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FACTORS ASSOCIATED WITH WITHDRAWAL SYMPTOMS AND ANGER AMONG PEOPLE RESUSCITATED FROM AN OPIOID OVERDOSE BY TAKE-HOME NALOXONE: EXPLORATORY MIXED METHODS ANALYSIS

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DECLARATIONS OF INTEREST

In the last 3 years, J.N. has received, through her University, research funding from Mundipharma Research Ltd and Camurus AB. N.J.K's PhD (2010 – 2015) was supported by a Wellcome Trust GlaxoSmithKline Translational Medicine Training Fellowship and, during this time, she received funds for travel, training and research materials from GlaxoSmithKline. N.J.K. has also been supported in attending educational meetings by the Lundbeck Institute (2010). 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, within the last 3 years, his employer (King's College London) has 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, S.D.C has consulted for: Alkermes, Charleston Labs, Clinilabs, Collegium, Depomed, Epiodyne, Inspirion Delivery Sciences, Janssen, KemPharm, Mallinckrodt, Nektar, Newron, Opiant, Otsuka, Pfizer, and Sun Pharma. She also has received honoraria from the World Health Organization. S.P., C.B., L.B., A.N.C.C., and J.D.J. have no disclosures to report.

Abstract

Introduction: Take-home naloxone (THN) is a clinically effective and cost-effective means of reducing opioid overdose fatality. Nonetheless, naloxone administration that successfully saves a person's life can still produce undesirable and harmful effects.

Aim: To better understand factors associated with two widely reported adverse outcomes following naloxone administration; namely the person resuscitated displays: i. withdrawal symptoms and ii. anger.

Methods: A mixed methods study combining a randomized controlled trial of overdose education and naloxone prescribing to people with opioid use disorder and semi-structured qualitative interviews with trial participants who had responded to an overdose whilst in the trial. All data were collected in New York City (2014–2019). A dataset (comprising demographic, pharmacological, situational, interpersonal, and overdose training related variables) was generated by transforming qualitative interview data from 47 overdose events into dichotomous variables and then combining these with quantitative demographic and overdose training related data from the main trial. Associations between variables within the dataset and reports of: i. withdrawal symptoms and ii. anger were explored using chi-squared tests, t-tests, and logistic regressions.

Results: A multivariate logistic regression found that people who had overdosed were significantly more likely to display anger if the person resuscitating them criticized, berated or chastised them during resuscitation (adjusted OR = 27 [95% CI = 4.0 – 295]). In contrast, they were significantly less likely to display anger if the person resuscitating them communicated positively with them (OR = 0.10 [95% CI = 0.01 – 0.78]). Both positive and negative communication styles were independently associated with anger, and communication was associated with 59% of the variance in anger. There was no evidence that people who displayed withdrawal symptoms were more likely to display anger than those not displaying withdrawal symptoms, and neither displaying withdrawal symptoms nor displaying anger were associated with using more drugs after resuscitation.

Conclusions: Contrary to common assumptions, withdrawal symptoms and anger following naloxone administration may be unrelated phenomena. Findings are consistent with previous research that has suggested that a lay responder's positive or reassuring communication style may lessen anger post overdose. Implications for improving THN programmes and naloxone administration are discussed.

Keywords

Naloxone; Overdose; Opioids; Withdrawal; Anger; Mixed Methods

1. INTRODUCTION

Opioid overdose deaths have been increasing in the United States and internationally (Kim et al., 2009; Rudd et al., 2016; Hedegaard et al., 2017; Roxburgh et al., 2017; Ciccarone, 2019). The timely administration of the opioid antagonist naloxone can prevent fatalities by temporarily counteracting the central nervous system-mediated respiratory depression associated with opioid overdose (Strang et al., 1996; Faulkner-Gurnstein, 2017; Strang et al.,

2019). Naloxone reverses all types of opioid overdoses, including those caused by heroin and pharmaceutical or synthetic opioid drugs; although its effectiveness in reversing overdoses involving fentanyl and/ or its analogs is unclear under some circumstances (Sommerville et al., 2017; Bardsley, 2019; Moe et al., 2020).

Medical staff in emergency departments and ambulance personnel have used naloxone to treat opioid overdoses for many years (Sporer et al., 1996; Clarke et al., 2005; Lenton et al., 2015). More recently, the drug has been made available to non-medically trained people, including people who use opioids and their friends and family, to use in the community wherever an overdose may occur (Strang et al., 1996; Darke and Hall, 1997; Mueller et al., 2015; McDonald et al., 2017; Behar et al., 2018). This pre-provision of naloxone to laypersons, in conjunction with instruction on how to manage an overdose whilst waiting for emergency medical care to arrive, is known as take-home naloxone (THN) (Strang et al., 1996).

The rate of successful overdose reversal following naloxone administration by laypersons has historically been very high (nearly 100% in some studies) (Dettmer et al., 2001; Clark et al., 2014; EMCDDA, 2015; Giglio et al., 2015; McDonald and Strang, 2016; Fairbairn et al. 2017) and THN is widely recognised as being effective and cost-effective in reducing opioid overdose mortality (Coffin and Sullivan, 2013; McDonald and Strang, 2016; Langham et al., 2018). Nonetheless, laws governing the possession of drugs, weak local and national support for harm reduction, and the stigma associated with addiction can all impede the successful implementation of THN (Dwyer et al., 2016; Mitchell and Higgens, 2016; Winstanley et al., 2016; Holloway et al., 2018). Other identified barriers to naloxone use include limited professional and lay person awareness of the availability of THN (Dietze et al., 2015; Mitchell and Higgens, 2016), as well as witnesses' reluctance to intervene because they are uncertain about how to identify an overdose (Richert, 2015; Dwyer et al., 2016; Heavey et al., 2018; Holloway et al., 2018) or are worried about police involvement, needle stick injuries, being personally too intoxicated to respond, or intervening when a person who has overdosed does not want help (Lagu et al., 2006; Wright et al., 2006; Richert, 2015; Neale et al., 2019).

One further, and frequently reported, factor undermining layperson preparedness to administer naloxone is concern that the person who has overdosed will respond by becoming angry, aggressive or even violent on regaining consciousness (Worthington et al., 2006; Sporer and Kral, 2007; Neale and Strang, 2015; Olsen et al., 2015; Richert, 2015; Sondhi et al., 2016; Faulkner-Gurstein, 2017; Heavey et al., 2018; Holloway et al., 2018; McAuley et al., 2018; Bessen et al., 2019). Within the literature, this phenomenon has been identified as resulting from 'over-antagonism'; that is, the dose of the antagonist naloxone given was more than pharmacologically needed to reverse the effects of the illicit agonists consumed (Neale and Strang, 2015). The anger of the person who has been resuscitated is variously attributed to the naloxone causing them to lose their 'high', to feel that they have wasted their drugs or money, or to experience uncomfortable or painful withdrawal symptoms (known as 'acute withdrawal syndrome') (Worthington et al., 2006; Kerr et al., 2008; Sporer and Kral, 2007; Neale and Strang 2015; Richert, 2015; Sondhi et al., 2016; UKMi, 2017; Heavey et al., 2018; Holloway et al., 2018; McAuley et al., 2018).

The reasons why people who have overdosed are given more naloxone than necessary have not been well studied. However, they are likely to include responder uncertainties regarding the amount and combination of drugs the person who has overdosed has consumed, poor understanding of naloxone pharmacology, first responder protocols that advocate a high naloxone dose, inability to titrate the dose of the different naloxone products, variable time periods before naloxone is first administered and then between any subsequent administrations, and other confounders such as the gender, weight and opioid tolerance of the person being resuscitated (Cantwell et al., 2005; Clarke et al., 2005; Lankenau et al., 2013; Neale and Strang, 2015; Fairbairn et al., 2017; Farrugia et al., 2019). In addition, lay responders may panic, forget to follow the dosing instructions they have been given, and accidentally ‘over treat’ or ‘over-antagonise’ the person who has overdosed (Neale et al., 2019).

Despite these various risk factors for over-antagonism, adverse events are not an inevitable outcome of naloxone administration and they may be mitigated by better information and guidelines on titrating naloxone dose against response (Neale and Strang, 2015) and by deploying routes of administration that arouse the person who has overdosed more slowly (i.e. subcutaneous or intramuscular rather than intravenous injections) (Horowitz, 1998; Wanger et al., 1998; Buajordet et al., 2004). Supporting this, research has found that some lay responders already actively seek to avoid inducing withdrawal by incrementally administering naloxone in small doses (Lankenau et al., 2013; Winston et al., 2015; Farrugia et al 2019; Neale et al., 2019) and that strategies for dose titration can be successfully built into overdose response training (Dettmer et al., 2001; Madah-Amiri et al., 2019). In addition, it has been suggested that adverse events could be prevented by better communication about naloxone, how it works, and its potential side effects at the point of treatment (Horowitz, 1998; Neale and Strang, 2015; Bessen et al., 2019). Reflecting this, Farrugia et al. (2019) found that lay responders seemed to manage conflict when administering naloxone by talking to, and reassuring, people as they were being resuscitated.

A naloxone reversal that successfully saves a person’s life can thus still produce suboptimal, undesirable, and harmful effects in the form of precipitated withdrawal symptoms, anger and aggression. These can undermine the effectiveness of THN programmes by prompting people who have overdosed to refuse or resist treatment and by increasing the likelihood that they might re-use opioids post resuscitation (Watson et al., 1998; Worthington et al., 2006; Richert, 2015; Neale and Strang, 2015; Black et al., 2017; UKMi, 2017; Bessen et al., 2019; Greene et al., 2019). Additionally, lay responders can become anxious or reluctant to administer naloxone in case they encounter hostility or aggression from the person being treated (Neale and Strang, 2015; Strang et al., 2018). Responding to such problems, the aim of this paper is to better understand factors associated with two widely reported adverse outcomes following naloxone administration; namely, the person resuscitated displays: i. withdrawal symptoms and ii. anger. In so doing, our objective is to identify ways of potentially improving both THN programmes and responses to emergency overdose events.

2. METHODS

2.1 Data sources

Our data derive from a convergent mixed methods study (Creswell and Plano Clark, 2018), combining quantitative data from a randomized controlled trial (RCT) of overdose education and naloxone prescribing to individuals with opioid use disorder and qualitative data from semi-structured interviews conducted with trial participants who had responded to an overdose whilst in the trial. Both the trial and the qualitative study received ethical approval from the New York State Psychiatric Institute (NYSPI) Institutional Review Board (IRB# 6723) and were conducted in the New York City (NYC) metropolitan area. Core information about each study component is described below.

2.1.1 RCT of overdose education and naloxone prescribing—The RCT (entitled: "Risks and benefits of overdose education and naloxone prescribing to heroin users") was conducted between September 2014 and October 2019 and funded by the National Institute on Drug Abuse (NIDA) (R01DA035207; NCT02535494). The primary aim was to determine whether more extensive overdose education could improve overdose outcomes compared to brief overdose education. Men and women (21-65 years of age) were eligible to participate provided that they met DSM-IV (American Psychiatric Association, 2000) criteria for opioid use disorder within the last 6 months regardless of current treatment status; spoke/read English; had no active psychiatric disorder that might interfere with participation; and had had no naloxone or cardiopulmonary resuscitation training within the past two years. In total, 403 participants were enrolled in the trial, of whom 228 completed follow up interviews at 1, 3, 6, and 12 months. Among other measures, follow up interviews assessed retention of naloxone training knowledge and captured key information surrounding any overdose events witnessed or experienced.

In NYC, organizations that work with people who use illicit opioids routinely offer largely standardized, brief overdose training that addresses risk factors, how to recognize an opioid overdose, and how to use naloxone. Trial participants either received the brief training (20-30 minutes) or an extended training that comprised the brief training plus a further two-hour session. The extended training reiterated and reinforced key information from the brief training, but additionally provided information about non-opioid overdose and taught cardiopulmonary resuscitation. Both the brief and extended training were conducted at Columbia University Irving Medical Center by research assistants who followed a written script to ensure that every participant received exactly the same information.

On completion of the training, all trial participants were given the option of receiving either intramuscular (IM) or intranasal (IN) naloxone as part of a naloxone rescue kit. All rescue kits included two doses of naloxone (regardless of formulation) plus a pair of latex gloves, a face shield for rescue breathing, sterile wipes, and an instructional handout. At the start of the trial, participants were offered the choice of an IM naloxone formulation comprising a needle and syringe with two glass vials (where the dose concentration was 0.4mg naloxone per 1ml solution in each vial, yielding a total dose of 0.8mg) or a multi-step atomized nasal naloxone spray assembled by combining a pre-filled luer-lock syringe with a nasal atomizer and spare vial (where the dose was 2mg/2ml in each vial [1mg/1ml to be administered to

each nostril] yielding a total possible dose of 4mg). In November 2015, the U.S. Food and Drug Administration approved a new concentrated nasal naloxone formulation (Narcan® nasal spray) that administers a single dose with a concentration of 4mg/0.1ml into one nostril (provided in a twin-pack yielding a total dose of 8mg). On NIDA's recommendation, the trial changed from providing the multistep IN naloxone to the single step Narcan® nasal spray in August 2017, although participants were still offered the option of receiving the IM device instead.

2.1.2 Semi-structured interviews—Between January 2016 and December 2018, 62 semi-structured interviews were conducted with 52 trial participants who reported being present at an overdose during one of their follow up assessments. Seven trial participants were interviewed more than once as they reported being present at multiple overdoses whilst in the trial: five were interviewed twice, one was interviewed three times, and one was interviewed four times. Sampling ensured a mix of males, females, overdose experiences, and naloxone formulations used. The time between the overdose event reported and the interview was also minimized as much as possible to maximize recall (most interviews were conducted within 3 months of the witnessed overdose; range 1 day to 6 months).

The primary aim of the qualitative interviews was to supplement the RCT data by collecting and analysing more detailed first-hand accounts of overdoses occurring post training in order to better understand and potentially improve the effectiveness of current overdose prevention programmes in NYC. Participation in the qualitative study was optional and followed a separate information giving and consenting process from the trial. All qualitative interviews were audio-recorded and conducted in private offices at the NYSPI. They lasted 20-65 minutes and were guided by an interview schedule that covered: demographic and psychosocial information, substance use and treatment, pre-trial overdoses experienced and witnessed, the last overdose witnessed since joining the trial (including how the person who overdosed responded to naloxone), and views on overdose training. Interview schedule questions were supplemented by prompts and probes to follow up issues raised by the participants. On completion of a qualitative interview, participants were compensated US $40.

2.2 Data handling and management

All quantitative trial data were entered, cleaned and stored at Columbia University, NYC. The audio files from the qualitative interviews were transcribed verbatim in the U.S. but the transcriptions were then encrypted and emailed to research team members in London, UK. Here, they were entered into the qualitative software programme MAXQDA v18 (VERBI Software, 2019) and coded by two team members who worked together to ensure consistency. The coding frame used was co-developed with a third team member and comprised deductive codes based on the interview schedule and more inductive codes emerging from the data. The coded data were then extracted from the qualitative software programme into Microsoft Word documents ready for analyses.

2.3 Analyses

2.3.1 Variable construction—Preliminary readings of the interview transcriptions and coded data revealed that although the study had a very high rate of successful reversals (96% of trial reversals were successful), there was widespread evidence of 'over-antagonism'. Specifically, participants often reported that the people they had resuscitated had displayed signs of opioid withdrawal and had become angry or aggressive. Meanwhile, further qualitative analyses of the interview data indicated that withdrawal symptoms and anger/aggression did not always occur together and, when they did occur together, they did not always follow the same sequential order (Parkin et al., 2020). As further qualitative analysis was unable to systematically test factors that might be associated with over-antagonism, we transformed key information from the qualitative interviews into dichotomous quantitative variables so that we could then combine these with variables from the trial and undertake a mixed methods analysis (Creswell and Plano Clark, 2018). In the mixed methods literature, this process of transforming qualitative data into numbers has been termed 'quantitization' (Tashakkori and Teddlie, 1998; Driscoll et al., 2007). Quantitization can, *inter alia*, show regularities and patterns in qualitative data that might otherwise be difficult to see, communicate or verify (Sandelowski et al., 2009).

To begin, the coded qualitative data relating to the last overdose event reported at each interview (n=62) were reviewed to ascertain whether (or not) withdrawal symptoms and, separately, whether (or not) anger, including aggression or violence, were reported. These results were then entered as two dichotomous variables ('withdrawal' [yes/no] and 'anger' [yes/no]) into the statistical software programme R (version 3.5.0) (R Core Team, 2013). The coded qualitative data were next further reviewed to create additional variables that were also entered into the R database along with quantitative variables relating to the same participants and overdoses from the main trial.

Variables were developed and selected based on the available study data and factors that, according to the team's reading of the literature and clinical understanding of the topic, seemed likely to make an overdose difficult to manage and/or to provoke either withdrawal symptoms or an angry reaction. They included demographic, pharmacological, situational, interpersonal, and overdose training related factors. One variable that was considered but reluctantly excluded was a naloxone dose variable. Whilst it would have been theoretically possible to convert the naloxone given at each overdose into a standardised dose, this would likely have produced misleading data as the amount of naloxone absorbed from different kits and formulations varies significantly (McDonald et al., 2018; Krieter et al., 2019). After several attempts to calculate a variable for 'naloxone dose absorbed', the team were not satisfied that the results were sufficiently reliable and so decided to use variables for 'intramuscular versus intranasal administration' and 'one naloxone dose versus more than one naloxone dose' instead. Table 1 describes the variables used in the analyses and the data source (interview or main trial) from which each variable was derived.

At this point, 15/62 overdose events (cases) had to be excluded because of missing information relating to how the person who had overdosed had responded to naloxone. Specific reasons for these missing data are shown in Figure 1. This left 47 overdose events

described by 40 participants: 11 cases of withdrawal only; 9 cases of anger only; 6 cases of withdrawal with anger; and 21 cases where neither withdrawal symptoms nor anger were reported. An analysis plan was then developed to explore associations between each of the variables of interest and reports of i. withdrawal (with or without anger; 17 overdoses: 11+6) and ii. anger (with or without withdrawal; 15 overdoses: 9+6).

2.3.2 Statistical analyses—All analyses were undertaken in R (version 3.5.0) (R Core Team, 2013). Descriptive analyses of variables were first conducted using counts and proportions for categorical variables and means and standard deviations for continuous variables (Table 2).

Exploratory analyses of variables associated with i. withdrawal and ii anger were then conducted. Yates' chi-squared tests (Yates, 1934) were used to identify possible associations between categorical independent variables and outcomes where values existed in all combinations of fields. This was not possible for one variable ('emergency services [911] attended the overdose event') as there were no instances where an ambulance did not attend and anger was not present. Continuous variables were examined for normality and t-tests were used to examine differences in means. The Bonferroni-corrected threshold for significance was set at $p = 0.0018$ (Bonferroni, 1936).

Associations that reached Bonferroni-corrected statistical significance were quantified using univariate logistic regressions, before these variables were combined in a single multivariate logistic regression. The model results are presented as regression coefficients and odds ratios (OR) with 95% confidence intervals (CI). The multivariate model was subsequently compared with the univariate model using Aikaike Information Criteria and a chi-squared test using the deviance and deviance residuals of both models. The variables were examined for multicollinearity by calculating the variance inhibitory factor.

Because of the small sample size, imputation of missing data was not reliable, so a complete case analysis was undertaken. Logistic regression was used to confirm that missing data were random or completely random. No predictor variable was significantly associated with complete case status.

3. RESULTS

3.1 Withdrawal symptoms

Withdrawal symptoms were more likely to be reported when more than one dose of naloxone was administered to the person who had overdosed (X^2 [df = 1, N = 46] = 4.0, p = 0.046); however, this did not meet the significance threshold following correction for multiple comparisons. Other pharmacological variables – fentanyl consumption, consumption of heroin only, injection of drugs, route of naloxone administration, subsequent use of drugs – were not associated with withdrawal. Additionally, no demographic, situational, interpersonal or overdose training related variable – sex of the person who had overdosed, person who had overdosed being concerned about loss of money or drugs, a pre-existing relationship between the participant and the person who had overdosed, participant's positive or negative communication during the reversal process, participant

having received brief or extended overdose training, and participant completing eight or more standard revival procedures – was associated with withdrawal (Table 3).

There were also no associations between whether (or not) withdrawal was reported and either the age of person who had overdosed or the participant's Opioid Overdose Knowledge Scale (OOKS) score (Williams et al., 2013) (Table 3).

3.2 Anger

Anger was less likely to be reported when participants communicated positively with the person who had overdosed by talking to them, explaining what had happened, and/or trying to calm them down (X_2 [df = 1, N = 42] = 14 $p < 0.001$). In contrast, anger was more likely to be reported when the participant communicated negatively with the person who had overdosed by criticizing, berating or chastising them during the resuscitation process (X_2 [df = 1, N = 42] = 20, $p < 0.001$). Anger was also more frequent when the person who had overdosed was concerned about loss of money or drugs after they had been resuscitated (X_2 [df = 1, N =47] = 5.8 $p = 0.016$), but the significance of the association did not survive correction for multiple comparisons. No other demographic, pharmacological, interpersonal or overdose training related variables – including sex of the person who had overdosed, consumption of fentanyl, consumption of heroin only, injection of drugs, route of naloxone administration, subsequent use of drugs, a pre-existing relationship between the participant and the person who had overdosed, the participant having received brief or extended overdose training, and the participant completing eight or more standard revival procedures – were associated with anger (Table 4).

There was also no association between anger and withdrawal symptoms or between anger and either the age of person who had overdosed or the participant's Opioid Overdose Knowledge Scale (OOKS) score (Williams et al., 2013) (Table 4).

Univariate logistic regression estimated the odds of the person who had overdosed displaying anger in reversals where there was positive communication as OR = 0.045 (95% CI 0.0072 – 0.21). The model was significant (X_2 [1] = 17.23, p <0.001), explaining 37% of the variance (Nagelkerke R^2) (Table 5). Univariate logistic regression estimated the odds of the person displaying anger in reversals where there was negative communication as OR = 50 (95% CI 8.9 – 457). The model was also significant (X_2 [1] = 24.20, p <0.001), explaining 50% of the variance (Nagelkerke R^2) (Table 5).

When positive and negative communication were combined in a single model, the association between both variables and anger continued to be significant. The adjusted odds ratio was 0.10 (95% CI 0.01 – 0.78) for positive communication and 27 (95% CI 4 – 295) for negative communication. Notably, the upper bound of the adjusted 95% confidence interval reflected more than a 20% reduction in odds of anger where there was positive communication and the lower bound of the adjusted 95% confidence interval represented an almost four-fold increase in the odds of anger where there was negative communication. The model was significant (X_2 [2] = 29.00, p <0.001) and accounted for 59% of the variance (Nagelkerke R^2) (Table 6).

When compared to the univariate model with negative communication as the sole predictor, the model including positive and negative communication provided a better fit (X_2 [1] = 11.7 p <0.001) and had a smaller Akaike Information Criterion (AIC [negative communication] = 34.6; AIC [positive communication model] = 41.5; AIC [all communication model] = 31.8), suggesting that both positive and negative communication were associated with anger. The model was examined for multicollinearity and the variance inflation factor was 1.002; demonstrating that multicollinearity was not present.

4. DISCUSSION

Our analyses were exploratory and inevitably have limitations. The sample size was initially small and cases then had to be deleted due to missing information on how the person who had overdosed had responded to receiving naloxone. A logistic regression including many variables was not possible, only very large effects could be detected and quantified, and the 95% confidence intervals of the point estimates for the odds ratios were wide. In addition, the analyses undertaken were neither pre-specified nor pre-registered; rather they were undertaken in response to inductive analyses of the qualitative data occurring whilst the trial was in progress. Accordingly, the variables used were based on the available data, rather than ideal measures, and focused on factors that seemed likely to be relevant from the team's reading of the literature and clinical understanding of the topic. This may have introduced bias into the analyses and we caution that other factors not explored, such as the naloxone dose absorbed, may also be relevant in explaining withdrawal and anger.

Despite these weaknesses, we believe that this the first research to combine demographic, pharmacological, situational, interpersonal and overdose training related factors to better understand why people often respond so negatively when their lives have just been saved by naloxone. We also note that it would be impossible to prospectively create a robust quantitative dataset that included all the variables that might be of interest given that sufficient real life emergency overdose events would be difficult to observe within the context of a research study; the accounts of those who overdosed, those who responded, and other bystanders would almost certainly yield inconsistencies; and there would be no reliable way of knowing what exact quantities and combination of substances and adulterants an individual had consumed prior to overdosing, their opioid tolerance at the point of overdose, or precisely how long intervals were between opioid use, first naloxone administration, and subsequent administrations.

Our analyses add to the existing literature by seeming to challenge a common assumption about opioid overdose reversals: that anger and aggression after a person has received naloxone occur in response to them experiencing withdrawal symptoms (Gaddis and Watson, 1992; Horowitz, 1998; Neale & Strang, 2015; Richert, 2015; Heavey et al., 2018; McAuley et al., 2018; Bessen et al., 2019; Farrugia et al., 2019). Instead, our findings suggest that withdrawal and anger could be independent phenomena. Withdrawal symptoms were potentially associated with receiving more than one naloxone dose, which seems logical given that withdrawal symptoms are likely to have strong pharmacological and physiological origins. Nonetheless, withdrawal was not associated with any other pharmacological or demographic variables. This seems surprising, but may be explained by

small effects which could not be detected using this size of sample, lack of current understanding regarding optimal dosing, and differences between the dosages and pharmacokinetics of the various naloxone products used (Goldfrank et al., 1986; Horowitz, 1998; Cantwell et al., 2005; Clarke et al., 2005; Fairbairn et al., 2017; UKMi, 2017).

In contrast, our findings indicate that anger may be more of a social phenomenon and less of a pharmacological or physiological response to naloxone administration. Consistent with previous research (Neale and Strang, 2015; Richert, 2015; Farrugia et al., 2019), we found that anger was potentially associated with a person who had overdosed being concerned about losing their money and drugs. Additionally, anger was strongly associated with the responder's positive or negative communication style (Neale and Strang, 2015; Bessen et al., 2019; Farrugia et al., 2019). Management of potential anger did not, however, appear to be affected by a responder's knowledge or attitude to overdose as measured by the Opioid Overdose Knowledge Scale (Williams et al., 2013), by their practical skills in managing an overdose (as measured by completion of 8 or more of 11 standard revival procedures), or by the training an individual had received in the study trial (brief or extended). Equally, and contra Farrugia et al. (2019), anger was not associated with whether the person who had overdosed knew the responder.

As previously stated, the primary purpose of naloxone administration is to prevent death. Nonetheless, it is also important to address any unintended harms associated with naloxone use (Neale and Strang, 2015; Strang et al., 2018). The risk of death from precipitated withdrawal symptoms and rebound toxicity is believed to be small (1 per cent or less), but it still exists (Worthington et al., 2006; UKMi, 2017). Withdrawal was reported in 17/47 (36%) of the overdose events we studied. However, we found no evidence that either withdrawal symptoms or anger were associated with people who had overdosed being known or presumed to go on to use more drugs post reversal. Despite this, people who had overdosed were known or presumed to have later re-used drugs in 7/35 (20%) of the overdose events for which data were available (Table 2). Reasons for post resuscitation substance use thus require further investigation and strategies to prevent it are urgently needed.

Anger was reported in 15/47 (32%) of the overdose events studied. According to previous research, anger and aggression can result in first responders being abused and attacked, can cause them to feel resentful about the ingratitude of those they have resuscitated, and can leave them anxious or reluctant to administer naloxone again (Neale and Strang, 2015; McAuley et al., 2018). Our analyses showed that anger was strongly linked to how well lay responders communicated with the person who had overdosed. It is therefore possible that lay responders may be able to placate a person they have resuscitated by explanation and reassurance (Neale and Strang, 2015; Farrugia et al., 2019). Equally, they might provoke them by criticism or rebuke. On the face of it, expecting people who have received relatively limited training to 'socially' manage complex and potentially aggressive and violent medical emergencies involving acquaintances or even strangers seems unrealistic. Yet, THN appears to be premised on the assumption that lay responders will behave in this highly skilful way and our data confirmed that this was, in fact, how they often reacted (Farrugia et al., 2019; Neale et al., 2019).

5. CONCLUSIONS

Delivering enough naloxone to ensure adequate resuscitation whilst avoiding the precipitation of withdrawal symptoms has been likened to walking a medical tightrope (Clarke et al., 2005). The increasing range of THN products and the emergence of more potent and faster-acting synthetic opioids, such as fentanyl, only serve to compound the administration complexity (Fairbairn et al., 2017). Unfortunately, our analyses do not yield any new suggestions for preventing withdrawal symptoms whilst guaranteeing a successful overdose reversal. Nonetheless, the data we have presented seem broadly supportive of existing recommendations to deliver naloxone carefully in incremental doses, to choose products that support the delivery of low incremental doses, and to provide training on the specific product selected for supply locally (WHO, 2014; Neale and Strang, 2015; UKMi, 2016).

Although more research is needed, our findings indicate ways that THN programmes might be improved to help address the angry outbursts that can occur after naloxone administration. Most obviously, more time and resources could be invested in training lay responders to understand how people who experience an opioid overdose may feel post resuscitation, why they may react negatively, and also how it may be possible to manage the situation and prevent problems from escalating by using positive communication and reassurance (Neale and Strang, 2015; Farrugia et al., 2019). This must not be presented in a way that either makes lay responders unnecessarily afraid that anger or violence will occur or leads them to feel that they have failed if the person who is being resuscitated cannot be placated. Nonetheless, training needs to recognize that people who have overdosed might react angrily. Moreover, it seems important to offer people who have been present at an opioid overdose support in talking through what happened, particularly any anger, aggression or violence directed at them.

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HIGHLIGHTS

- Withdrawal symptoms and anger can undermine willingness to administer naloxone
- Withdrawal symptoms and anger after naloxone administration may be unrelated
- Positive communication style is associated with less anger after naloxone
- Negative communication style is associated with more anger after naloxone
- Training programmes should support lay responders in managing anger after naloxone

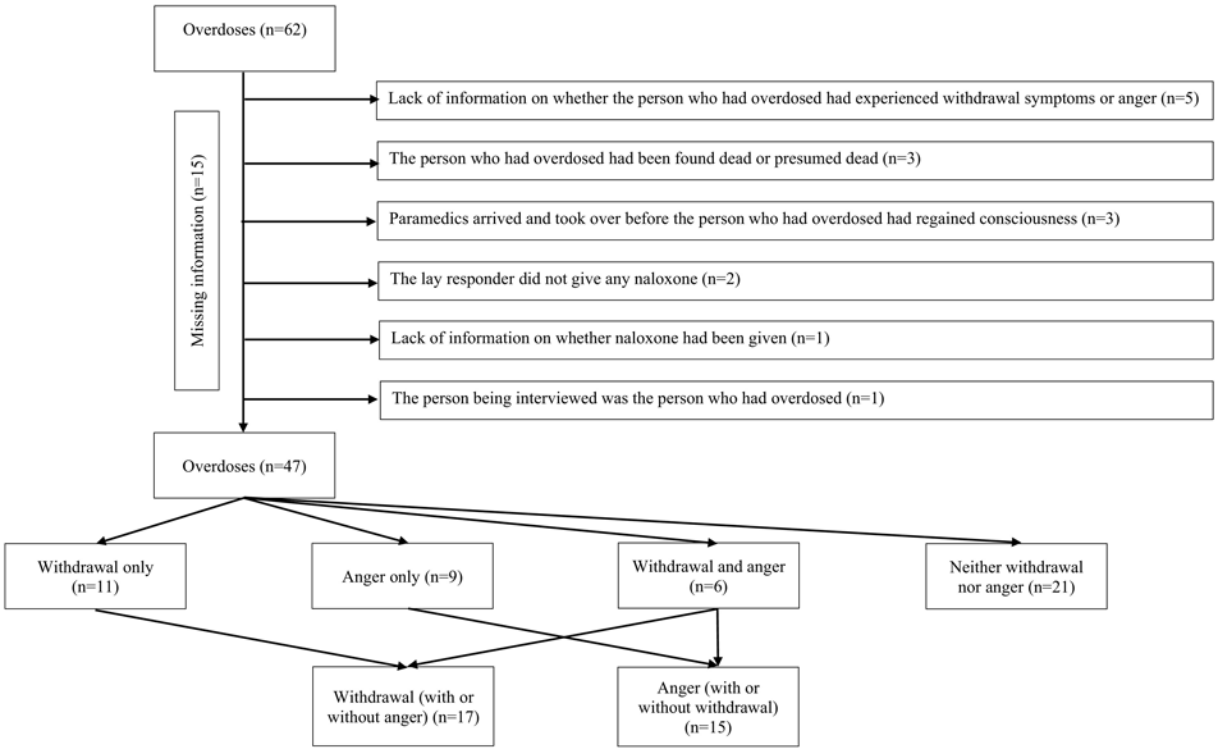

FIGURE 1:
SELECTION OF OVERDOSE EVENTS FOR INCLUSION IN THE ANALYSES

TABLE 1:

VARIABLES CONSTRUCTED FOR THE MIXED METHODS ANALYSIS

Variable	Data source[1]
Demographic	
Sex of person who overdosed is male v female	Interview
Age of person who overdosed (years)	Main trial
Pharmacological	
Person who overdosed consumed fentanyl prior to overdosing (no v yes)	Interview
Person who overdosed consumed heroin and no other substances prior to overdosing (no v yes)	Interview
Person who overdosed injected drugs prior to overdosing (no v yes)	Interview
Intramuscular naloxone was used to reverse the overdose (no v yes)	Interview
More than one dose of naloxone (IM or IN) was administered to the person who overdosed (no v yes)	Interview
Person who overdosed was known or presumed to have gone on to use more drugs post reversal (no v yes)	Interview
Situational	
Emergency services (911) attended the overdose event (no v yes)	Interview
Person who overdosed expressed concern about loss of money or drugs post resuscitation (no v yes)	Interview
Interpersonal	
Participant had a pre-existing relationship with the person who overdosed as they were a family member or friend (no v yes)	Interview
Participant communicated positively with the person who overdosed during the reversal process (no v yes)[2]	Interview
Participant communicated negatively with the person who overdosed during the reversal process (no v yes)[3]	Interview
Overdose training related	
Participant received extended (rather than brief) overdose training (no v yes)	Main trial
Participant's Opioid Overdose Knowledge Scale (OOKS) score at their last assessment prior to the overdose (range 0-45)[4]	Main trial
Participant completed 8 or more of 11 standard revival procedures (no v yes)[5]	Interview

[1]Responses are based on participant self-reports (via their follow up assessments for the trial or the qualitative interviews) unless otherwise stated.

[2]Participant talked to the person who had overdosed, explained what was happening and/ or tried to calm them down (based on researcher assessment of the interview data).

[3]Participant criticized, berated or chastised the person who had overdosed or reacted angrily when the person who had overdose complained or reacted negatively (based on researcher assessment of the interview data).

[4]The Opioid Overdose Knowledge Scale (Williams et al., 2014) is a validated self-completed instrument used to assess the level of knowledge of opioid overdose management among addiction professionals, patients and family members. It records knowledge about risk factors for having an opioid overdose, signs of an opioid overdose, actions to be taken in an overdose situation, naloxone effects and administration, adverse effects, and aftercare procedures.

[5]Participant completed 8 or more of the following 11 standard overdose response procedures (based on researcher assessment of the interview data): 1. Recognized overdose symptoms; 2. Called out the name of the person who had overdosed; 3. Shaked, touched, shouted at the person who had overdosed to waken them; 4. Checked the eyes, pulse and breathing of the person who had overdosed; 5. Checked the person who had overdosed for the colour of their skin, lips, fingernails; 6. Called the Emergency Services before administering naloxone; 7. Placed the person who had overdosed in the recovery position; 8. Administered cardiopulmonary resuscitation; 9. Gave rescue breathing; 10. Successfully assembled the naloxone kit; 11. Delivered naloxone.

TABLE 2:

FREQUENCY OF VARIABLES

Categorical variables						
Variable	**No**		**Yes**		**Missing**	
	n	%	n	%	n	%
Outcomes						
Withdrawal	30	63.8	17	36.1	0	0
Anger	32	68.1	15	32.0	0	0
Demographic						
Sex of person who overdosed	Male		Female			
	34	72.3	13	27.7	0	0
Pharmacological						
Fentanyl taken	36	76.6	10	21.3	1	2.1
Heroin only taken	24	51.0	22	46.8	2	2.1
Drugs injected	12	25.5	28	59.6	7	14.9
IM naloxone given	36	76.6	10	21.3	1	2.1
More than one dose of naloxone given	21	44.7	25	53.2	1	2.1
Known or presumed re-use of drugs post resuscitation	28	59.6	7	14.9	12	25.5
Situational						
Emergency services attended	16	34.0	30	63.8	1	2.1
Person who overdosed expressed concern about loss of money or drugs	29	61.7	18	38.2	0	0
Interpersonal						
Pre-existing relationship between participant and person who overdosed	25	53.2	22	46.8	0	0
Positive communication during the resuscitation process	14	29.8	28	59.6	5	10.6
Negative communication during the resuscitation process	28	59.6	14	29.8	5	10.6
Overdose training related						
Participant received extended overdose training	13	27.7	34	72.3	0	0
8 or more standard revival procedures completed	31	66.0	15	31.9	1	2.1
Continuous variables						
Variable	**Mean**	**SD**	**Median**	**Range**	**Missing n**	**Missing %**
Age of person who overdosed	40.5	12.49	40	19-62	0	0
Opioid Overdose Knowledge Scale (OOKS) score	39.3	3.46	40	25-44	6.4	3

TABLE 3:

TEST STATISTICS FOR WITHDRAWAL

Variable	X_2	**df**	**N**	***p***
Demographic				
Sex of person who overdosed	0.29	1	47	0.588
Pharmacological				
Person who overdosed consumed fentanyl prior to overdosing	0.36	1	46	0.554
Person who overdosed consumed heroin and no other substances prior to overdosing	2.59	1	45	0.100
Person who overdosed injected drugs prior to overdosing	0.05	1	40	0.833
Intramuscular naloxone was used to reverse the overdose	0.02	1	46	0.885
More than one dose of naloxone (IM or IN) was administered to the person who overdosed	**4.0**	**1**	**46**	**0.046***
Person who overdosed was known or presumed to have gone on to use more drugs post reversal	0.96	1	35	0.327
Situational				
Person who overdosed expressed concern about loss of money or drugs on resuscitation	0.38	1	47	0.911
Interpersonal				
Participant had a pre-existing relationship with the person who overdosed as they were a family member or friend	0.88	1	47	0.588
Participant communicated positively with the person who overdosed during the reversal process	0.01	1	42	0.911
Participant communicated negatively with the person who overdosed during the reversal process	0.01	1	42	0.911
Overdose training related				
Participant received extended overdose training	0.02	1	47	0.891
Participant completed 8 or more of 11 standard revival procedures	1.6	1	46	0.202
Variable	***t***	**Mean (SD) Withdrawal −**	**Mean (SD) Withdrawal +**	***p***
Age of person who overdosed (years)	−0.14547	40 (13)	41 (11)	0.885
Opioid Overdose Knowledge Scale (OOKS) score	0.20035	39 (2.7)	40 (4.6)	0.843

TABLE 4:

TEST STATISTICS FOR ANGER

Variable	X_2	**df**	**N**	***p***
Demographic				
Sex of person who overdosed		1	47	
Pharmacological				
Person who overdosed exhibited withdrawal symptoms	0.002	1	47	0.961
Person who overdosed consumed fentanyl prior to overdosing	4.9×10^{-31}	1	46	1
Person who overdosed consumed heroin and no other substances prior to overdosing	1.9	1	45	0.160
Person who overdosed injected drugs prior to overdosing	3.1	1	40	0.077
Intramuscular naloxone was used to reverse the overdose	0.12	1	46	0.723
More than one dose of naloxone (IM or IN) was administered to the person who overdosed	0.51	1	46	0.476
Person who overdosed was known or presumed to have gone on to use more drugs post reversal	0.46	1	35	0.499
Situational		1		
Person who overdosed expressed concern about loss of money or drugs post resuscitation	**5.8**	**1**	**47**	**0.016**
Interpersonal				
Participant had a pre-existing relationship with the person who overdosed as they were a family member or friend	0.11	1	47	0.744
Participant communicated positively with the person who overdosed during the reversal process	**14**	**1**	**42**	**<0.001**
Participant communicated negatively with the person who overdosed during the reversal process	**20**	**1**	**42**	**<0.001**
Overdose training related				
Participant received extended overdose training	1.3×10^{-31}	1	47	1
Participant completed 8 or more of 11 standard revival procedures	0.53	1	46	0.467
Variable	***t***	**Mean (SD) Anger −**	**Mean (SD) Anger +**	***p***
Age of person who overdosed (years)	1.52	42 (12)	37 (12)	0.139
Opioid Overdose Knowledge Scale (OOKS) score	−1.28	39 (3.9)	40 (23.0)	0.207

TABLE 5:

UNIVARIATE LOGISTIC REGRESSION – COMMUNICATION AND ANGER

Variable	B (SE)	95% CI for odds ratio		
		Lower	Odds ratio	Upper
Constant	1.3 (0.65)			
Positive communication	−3.1 (0.85)	0.0072	0.045	0.21*
Constant	−2.1 (0.61)			
Negative communication	3.9 (1.0)	8.9	50	457**

*R^2 = 0.31 (Hosmer-Lemeshow), 0.14 (Cox-Snell), 0.37 (Nagelkerke). Model $X_2(1) = 17.23$, $p < 0.001$

**R^2 = 0.44 (Hosmer-Lemeshow), 0.19 (Cox –Snell), 0.50 (Nagelkerke). Model $X_2(1) = 24.20$, $p < 0.001$

TABLE 6:

MULTIVARIATE LOGISTIC REGRESSION – COMMUNICATION AND ANGER

Variable	B (SE)	95% CI for odds ratio		
		Lower	Odds ratio	Upper
Constant	−0.46 (0.95)			
Positive communication	−2.3 * (1.1)	0.010	0.10	0.78
Negative communication	3.3 ** (1.1)	4.0	27	295

R^2 = 0.53 (Hosmer-Lemeshow), 0.23 (Cox –Snell), 0.59 (Nagelkerke). Model $X_2(2) = 29.00$, $p < 0.001$.

* $p < 0.05$

** $p < 0.01$

VIF 1.002