, 1–2, 1117. [PubMed: 9541033]

Wermeling DP (2015). Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access. Therapeutic Advances in Drug Safety, 6, 1, 20–31. [PubMed: 25642320]

Williams AV, Marsden J and Strang J, (2014). Training family members to manage heroin overdose and administer naloxone: randomized trial of effects on knowledge and attitudes. Addiction 109 (2), pp. 250–59. [PubMed: 24103087]

World Health Organization (2014). Community management of opioid overdose. Geneva, World Health Organization.

**Table 1:**

Reversal outcomes obtained from blended analysis (situational analysis, inductive content analysis and deductive clinical analysis)

| Reversal outcome described by participants' lived experience of event (inductive analysis) | Reversal outcome as interpreted by researchers' clinical knowledge (deductive analysis) | Label to describe outcome (situational analysis) | Number of overdose events |
|---|---|---|---|
| Assorted (short-lived) physiological and psychological effects | Expected outcome and not clinically remarkable | Not rage, not withdrawal | **22** |
| 'Dopesick / sick' | **Minor** withdrawal symptoms (×9) | Withdrawal symptoms | **11** |
| | **Major** withdrawal symptoms (×2) | | |
| 'Rage' | **Low** level rage (×8) | Rage | **23** |
| | **High** level rage (×15) | | |
| ***Total*** | **56** | **56** | **56** |

**Table 2:**

Responses to naloxone observed by people who use opioids and labelled as 'not rage, not withdrawal'

| Type of Response | Not rage, not withdrawal | Illustration of Response and Outcome (emphases added) |
|---|---|---|
| **Physiological** | Breathing difficulties and perspiration | Respondent: He like, like when you come out of the water and then you want to … *breathing again like that*.<br>Interviewer: Yeah, kind of a big deep breath. Was he able to speak, did he say anything.<br>Respondent: No, no, not for a while. He was *sweating* and he was … it was nervous it was so we call 911. We called 911. (Participant 43) |
| | Breathing difficulties | Interviewer: And then but he already woke up after the first (dose), right?<br>Respondent: Yeah had started going—like he was like *gasping* but he started coming around. (Participant 32) |
| | Confusion, disbelief and perspiration | Respondent: (After the dose) … he's like '*what's going on*?' He didn't even realize what's going on. It was like he just was sleeping; and he just woke up. 'What's going on? What happened?' 'Calm down first of all; calm down man. You just OD'd'. '*What? Oh my god; no; don't tell me that.*'…. I went and got a towel you know he started *sweating*. (Participant 41) |
| | Flatulence and burning sensation in chest | Respondent: (After the dose) and he said like, he got to *burp*, he feel like he got to burp you know, his *chest was burning*. He had to burp. So we walked to the bathroom, he sat there at the toilet for about five minutes, and he burped. (Participant 49): |
| | Fatigue | Interviewer: Like he didn't seem dope sick (after the naloxone)?<br>Respondent: No. I can't say he was dope sick because I don't know if he had a habit or not, you see what I'm saying? But the effect of it, it was like you can tell everything just was out of him. *He was out of it*, and…<br>Interviewer: Out of it like he seemed tired?<br>Respondent: Yeah like *fatigued*. (Participant 23) |
| | Fatigue and confusion | Interviewer: Did he go back into it after that first (dose)?<br>Respondent: No, but it seemed like … *it took a lot out of him* I guess or whatever.<br>Interviewer: What do you mean when you say he came out of it? Did his eyes perk up, did he sit up, did he speak? Describe that a little bit more for me.<br>Respondent: He spoke.<br>Interviewer: What did he say?<br>Respondent: Basically, uh, '*what happened*' really. (Participant 15) |
| **Emotional** | Shock | Interviewer: How did he seem to you?<br>Respondent: He was in *shock*.<br>Interviewer: Shock?<br>Respondent: Kinda *upset*. Like "What happened?" I said, "Yo boy you OD'd bro." He goes, "*Oh shit, oh shit, for real?*" I said, "Yeah boy you almost called the ambulance." (Participant 16) |
| | Shock and disbelief | Interviewer: Was he complaining of any other symptoms afterwards?<br>Respondent: Nothing; he was just sitting there like *he couldn't believe* ….<br>Interviewer: He's in *shock*?<br>Respondent: Yes, shock. *He couldn't believe what just happened*. (Participant 41) |
| | Confusion, amnesia and hilarity | Respondent: So, I hit him. I gave him a shot. And I think it took about a minute; and he just came out of it. And came out of it *confused*.<br>Interviewer: What did he say; do you remember?<br>Respondent: Like what we doing here? *He didn't remember nothing*. He was like confused. Then he remembered and basically like *started laughing*. (Participant 10) |
| | Gratitude and remorse | Interviewer: What did that look like? What was she doing after she responded?<br>Respondent: *Started crying*. She said, *thank you* for saving my life. *I don't want to die*. (Participant 40) |
| | Paranoia and confusion | Respondent: And then I hit her, half in one nostril and nothing and then nothing. And then I hit her with the other and then she started… you know? Like I was telling xxx, when she came to, she was not scared but like *paranoid*. Like *didn't know what the hell was going on*. (Participant 02) |
| **Poor Communication** | Inability to talk and nasal problems | Respondent: And then I was smacking him around and I said 'c'mon, what's going on?' You know? He goes '*ehmhm*', he's *babbling* on something. So later on, minutes later, after he had come around to it, I don't know if the naloxone helped or didn't help but somehow it affected his nasal, whatever it was, maybe he had some type of *annoyance with his nasal* and he was going (inaudible) and so I gave him some tissue and stuff. I says, '*if you don't talk to me I'm going to hit you again*. I'm going to blast you again'. And then he goes, 'No, no, I don't wanna' and then he started getting a little more responsive. (Participant 26) |
| | Incoherence | Interviewer: But he had no other reaction? Did he talk?<br>Respondent: I don't know, *mumbled*, that's it. |

| Type of Response | Not rage, not withdrawal | Illustration of Response and Outcome (emphases added) |
|---|---|---|
| | | Interviewer: Okay, so he was definitely awake.<br>Respondent: Yeah of course.<br>Interviewer: Did he have any signs of withdrawal, any reactions that you observed?<br>Respondent: No.<br>Interviewer: Could you understand what he said?<br>Respondent: *No.* (Participant 34) |
| | Dazed | Respondent: After the second dose yeah, she responded right away.<br>Interviewer: How did it seem?<br>Respondent: *She's looking at me*, you know, because I'm in the back seat with the doors open. I'm like dude, 'you just overdosed. So, don't freak out, you know?' I was like 'yeah obviously this shit was good and you did too much'. (Participant 01) |
| **Amnesia** | Confusion, amnesia and hilarity (from above) | Respondent: So, I hit him. I gave him a shot. And I think it took about a minute; and he just came out of it. And came out of it *confused*.<br>Interviewer: What did he say; do you remember?<br>Respondent: Like what we doing here? *He didn't remember nothing*. He was like confused. Then he remembered and basically like *started laughing*. (Participant 10) |
| | Unable to remember events | Interviewer: … so he woke up and didn't know what was going on. Anything else?<br>Respondent: No. He asked me *what happened*. I told him 'you OD. You passed out.' (Participant 50) |
| | Unable to remember events | Respondent: … that's all I recall; they said since I was acting funny; they shot me with it and I say you shot…? *And I couldn't remember that*. I could not remember that. And that's all I said. And the reason I know they shot me with it, because you know, I have the bottle to prove that the needle is out; and then, I had caught some pain like the next day. (Participant 09 describing his own overdose reversal) |
| **Gratitude** | Expressing thanks | Interviewer: Was she concerned? How did she seem?<br>Respondent: Yeah, *she's thanking me*, and he's crying, because my husband's saving her husband right next to her, you know? (Participant 01) |
| | Expressing thanks and remorse (from above) | Interviewer: What did that look like? What was she doing after she responded?<br>Respondent: *Started crying*. She said, *thank you* for saving my life. *I don't want to die*. (Participant 40) |
| **Deliberate cognisance** | Amnesia with definitive decision-making | Respondent: And after he came back through, I was like uh, and I told him *what happened*. And he was like 'no, don't call the ambulance. *Don't call the ambulance*'. I was like 'but you need to go to the hospital.' And he was like 'no I'm okay, I'm okay, I won't go with the ambulance.' (Participant 37) |

**Table 3:**

Naloxone Kit, Dose and Outcomes

| Type of Naloxone Kit | Number of overdose events | Single Dose | Multiple Dose | Rage | Withdrawal Symptoms |
|---|---|---|---|---|---|
| **IM 0.4 mg** | 13 | 7 | 6 | 4 × Single Dose<br>2 × Multiple Dose | 2 × Multiple Dose |
| **IN 2 mg** | 33 | 14 | 19 | 7 × Single Dose<br>5 × Multiple Dose | 1 × Single Dose<br>7 × Multiple Dose |
| **IN 4 mg** | 9 | 7 | 2 | 3 × Single Dose<br>1 × Multiple Dose | 1 × Multiple Dose |
| **Kit Not Known** | 1 | 0 | 1 | 1 × Multiple Dose | 0 |
| **Total** | **56** | **28** | **28** | **23** (14 × Single Dose + 9 × Multiple Dose) | **11** (1 × Single Dose + 10 × Multiple Dose) |