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Complete List of Authors:	Okolie, Chukwudi; Swansea University, College of Medicine Evans, Bridie; Swansea University, Medicine John, Ann; Swansea University, Farr Institute Moore, Chris; Welsh Ambulance Services NHS Trust, Medical and Clinical Services Directorate Russell, Daphne; Swansea University, College of Medicine Snooks, Helen; Swansea University, Medicine
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Community-based interventions to prevent fatal overdose from illegal drugs: a systematic review protocol

Chukwudi Okolie[1*]; Bridie Angela Evans[1]; Ann John[1]; Chris Moore[2] ; Daphne Russell[1]; Helen Snooks[1]

[1] College of Medicine, Swansea University, Singleton Park, Swansea, SA2 8PP, United Kingdom

[2] Welsh Ambulance Services NHS Trust, Blackweir Ambulance Station, North Road, Cardiff, CF10 3DX

*Corresponding author: Dr Chukwudi Okolie, College of Medicine, Swansea University, Singleton Park, Swansea, SA2 8PP, UK. Telephone: +44 (0)1792 606509. E-mail address: c.o.okolie@swansea.ac.uk

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ABSTRACT

Introduction

Drug overdose is the most frequent cause of death amongst people who misuse illegal drugs. People who inject these drugs are 14 to 17 times more likely to die than their non-drug using peers. Various strategies to reduce drug related deaths have failed to meet target reductions. Research into community-based interventions for preventing drug overdose deaths is promising. This review seeks to identify published studies describing community-based interventions and to evaluate their effectiveness at reducing drug overdose deaths.

Methods and analysis

We will systematically search key electronic databases using a search strategy which groups terms into four facets: 1. Overdose event. 2. Drug classification. 3. Intervention. 4. Setting. Searches will be limited where possible to international literature published in English between 1998 and 2014. Data will be extracted by two independent reviewers using a pre-defined table adapted from the Cochrane Collaboration handbook. The quality of included studies will be evaluated using the Cochrane Collaboration's tool for assessing risk of bias. We will conduct a meta-analysis for variables which can be compared across studies, using statistical methods to control for heterogeneity where appropriate. Where clinical or statistical heterogeneity prevents a valid numerical synthesis, we will employ a narrative synthesis to describe community-based interventions, their delivery and use, and how effectively they prevent fatal overdoses.

Ethics and dissemination

We will publish findings from this systematic review in a peer-reviewed scientific journal and present results at national and international conferences. It will be disseminated electronically and in print.

Trial registration number: PROSPERO CRD42015017833

Strengths and limitations of this study

- Our systematic review will provide a comprehensive assessment of the methods used to prevent deaths from drug overdose in the community setting
- The results of this review will have impact for policy and practice by providing relevant data to identify and describe existing community-based interventions and assess evidence about their effectiveness in preventing fatalities.
- A potential limitation to this work may be a lack of available high quality studies. However, it may also identify research gaps so that future studies can target areas where further knowledge can contribute towards the greatest impact on reducing drug overdose deaths.

INTRODUCTION

Drug overdose is the most frequent cause of death amongst people who misuse illegal drugs [1]. In England and Wales, nearly 3000 drug poisoning deaths (involving both legal and illegal drugs) were registered in 2013 [2]. As in previous years, just over two-thirds (2,032) of these deaths were in males, an increase of 19% over the previous year and the highest since 2009. The equivalent number of female deaths was 923, an increase of 4% over 2012, and the highest since 2004 [2, 3]. Drug poisoning accounted for nearly one in seven deaths among people in their 20s and 30s [2]. Annual mortality rates for injecting drug users is 14-17 times greater than for their non-drug using peers [4, 5]. Numbers of fatal drug overdoses exceeds deaths caused by diseases in this group in many countries [4, 6-10]. Drug overdose is the second highest cause of death in the United States after vehicle fatalities while deaths from opiate overdose in the UK are among the highest in Europe [11]. Drug overdose death rates have been rising for decades. In the USA, fatal drug overdoses increased by more than 400% between 1980 and 1999 and more than doubled between 1999 and 2005.

Between 10% and 40% of people have tried an illegal drug in their lifetime [12, 13]. Death rates are higher for males although the number of female deaths in the UK is growing and rose by 10% between 2009 and 2010. UK death rates are highest among the 30-39 year age group while overdose is the number one injury rated killer among 35-54 year olds in the United States [3, 11, 14]. Drug misuse deaths are five times higher in deprived parts of England and Wales [15]. Heroin and other related opiates are responsible for the highest mortality rates among drug users [12]. Deaths attributed to drug overdose are typically seen in older, heroin-dependent males not in drug treatment at the time of death [16]. Risk of death is also increased by use of more than one drug, injecting drugs, homelessness, sexual orientation and changes in tolerance to a drug. Drug users released from prison in Australia, the USA and UK are up to 40 times more likely to die from an overdose than similar individuals from the general population [14, 16-24].

In the European Union, government strategies to cut drug related deaths have failed to meet target reductions [25]. The World Health Organisation recommends countries have drug strategies based on national epidemiological data and effectiveness of methods to reduce dependency and death [26]. The UK government target, set in 1999 to reduce drug related deaths by 20% by 2004, was not met [13, 14]. The current approach aims to prevent drug use and support recovery from drug dependence and includes a priority to gather research

evidence about effective approaches to drugs prevention [27]. The National Treatment Agency and Department of Health have named carers as one of the key groups to be targeted to reduce the risks of overdose. Treatment for opioid overdose is by administration of naloxone hydrochloride (also known as Narcan), either intravenously (IV) or intramuscularly when IV access is not possible [28]. In the UK, naloxone may be administered by emergency care practitioners in the Emergency Department (ED) and by emergency ambulance personnel in the community.

Research about opioid dependence has focused on drug treatments with the aim of achieving long term detoxification, abstinence or maintenance. A number of systematic reviews have established efficacy of various pharmacological treatments by comparing them with each other or compliance with abstinence programmes. For example, one suggests that psychosocial treatments may increase adherence to detoxification programmes [29-31]. Research into community-based treatment and prevention programmes has begun to show some successful approaches to preventing drug overdose deaths, including among former prison offenders and through safe injecting facilities [32-35]. Since the 1990s, interest has grown in reducing overdose deaths by providing 'take-home' naloxone to users, families and drug services [36-39]. Witnesses at an overdose event are willing to intervene and training, such as in CPR or naloxone delivery, can enhance an effective response [40, 41].

The World Health Organisation has summarised a range of psychosocially assisted pharmacological treatments for opioid dependence [26]. However, the range of interventions available and their effectiveness to treat or prevent overdose deaths has not been assessed. There is also a lack of evidence about best methods to administer and deliver treatments in the pre-hospital setting. Meanwhile, there have been calls for research into preventative interventions for drug users at high risk of death in order to reduce the rising numbers of fatal and non-fatal overdoses [42-44]. A recent systematic review [45] looked at the effectiveness of community-based opioid overdose prevention programmes (OOPPs) that included the distribution of naloxone. This review did not include the emergency medical services nor harm reduction programmes such as supervised injection facilities (SIFs). They did not conduct a meta-analysis on their data and the review did not adhere strictly to PRISMA guidelines. There are currently no other reviews assessing the effectiveness of SIFs. Given the high mortality associated with drug overdose it is essential to undertake a review assessing the effectiveness of every type of overdose prevention programme offered in the community.

We present the protocol of a systematic review to assess the effectiveness of methods to prevent deaths from drug overdose in the community setting.

This protocol is prepared and presented in accordance with the PRISMA guidelines [46].

Objectives

This systematic review will:

1. Identify published studies describing interventions delivered in the community to prevent fatal overdoses of illegal drugs
2. Evaluate the effectiveness of these interventions to reduce overdose deaths

METHODS

Criteria for considering studies for the review

We will include studies reporting effectiveness data about interventions delivered to drug users in order to prevent a fatality from a future overdose in the community. The intervention should be initiated or delivered in the community. We will consider all published studies from 1 January 1998, reported in English.

We will exclude studies reporting use of drugs not listed on the UK Misuse of Drugs Act 1971. Interventions to treat a presenting overdose, manage drug dependency or without an overdose prevention component will be excluded. However, we will include studies which report referral to maintenance treatments if these are part of a multi-faceted intervention to prevent overdose.

Inclusion and exclusion criteria are shown in Table 1

Table 1: Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Drug users who are at risk of overdose on illegal drugs or who present to emergency or drug services because of use of illegal drugs, where illegal drugs are those listed under the UK Misuse of Drugs Act 1971	People who overdose or are at risk of overdose on drugs not listed on the UK Misuse of Drugs Act 1971
Intervention	Intervention to prevent a fatality from a future overdose in the community	• Treatment for a presenting overdose • Treatment to manage drug dependency • Interventions without an acute overdose prevention component e.g. maintenance therapy, naltrexone
Context	Intervention initiated or delivered in the pre-hospital or community setting	Intervention initiated in hospital
Outcomes	Effectiveness data, with any type of comparator e.g. randomised trial, before-and-after study, controlled cohort study, interrupted time series etc.	• No effectiveness data • No comparator or control
Study limits	• Published between 1998-2014 • English language	

Search strategy for identifying relevant studies

We will undertake a systematic review following PRISMA guidelines for undertaking and reporting systematic reviews [46]. We will adhere to Cochrane-recommended key stages of a systematic review [47].

We will systematically search the following electronic databases: PubMed, CINAHL, Cochrane (clinical trials database), EMBASE, PsychInfo, HMIC, and the National Library for Health using a search strategy (Appendix I) which groups terms into four facets:

1. Overdose event
2. Drug classification
3. Intervention
4. Setting

We will use Medical Subject Headings (MeSH) and key word terms where available. Searches will be limited where possible to international literature published in English between 1998 and 2014. The literature search strategy will be adapted to suit each database.

We will manually search the reference lists of eligible studies and relevant reviews and trace their citations using Web of Knowledge. We will save search results in the electronic reference management system EndNote (version X7).

Selection of studies for inclusion in the review

We will undertake a two stage screening process for selection of studies. One reviewer (CO) will screen titles and abstracts against inclusion criteria to identify potentially eligible texts. A second reviewer (BAE) will independently check 10% of the decisions including anywhere the first reviewer is uncertain. Two reviewers (CO & CM) will independently assess full text articles to identify texts to be included in the review, and examine the reference lists of all selected articles to identify other potentially eligible studies. Any disagreements at either stage will be referred to a third reviewer (AJ).

Data extraction

Two reviewers (CO & CM) will independently extract data using a pre-defined table adapted from the Cochrane Collaboration handbook [47] which we will pilot and adjust as necessary. We will extract general information (authors, year, country, publication details), study characteristics (study design, setting, sample size, response rate), description of intervention and outcomes as well as additional data on fatal and non-fatal poisoning numbers and rates. Both reviewers will compare collected data. Any disagreements will be referred to a third reviewer (DR).

Assessment of the quality of included studies

We will evaluate the quality of included studies using the Cochrane Collaborations' tool for assessing risk of bias [47]. This tool assesses seven specific domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other sources of bias. A judgement of 'Low risk' of bias, 'High risk' of bias, or 'Unclear risk' of bias will be assigned relating to the risk of bias within each entry and presented in a table.

Data synthesis

We will summarise effectiveness data by intervention and context. We will, conduct a meta-analysis for variables which can be compared across studies, using statistical methods to control for heterogeneity where appropriate [48]. Where there is sufficient clinical or statistical heterogeneity to prevent a valid numerical synthesis, we will employ a narrative synthesis [49] to describe community-based interventions, their delivery and use, and how effectively they prevent fatal overdoses.

Presenting and reporting results

We will present results according to the PRISMA reporting guidance [46]. The study selection will be described in a flowchart, with reasons given for excluding papers. Quantitative data will be presented in tables and forest plots where appropriate. We will provide narrative summaries describing characteristics of included studies, details of the interventions, how they are delivered and their effects.

Dissemination

We will publish findings from this systematic review in a peer-reviewed scientific journal and present results at national and international conferences. We will also make our results available to UK policy makers and the Association of Ambulance Chief Executives (UK), National Ambulance Services Medical Directors (UK) and the Wales National Implementation Board for Drug Poisoning Prevention.

Ethics

This study will use published data, so ethical permissions are not required. However, we will adhere to ethical and governance standards in the management of our data and presentation of findings.

Conclusion

Drug overdose is the most frequent cause of death amongst people who use illegal drugs [1]. Government drug strategies to cut drug related deaths have failed to meet target reductions. There is growing interest in alternatives to detoxification, abstinence or maintenance to prevent drug related deaths. Carers have been identified as a route to achieve this while some evidence suggests community-based treatment and prevention programmes may be successful. We anticipate this review will have impact for policy and practice by providing

relevant data to identify and describe existing community-based interventions and assess evidence about their effectiveness in preventing fatalities. A potential limitation to this work may be a lack of available high quality studies. However, it may also identify research gaps so that future studies can target areas where further knowledge can contribute towards the greatest impact on reducing death rates in this vulnerable population.

Competing interests

The authors are unaware of any conflict of interests

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Contributorship statement

HS, BAE, AJ, and DR contributed to the conception of the study. All authors contributed to the study design. The manuscript protocol was drafted by CO. Screening of studies for inclusion will be undertaken by CO, CM, and BAE. AJ will arbitrate in case of disagreements. Data extraction will be undertaken by CO and CM. DR will arbitrate in case of disagreements. All authors approved the publication of the protocol.

Data sharing statement

There is currently no data available for sharing at the protocol stage. On completion of the study our data will be fully available on request.

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Appendix I: Search strategy for a review of community based interventions to prevent fatal overdoses from illegal drugs

This search strategy will be used in PubMed and adapted for each of the other databases.

KEY: Mesh = exploded Mesh heading
Supplementary Concept=These are index terms in PubMed used in particular for chemicals and drugs.
[tiab]= title / abstract

1	"Drug-Related Side Effects and Adverse Reactions"[Mesh]
2	"Drug Overdose"[Mesh]
3	poisoning[tiab]
4	overdose[tiab]
5	toxic[tiab]
6	toxicity[tiab]
7	(OR/1-6)
8	"Designer Drugs"[Mesh] OR "Street Drugs"[Mesh] OR "Hallucinogens"[Mesh]
15	"Methadyl Acetate"[Mesh]
16	"Alphaprodine"[Mesh]
17	"Bufotenin"[Mesh] OR "magic mushrooms"
18	buprenorphine[Mesh] OR buprenorphine[tiab]
19	“Coca”[Mesh]
20	"Cocaine"[Mesh] (exp includes Crack)
22	Krokodil[tiab] OR Desomorphine[tiab]
23	"Dextromoramide"[Mesh]
24	"Heroin"[Mesh] OR diamorphine[tiab]
25	"18,19-dihydroetorphine" [Supplementary Concept]
26	"Dihydromorphine"[Mesh]
28	"dipipanone" [Supplementary Concept]
29	"Morphinans"[Mesh]
30	“etryptamine” [Supplementary Concept]
31	"Fentanyl"[Mesh]
34	“ketobemidone” [Supplementary Concept]
36	"lofentanil" [Supplementary Concept]
37	"Lysergic Acid Diethylamide"[Mesh]
38	“Mescaline”[Mesh]
39	"Methadone"[Mesh]
40	("MDMA"[tiab] OR methylenedioxymethamfetamine[tiab])
42	“Opium”[Mesh]
45	"Isonipecotic Acids"[Mesh]
47	"Phenoperidine"[Mesh]
49	“piminodine” [Supplementary Concept]
52	Methylamphetamine[tiab]
55	Psilocybine[Mesh]
56	tapentadol [Supplementary Concept] OR ("Angel Dust")
57	“remifentanil” [Supplementary Concept]
58	“Tilidine”[Mesh]
59	Phencyclidine[Mesh]
61	"Amphetamines"[Mesh]
62	Barbiturates[Mesh]
63	Cannabinol[Mesh] OR “Cannibis”[Mesh]
64	Marijuana Abuse[Mesh]
70	"Glutethimide"[Mesh]
71	“Methaqualone”[Mesh] OR Mandrax[tiab]
72	“monomethylpropion” [Supplementary Concept]
75	“Methylphenidate"[Mesh]

76 "O-demethyltramadol" [Supplementary Concept] OR Tramadol[Mesh]
77 "2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone" [Supplementary Concept] OR methoxetamine[tiab]
78 "Phencyclidine"[Mesh]
80 Phenmetrazine[Mesh]
82 Amitriptyline[Mesh]
83 Anabolic Agents[Mesh]
84 Aminorex[Mesh]
85 "Benzodiazepines"[Mesh]
89 "Dextropropoxyphene"[Mesh]
92 Gamma-butyrolactone[tiab] OR "4-Butyrolactone"[Mesh] OR GBL[tiab]
93 Gamma hydroxybutrate[tiab] OR GHB[tiab]
94 Ketamine[Mesh]
95 Meprobamate[Mesh]
97 Methaqualone[Mesh]
99 Pemoline[Mesh]
101 "Phenmetrazine"[Mesh]
102 "pyrovalerone" [Supplementary Concept]
104 "zolpidem" [Supplementary Concept]
105 "Androstenediol"[Mesh]
106 "Chorionic Gonadotropin"[Mesh]
107 "Clenbuterol"[Mesh]
108 Non-human chorionic gonadotrophin[tiab]
109 Somatotropin[tiab]
110 Somatrem[tiab]
111 Somatropin[tiab]
112 "Zeranol"[Mesh]
113 "Zilpaterol" [Supplementary Concept]
114 OR/(8-113)
115 care[tiab] OR treatment[tiab] OR intervention[tiab] OR prevention[tiab] OR rapid assessment response[tiab] OR rapid appraisal[tiab] OR crisis[tiab] OR management[tiab] OR critical[tiab] OR therapy[tiab] OR care pathway[tiab] OR referral[tiab] OR opiate antagonist[tiab] OR opiod antagonist[tiab] OR opiate reversal[tiab] OR opiod reversal[tiab]

116 (115 AND 114 AND 7)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4, 5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6, 7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7, 8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	14,15
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7, 8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7, 10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2 for each meta-analysis.	9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

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Community-based interventions to prevent fatal overdose from illegal drugs: a systematic review protocol

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Community-based interventions to prevent fatal overdose from illegal drugs: a systematic review protocol

Chukwudi Okolie[1*]; Bridie Angela Evans[1]; Ann John[1]; Chris Moore[2] ; Daphne Russell[1]; Helen Snooks[1]

[1] College of Medicine, Swansea University, Singleton Park, Swansea, SA2 8PP, United Kingdom

[2] Welsh Ambulance Services NHS Trust, Blackweir Ambulance Station, North Road, Cardiff, CF10 3DX

*Corresponding author: Dr Chukwudi Okolie, College of Medicine, Swansea University, Singleton Park, Swansea, SA2 8PP, UK. Telephone: +44 (0)1792 606509. E-mail address: c.o.okolie@swansea.ac.uk

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ABSTRACT

Introduction

Drug overdose is the most frequent cause of death amongst people who misuse illegal drugs. People who inject these drugs are 14 to 17 times more likely to die than their non-drug using peers. Various strategies to reduce drug related deaths have failed to meet target reductions. Research into community-based interventions for preventing drug overdose deaths is promising. This review seeks to identify published studies describing community-based interventions and to evaluate their effectiveness at reducing drug overdose deaths.

Methods and analysis

We will systematically search key electronic databases using a search strategy which groups terms into four facets: 1. Overdose event. 2. Drug classification. 3. Intervention. 4. Setting. Searches will be limited where possible to international literature published in English between 1998 and 2014. Data will be extracted by two independent reviewers using a pre-defined table adapted from the Cochrane Collaboration handbook. The quality of included studies will be evaluated using the Cochrane Collaboration's tool for assessing risk of bias. We will conduct a meta-analysis for variables which can be compared across studies, using statistical methods to control for heterogeneity where appropriate. Where clinical or statistical heterogeneity prevents a valid numerical synthesis, we will employ a narrative synthesis to describe community-based interventions, their delivery and use, and how effectively they prevent fatal overdoses.

Ethics and dissemination

We will publish findings from this systematic review in a peer-reviewed scientific journal and present results at national and international conferences. It will be disseminated electronically and in print.

Trial registration number: PROSPERO CRD42015017833

Strengths and limitations of this study

- Our systematic review will provide a comprehensive assessment of the methods used to prevent deaths from drug overdose in the community setting
- The results of this review will have impact for policy and practice by providing relevant data to identify and describe existing community-based interventions and assess evidence about their effectiveness in preventing fatalities.
- A potential limitation to this work may be a lack of available high quality studies. This may reflect the difficulty of conducting studies in this setting and population, as well as publication bias.
- These issues have the potential to lead to significant heterogeneity between studies which will impact on any meta-analysis. Sub group analysis will be conducted to address this problem where possible.
- Study selection, data extraction and assessment of risk of bias will be conducted independently by two authors.
- However, it may also identify research gaps so that future studies can target areas where further knowledge can contribute towards the greatest impact on reducing drug overdose deaths.

INTRODUCTION

Drug overdose is the most frequent cause of death amongst people who misuse illegal drugs [1]. In England and Wales, nearly 3000 drug poisoning deaths (involving both legal and illegal drugs) were registered in 2013 [2]. As in previous years, just over two-thirds (2,032) of these deaths were in males, an increase of 19% over the previous year and the highest since 2009. The equivalent number of female deaths was 923, an increase of 4% over 2012, and the highest since 2004 [2, 3]. Drug poisoning accounted for nearly one in seven deaths among people in their 20s and 30s [2]. Annual mortality rates for injecting drug users is 14-17 times greater than for their non-drug using peers [4, 5]. Numbers of fatal drug overdoses exceeds deaths caused by diseases in this group in many countries [4, 6-10]. Drug overdose is the second highest cause of death in the United States after vehicle fatalities while deaths from opiate overdose in the UK are among the highest in Europe [11]. Drug overdose death rates have been rising for decades. In the USA, fatal drug overdoses increased by more than 400% between 1980 and 1999 and more than doubled between 1999 and 2005.

Between 10% and 40% of people have tried an illegal drug in their lifetime [12, 13]. Death rates are higher for males although the number of female deaths in the UK is growing and rose by 10% between 2009 and 2010. UK death rates are highest among the 30-39 year age group while overdose is the number one injury rated killer among 35-54 year olds in the United States [3, 11, 14]. Drug misuse deaths are five times higher in deprived parts of England and Wales [15]. Heroin and other related opiates are responsible for the highest mortality rates among drug users [12]. Deaths attributed to drug overdose are typically seen in older, heroin-dependent males not in drug treatment at the time of death [16]. Comorbidity with a mental disorder may be an important factor associated with the risk of drug overdose. A recent meta-analysis investigating the association between depression and non-fatal overdoses among drug users, found substantial evidence supporting the role of depressive disorders in increasing the risk of drug overdose [17]. However, factors mediating the relationship between depressive disorders and drug overdose are unknown. Risk of death from drug overdose is also increased by use of more than one drug, injecting drugs, homelessness, sexual orientation and changes in tolerance to a drug. Drug users released from prison in Australia, the USA and UK are up to 40 times more likely to die from an overdose than similar individuals from the general population [14, 16, 18-25].

In the European Union, government strategies to cut drug related deaths have failed to meet target reductions [26]. The World Health Organisation recommends countries have drug strategies based on national epidemiological data and effectiveness of methods to reduce

dependency and death [27]. The UK government target, set in 1999 to reduce drug related deaths by 20% by 2004, was not met [13, 14]. The current approach aims to prevent drug use and support recovery from drug dependence and includes a priority to gather research evidence about effective approaches to drugs prevention [28]. The National Treatment Agency and Department of Health have named carers as one of the key groups to be targeted to reduce the risks of overdose. Treatment for opioid overdose is by administration of naloxone hydrochloride (also known as Narcan), either intravenously (IV) or intramuscularly when IV access is not possible [29]. In the UK, naloxone may be administered by emergency care practitioners in the Emergency Department (ED) and by emergency ambulance personnel in the community.

Research about opioid dependence has focused on drug treatments with the aim of achieving long term detoxification, abstinence or maintenance. A number of systematic reviews have established efficacy of various pharmacological treatments by comparing them with each other or compliance with abstinence programmes. For example, one suggests that psychosocial treatments may increase adherence to detoxification programmes [30-32]. Research into community-based treatment and prevention programmes has begun to show some successful approaches to preventing drug overdose deaths, including among former prison offenders and through safe injecting facilities [33-36]. Since the 1990s, interest has grown in reducing overdose deaths by providing 'take-home' naloxone to users, families and drug services [37-40]. Witnesses at an overdose event are willing to intervene and training, such as in CPR or naloxone delivery, can enhance an effective response [41, 42].

The World Health Organisation has summarised a range of psychosocially assisted pharmacological treatments for opioid dependence [27]. However, the range of interventions available and their effectiveness to treat or prevent overdose deaths has not been assessed. There is also a lack of evidence about best methods to administer and deliver treatments in the pre-hospital setting. Meanwhile, there have been calls for research into preventative interventions for drug users at high risk of death in order to reduce the rising numbers of fatal and non-fatal overdoses [43-45]. A recent systematic review [46] looked at the effectiveness of community-based opioid overdose prevention programmes (OOPPs) that included the distribution of naloxone. This review did not include the emergency medical services nor harm reduction programmes such as supervised injection facilities (SIFs). They did not conduct a meta-analysis on their data and the review did not adhere strictly to PRISMA-P guidelines. There are currently no other reviews assessing the effectiveness of SIFs. Given

the high mortality associated with drug overdose it is essential to undertake a review assessing the effectiveness of every type of overdose prevention programme offered in the community.

We present the protocol of a systematic review to assess the effectiveness of methods to prevent deaths from drug overdose in the community setting.

This protocol is prepared and presented in accordance with the PRISMA-P guidelines [47].

Objectives

This systematic review will:

1. Identify published studies describing interventions delivered in the community to prevent fatal overdoses of illegal drugs
2. Evaluate the effectiveness of these interventions to reduce overdose deaths

METHODS

Criteria for considering studies for the review

We will include studies reporting effectiveness data about interventions delivered to drug users in order to prevent a fatality from a future overdose in the community. The intervention should be initiated or delivered in the community. We will consider all published studies from 1 January 1998, reported in English.

We will exclude studies reporting use of drugs not listed on the UK Misuse of Drugs Act 1971. Interventions to treat a presenting overdose, manage drug dependency or without an overdose prevention component will be excluded. However, we will include studies which report referral to maintenance treatments if these are part of a multi-faceted intervention to prevent overdose.

Inclusion and exclusion criteria are shown in Table 1

Table 1: Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Drug users who are at risk of	People who overdose or are at risk

	overdose on illegal drugs or who present to emergency or drug services because of use of illegal drugs, where illegal drugs are those listed under the UK Misuse of Drugs Act 1971	of overdose on drugs not listed on the UK Misuse of Drugs Act 1971
Intervention	Intervention to prevent a fatality from a future overdose in the community	• Treatment for a presenting overdose • Treatment to manage drug dependency • Interventions without an acute overdose prevention component e.g. maintenance therapy, naltrexone
Context	Intervention initiated or delivered in the pre-hospital or community setting	Intervention initiated in hospital
Outcomes	Effectiveness data (e.g. Fatal overdose rate, knowledge about use of naloxone, overdose reversal), with any type of comparator e.g. randomised trial, before-and-after study, controlled cohort study, interrupted time series etc.	• No effectiveness data • No comparator or control
Study limits	• Published between 1998-2014 • English language	

Search strategy for identifying relevant studies

We will undertake a systematic review following PRISMA-P guidelines for reporting systematic reviews [47]. We will adhere to Cochrane-recommended key stages of a systematic review [48].

We will systematically search the following electronic databases: PubMed, CINAHL, Cochrane (clinical trials database), EMBASE, PsychInfo, HMIC, and the National Library for Health using a search strategy (Appendix I) which groups terms into four facets:

1. Overdose event
2. Drug classification
3. Intervention
4. Setting

We will use Medical Subject Headings (MeSH) and key word terms where available. Searches will be limited where possible to international literature published in English between 1998 and 2014. The literature search strategy will be adapted to suit each database.

We will manually search the reference lists of eligible studies and relevant reviews and trace their citations using Web of Knowledge. We will save search results in the electronic reference management system EndNote (version X7).

Selection of studies for inclusion in the review

We will undertake a two stage screening process for selection of studies. One reviewer (CO) will screen titles and abstracts against inclusion criteria to identify potentially eligible texts. A second reviewer (BAE) will independently check 10% of the decisions including anywhere the first reviewer is uncertain. Two reviewers (CO & CM) will independently assess full text articles to identify texts to be included in the review, and examine the reference lists of all selected articles to identify other potentially eligible studies. Any disagreements at either stage will be referred to a third reviewer (AJ).

Data extraction

Two reviewers (CO & CM) will independently extract data using a pre-defined table adapted from the Cochrane Collaboration handbook [48] which we will pilot and adjust as necessary. We will extract general information (authors, year, country, publication details), study characteristics (study design, setting, sample size, response rate), description of intervention and outcomes as well as additional data on fatal and non-fatal poisoning numbers and rates. Both reviewers will compare collected data. Any disagreements will be referred to a third reviewer (DR).

Measures of treatment effects

Data will be presented as the relative risk (RR) with 95% CIs for dichotomous outcomes. Standard mean difference (SMD) with 95% CI will be used for continuous outcomes. Analyses will involve all participants in the treatment groups to which they were allocated (if such data are available).

Assessment of the quality of included studies

We will evaluate the quality of included studies using the Cochrane Collaborations' tool for assessing risk of bias [48]. This tool assesses seven specific domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other sources of bias. A judgement of 'Low risk' of bias, 'High risk' of bias, or 'Unclear risk' of bias will be assigned relating to the risk of bias within each entry and presented in a table.

Data synthesis

Data synthesis will be conducted using a software program from the Cochrane Collaboration (Review Manager [RevMan] V.5.3 for Windows). We will summarise effectiveness data by intervention and context. We will, conduct a meta-analysis for variables which can be compared across studies, using statistical methods to control for heterogeneity where appropriate and use subgroup analysis where appropriate [49]. For dichotomous data, we will combine the RRs of each study and calculate values for 95% CI using a fixed-effect model if significant heterogeneity is not detected; we will employ a random effect model if significant heterogeneity is detected. For continuous data, we will combine the SMD of each study and calculate the 95% CI according to the outcome. We will conduct a sensitivity analysis to remove the impact of low quality studies where significant heterogeneity still exists after subgroup analysis.

Where there is sufficient clinical or statistical heterogeneity to prevent any valid numerical synthesis, we will employ a narrative synthesis using the approach developed by Popay et al [50] to describe community-based interventions, their delivery and use, and how effectively they prevent fatal overdoses. This approach is supported by the Cochrane Collaboration, and was developed to address weaknesses identified in synthesis of heterogenous data.

Presenting and reporting results

We will present results according to the PRISMA-P reporting guidance [47]. The study selection will be described in a flowchart, with reasons given for excluding papers. Quantitative data will be presented in tables and forest plots where appropriate. We will provide narrative summaries describing characteristics of included studies, details of the interventions, how they are delivered and their effects.

Dissemination

We will publish findings from this systematic review in a peer-reviewed scientific journal and present results at national and international conferences. We will also make our results available to UK policy makers and the Association of Ambulance Chief Executives (UK), National Ambulance Services Medical Directors (UK) and the Wales National Implementation Board for Drug Poisoning Prevention.

Ethics

This study will use published data, so ethical permissions are not required. However, we will adhere to ethical and governance standards in the management of our data and presentation of findings.

Conclusion

Drug overdose is the most frequent cause of death amongst people who use illegal drugs [1]. Government drug strategies to cut drug related deaths have failed to meet target reductions. There is growing interest in alternatives to detoxification, abstinence or maintenance to prevent drug related deaths. Carers have been identified as a route to achieve this while some evidence suggests community-based treatment and prevention programmes may be successful. We anticipate this review will have impact for policy and practice by providing relevant data to identify and describe existing community-based interventions and assess evidence about their effectiveness in preventing fatalities. A potential limitation to this work may be a lack of available high quality studies. However, it may also identify research gaps so that future studies can target areas where further knowledge can contribute towards the greatest impact on reducing death rates in this vulnerable population.

Competing interests

No, there are no competing interests.

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Contributorship statement

HS, BAE, AJ, and DR contributed to the conception of the study. All authors contributed to the study design. The manuscript protocol was drafted by CO. Screening of studies for inclusion will be undertaken by CO, CM, and BAE. AJ will arbitrate in case of disagreements. Data extraction will be undertaken by CO and CM. DR will arbitrate in case of disagreements. All authors approved the publication of the protocol.

Data sharing statement

There is currently no data available for sharing at the protocol stage. On completion of the study our data will be fully available on request.

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Appendix I: Search strategy for a review of community based interventions to prevent fatal overdoses from illegal drugs

This search strategy will be used in PubMed and adapted for each of the other databases.

KEY: Mesh = exploded Mesh heading
Supplementary Concept=These are index terms in PubMed used in particular for chemicals and drugs.
[tiab]= title / abstract

1	"Drug-Related Side Effects and Adverse Reactions"[Mesh]
2	"Drug Overdose"[Mesh]
3	poisoning[tiab]
4	overdose[tiab]
5	toxic[tiab]
6	toxicity[tiab]
7	(OR/1-6)
8	"Designer Drugs"[Mesh] OR "Street Drugs"[Mesh] OR "Hallucinogens"[Mesh]
15	"Methadyl Acetate"[Mesh]
16	"Alphaprodine"[Mesh]
17	"Bufotenin"[Mesh] OR "magic mushrooms"
18	buprenorphine[Mesh] OR buprenorphine[tiab]
19	“Coca”[Mesh]
20	"Cocaine"[Mesh] (exp includes Crack)
22	Krokodil[tiab] OR Desomorphine[tiab]
23	"Dextromoramide"[Mesh]
24	"Heroin"[Mesh] OR diamorphine[tiab]
25	"18,19-dihydroetorphine" [Supplementary Concept]
26	"Dihydromorphine"[Mesh]
28	"dipipanone" [Supplementary Concept]
29	"Morphinans"[Mesh]
30	“etryptamine” [Supplementary Concept]
31	"Fentanyl"[Mesh]
34	“ketobemidone” [Supplementary Concept]
36	"lofentanil" [Supplementary Concept]
37	"Lysergic Acid Diethylamide"[Mesh]
38	“Mescaline”[Mesh]
39	"Methadone"[Mesh]
40	("MDMA"[tiab] OR methylenedioxymethamfetamine[tiab])
42	“Opium”[Mesh]
45	"Isonipecotic Acids"[Mesh]
47	"Phenoperidine"[Mesh]
49	“piminodine” [Supplementary Concept]
52	Methylamphetamine[tiab]
55	Psilocybine[Mesh]
56	tapentadol [Supplementary Concept] OR ("Angel Dust")
57	“remifentanil” [Supplementary Concept]
58	“Tilidine”[Mesh]
59	Phencyclidine[Mesh]
61	"Amphetamines"[Mesh]
62	Barbiturates[Mesh]
63	Cannabinol[Mesh] OR “Cannibis”[Mesh]
64	Marijuana Abuse[Mesh]
70	"Glutethimide"[Mesh]
71	“Methaqualone”[Mesh] OR Mandrax[tiab]
72	“monomethylpropion” [Supplementary Concept]
75	“Methylphenidate"[Mesh]

76 "O-demethyltramadol" [Supplementary Concept] OR Tramadol[Mesh]
77 "2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone" [Supplementary Concept] OR methoxetamine[tiab]
78 "Phencyclidine"[Mesh]
80 Phenmetrazine[Mesh]
82 Amitriptyline[Mesh]
83 Anabolic Agents[Mesh]
84 Aminorex[Mesh]
85 "Benzodiazepines"[Mesh]
89 "Dextropropoxyphene"[Mesh]
92 Gamma-butyrolactone[tiab] OR "4-Butyrolactone"[Mesh] OR GBL[tiab]
93 Gamma hydroxybutrate[tiab] OR GHB[tiab]
94 Ketamine[Mesh]
95 Meprobamate[Mesh]
97 Methaqualone[Mesh]
99 Pemoline[Mesh]
101 "Phenmetrazine"[Mesh]
102 "pyrovalerone" [Supplementary Concept]
104 "zolpidem" [Supplementary Concept]
105 "Androstenediol"[Mesh]
106 "Chorionic Gonadotropin"[Mesh]
107 "Clenbuterol"[Mesh]
108 Non-human chorionic gonadotrophin[tiab]
109 Somatotropin[tiab]
110 Somatrem[tiab]
111 Somatropin[tiab]
112 "Zeranol"[Mesh]
113 "Zilpaterol" [Supplementary Concept]
114 OR/(8-113)
115 care[tiab] OR treatment[tiab] OR intervention[tiab] OR prevention[tiab] OR rapid assessment response[tiab] OR rapid appraisal[tiab] OR crisis[tiab] OR management[tiab] OR critical[tiab] OR therapy[tiab] OR care pathway[tiab] OR referral[tiab] OR opiate antagonist[tiab] OR opiod antagonist[tiab] OR opiate reversal[tiab] OR opiod reversal[tiab]

116 (115 AND 114 AND 7)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	10
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	10
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4, 5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6, 7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7, 8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database,	14, 15

		including planned limits, such that it could be repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8, 9, 10
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7, 8, 10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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