

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

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## ABSTRACT

**Introduction:** Drug overdose is the most frequent cause of death among people who misuse illegal drugs. People who inject these drugs are 14–17 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 and (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 predefined 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.

## INTRODUCTION

Drug overdose is the most frequent cause of death among people who misuse illegal drugs.<sup>1</sup> In England and Wales, nearly 3000 drug poisoning deaths (involving both legal and illegal drugs) were registered in 2013.<sup>2</sup>

## 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. Subgroup 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.

As in previous years, just over two-thirds (2032) 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.<sup>2–3</sup> Drug poisoning accounted for nearly one in seven deaths among people in their 20s and 30s.<sup>2</sup> Annual mortality rates for injecting drug users is 14–17 times greater than for their non-drug using peers.<sup>4–5</sup> Numbers of fatal drug overdoses exceeds deaths caused by diseases in this group in many countries.<sup>4–10</sup> Drug overdose is the second highest cause of death in the USA after vehicle fatalities while deaths from opiate overdose in the UK are among the highest in Europe.<sup>11</sup> 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.<sup>12 13</sup> 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 USA.<sup>3 11 14</sup> Drug misuse deaths are five times higher in deprived parts of England and Wales.<sup>15</sup> Heroin and other related opiates are responsible for the highest mortality rates among drug users.<sup>12</sup> Deaths attributed to drug overdose are typically seen in older, heroin-dependent males not in drug treatment at the time of death.<sup>16</sup> 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.<sup>17</sup> 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.<sup>14 16 18–25</sup>

In the European Union, government strategies to cut drug-related deaths have failed to meet target reductions.<sup>26</sup> The WHO recommends countries have drug strategies based on national epidemiological data and effectiveness of methods to reduce dependency and death.<sup>27</sup> The UK government target, set in 1999 to reduce drug-related deaths by 20% by 2004, was not met.<sup>13 14</sup> 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.<sup>28</sup> 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 or intramuscularly when intravenous access is not possible.<sup>29</sup> In the UK, naloxone may be administered by emergency care practitioners in the emergency department 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.<sup>30–32</sup> 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.<sup>33–36</sup> Since the 1990s, interest has grown in reducing overdose deaths by providing ‘take-home’ naloxone to users, families and drug services.<sup>37–40</sup> Witnesses at an overdose event are willing to intervene and training, such as in cardiopulmonary resuscitation or naloxone delivery, can enhance an effective response.<sup>41 42</sup>

The WHO has summarised a range of psychosocially assisted pharmacological treatments for opioid dependence.<sup>27</sup> 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 prehospital 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.<sup>43–45</sup> A recent systematic review<sup>46</sup> looked at the effectiveness of community-based opioid overdose prevention programmes 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.<sup>47</sup>

## 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 multifaceted intervention to prevent overdose.

Inclusion and exclusion criteria are shown in [table 1](#).

### Search strategy for identifying relevant studies

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

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 (see online supplementary 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 and 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 and CM) will independently extract data using a predefined table adapted from the Cochrane Collaboration handbook<sup>48</sup> 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.<sup>48</sup> This tool assesses seven specific domains: sequence generation, allocation concealment, blinding of participants

**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	<ul style="list-style-type: none"> <li>▶ Treatment for a presenting overdose</li> <li>▶ Treatment to manage drug dependency</li> <li>▶ Interventions without an acute overdose prevention component eg, maintenance therapy, naltrexone</li> </ul>
Context	Intervention initiated or delivered in the prehospital or community setting	Intervention initiated in hospital
Outcomes	Effectiveness data (eg, fatal overdose rate, knowledge about use of naloxone, overdose reversal), with any type of comparator eg, randomised trial, before-and-after study, controlled cohort study, interrupted time series etc	<ul style="list-style-type: none"> <li>▶ No effectiveness data</li> <li>▶ No comparator or control</li> </ul>
Study limits	<ul style="list-style-type: none"> <li>▶ Published between 1998–2014</li> <li>▶ English language</li> </ul>	

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) V5.3 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.<sup>49</sup> 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*<sup>50</sup> 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 heterogeneous data.

### Presenting and reporting results

We will present results according to the PRISMA-P reporting guidance.<sup>47</sup> The study selection will be described in a flow chart, 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 policymakers 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 among people who use illegal drugs.<sup>1</sup> 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.

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**Contributors** 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.

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