European Monitoring Centre
for Drugs and Drug Addiction

ISSN 2315-1463

EMCDDA PAPERS

Preventing fatal overdoses: a systematic review of the effectiveness of take-home naloxone

Abstract: Drug overdose is one of the major causes of death among young people in Europe. Naloxone is an effective antidote that can reverse opioid (including synthetic opioid) intoxication. As overdoses quite often occur in the presence of peers or family members, programmes that enable bystanders to provide first aid and administer naloxone before an ambulance arrives can save lives.

We conducted a systematic review of the available studies on take-home naloxone to reverse opioid overdose and included 21 studies for analysis (with various study designs). There is evidence from one interrupted time-series study, involving 2 912 opioid users at risk of overdose in 19 communities followed up for seven years, that educational and training interventions complemented by take-home naloxone decrease overdose-related mortality.

There is weaker, but consistent, evidence that similar interventions for opioid-dependent patients and their peers effectively improve knowledge while forming positive attitudes to the correct use of naloxone and the management of witnessed overdoses.

Keywords naloxone overdose opioids systematic review

Recommended citation: European Monitoring Centre for Drugs and Drug Addiction (2015), *Preventing fatal overdoses: a systematic review of the effectiveness of take-home naloxone,* EMCDDA Papers, Publications Office of the European Union, Luxembourg.

Background

Drug use is one of the major causes of health problems and mortality among young people in Europe, and it can account for a considerable proportion of deaths among adults. The risk of premature death among injecting drug users can be 15 times higher than in the general population of the same age group (Mathers et al., 2013). Some studies show that one third to one half of deaths among drug users may be caused by overdose (Bargagli et al., 2006; Degenhardt et al., 2011; EMCDDA, 2011, 2013a). Combined with acquired immune deficiency syndrome (AIDS), overdose represents the primary cause of death among people who inject drugs.

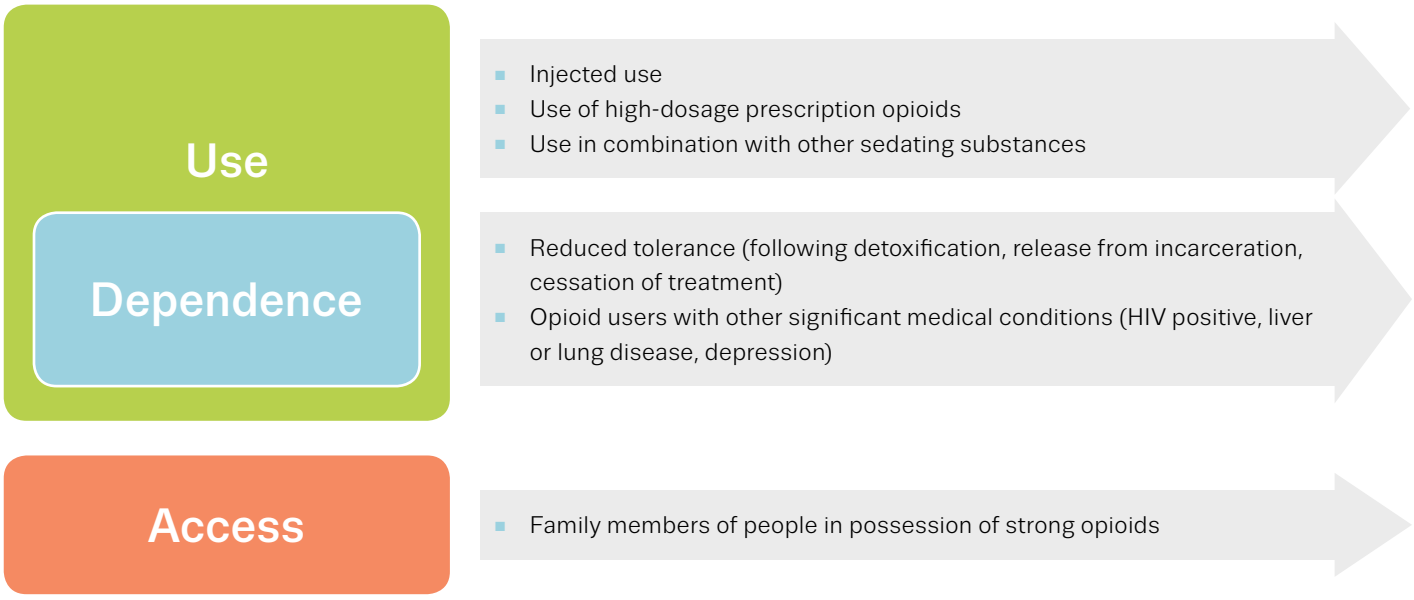
Drug overdose accounts for approximately 3.5 % of all deaths in adult males under 40 years of age (Eurostat, 2012, cited in EMCDDA, 2013a). In absolute numbers in 2012, for example, there were 6 100 overdose deaths across Europe.

In particular, the use of heroin and other opioids contributes disproportionately to drug-related deaths: overdose represents a common event among opioid users (EMCDDA, 2011, 2013a). Injecting drug use in Europe is becoming less prevalent (EMCDDA, 2013b) but mortality among injectors remains high (Mathers et al., 2013), and injecting drug use is associated with increased risk for fatal and non-fatal overdoses compared with non-injected routes of administration (Darke et al., 2007). Among the substances associated with the risk of overdose are opioids (including prescription and non-medical use) and non-opioids (e.g. benzodiazepines), as well as use of a combination of substances (polysubstance use) (Giraudon et al., 2013). In addition, in a substantial number of deaths, evidence of polydrug use (heroin in combination with other central nervous system depressants such as alcohol or benzodiazepines) was found. Among the new psychoactive substances (NPSs) are synthetic opioids, which have emerged as a key concern because of links to serious adverse events such as fatal and non-fatal intoxications (EMCDDA, 2014a), for example fentanyls causing fatal overdoses, particularly in east and central European countries (EMCDDA, 2012).

Overdose risk is influenced by individual, situational and organisational factors (Figure 1). Beyond the type of substance used and the route of administration, the circumstances of use also affect the probability of overdose.

Risk factors can include interrupted treatment provision because of discontinuous treatment and care, completion of the detoxification process or discharge from drug-free treatment (Cornish et al., 2010). In fact, although the majority of deaths occur in individuals with a history of opioid addiction, most of these individuals commonly have a reduced tolerance to opioids at the time of their death (Darke et al., 2007). This implies an increased risk linked to relapse into use after a period of abstinence, for example following release from detention (Binswanger et al., 2013; Zlodre and Fazel, 2012). Furthermore, occasional users of NPSs can also experience opioid overdose (EMCDDA, 2013b).

FIGURE 1
Risk factors for overdose



Adapted from WHO (2014). HIV, human immunodeficiency virus

Overdose prevention interventions

Several interventions are implemented with the direct aim of preventing opioid overdose, whereas other interventions have an indirect effect on reducing overdoses and overdose mortality.

These interventions act at different stages and levels of risk and they can address (i) the general population, such as drug-use prevention interventions; (ii) drug users, for example induction into treatment; (iii) active drug users, as is the case with harm reduction strategies; and (iv) those experiencing an ongoing overdose, in order to reduce lethality (Figure 2).

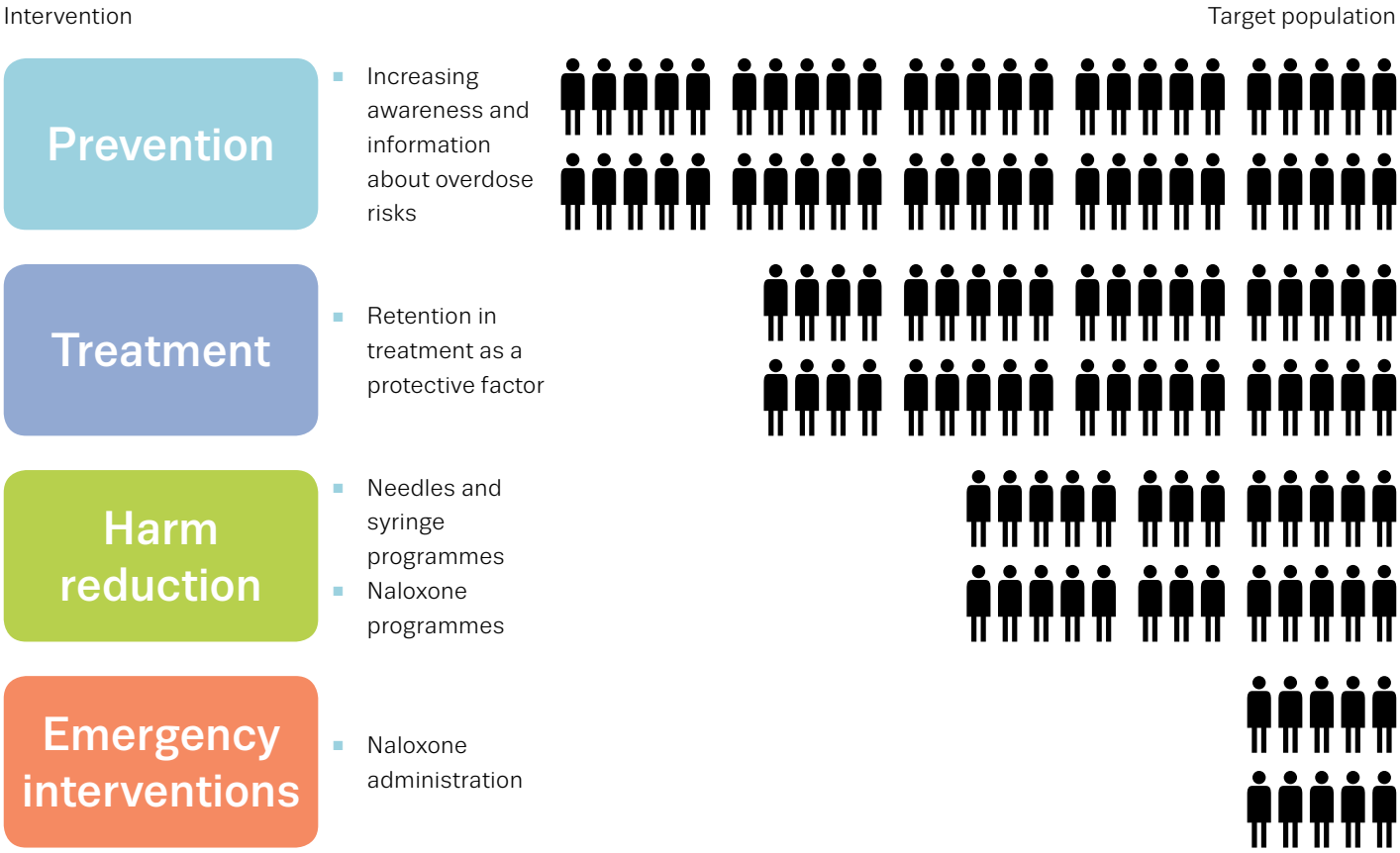
Cause of death in opioid overdose and the role of naloxone

Opioid overdose is characterised by drowsiness or coma, decreased respiratory rate, abnormally slow breathing, pinpoint pupils and possibly apnoea (Boyer Edward, 2012). Death from opioid overdose is caused primarily by respiratory depression leading to cardiac arrest. Naloxone is an opioid antagonist that can reverse the effects of opioids, including respiratory depression, in the body within a few minutes. In the absence of an agonist drug (such as an opioid) naloxone is almost inert, but in individuals who are in acute respiratory depression caused by an opioid overdose naloxone can normalise respiration, level of consciousness, pupil size, bowel activity and other signs and symptoms of overdose (Katzung, 1995). As naloxone, like naltrexone, has antagonistic effects, it can precipitate opioid withdrawal syndrome in those under the influence of opioid agonists.

It is standard practice for ambulance personnel to administer naloxone to victims of acute opioid overdose, as well as perform resuscitation techniques. When emergency personnel intervene in sufficient time, opioid overdoses can be effectively reversed. Nevertheless, it has been observed that although bystanders are present during the majority of overdoses they fail to call for ambulance services. The person most likely to be present during an overdose is another drug user, and a large proportion of heroin users have witnessed an overdose (Darke et al., 2007; Frischer and Baldacchino, 2012). Therefore, they are reluctant to call for medical help for fear of possible legal consequences for themselves (Frischer and Baldacchino, 2012).

On the other hand, it has been reported that laypeople present during overdoses attempt a variety of methods to rescue the

FIGURE 2
Targets of overdose prevention



victim, including a number of ineffective techniques. These include injection of other drugs (such as cocaine) or salt and allowing the victim to ingest ice or bathe in cold water (Strang et al., 2013). These and other potentially harmful practices show the willingness of bystanders to help.

The distribution of naloxone to potential victims of heroin overdose and to those who may happen to assist during an opioid overdose — together with a brief educational intervention that aims to instruct how to recognise an overdose, assist the patient and administer naloxone — has been proposed as an innovative approach to reduce overdose fatalities (Clark, 2014). Specifically, programmes for the distribution of naloxone aim to increase the availability of naloxone in the community and, consequently, decrease overdose fatalities.

What naloxone formulations are available?

Naloxone injection is a liquid formulation that can be injected intravenously, intramuscularly or subcutaneously. Prefilled auto-injection devices containing a solution for injection into a muscle or under the skin also exist, as well as devices to administer naloxone intranasally (sprayed into the nose) (MedlinePlus, accessed May 2014). Nevertheless, intranasal administration is an off-label use (WHO, 2014).

Why is this review important?

Implementation of take-home naloxone has been recommended in the UK by the Advisory Council on the Misuse of Drugs (ACMD, 2012) since 2000, recognising the potential contribution of this intervention to the reduction in the number of overdose mortalities and the need for naloxone to be more widely available. Naloxone administration is available in seven European countries, namely Denmark, Germany, Estonia, Spain, Italy, United Kingdom and Norway (see Annex 1 and EMCDDA, 2014b). It is therefore important to exchange existing knowledge on such an intervention to enable potential implementers to take informed decisions.

Objective

The objective of this overview is to assess the effect of take-home emergency naloxone and educational intervention on knowledge improvement, naloxone use, management of overdoses witnessed and death as a result of overdose.

Methods

We included randomised controlled trials (RCTs), controlled clinical trials (CCTs), controlled cohort studies, interrupted time-series analyses, cross-sectional surveys, case series and population-based results of programme implementations. We considered studies enrolling current or former opioid injectors, their parents and their peers. All participants were included regardless of age, gender and nationality. The experimental intervention was take-home emergency naloxone accompanied or not by explanatory leaflets, education and training for opioid users, peers and families; the control intervention was intervention as usual (e.g. information on the risks of overdose) or no intervention.

The types of outcomes were as follows: (a) knowledge, management and first aid in overdose cases; (b) attitudes towards naloxone (acceptability and willingness to use); (c) management of witnessed overdoses — use of naloxone and adequacy of care given to the patient; (d) adverse events following administration of naloxone to reverse overdose; and (e) deaths due to overdose.

Search strategy

The following electronic databases were searched (Figure 3): Cochrane Drugs and Alcohol Group (CDAG) Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL) Issue 6, 2013; PubMed (also known as MEDLINE, 1996 to June 2013); EMBASE (Elsevier, EMBASE.com, 1974 to June 2013); the Cumulative Index to Nursing and Allied Health Literature (CINAHL, EBSCOhost, 1982 to June 2013); and the Web of Science (1991 to June 2013). The detailed search strategy for each database is reported in Annex 4.

The following were also searched: (a) the reference lists of all relevant papers to identify further studies; (b) some of the main electronic sources of ongoing trials, including metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en); (c) conference proceedings likely to contain trials relevant to the review (College on Problems of Drug Dependence — CPDD); and (d) national focal points for drug research (e.g. National Institute of Drug Abuse and National Drug and Alcohol Research Centre).

The search was not limited by language of publication.

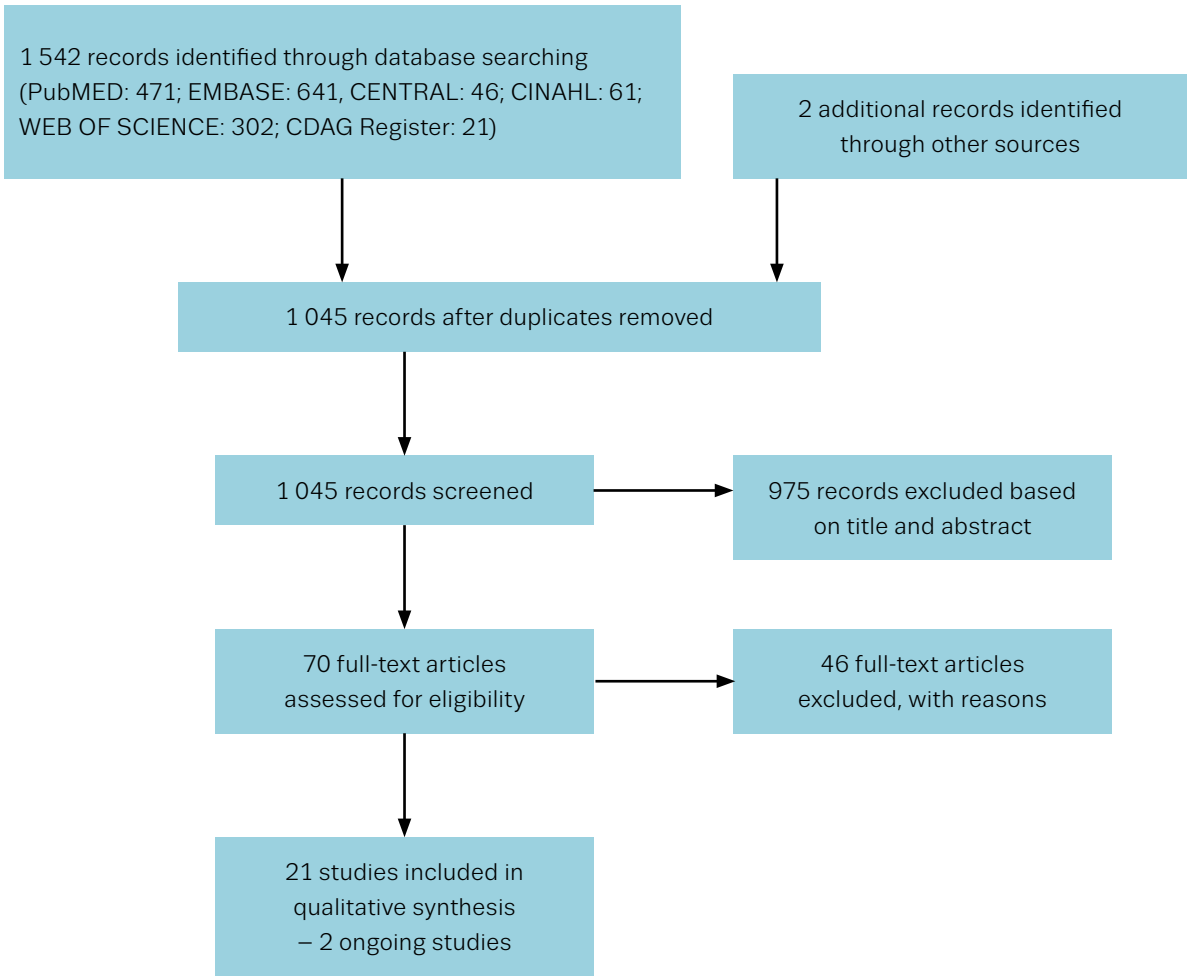
Data collection and analysis

Two authors independently inspected the search hits by reading titles and abstracts. The full text of each potentially

relevant study located in the search was obtained and independently assessed for inclusion. Doubts were resolved through discussion between the authors. Data were extracted from included studies using a structured data extraction form. One author extracted data and a second investigator checked it. Differences were resolved through discussion and consensus. A risk-of-bias assessment for RCTs and CCTs was performed using the approach recommended by the Cochrane handbook; the first step is to describe what is reported in the study and the second is to judge the risk of bias in terms of low, high or unclear risk (Higgins and Green, 2011).

For a detailed description of the criteria used in this overview to assess each type of study design, see Annex 5.

FIGURE 3
Flow chart of study assessment and selection



What is 'bias'?

The main objective of epidemiological research is to find explanations for the manifestation of diseases in the population. Bias is a false result influenced by uncontrolled factors. A typical example of bias is an unwanted selection of the population studied so that the sample does not adequately represent the target population. Bias has been defined as 'incorrect assessment of the association between an exposure and an effect in the target population' (Delgado-Rodríguez, 2004, p. 635). The quality of studies is highly linked to the reduction of possible bias. There are many known types of bias, including **selection bias**, the risk of selecting the sample for uncontrolled characteristics (Delgado-Rodríguez, 2004); **indication bias**, which emerges from RCTs when patients, instead of being assigned to treatment randomly, are assigned on the basis of some characteristic, for example a higher susceptibility to a disease; **detection bias**, when some patients have a higher chance of being diagnosed because they are tested more often owing to a concurrent condition (e.g. those with diabetes who are tested daily have more chance of testing positive for hyperglycaemia than those who are not tested); **assessment bias**, when the professionals assessing the results of an intervention are influenced by their knowledge of the interventions provided (a typical example is a nurse who measures body temperature more often or more accurately in patients given placebo than in those given the active substance); and **performance bias**, when patients are given different interventions not on the basis of random allocation but because of some other characteristic or situation. In addition, **publication bias** is a distortion in the availability of studies. It has been observed that studies with positive results have more probability of being published and, in general, are published faster and in higher impact journals (Dubben and Beck-Bornholdt, 2005).

Why are some studies defined as 'blinded'?

Blinding refers to all the strategies that are put in place to prevent knowledge of the intervention influencing behaviour (of patients, clinicians, carers or outcome assessors), which could lead to biased results. In a RCT, patients are usually blinded to the intervention so that they cannot over- or under-report some symptoms. The same strategy applies to the assessors. The term 'double blinded' describes a situation in which neither the patient nor the assessor of the outcome (e.g. the professional asking questions) is aware of the treatment provided to the specific patient.

Excluded articles

Forty-six full text articles were excluded (see 'Excluded studies (articles)' in References). The reasons for exclusion were as follows: study design not in the inclusion criteria (narrative review, editorial, letter, case report) (n = 18); types of intervention not in the inclusion criteria (take-home naloxone not provided) (n = 17); outcome of interest not provided (n = 7); poster or abstract of already included study (n = 4).

Results

Included studies

Twenty-two publications, covering 21 studies, were included in the present overview (two publications referred to the same study whereas one publication reported the results of two programmes). For more details see Annex 1.

Study design and location

One study was a RCT, three were case-series and 17 were pre-post studies.

Furthermore, two ongoing trials were identified and the descriptions of the protocols are reported in the Conclusions (pp. 11–12).

Of the included studies, 14 were carried out in the USA, five in the UK, one in Canada and one in the UK and Germany.

Participants

In all the included studies participants were opioid users and their parents or carers. In one study (Walley et al., 2013a) participants were patients enrolled on methadone maintenance programmes. The sample size varied greatly, ranging from 19 to 53 032 subjects enrolled and assessed.

TABLE 1
Interventions and comparisons

Intervention	Comparison	References
Naloxone hydrochloride (2 mg/2 ml prefilled syringe) for taking away and 1-hour training session	The control group was asked only to read a short booklet on overdose risk factors, opioid overdose signs, actions to take in an overdose and basic information about naloxone	Williams et al. (2014)
Educational and training programme with the provision of take-home naloxone	No comparison	Gaston et al. (2009), Seal et al. (2005), Strang et al. (2008)
Implementation of education and naloxone distribution programmes realised at city or regional level	N/A (but one study compared different levels of intensity of intervention)	Bennett and Holloway (2012), Bennett et al. (2011), Dettmer et al. (2001), Enteen et al. (2010), Galea et al. (2006), Gaston et al. (2009), Heller and Stancliff (2007), Leece et al. (2013), McAuley et al. (2010), Maxwell et al. (2006), Piper et al. (2008), Tobin et al. (2009), Wagner et al. (2010), Walley et al. (2013a), Walley et al. (2013b), Wheeler et al. (2012), Yokell et al. (2011)
Implementation of education and intranasal naloxone distribution programmes realised at city or regional level	N/A	Doe-Simkins et al. (2009)

N/A, not applicable.

Interventions

In all the included studies (Table 1) the intervention consisted of (i) education and information on the identification of overdose risk factors, the usual signs of opiate overdose, appropriate methods for dealing with an overdose, the use of naloxone, methods for administering naloxone, period of time over which naloxone is effective and recommended injection sites; (ii) practical training; and (iii) provision of one or two doses of naloxone as prefilled syringes. In three studies the device for administering intranasal naloxone was provided to participants.

Outcome measures

The outcome measures were as follows:

Knowledge of risk factors of overdose, signs of opiate overdose, correct use of naloxone, management of witnessed overdose: training provision is aimed at enabling laypeople to proactively manage an overdose occurrence. For this reason, some of the studies primarily measure how effective the training interventions were in communicating the basic information required in such an occurrence. These outcomes were covered by eight studies (Bennett and Holloway, 2012; Gaston et al., 2009; McAuley et al., 2010; Seal et al., 2005; Strang et al., 2008; Tobin et al., 2009; Wagner et al., 2010; Williams et al., 2014).

Attitudes: willingness to use naloxone, confidence in and acceptability of naloxone. Acquisition of knowledge may not be associated with preparedness to put it into practice, especially under emotional circumstances. These outcomes were covered by seven studies (Bennett and Holloway, 2012; Galea et al., 2006; McAuley et al., 2010; Strang et al., 2008; Tobin et al., 2009; Wagner et al., 2010; Williams et al., 2014).

Study design

Several study designs are available in the epidemiologist's toolbox to assess the effectiveness of interventions. The choice of study design is influenced by many factors, including the type of research question, the resources available, the setting and how common a health condition is. The studies included in the present review are:

randomised controlled studies — typically used to assess the effectiveness of interventions, this study design randomly allocates patients to one intervention or a control;

clinical controlled studies — studies in which patients are assigned to one intervention or a control, but not randomly;

case-series studies — studies in which a consecutive series of patient cases described;

time-series studies — studies in which the end points (e.g. the mortality in a town) are measured at different points in time;

pre–post studies — studies in which the end points are measured before and after the study interventions.

Overdose management: including calling for an ambulance, putting the patient in the recovery position and performing cardiopulmonary resuscitation. Twelve studies assessed whether or not the target population followed the instructions given during the training sessions (Bennett et al., 2011;

Bennett and Holloway, 2012; Dettmer et al., 2001; Doe-Simkins et al., 2009; Enteen et al., 2010; Galea et al., 2006; Gaston et al., 2009; McAuley et al., 2010; Piper et al., 2008; Seal et al., 2005; Tobin et al., 2009; Wagner et al., 2010).

Naloxone administration: all but three studies (Heller and Stancliff, 2007; Maxwell et al., 2006; Wheeler et al., 2012) reported the number of times when naloxone was given to patients, but only 13 studies reported the number of overdoses witnessed, allowing calculation of the percentage of overdoses in which naloxone was given. Two studies (Leece et al., 2013; Tobin et al., 2009) did not report the number of overdoses witnessed, but only the number of participants who used naloxone, without specifying if they did so on one or more occasions.

Request for naloxone refill, naloxone lost or stolen: a proxy outcome for actual use and/or interest in using the naloxone at occurrence. These outcomes were covered by nine studies (Bennett et al., 2011; Doe-Simkins et al., 2009; Enteen et al., 2010; Galea et al., 2006; Gaston et al., 2009; Piper et al., 2008; Tobin et al., 2009; Wagner et al., 2010; Walley et al., 2013a and b).

Death due to overdose: 11 studies (Bennett et al., 2011; Bennett and Holloway, 2012; Dettmer et al. 2001; Doe-Simkins et al., 2009; Enteen et al., 2010; Galea et al., 2006; McAuley et al., 2010; Piper et al., 2008; Seal et al., 2005; Strang et al., 2008; Wagner et al., 2010) assessed this outcome among subjects with overdoses witnessed by study participants; one study (Walley et al., 2013b) reported overdose deaths in communities covered by the intervention compared with communities not covered by the intervention. Three studies (Heller and Stancliff, 2007; Maxwell et al., 2006; Wheeler et al., 2012) reported only the total number of overdoses reversed.

Methodological quality

The assessment of methodological quality using standardised criteria was possible for only two studies: the RCT (Williams et al., 2014) and the interrupted time-series study (Walley et al., 2013b). Three studies were uncontrolled case series and all the other studies used a pre–post (or only post) evaluation design without a control group for which standardised and validated checklists for quality assessment were not available.

The RCT was judged to be at low risk of selection bias but at high risk of performance and detection bias. This is because it was an open-label study with subjective outcome measures based on self-reported data. It was also judged to be at risk of attrition bias because the analysis was done on a per-protocol basis with a high rate of patients lost at follow-up and unbalanced between the arms of the study (Annex 2).

The interrupted time-series (ITS) analysis (Walley et al., 2013b) was judged to be at low risk of bias for all the items assessed (clearly defined point in time when the intervention occurred; at least three data points before, and three after, the intervention; protection against secular changes; protection against detection bias; blinded assessment of primary outcomes) and at unclear risk of bias for the completeness of data sets (Annex 2).

Even if a validated checklist was not available to assess the risk of bias of the other study designs, we noted that the generalisability of the results is limited. All but one study (Bennett and Holloway, 2012) had no control groups. Bennett and Holloway (2012) had a control group of 50 participants compared with 521 individuals exposed to the intervention. Four studies (Galea et al., 2006; Gaston et al., 2009; McAuley et al., 2010; Seal et al., 2005) included a very small number of patients (n = 25, n = 70, n = 19 and n = 24, respectively) and the method for the sample selection was not reported. In five studies there were many patients lost at follow-up: 20 % in Galea et al. (2006), 35 % in Gaston et al. (2009), 23 % in Strang et al. (2008), 66 % in Tobin et al. (2009) and 29 % in Wagner et al. (2010). In Piper et al. (2008) detailed information on the management of overdose was reported for 61 % of the overdoses for which naloxone was administered. In five studies (Bennett et al., 2011; Bennett and Holloway, 2012; Dettmer et al., 2001; Enteen et al., 2010; Yokell et al., 2011) the results about naloxone use and management of overdose were reported only for those participants who voluntarily reported back and/or returned for a refill of naloxone, who constituted a small percentage of the overall sample: 33 % in Bennett et al. (2011), 5.3 % in Bennett and Holloway (2012), 41 % in Dettmer et al. (2001), 24 % in Enteen et al. (2010) and 8.3 % in Yokell et al. (2011). In Leece et al. (2013), Maxwell et al. (2006) and Wheeler et al. (2012) there was no information about the method used for collecting data on the management of overdose. All the outcomes were self-reported.

Effect of the interventions

Overall, the available studies considered in the present overview showed that naloxone provision among drug users and their peers may be an effective strategy to reduce fatal overdoses (Table 2). The outcomes measured included the improvement of knowledge on how to manage an overdose and the willingness to put into practice the acquired knowledge, along with the process and the outcomes of overdose management. The studies also measured the percentage of naloxone administration in the event of overdose and the requests to refill naloxone, and the fatal cases in spite of naloxone administration.

TABLE 2
Description of effects of the interventions across the studies

Population	Outcome	Intervention	Effects	Number of studies	Quick guide	References
Drug users and their peers	Knowledge about signs of overdose, correct management of patients, naloxone use	Targeted training plus naloxone provision	The RCT showed a significant difference in improvement in knowledge after the training compared with the baseline between the experimental and the control groups. All the other uncontrolled studies showed an improvement in knowledge after the training compared with the baseline results	8	++	Bennett and Holloway (2012), Gaston et al. (2009), McAuley et al. (2010), Seal et al. (2005), Strang et al. (2008), Tobin et al. (2009), Wagner et al. (2010), Williams et al. (2014)
	Attitudes: willingness to use naloxone, confidence in and acceptability of naloxone		The RCT showed a significant improvement in attitudes after the training. Of the uncontrolled studies, three showed a significant improvement, one reported only the post-intervention results and three did not show improvement	7	+	Bennett and Holloway (2012), Galea et al. (2006), McAuley et al. (2010), Strang et al. (2008), Tobin et al. (2009), Wagner et al. (2010), Williams et al. (2014)
	Management of overdose		Ambulance call: median 30 % of overdose witnessed — self-reported (range 10–85 %); median of 54.5 % of overdose witnessed — active follow-up (range 19–100 %) Recovery position: 40 % of overdoses (three studies self-reported) CPR: 61 % of overdoses (six studies, self-reported) Naloxone refill: median of 59.5 % (range 23–80 %) of overdose witnessed – active follow-up in four studies	12	+	Bennett et al. (2011), Bennett and Holloway (2012), Dettmer et al. (2001), Doe-Simkins et al., (2009), Enteen et al., (2010), Galea et al. (2006), Gaston et al. (2009), McAuley et al. (2010), Piper et al. (2008), Seal et al. (2005), Tobin et al. (2009), Wagner et al. (2010)
	Naloxone administration		Percentage of overdoses witnessed in which naloxone was administered (by the target population) In the RCT naloxone was given in 28 % of overdoses witnessed. In the two studies based on self-report, naloxone was administered in 76 % and 50 % of overdoses witnessed. In seven studies based on active follow-up by study researchers naloxone was used in a median of 67 % (range 0–100 %) of overdoses witnessed One study reported the percentage of participants who administered naloxone (44 %) and one study reported 17 naloxone administrations during the first 8 months, all with successful outcomes	11	++	Dettmer et al. (2001), Doe-Simkins et al. (2009), Galea et al. (2006), Gaston et al. (2009), Leece et al. (2013), McAuley et al. (2010), Seal et al. (2005), Strang et al. (2008), Wagner et al. (2010), Williams et al. (2014), Yokell et al. (2011)

Population	Outcome	Intervention	Effects	Number of studies	Quick guide	References
Communities	Reducing death due to overdose		One ITS showed that the risk for opioid-related overdose fatalities was significantly lower both in communities with high programme implementation and in communities with low programme implementation when compared with communities without programme implementation (high vs. none: adjusted RR 0.54, 95 % CI 0.39–0.76; low vs. none: adjusted RR 0.73, 95% CI 0.57–0.91) One study reported that 83 % of overdoses that occurred during the study were reversed but no information was available for the remaining 17 %. In four studies information on survival status collected from voluntary participants reporting fatal overdoses (despite naloxone administration) ranged from 0 % to 4%; the median percentage of death was 0.8 % In six other studies with active follow-up fatal overdoses (despite naloxone provision) ranged from 0 % to 33 % Three studies reported the total number of overdoses reversed (no information is given about the number of overdoses for which naloxone was administered)	13	++	Bennett et al. (2011), Bennett and Holloway (2012), Dettmer et al. (2001 – Berlin and Jersey), Doe-Simkins et al. (2009), Enteen et al. (2010), Galea et al. (2006), McAuley et al. (2010), Piper et al. (2008), Seal et al. (2005), Strang et al. (2008), Wagner et al. (2010), Walley et al. (2013)

++ = the studies including the outcome gave consistently favourable results; + = the studies measuring the outcomes gave varied results.
CI, confidence interval; CPR, cardiopulmonary resuscitation; ITS, interrupted time series; RCT, randomised controlled trial; RR, relative risk.

Discussion

Summary of the main results

Improving knowledge on opioid overdose and enabling preparedness to intervene

This outcome included knowledge about signs of overdose, the correct management of patients and naloxone use; and attitudes (willingness to use naloxone, confidence in and acceptability of naloxone). The educational and training intervention with naloxone provision seems to be effective in improving knowledge about signs of overdose, the correct management of patients and naloxone use in all the retrieved studies, including the randomised trial and the uncontrolled pre–post studies. The one randomised trial also suggests that attitudes towards the use of naloxone have improved. The management of witnessed overdoses seems to be positively influenced by the educational and training intervention in patients who returned for naloxone refill or who were not lost at follow-up.

Management of witnessed overdose (naloxone administration)

Naloxone was administered in a median of 67 % of overdoses witnessed by participants who returned for naloxone refill or who were not lost at follow-up (Table 2). The data come only from uncontrolled studies.

Death due to overdose and survival rate

The risk of opioid-related overdose fatalities was significantly lower in communities providing naloxone distribution and overdose management education than in communities without programme implementation. This was shown in an ITS analysis of more than 2 900 subjects from 19 communities with a follow-up of 7 years (Walley et al., 2013b). Furthermore, all the other studies found a high survival rate.

Potential bias in the review process

It was not possible to assess the risk of publication bias using a funnel plot because a meta-analysis was not performed. Unpublished studies were searched on websites of conference proceedings, ongoing trials were searched, comprehensive bibliographic searches of many databases, unrestricted by date or language, were undertaken and reference lists of retrieved studies and narrative reviews were inspected. For these reasons the probability that relevant studies on this topic have been missed is small, but the possibility of some unpublished studies not being retrieved cannot be ruled out.

Conclusions

There is evidence that educational and training interventions with provision of take-home naloxone decrease overdose-related mortality.

There is weaker, but consistent, evidence that educational and training interventions with naloxone provision for opioid-dependent patients and their peers is effective in improving knowledge about and creating positive attitudes to the correct use of naloxone and management of witnessed overdoses. There is sparse evidence that people return for naloxone refill.

Take-home naloxone provision is an emergency life-saving intervention. As with other types of public health programmes relying on layperson interventions in critical situations, it is difficult to assess their effectiveness with properly designed experimental studies. By analogy with the provision of public access defibrillators (PADs) for out-of-hospital cardiac arrest, for example, the factors contributing to survival rates are many and difficult to control in an experimental study design. Nevertheless, although the evidence in support of PADs is scarce, the available systematic reviews of the literature suggest the implementation of such an intervention (Clare, 2006; Smith et al., 2007) for the actual or potential reduction of fatal cases.

Prospective controlled cohort studies of good methodological quality comparing communities where the intervention is implemented with communities where it is not implemented or implemented at a lower intensity may contribute to the supporting evidence. Those studies should be based on current multiple-source data collections (including emergency and hospital data, along with mortality data) and may assess the impact of the intervention on public health and participants' behaviour (incidence of overdose, management of witnessed overdose, outcome of overdoses, naloxone provision and naloxone refill).

New initiatives have emerged quickly over recent years in various regions of the world. This is driven in part by the epidemic of opioid-related deaths (heroin and non-heroin) in the USA. In Europe, naloxone programmes are now broadly available. Since September 2013, Estonia has had a naloxone programme to tackle the alarming increase in deaths caused by illicit use of fentanyl. Most recently, Norway began a pilot of a nasal spray naloxone programme.

In this context, the rapid identification and dissemination of the available evidence can be helpful to refine these programmes, if needed, or to scale up their implementation and coverage.

Furthermore, some studies are ongoing and their results will greatly contribute to the body of evidence. These include the N-ALIVE trial (Strang et al., 2013), which plans to involve 5 600 prisoners on release in the initial pilot randomised phase then extend to its randomised sample size of 56 000 for the full trial. Participants will receive emergency naloxone with instructions for it to be given by the much simpler intramuscular route. The PATHFINDER feasibility study South Wales (Moore, ongoing) aims to assess whether it is possible for paramedics to supply take-home naloxone kits to patients whom they have treated and who have subsequently recovered from an opioid overdose. Paramedics will be randomly allocated to training over the first 4 months of the 12-month trial. Patients attended to by paramedics who have been trained and issued with take-home naloxone kits for distribution will fall into the intervention group. Patients attended to by paramedics following usual practice (until they receive their training and take-home naloxone kits) will fall into the control group. Many outcomes will be assessed, with the aim of defining the primary outcome of the definitive trial.

This overview reached similar conclusions to those of a recently published review (Clark et al., 2014) that included 19 of the 21 studies in our work, including the RCT by Williams et al. (2014), which probably contributed to our more confident conclusions.

With regard to guidelines to support the implementation of naloxone availability outside the healthcare system, the World Health Organization published a document for global use. Some European countries have national guidelines; these can be found in the EMCDDA's Best practice portal.

References

Included studies

1. Bennett, A. S., Bell, A., Tomedi, L., Hulsey, E. G. and Kral, A. H. (2011), 'Characteristics of an overdose prevention, response, and naloxone distribution program in Pittsburgh and Allegheny County, Pennsylvania', *Journal of Urban Health* 88, pp. 1020–1030.
2. Bennett, T. and Holloway, K. (2012), 'The impact of take-home naloxone distribution and training on opiate overdose knowledge and response: an evaluation of the THN Project in Wales', *Drugs: Education Prevention and Policy* 19, pp. 320–328.
3. Dettmer, K., Saunders, B. and Strang, J. (2001), 'Take home naloxone and the prevention of deaths from opiate overdose: two pilot schemes', *BMJ* 322, pp. 895–896.
4. Doe-Simkins, M., Walley, A. Y., Epstein, A. and Moyer, P. (2009), 'Saved by the nose: bystander-administered intranasal naloxone hydrochloride for opioid overdose', *American Journal of Public Health* 99, pp. 788–791.
5. Enteen, L., Bauer, J., McLean, R., et al. (2010), 'Overdose prevention and naloxone prescription for opioid users in San Francisco', *Journal of Urban Health* 87, pp. 931–941.
6. Galea, S., Worthington, N., Piper, T. M., Nandi, V. V., Curtis, M. and Rosenthal, D. M. (2006), 'Provision of naloxone to injection drug users as an overdose prevention strategy: early evidence from a pilot study in New York City', *Addictive Behaviors* 31, pp. 907–912.
7. Gaston, R. L., Best, D., Manning, V. and Day, E. (2009), 'Can we prevent drug related deaths by training opioid users to recognise and manage overdoses?', *Harm Reduction Journal* 6, p. 26.
8. Heller, D.I. and Stancliff, S. (2007), 'Providing naloxone to substance users for secondary administration to reduce overdose mortality in New York City', *Public Health Reports* 122, pp. 393–397.
9. Leece, P. N., Hopkins, S., Marshall, C., et al. (2013), 'Development and implementation of an opioid overdose prevention and response program in Toronto, Ontario', *Revue Canadienne de Santé Publique* 104, pp. e200–e204.
10. McAuley, A., Lindsay, G., Woods, M. and Louttit, D. (2010), 'Responsible management and use of a personal take-home naloxone supply: a pilot project', *Drugs: Education, Prevention, and Policy* 17, pp. 388–399.
11. Maxwell, S., Bigg, D., Stanczykiewicz, K. and Carlberg-Racich, S. (2006), 'Prescribing naloxone to actively injecting heroin users: a program to reduce heroin overdose deaths', *Journal of Addictive Diseases* 25, pp. 89–96.
12. Piper, T. M. , Stancliff, S., Rudenstine, S., et al. (2008), 'Evaluation of a naloxone distribution and administration program in New York City', *Substance Use & Misuse* 43, pp. 858–870.
13. Seal, K. H., Thawley, R., Gee, L., et al. (2005), 'Naloxone distribution and cardiopulmonary resuscitation training for injection drug users to prevent heroin overdose death: a pilot intervention study', *Journal of Urban Health* 82, pp. 303–311.
14. Strang, J., Manning, V., Mayet, S., et al. (2008), 'Overdose training and take-home naloxone for opiate users: prospective cohort study of impact on knowledge and attitudes and subsequent management of overdoses', *Addiction* 103, pp. 1648–1657.
15. Tobin, K. E., Sherman, S. G., Beilenson, P., Welsh, C. and Latkin, C. A. (2009), 'Evaluation of the Staying Alive programme: training injection drug users to properly administer naloxone and save lives', *International Journal of Drug Policy* 20, pp. 131–136.
16. Wagner, K. D., Valente, T. W., Casanova, M., et al. (2010), 'Evaluation of an overdose prevention and response training programme for injection drug users in the Skid Row area of Los Angeles, CA', *International Journal of Drug Policy* 21, pp. 186–193.
17. Walley, A. Y., Doe-Simkins, M., Quinn, E., Pierce, C., Xuan, Z. and Ozonoff, A. (2013a), 'Opioid overdose prevention with intranasal naloxone among people who take methadone', *Journal of Substance Abuse Treatment* 44, pp. 241–247.

18. Walley, A. Y., Xuan, Z., Hackman, H. H., et al. (2013b), 'Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis', *BMJ* 346, p. f174.

19. Wheeler, E., Davidson, P. J., Jones, T. S. and Irwin, K. S. (2012), 'Community-based opioid overdose prevention programs providing naloxone — United States, 2010', *Morbidity and Mortality Weekly Report* 61, pp. 101–104.

20. Williams, A. V., Marsden, J. and Strang, J. (2014), 'Training family members to manage heroin overdose and administer naloxone: randomized trial of effects on knowledge and attitudes', *Addiction* 109, pp. 250–259.

21. Yokell, M. A., Green, T. C., Bowman, S., McKenzie, M., Rich, J. D. (2011), 'Opioid overdose prevention and naloxone distribution in Rhode Island', *Medicine and Health Rhode Island* 94, pp. 240–242.

Excluded studies (articles)

1. Anonymous (2010), 'Naloxone distribution saves more than 400 lives in SF overdose project', *DATA: The Brown University Digest of Addiction Theory & Application* 29, pp. 4–5.

2. Anonymous (2012), 'Community-based opioid overdose prevention programs providing naloxone — United States, 2010', *Morbidity and Mortality Weekly Report* 61, pp. 101–105.

3. Ashton, H. and Hassan, Z. (2006), 'Best evidence topic report. Intranasal naloxone in suspected opioid overdose', *Emergency Medicine Journal* 23, pp. 221–223.

4. Ashworth, A. J. and Kidd, A. (2001), 'Take home naloxone for opiate addicts. Apparent advantages may be balanced by hidden harms', *BMJ* 323, p. 935.

5. Baca, C. T. and Grant, K. J. (2005), 'Take-home naloxone to reduce heroin death', *Addiction* 100, pp. 1823–1831.

6. Bigg, D. (2002), 'Data on take home naloxone are unclear but not condemnatory', *BMJ* 324, p. 678.

7. Blackwood, G. (2001), 'Take home naloxone for opiate addicts. Figures in Jersey give no support to scheme's effectiveness' *BMJ* 323, pp. 934–935; author reply p. 935.

8. Campopiano, M. (2009), 'Overdose prevention and naloxone prescribing in a narcotic addiction treatment program (NATP)', *Substance Abuse* 30, p. 90.

9. Darke, S. (1999a), 'Attacking overdose on the home front', *Addiction* 94, pp. 205–206; discussion p. 207.

10. Darke, S. (1999b), 'Comments on Strang et al's "Preventing opiate overdose fatalities with take-home naloxone: pre-launch study of possible impact and acceptability" attacking overdose on the home front', *Addiction* 94, pp. 205–206.

11. Davis, C., Webb, D. and Burris, S. (2013), 'Changing law from barrier to facilitator of opioid overdose prevention', *Journal of Law, Medicine & Ethics* 41(Suppl 1), pp. 33–36.

12. George, S. and Moreira, K. (2008), 'A guide for clinicians on take home naloxone prescribing', *Addictive Disorders & Their Treatment* 7, pp. 163–167.

13. George, S., Boulay, S. and Begley, D. (2010), '"I saved a life": a heroin addict's reflections on managing an overdose using "take home naloxone"', *BMJ Case Reports* p. ii, bcr0520102986.

14. Graham, C. A., McNaughton, G. W., Ireland, A. J. and Cassells, K. (2001), 'Take home naloxone for opiate addicts. Drug misusers may benefit from training in cardiopulmonary resuscitation', *BMJ* 323, p. 934; author reply p. 935.

15. Green, T. C., Heimer, R. and Grau, L. E. (2008), 'Distinguishing signs of opioid overdose and indications for naloxone: an evaluation of six overdose training and naloxone distributions programs in the United States', *Addiction* 103, pp. 979–989.

16. Hill, D. and Mcauley, A. (2012), 'A comparative study of stakeholder views on take-home naloxone services', *Journal of Substance Use* 17, pp. 430–441.

17. Hurley, R. (2011), 'Pilot scheme shows that giving naloxone to families of drug users would save lives', *BMJ* 343, p. d5445.

18. Jones, J. D., Roux, P., Stancliff, S., Matthews, W. and Comer, S. D. (2014), 'Brief overdose education can significantly increase accurate recognition of opioid overdose among heroin users', *International Journal of Drug Policy* 25, pp. 166–170.

19. Kerr, D., Dietze, P., Kelly, A. M. and Jolley, D. (2008), 'Attitudes of Australian heroin users to peer distribution of naloxone for heroin overdose: perspectives on intranasal administration', *Journal of Urban Health* 85, pp. 352–360.

20. Lagu, T., Anderson, B. J. and Stein, M. (2006), 'Overdoses among friends: drug users are willing to administer naloxone to others', *Journal of Substance Abuse Treatment* 30, pp. 129–133.

21. Lenton, S. (2008), 'Case for peer naloxone further strengthened — commentary', *Addiction* 103, pp. 1658–1659.

22. Lenton, S. and Hargreaves, K. (2000a), 'A trial of naloxone for peer administration has merit, but will the lawyers let it happen?', *Drug and Alcohol Review* 19, pp. 365–369.

23. Lenton, S. R. and Hargreaves, K. M. (2000b), 'Should we conduct a trial of distributing naloxone to heroin users for peer administration to prevent fatal overdose?', *Medical Journal of Australia* 173, pp. 260–263.

24. Lenton, S. R., Dietze, P. M., Degenhardt, L., Darke, S. and Butler, T. G. (2009), 'Now is the time to take steps to allow peer access to naloxone for heroin overdose in Australia', *Drug and Alcohol Review* 28, pp. 583–585.

25. Lenton, S., Dietze, P., Van Beek, I., Lintzeris, N. and Wiggins, N. (2010), 'Symposium — policy and practice — increasing community access to naloxone to prevent opioid overdose deaths: lessons for Australia', *Drug and Alcohol Review* 29, pp. 40–41.

26. Mountain, D. (2001), 'Take home naloxone for opiate addicts. Big conclusions are drawn from little evidence', *BMJ* 323, p. 934; author reply p. 935.

27. Oldham, N. S. and Wright, N. M. J. (2003), 'A UK policy on "take home naloxone" for opiate users — strategy or stalemate?', *Drugs: Education, Prevention, and Policy* 10, pp. 105–119.

28. Piper, T. M., Rudenstine, S., Stancliff, S., et al. (2007), 'Overdose prevention for injection drug users: lessons learned from naloxone training and distribution programs in New York City', *Harm Reduction Journal* 4, p. 3.

29. Seal, K. H., Downing, M., Kral, A. H., et al. (2003), 'Attitudes about prescribing take-home naloxone to injection drug users for the management of heroin overdose: a survey of street-recruited injectors in the San Francisco Bay Area', *Journal of Urban Health* 80, pp. 291–301.

30. Snooks, H., Russell, D., Brown, C., et al. (2011), 'How can we prevent overdoses and what works? A systematic review of interventions for non-fatal poisonings', *Emergency Medicine Journal* 28, pp. 5–6.

31. Sporer, K. A. (2003), 'Strategies for preventing heroin overdose', *BMJ* 326, pp. 442–444.

32. Sporer, K. (2008), 'Prescription naloxone: a novel approach to opiate overdose prevention', *Clinical Toxicology* 46, pp. 353–354.

33. Sporer, K. A. and Kral, A. H. (2007), 'Prescription naloxone: a novel approach to heroin overdose prevention', *Annals of Emergency Medicine* 49, pp. 172–177.

34. Sporer, K. A., Firestone, J. and Isaacs, S.M. (1996), 'Out-of-hospital treatment of opioid overdoses in an urban setting', *Academic Emergency Medicine* 3, pp. 660–667.

35. Strang, J. (1999), 'Comments on Strang et al's "Preventing opiate overdose fatalities with take-home naloxone: pre-launch study of possible impact and acceptability" — take-home naloxone: the next steps', *Addiction* 94, p. 207.

36. Strang, J., Darke, S., Hall, W., Farrell, M. and Ali, R. (1996), 'Heroin overdose: the case for take-home naloxone', *BMJ* 312, pp. 1435–1436.

37. Strang, J., Powis, B., Best, D., et al. (1999), 'Preventing opiate overdose fatalities with take-home naloxone: pre-launch study of possible impact and acceptability', *Addiction* 94, pp. 199–204.

38. Strang, J., Best, D., Man, L.-H., Noble, A. and Gossop, M. (2000), 'Peer-initiated overdose resuscitation: fellow drug users could be mobilised to implement resuscitation', *International Journal of Drug Policy* 11, pp. 437–445.

39. Strang, J., Manning, V., Mayet, S., et al. (2008), 'Family carers and the prevention of heroin overdose deaths: unmet training need and overlooked intervention opportunity of resuscitation training and supply of naloxone', *Drugs: Education, Prevention, and Policy* 15, pp. 211–218.

40. Wakeman, S. E., Bowman, S. E., McKenzie, M., Jeronimo, A. and Rich, J. D. (2009), 'Preventing death among the recently incarcerated: an argument for naloxone prescription before release', *Journal of Addictive Disorders* 28, pp. 124–129.

41. Walley, A. Y., Doe-Simkins, M., Quinn, E., Pierce, C., Ozonoff, A. and Xuan, ZM. (2012a), 'Opioid overdose prevention with intranasal naloxone among people who use methadone', *Substance Abuse* 33, pp. 210–211.

42. Walley, A. Y., Xuan, Z. M., Hackman, H., et al. (2012b), 'Is implementation of bystander overdose education and naloxone distribution associated with lower opioid-related overdose rates in Massachusetts?' *Substance Abuse* 33, p. 206.

43. Williams, A., Reed, K., Groshkova, T., et al. (2010), 'Training family members and carers of opiate users in overdose management and naloxone administration: a randomised trial', *Drug and Alcohol Review* 29, pp. 81–82.

44. Williams, A. V., Strang, J. and Marsden, J. (2013), 'Development of Opioid Overdose Knowledge (OOKS) and Attitudes (OOAS) Scales for take-home naloxone training evaluation', *Drug and Alcohol Dependence* 132, pp. 383–386.

45. Wright, N., Oldham, N., Francis, K. and Jones, L. (2006), 'Homeless drug users' awareness and risk perception of peer "take home naloxone" use — a qualitative study', *Substance Abuse Treatment, Prevention, and Policy* 1, p. 28.

46. Zaller, N. D., Yokell, M. A., Green, T. C., Gaggin, J. and Case, P. (2013), 'The feasibility of pharmacy-based naloxone distribution interventions: a qualitative study with injection drug users and pharmacy staff in Rhode Island', *Substance Use and Misuse* 48, pp. 590–599.

Ongoing studies

Moore, C. 'Paramedic Administered Take Home kits: Feasible Intervention for Naloxone Distribution in Emergency Response (PATHFINDER) to opioid overdose: a feasibility study for a randomised controlled trial'. Available at: www.controlled-trials.com (doi: 10.1186/ISRCTN98216498, last accessed Nov. 2014).

Strang, J., Bird, S. M. and Parmar, M. K. (2013), 'Take-home emergency naloxone to prevent heroin overdose deaths after prison release: rationale and practicalities for the N-ALIVE randomized trial', *Journal of Urban Health* 90, pp. 983–996.

Studies awaiting classification

Kan, M., Gall, J. A., Latypov, A., et al. (2014), 'Effective use of naloxone among people who inject drugs in Kyrgyzstan and Tajikistan using pharmacy- and community-based distribution approaches', *International Journal of Drug Policy* (doi: 10.1016/j.drugpo.2014.01.005).

Lenton, S. R., Dietze, P. M., Degenhardt, L., Darke, S. and Butler, T. G. (2009), 'Naloxone for administration by peers in cases of heroin overdose', *Medical Journal of Australia* 191, p. 469.

Other references

Advisory Council on the Misuse of Drugs (ACMD) (2012), *Consideration of naloxone*, London, The Stationery Office.

Bargagli, A. M., Hickman, M., Davoli, M., et al. (2006), 'Drug-related mortality and its impact on adult mortality in eight European countries', *European Journal of Public Health* 16, pp. 198–202.

Binswanger, I. A., Blatchford, P. J., Mueller, S. R. and Stern, M. F. (2013), 'Mortality after prison release: opioid overdose and other causes of death, risk factors, and time trends from 1999 to 2009', *Annals of Internal Medicine* 159, pp. 592–600.

Boyer Edward, W. (2012), 'Management of opioid analgesic overdose', *New England Journal of Medicine* 367, pp. 146–155.

Clare, C. (2006), 'Do public access defibrillation (PAD) programmes lead to an increase of patients surviving to discharge from hospital following out of hospital cardiac arrest? A literature review', *International Journal of Nursing Studies* 43, pp. 1057–1062.

Clark, A , Wilder, C. and Winstanley, E. (2014), 'A systematic review of community opioid overdose prevention and naloxone distribution programs', *Journal of Addiction Medicine* 8, pp 153–63.

Cornish, R., Macleod, J., Strang, J., Vickerman, P. and Hickman, M. (2010), 'Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database', *BMJ* 341, p. c5475.

Darke, S., Degenhardt, L. and Mattick, R. (2007), *Mortality amongst illicit drug users: epidemiology, causes and interventions*, Cambridge University Press, Cambridge.

Degenhardt, L., Bucello, C., Mathers, B., et al. (2011), 'Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies', *Addiction* 106, pp. 32–51.

Delgado-Rodríguez, M. and Llorca, X. (2004), 'Bias', *Journal of Epidemiology and Community Health* 58, pp. 635–641.

Dubben, H. and Beck-Bornholdt, H. (2005), 'Systematic review of publication bias in studies on publication bias', *BMJ* 331(7514), pp. 433–434. doi:10.1136/bmj.38478.497164.F7

EMCDDA (2011), *Mortality related to drug use in Europe: public health implications*, Publications Office of the European Union, Luxembourg.

EMCDDA (2012), *EMCDDA Trendspotter study on fentanyl in Europe*, Publications Office of the European Union, Luxembourg.

EMCDDA (2013a), *Perspectives on drugs. Preventing overdose deaths in Europe.* Available at: http://www.emcdda.europa.eu/topics/pods/preventing-overdose-deaths (last accessed Nov. 2014).

EMCDDA (2013b), *European Drug Report 2013: Trends and developments*, Publications Office of the European Union, Luxembourg. Available at: http://www.emcdda.europa.eu/publications/edr/trends-developments/2013

EMCDDA (2014a), *EMCDDA–Europol 2013 Annual Report on the implementation of Council Decision 2005/387/JHA*, Implementation reports, Publications Office of the European Union, Luxembourg.

EMCDDA (2014b), *European Drug Report 2014: Trends and developments*, Publications Office of the European Union, Luxembourg.

Frischer, M. and Baldacchino, A. (2012), *Preventing opioid overdoses in Europe: a critical assessment of known risk factors and preventative measures.* Available at: http://www.emcdda.europa.eu/scientific-studies/2012/preventing-overdoses

Giraudon, I., Vicente, J., Matias, J., Mounteney, J. and Griffiths, P. (2012), 'Reducing drug related mortality in Europe — a seemingly intractable public health issue', *Adicciones* 24, pp. 3–7.

Giraudon, I., Lowitz, K., Dargan, P., Wood, D. and Dart, R. (2013), 'Prescription opioid abuse in the UK', *British Journal of Clinical Pharmacology* 76, pp. 823–824.

- Higgins, J. P. T. and Green, S., editors (2011), *Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0* (updated May 2011), The Cochrane Collaboration. Available at: www.cochrane-handbook.org
- HM Government (2008), *Drugs: protecting families and communities. The 2008 Drug Strategy,* Report No.: CDSD9. Central Office of Information on behalf of HM Government, London.
- Katzung, B. G. (1995), *Basic and clinical pharmacology*, 6th edition, Prentice-Hall International, London.
- Mathers, B. M., Degenhardt, L., Bucello, C., Lemon, J., Wiessing, L. and Hickman, M. (2013), 'Mortality among people who inject drugs: a systematic review and meta-analysis', *Bulletin of the World Health Organization* 91, pp. 102–123.
- Medline plus, 'Naloxone injection'. Available at: http://www.nlm.nih.gov/medlineplus/druginfo/meds/a612022.html (last accessed Nov. 2014).
- Smith, L. M., Davidson, P. M., Halcomb, E. J. and Andrew, S. (2007), 'Can lay responder defibrillation programmes improve survival to hospital discharge following an out-of-hospital cardiac arrest?', *Australian Critical Care* 20, pp. 137–145.
- Strang, J., Bird, S. M. and Parmar, M. K. (2013), 'Take-home emergency naloxone to prevent heroin overdose deaths after prison release: rationale and practicalities for the N-ALIVE randomized trial', *Journal of Urban Health* 90, pp. 983–996.
- World Health Organziation (2014), 'Community management of opioid overdose', Geneva. Available at: http://apps.who.int/iris/bitstream/10665/137462/1/9789241548816_eng.pdf?ua=1&ua=1 (last accessed Nov. 2014).
- Zlodre, J. and Fazel, S. (2012), 'All-cause and external mortality in released prisoners: systematic review and meta-analysis', *American Journal of Public Health* 102, pp. e67–75.

Annex 1

Characteristics of included studies

Author (year)	Study design	Participants	Name of the programme	Country	Intervention	Outcome measures	Length of follow-up
Bennett et al. (2011)	Prospective uncontrolled study assessing programme implementation	426 clients who utilised the needle exchange site, participated in overdose prevention programme and received naloxone 141 (33.1 %) returned for naloxone refill and were assessed at follow-up	**Overdose prevention program in Pittsburgh, Pennsylvania**	USA	Education: risk factors for overdose Training: management of overdose, use of naltrexone Naloxone provision	Overdose witnessed Naloxone use Death Naloxone refill Management of overdose	42 months
Bennett and Holloway (2012)	Prospective controlled study assessing programme implementation	525 (experimental group, trained and receiving take-home naloxone packs) 50 (control group) 28/525 (5.3 %) returned for naloxone refill Follow-up assessment for the overall sample for knowledge and attitudes, only for the 28 who returned for naloxone refill and 38/50 (86 %) of the control group for management of overdoses	**Take-home naloxone (THN) programme**	Wales, UK	Education: signs and risk factors for overdose Training: management of overdose, use of naloxone Naloxone provision	Overdose witnessed Naloxone use Death Management of overdose Knowledge Attitudes	6 months
Dettmer et al. (2001)	Prospective uncontrolled study assessing programme implementation	**Berlin Project:** 124 opiate misusers received the training and were provided with naloxone; 40 (32.2 %) voluntarily reported back and were assessed at follow-up **Jersey Project:** 101 drug misusers in contact with local drug services and provided with naloxone	**Berlin Project** **Jersey Project**	Germany UK	Training: management of overdose, use of naloxone Naloxone provision	Overdose witnessed Management of overdose Naloxone use Death Adverse events	16 months
Doe-Simkins et al. (2009)	Prospective uncontrolled study assessing programme implementation	385 participants trained and received intranasal naloxone 278 contacted at follow-up	**Saved by the Nose**	USA	Techniques in overdose prevention	Overdose witnessed Management of overdose Naloxone use Death	15 months
Enteen et al. (2010)	Prospective uncontrolled study assessing programme implementation	1 942 individuals who were trained and provided with naloxone 470 (24 %) returned for naloxone refill and were assessed at follow-up	**Drug Overdose Prevention and Education (DOPE) Project, San Francisco**	USA	Education: signs and symptoms of overdose Training: management of overdose, use of naloxone Naloxone provision	Management of overdose Naloxone use Death Naloxone refill Adverse events	6 years
Galea et al. (2006)	Prospective uncontrolled study assessing programme implementation	25 volunteer individuals trained and provided with naloxone 20 (80 %) assessed at active follow-up	**Overdose Prevention and Reversal Program, New York**	USA	Education: signs and symptoms of overdose Training: management of overdose, use of naloxone Naloxone provision	Overdose witnessed Management of overdose Naloxone use Death Attitudes	3 months
Gaston et al. (2009)	Prospective uncontrolled study assessing programme implementation	70 patients diagnosed with opioid dependence syndrome and provided with naloxone 46 (65 %) assessed at active follow-up	Study based on the **National training evaluation programme in England**	England, UK	Education: signs and symptoms of overdose Training: management of overdose, use of naloxone Naloxone provision	Overdose witnessed Management of overdose Naloxone use Knowledge	6 months

Author (year)	Study design	Participants	Name of the programme	Country	Intervention	Outcome measures	Length of follow-up
Heller and Stancliff (2007)	Prospective uncontrolled study assessing programme implementation	More than 1 800 opioid dependents trained as overdose responders and provided with overdose prevention kits	**Overdose prevention program in New York City**	USA	Education: signs and symptoms of overdose Medical evaluation Training: management of overdose, use of naloxone Naloxone provision	Reversal rate	18 months
Leece et al. (2013)	Prospective uncontrolled study assessing programme implementation	209 clients trained and provided with a take-home naloxone pack	**POINT program in Toronto**	Canada	Education: signs and symptoms of overdose Medical evaluation Training: management of overdose, use of naloxone Naloxone provision	Knowledge retention, experiences related to overdose and overdose response, willingness and confidence to administer naloxone, barriers to implementing the resuscitation protocol, and risky drug use behaviours	8 months
McAuley et al. (2010)	Prospective uncontrolled study assessing programme implementation	19 clients trained and provided with a take-home naloxone pack 17 (89 %) assessed at active follow-up	**Lanarkshire Naloxone (Narcan) pilot**	Scotland, UK	Education: signs, symptoms and risk factors of overdose Training: management of overdose (basic life support), use of naloxone Naloxone provision	Overdose witnessed Management of overdose Death Naloxone use Knowledge Attitudes	6 months
Maxwell et al. (2006)	Prospective uncontrolled study assessing programme implementation	Number of participants not reported Every week Chicago Recovery Alliance's outreach workers directly contact over 340 IDUs, who have gone on to reach an additional 780 people since 2001	**Chicago Recovery Alliance naloxone project**	USA	Standardised education about overdose and naloxone	Overdose reversed	8 years
Piper et al. (2008)	Prospective uncontrolled study assessing programme implementation	122 opioid-dependent participants trained and provided with naloxone None lost at active follow-up but detailed information only on 50 overdoses witnessed	**SKOOP (Skills and Knowledge on Overdose Prevention) in New York City**	USA	Education: signs, symptoms and risk factors of overdose Training: management of overdose, use of naloxone Naloxone provision	Overdose witnessed Management of overdose Death Naloxone use Naloxone refill Attitudes	8 months
Seal et al. (2005)	Case series	24 IDUs trained and provided with naloxone None lost at active follow-up	**Pilot overdose prevention and management programme in San Francisco**	USA	Education: signs, symptoms and risk factors of overdose Training: management of overdose, use of naloxone Naloxone provision	Overdose witnessed Management of overdose Knowledge	6 months
Strang et al. (2008)	Prospective uncontrolled study	239 opiate users trained and provided with naloxone Assessed at post training: 202 (84.5 %) Assessed at active follow-up: 186 (77.8 %)	**National initiative to provide training in the management of overdose**	England, UK	Education: signs, symptoms and risk factors of overdose Training: management of overdose, use of naloxone Naloxone provision	Overdose witnessed Naloxone use Knowledge Attitudes	3 months
Tobin et al. (2009)	Prospective uncontrolled study assessing programme implementation	250 individuals trained and provided with naloxone 85 assessed at active follow-up	**Staying Alive (SA) program, Baltimore**	USA	Education: signs, symptoms and risk factors of overdose Training: management of overdose, use of naloxone Naloxone provision	Overdose witnessed Management of overdose Naloxone use Knowledge Attitudes	6 months

Author (year)	Study design	Participants	Name of the programme	Country	Intervention	Outcome measures	Length of follow-up
Wagner et al. (2010)	Prospective uncontrolled study assessing programme implementation	93 drug users trained and provided with naloxone 66 (71.5 %) enrolled in the study 47 (50.5 %) assessed at active follow-up	**Overdose prevention and response training program in Los Angeles**	USA	Education: signs, symptoms and risk factors of overdose Training: management of overdose, use of naloxone Naloxone provision	Overdose witnessed Management of overdose Naloxone use Death Knowledge Attitudes Naloxone refill	3 months
Walley et al. (2013a)	Prospective uncontrolled study assessing programme implementation From September 2008 and December 2010	1 553 participants taking methadone	**Overdose Education and Naloxone Distribution (OEND) Program**	USA	Education: signs, symptoms and risk factors of overdose Training: management of overdose, use of naloxone Naloxone provision	Overdose witnessed Naloxone use	27 months
Walley et al. (2013b)	Interrupted time-series analysis from 2002 to 2009	2 912 opioid users at risk for overdose, social service agency staff, family and friends of opioid users in 19 communities	**Overdose Education and Naloxone Distribution (OEND) Program, Massachusetts**	USA	Education: signs, symptoms and risk factors of overdose Training: management of overdose, use of naloxone Naloxone provision	Annual opioid-related rates of overdose fatalities	7 years
Wheeler et al. (2012)	Prospective uncontrolled study assessing programme implementation	53 032 participants trained and provided with a take-home naloxone pack	**48 programmes in USA**	USA	Opioid overdose education	Overdose reversal	14 years
Williams et al. (2014)	Randomised clinical trial	187 randomised, 123 (65 %) assessed at follow-up	**Emergency recovery procedures and take-home naloxone administration training**	UK	Education: oral presentation on overdose management and naloxone administration; 8-minute film which dramatises real opioid overdose stories Training: management of overdose, use of naloxone Naloxone provision	Overdose witnessed Naloxone use Knowledge Attitudes	3 months
Yokell et al. (2011)	Prospective uncontrolled study assessing programme implementation	120 individuals trained and provided with naloxone 10 (0.083 %) voluntarily returned and were assessed at follow-up	**PONI (Preventing Overdose and Naloxone Intervention), Rhode Island**	USA	Education: signs, symptoms and risk factors of overdose Training: management of overdose, use of naloxone Naloxone provision	Overdose witnessed Naloxone use	3 months

IDU, injecting drug user.

Annex 2

Effects of the interventions

Author (year)	Results		Survival/adverse events/death	Naloxone refill/lost/stolen/ confiscated	Authors' conclusions and quality of evidence (when available)
	Overdose witnessed/ attitudes/knowledge	Overdose management: naloxone administration, recovery position and CPR			
Bennett et al. (2011)	Overdose witnessed: not reported Attitudes: 89/141 (63.1 %) used naloxone Knowledge [appropriate use of naloxone (overdose caused by opioids)]: 98 %	Naloxone: 249 (episodes administered by 89 persons) Recovery position: no information CPR: 152/249 (61 %) Ambulance call: 25/249 (10 %)	Survival: 96 % Adverse events: no information Death: 0.8 % Unknown outcome: 3.2 %	Refill: 141/426 (33.1 %) Refill for reason different from overdose: 52, of which naloxone lost 48.1 %; confiscated by police 12 %; stolen 4 %, other reasons (37 %)	The majority (96 %) of participants reported positive outcomes (e.g. person lived, was not in a coma and did not have brain damage) in the overdose situations where they administered naloxone to a peer. This indicates the feasibility of developing programmes that equip active drug users with the skills to prevent, recognise and respond to an overdose in community settings. Training in the effective administration of naloxone can be provided to drug users in a community setting and can prevent overdose fatalities. Participants who used naloxone reported very few problems, and only two fatalities were recorded
Bennett and Holloway (2012)	*Overdose witnessed* Experimental: not reported Control: 38 *Attitudes* Willingness to use naloxone: pre 88 %, post 98 % ($p < 0.001$) Willingness to do mouth-to-mouth resuscitation: pre 79 %, post 88 % ($p< 0.001$) Willingness put in recovery position: pre 96 %, post 99 % ($p = 0.007$) Willingness to phone emergency services: pre 97 %, post 99 % ($p= 0.267$) *Knowledge* Relative change in correctly identified responses before and after training Overdose risk factors: +12.7 % Signs of opiate overdose: +12.5 % Management of overdose: +11.3 % Use of naloxone: +6.4 % Method for administering naloxone: +13.4%	*Naloxone* Experimental: 28 Control: 38 *Recovery position* Experimental: 21/28 (81 %) Control: 14/38 (40 %) *CPR* Experimental: 10/28 (40 %) Control: 18/38 (53 %) *Ambulance call* Experimental: 23/28 (85 %) Control: 21/38 (60 %)	Survival: 27/28 (96.5 %) Adverse events: no information *Death* Experimental: 1 (4 %) Control: 1 (3 %)	Refill: 28/525 (5.3 %)	Training in overdose management and the use of naloxone can significantly improve knowledge and willingness to take action. Take-home naloxone training helped drug users to use naloxone successfully in overdose events

Author (year)	Results		Survival/adverse events/death	Naloxone refill/lost/stolen/ confiscated	Authors' conclusions and quality of evidence (when available)
Dettmer et al. (2001, Berlin)	Overdose witnessed: 29 Attitudes: no information Knowledge: no information	Naloxone: 22/29 (76 %) Recovery position: no information CPR: no information Ambulance call: 9/29 (31 %)	Survival: 100 % Adverse effects: in 34 % of instances naloxone provoked a sudden onset of opiate withdrawal; no other side-effects were reported	No information	Early reports are encouraging. No deaths have been reported, and 10 % of distributed naloxone has saved lives. A study of the wider distribution of take-home naloxone is now required
Dettmer et al. (2001, Jersey)	Overdose witnessed: not reported Attitudes: no information Knowledge: no information	Naloxone: 5 overdoses out of 101 drug users. Recovery position: no information CPR: no information Ambulance call: no information	Survival: 100 % Adverse events: no adverse consequences other than withdrawal symptoms of resuscitation reported Death: none	No information	Early reports are encouraging. No deaths have been reported, and 10 % of distributed naloxone has saved lives. A study of the wider distribution of take-home naloxone is now required
Doe-Simkins et al. (2009)	Overdose witnessed: 74/278 (26.6 %) Attitudes: no information Knowledge: no information	Naloxone: 74 (100 %) Recovery position: no information CPR: no information Ambulance call: 21/74 (28.4 %)	Survival: 100 % Adverse events: two withdrawal symptoms Death: none	Refill: 57/274 (20.8 %) Stolen: 2 (3.5 %) Confiscated: 2 (3.5 %)	Overdose prevention education with distribution of intranasal naloxone is a feasible public health intervention to address opioid overdose
Enteen et al. (2010)	Overdose witnessed: no data Attitudes: no data Knowledge: no data	Naloxone: 399 Recovery position: no information CPR: no information Ambulance call: 116/399 (29 %)	Reversion due to naloxone: 333/399 (83 %): Unknown outcome: 36/399 (9 %) *Adverse events* Seizure:1 % Vomiting:13 % Victim was angry or 'dope sick': 9 % Death: 6 (1.5 %)	Patients returned for naloxone refill: 470/1942 (24 %) Number of refills: 1 020 Lost: 499/1 020 (49 %) Confiscated: 122/1 020 (12 %) Refill for naloxone administration: 399/1 020 (40 %)	Participation has grown steadily among individuals at high risk of witnessing overdose events, and findings indicate that participants are motivated to receive refills following naloxone loss or use. Among trained participants who report using naloxone, 9 in 10 report positive outcomes. Few serious side-effects or deaths were reported. The findings presented here add to a growing body of evidence that supports the positive impact of naloxone prescription programmes as an intervention to prevent potentially fatal overdose events
Galea et al. (2006)	Overdose witnessed: 26 (information on 17); ambulance called: 9/11 (82 %) Attitudes: 15/20 (75 %) felt comfortable or very comfortable using naloxone; 12/20 (60 %) kept naloxone with them at all times or in their house, where they usually used drugs	Naloxone: 10/17 (59 %) Recovery position: no information CPR: no information Ambulance call: 9/11 (82 %)	Overdose reversed: 100 % No adverse effects reported	Stolen: 4/20 (20 %)	This initial evidence suggests that naloxone administration by injecting drug users as part of a comprehensive overdose prevention strategy is feasible in New York City and may be a practicable means of reducing overdose deaths on a larger scale. Participants in this assessment reported high levels of comfort with naloxone administration and no adverse consequences following administration. All instances of naloxone use during this brief period of assessment appeared to be appropriate and associated with near-immediate reversal of the opiate overdose. The limited available evidence in this regard concurs that there are few complications or problems with naloxone administration in this context

Author (year)	Results		Survival/adverse events/death	Naloxone refill/lost/stolen/ confiscated	Authors' conclusions and quality of evidence (when available)
Gaston et al. (2009)	Overdose witnessed: 16 by 9 individuals Attitudes: most participants did not carry naloxone with them consistently and, consequently, it was generally not available if they witnessed an overdose *Knowledge* Mean score Recognition of overdose: baseline 5.5, follow-up 6.0 ($p < 0.05$) Actions to take in case of overdose events: baseline 5.6, follow-up 9.3 ($p < 0.001$)	Naloxone: 0/16 Recovery position: 2/16 CPR: mouth to mouth: 2/16 Ambulance call: 3/16	Survival: 6/16 *Adverse events* Death: 1/16 (found already dead) No information: 9	Lost: 3/70 (6.5 %)	Training opiate users in the recognition and management of opiate overdoses had a significant impact on their awareness, knowledge and confidence, and increased their likelihood of intervening in high-risk situations
Heller and Stancliff (2007)	Overdose witnessed: not specified Attitudes: no information Knowledge: no information	Naloxone: no information Recovery position: no information CPR: no information Ambulance call: no information	Reversal rate: 9 % (162/1 800) at 18-month follow-up	No information	The local success achieved in rapid programme development and implementation relied on the collaborative and complementary efforts of all stakeholders. The intervention now shows promise for addressing and reducing overdose mortality via community-based, public and medical systems of care in New York City
Leece et al. (2013)	Naloxone administration: 17/209 (8.13 %)	Naloxone administration: 17 (8.13 %) Recovery position: no information CPR: no information Ambulance call: no information	Survival, adverse events: no information Death: none	No information	The authors are encouraged by the initial development and implementation experience with the naloxone programme and its potential to save lives in Toronto. An outcomes and process evaluation is planned for the future
McAuley et al. (2010)	Overdose witnessed: 3 17 clients (89%) were followed up at 2 months: 16 (94 %) claimed to still have naloxone, 12 (75 %) witnessed by key workers 17 clients (89 %) were followed up at 6 months: 17 (100 %) claimed to still have naloxone, 15 (88 %) witnessed by key workers *Knowledge* Cumulative score mean (SD): pre 7.03 (2.27); 2-month follow-up 10.54 (1.94); 6-month follow-up 10.33 (2.42) *Attitudes (confidence)* Cumulative mean score (SD): pre 19.63 (5.40); 2-month follow-up 28 (2.41); 6-month follow-up 29.60 (0.89)	Naloxone: 2 (67 %) *Recovery position and CPR* Basic life support initiated: 3 (100 %) Ambulance call: 3 (100 %)	Saves ([1]): 2 (67 %) Death: 1 (33 %)	No information	These data suggest that Scottish drug users can be trained to identify and respond to an opiate overdose utilising basic life support and naloxone administration skills. These results suggest that a majority of opiate users can responsibly manage their own personal take-home naloxone supply when trained appropriately

Author (year)	Results		Survival/adverse events/death	Naloxone refill/lost/stolen/ confiscated	Authors' conclusions and quality of evidence (when available)
Maxwell et al. (2006)	Overdose witnessed: no information Attitudes: no information Knowledge: no information	Naloxone prescription: 3 500 doses Recovery position: no information CPR: no information Ambulance call: no information	Reversed: 319 Adverse effects: 1 vomit; 1 seizures [alprazolam use (6–8 mg/day)]; one rescuer reported using five sequential doses (0.4 mg each), each having a partial reviving effect, before full reversal was achieved Death: 1	No information	Participants were educated, and naloxone prescribed, throughout an extensive harm reduction outreach network. Approximately 3 500 10-dose vials of naloxone were prescribed. No clinical, legal or liability repercussions ensued. There were reports of 319 peer reversals, with only one unsuccessful reversal reported. Only two reports of adverse events have been received: one case of severe opiate abstinence syndrome (OAS) and one case of seizures (in a participant with high-dose alprazolam use)
Piper et al. (2008)	Overdose witnessed: not reported Overdose caused by heroin: 44/50 (88 %) Attitudes: 97 (82.2 %) said they felt comfortable or very comfortable using naloxone if indicated; 31 (27.0 %) reported having kept the naloxone with them at all times or in their house, where they usually used drugs	Naloxone: 82 Recovery position: 36/50 (72 %) CPR: 27/50 (54 %) Ambulance call: 37/50 (74 %)	Reversed: 68 (83.0 %) Outcome unknown: 14 (17.1 %)	Refilled more than once: 36/122 (30 %) Stolen: 28/122 (24 %)	Drug users can be trained to respond to heroin overdose with naloxone and save lives. Naloxone administration by injecting drug users may be used as part of a comprehensive overdose prevention strategy for reducing overdose deaths on a larger scale. Participants in this evaluation reported high levels of comfort with naloxone administration and no adverse consequences following administration
Seal et al. (2005)	Overdose witnessed: 20 *Knowledge* >50 % correct responses Identifying a heroin overdose: baseline 0 (0), follow-up 13 (53 %); $p < 0.001$ Risk factors for heroin overdose: baseline 2 (8 %), follow-up 16 (68 %); $p = 0.003$ Heroin overdose prevention strategies: baseline 1 (6 %), follow-up 8 (32 %); $p = 0.040$ Correct uses of naloxone: baseline 21 (91 %), follow-up 23 (95 %); $p = 1.000$	Naloxone: 15/20 (75 %) Recovery position: no information CPR: 16/20 (80 %) Ambulance called: 5/20 (25 %)	Death: none	No information	Injecting drug users can be trained to respond to heroin overdose emergencies by performing CPR and administering naloxone. Future research is needed to evaluate the effectiveness of this peer intervention to prevent fatal heroin overdose

Author (year)	Results		Survival/adverse events/death	Naloxone refill/lost/stolen/ confiscated	Authors' conclusions and quality of evidence (when available)
Strang et al. (2008)	Overdose witnessed: 18 *Knowledge* 1. Risk factors for opiate overdose: Participants correctly recognising all seven risk factors: pre-training 31.9 %, post training 63.8 % Number of correctly identified risk factors: pre-training mean 5.3 (SD 1.67), post-training mean 6.1 (SD 1.5); $p < 0.001$ 2. Signs of opiate overdose Mean correct answers (out of 8): pre-training 5.6 (SD = 1.3), post-training 6.7 (SD = 1.2); $p < 0.001$ 3. Appropriate actions to take in an opiate overdose situation Mean score (maximum 11): pre-training 5.9 (SD = 2.3), post-training 8.6 (SD = 2.1); $p < 0.001$ *Overall knowledge of overdose* Mean score (maximum 26): pre-training 16.7 (SD = 3.7), post-training 21.4 (SD = 3.4); $p < 0.001$ *Knowledge of naloxone* Naloxone only for the reversal of opiate overdose: before training 77 % (159 of 206), after training 96 % (191 of 200) Naloxone does not reverse cocaine, amphetamines, alcohol, benzodiazepines overdose: before training 80 %, after training between 95 % and 98 % *Attitudes* Willingness to administer naloxone: before training, 77 % (151/196), after training 99 %; $n = 192/194$ ($p < 0.001$) *Three follow-up results* Knowledge of signs of overdose: post-training 6.6 (SD 1.2), follow-up 6.5 (1.1); $p = 0.47$	Naloxone: 12/18 (66.6 %) Recovery position and calling an ambulance: N/A	Survival: 12/12 (100 %) Adverse events: 1 precipitation of opiate withdrawal or hostility at abrupt opiate reversal Death: 1 (naloxone not used)	No information	With overdose management training, opiate users can be trained to execute appropriate actions to assist the successful reversal of potentially fatal overdose. Wider provision may reduce drug-related deaths further. Future studies should examine whether public policy on wider overdose management training and naloxone provision could reduce the extent of opiate overdose fatalities, particularly at times of recognised increased risk

Author (year)	Results		Survival/adverse events/death	Naloxone refill/lost/stolen/ confiscated	Authors' conclusions and quality of evidence (when available)
	Knowledge of appropriate actions: post training 8.6 (SD 2.1), follow-up 9.4 (1.2); $p < 0.001$ *Attitudes* Confidence in the use of naloxone Confident in their ability to recognise an opiate overdose: 98 % (169 of 173) Able to manage an overdose situation: 97 % (167/172) Would call for an ambulance: 98 % (168/172)				
Tobin et al. (2009)	*Overdose witnessed* Number of overdoses not reported, number of patients reporting witnessing an overdose pre and post: 43 *Change in knowledge* Knowledge of naloxone: improved from baseline 39/85 (46 %); good at both time points 16/85 (19 %); not improved or decreased 30/85 (35 %) *Change in attitudes* Level of comfort: improved from baseline 21/85 (25 %); good at both time points 38/85 (45 %); not improved or decreased 27/85 (32 %)	Naloxone: 19/43 (44 %) Recovery position: no information CPR: pre 8/43 (19 %), post 23/49 (23 %) Ambulance call: pre 28/43 (65 %), post: 21/43 (49 %)		Naloxone lost: none Naloxone stolen: none	This study indicates that the Staying Alive (SA) programme was effective in increasing the use of naloxone during opiate overdoses, resulting in 22 reversals by 19 individuals. On average, the frequency of inappropriate responses (leaving the victim or applying pain) decreased. This study provides additional evidence to support the effectiveness of overdose prevention training programmes that include skills building from drug users to administer naloxone
Wagner et al. (2010)	Overdoses witnessed: 35 by 22 individuals *Knowledge* Overall knowledge index: baseline mean 76.5 (SD 15.4), follow-up: 91.5 (SD 9.6); $p < 0.0001$ A statistically significant increase was observed for three items about the appropriate use and effects of naloxone. No significant changes were observed in items about risk factors for overdose or overdose symptoms	Naloxone: 28/35 (80 %) Recovery position: no information CPR: 23/35 (65.7 %) Ambulance call: 21/35 (60 %)	Fatal overdoses 4/35 (11.4 %)	Refill: 14/47 (29.8 %) Lost or stolen: 6 Confiscated: 4 Other: 4	This study contributes to the growing literature suggesting that overdose prevention and response training programmes for drug users may be associated with changes in knowledge and overdose response behaviour, with few negative consequences and the possibility of unforeseen benefits such as reductions in drug use or increased engagement with drug treatment

Author (year)	Results		Survival/adverse events/death	Naloxone refill/lost/stolen/ confiscated	Authors' conclusions and quality of evidence (when available)
	Attitudes No significant changes were observed in attitudes about overdose response, including likelihood of administering naloxone, likelihood of calling emergency services or worry about arrest after calling emergency services (all $p > 0.05$)				
Walley et al. (2013a)	Overdose witnessed: not reported	Naloxone: 327 Recovery position, CPR and ambulance call: no information	Overdose rescues: 92 reported by 62 enrolees who reported taking any methadone in the past 30 days	Refill: 286 (from a subsample of 1 553 patients taking methadone from September 2008 to December 2010)	OEND training for individuals who take methadone can be successfully implemented in a variety of settings. People who take methadone have high rates of overdose risk factors and high exposure to witnessed overdose, and can use naloxone to reverse an overdose
Walley et al. (2013b)	Overdose witnessed: 327 *Opioid-related death rates* Low implementer community vs. no implementation: adjusted RR 0.73, 95 % CI 0.57–0.91 High implementer community vs. no implementation: adjusted RR 0.54, 95 % CI 0.39–0.76 *Non-fatal opioid overdose-related acute care hospital utilisations* Low implementer community vs. no implementation: adjusted RR 0.93, 95 % CI 0.80–1.08 High implementer community vs. no implementation: adjusted RR 0.92, 95 % CI 0.75–1.13	Naloxone, recovery position, CPR and ambulance call: no information	N/A	N/A	Death rates from opioid overdose were reduced in communities where an overdose education and naloxone distribution programme was implemented compared with no implementation. This provides observational evidence that an overdose education and nasal naloxone distribution programme is an effective public health intervention to address the epidemic of fatal opioid overdose. OEND implementation seemed to have a dose-related impact, where the higher the cumulative rate of OEND implementation, the greater the reduction in death rates. *Quality assessment* Clear defined point in time when the intervention occurred Three data points before, and three after, the intervention Intervention occurred independently of other changes over time Intervention unlikely to affect data collection (e.g. sources and methods of data collection were the same before and after the intervention) Explicit statement by authors that the primary outcome variables were assessed blindly or the outcome variables were objective, e.g. length of hospital stay, drug levels as assessed by a standardised test Unclear completeness of data set (compare also with Annex 5)
Wheeler et al. (2012)	Overdose reversal: 10 171 Naloxone distributed to 53 032 persons	Naloxone, recovery position, CPR and ambulance call: no information	Reversed: 10 171	No information	To address the high rates of opioid drug overdose deaths, public health agencies could, as part of a comprehensive prevention programme, implement community-based opioid drug overdose prevention programmes, including training and providing naloxone to potential overdose witnesses, and systematically assess the impact of these programmes

Author (year)	Results		Survival/adverse events/death	Naloxone refill/lost/stolen/ confiscated	Authors' conclusions and quality of evidence (when available)
Williams et al. (2014)	Overdose witnessed: experimental 7, control 6 Naloxone used: experimental 2/7 (28 %), control: 0/6 Change in knowledge (OOKS): experimental 6.47 (95 % CI 5.09–7.85), control: 0.81 (95 % CI –0.96 to –2.57) Between-group difference in change: 4.08 (95 % CI 2.10–6.06) Change in attitudes: experimental 14.10 (95 % CI 0.73–17.47), control 7.18 (95 % CI 3.48–10.87) Between-group difference in change: 7.47 (95 % CI 13–11.82)	*Naloxone* Experimental: 2/7 (28 %) Control: 0/6 Recovery position: mostly (data not reported) CPR: no information Ambulance call: mostly (data not reported)	N/A	N/A	Take-home naloxone training for family members of heroin users increases opioid overdose-related knowledge and competence and these benefits are well retained after 3 months. *Quality assessment* Selection bias: random sequence generation — low risk of bias Selection bias: allocation concealment — low risk of bias Performance bias: blinding of participants and providers (subjective and objective outcomes) — high risk of bias Detection bias: blinding of outcome assessor (subjective and objective outcomes) — unclear risk of bias (compare also with Annex 5)
Yokell et al. (2011)	Overdose witnessed: 10 Knowledge: five used their overdose response training and did not find it necessary to administer naloxone The passive nature of PONI's reporting system limited the collection of participant follow-up data and could be the reason for the very high rate of patients lost at follow-up	Naloxone: 5/10 (50 %) Recovery position: no information CPR: no information Ambulance call: no information	N/A	N/A	PONI is the first opioid overdose prevention programme in Rhode Island and has met with great success in the training of the first 120 participants. The major challenge faced by PONI has been its limited size. Expanding PONI would provide critical, life-saving knowledge to opioid users and their friends and families, which could ultimately avert countless opioid overdoses and subsequent deaths

([1]) A 'save' is any situation where the ambulance service observed and confirmed that the administered naloxone was the key element in saving the person's life.
CPR, cardiopulmonary resuscitation; N/A, not applicable; OEND, Overdose Education and Naloxone Distribution; OOKS, Opioid Overdose Knowledge Scale; PONI, Preventing Overdose and Naloxone Intervention.

Annex 3

Naloxone programmes in Europe (October 2014 — Technical meeting on naloxone provision) data from personal communications not checked with other sources

Country	Programme/study	Organisation, (timeframe) and main components, location
Germany	A three-year model project of take-home naloxone in Germany	Fixpunkt (1998–1999) Components: first-aid training and naloxone distribution for opiate users in Berlin
Denmark	Naloxone programme	State financed (2013–15) Components: naloxone programme in four Danish municipalities with open drug scenes
Norway	Nasal naloxone programme	Norwegian Minister of Health (April 2014–) Components: national overdose prevention strategy including the introduction of take-home naloxone nasal spray (for users, relatives and staff in low-threshold facilities), Oslo and Bergen
Estonia	Take-home naloxone programme	National Institute for Health Development (2013–) Components: take-home naloxone pilot programme, Estonia
Scotland, UK	Take-home naloxone programme	The Scottish Government (2010-) Components: take-home naloxone programme in 2010; current target is to reach 25 % of problem/high-risk drug users in Scotland by March 2015
Spain	Network of drug abuse care centres of Catalonia in an overdose prevention programme	Catalonia network of centres Components: methadone programmes, consumption rooms, education and naloxone distribution care centres and harm reduction facilities, Catalonia
Italy	Naloxone peer distribution programme via pharmacies	Naloxone in vial for injection is available over the counter from pharmacies (Official Pharmacopeia, Tables II and IV)

Annex 4

Search strategies

Database	Drugs and Alcohol Group Specialized Register (in CRS)
Search strategy	#1 ((opiat* OR opioid* OR heroin* OR narcot*):TI, AB, XDI) #2 ((overdos* OR intoxicat* OR poison*)) #3 #1 AND #2 #4 (Narcan OR naloxone) #5 #3 AND #4
Date of search	10/07/2013
Results	21

Database	CENTRAL (The Cochrane Library)
Search strategy	#1 MeSH descriptor: [Opioid-Related Disorders] explode all trees #2 (opiat* or opioid* or heroin* or narcot*):ti,ab,kw (Word variations have been searched) #3 #1 or #2 #4 MeSH descriptor: [Drug Overdose] explode all trees #5 (overdos* or intoxicat* or poison*):ti,ab,kw (Word variations have been searched) #6 #4 or #5 #7 MeSH descriptor: [Naloxone] explode all trees #8 naloxone:ti,ab,kw (Word variations have been searched) #9 narcan:ti,ab,kw (Word variations have been searched) #10 MeSH descriptor: [Narcotic Antagonists] this term only #11 ((narcotic or opiate or opioid) near/3 antagonist*):ti,ab #12 #7 or #8 or #9 or #10 or #11 #13 #3 and #6 and #12
Date of search	Issue 7, 2013
Results	50

Database	PubMed
Search strategy	(((((“drug overdose”[MeSH Terms]) OR overdos*[Title/Abstract]) OR intoxicat*[Title/Abstract])) AND ((((opiat*[tiab] OR opioid*[tiab] OR heroin*[tiab] OR narcot*[tiab])))) OR “Opioid-Related Disorders”[MeSH])) AND (((naloxone[MeSH Terms]) OR naloxone[Title/Abstract]) OR narcan[Title/Abstract])
Date of search	10/07/2013

Results	471

Database	EMBASE (embase.com)
Search strategy	'opiate addiction'/exp opiat*:ab,ti OR opioid*:ab,ti OR heroin*:ab,ti OR narcot*:ab,ti #1 OR #2 'drug overdose'/exp overdos*:ab,ti OR intoxicat*:ab,ti #4 OR #5 #3 AND #6 'naloxone'/exp naloxone:ab,ti OR narcan:ab,ti #8 OR #9 #7 AND #10 'animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal cell'/exp OR 'animal tissue'/exp OR 'nonhuman'/exp 'human'/exp OR 'normal human'/exp #12 AND #13 #12 NOT #14 #11 NOT #15 AND [embase]/lim
Date of search	10/07/2013
Results	641

Database	CINAHL
Search strategy	(MH "Substance Abuse+") TI opiat* OR TI opioid* OR TI heroin* OR TI narcot* or AB opiat* OR AB opioid* OR AB heroin* OR AB narcot* S1 OR S2 (MM "Overdose") TI overdos* OR TI intoxicat* OR TI poison* OR AB overdos* OR AB intoxicat* OR AB poison* S4 OR S5 (MH "Naloxone+") TX Naloxone TX Naloxone S7 OR S8 OR S9 S3 AND S6 AND S10 Limiters - Exclude MEDLINE records
Date of search	10/07/2013
Results	61

Database	Web of Science
Search strategy	Topic=((opiat* OR opioid* OR heroin* OR narcot*)) AND Topic=(overdos*) AND Topic=((Narcan OR naloxone)) Timespan=All years. Databases=SCI-EXPANDED, SSCI, A&HCI.
Date of search	10/07/2013
Results	302

Annex 5

Criteria for risk of bias assessment: randomised controlled trials

Item	Judgement	Description
1. Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process, such as random number tables, computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing lots, minimisation
	High risk	The investigators describe a non-random component in the sequence generation process, such as odd or even date of birth, date (or day) of admission, hospital or clinic record number, alternation, judgement of the clinician, results of a laboratory test or a series of tests, availability of the intervention
	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk
2. Allocation concealment (selection bias)	Low risk	Investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes
	High risk	Investigators enrolling participants could possibly foresee assignments because one of the following methods was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed, non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear risk	Insufficient information to permit judgement of low or high risk. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement
3. Blinding of participants and providers (performance bias) Objective outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding. Blinding of participants and key study personnel is ensured, and it is unlikely that the blinding could have been broken
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding. Blinding of key study participants and personnel is attempted, but it is likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgement of low or high risk
4. Blinding of participants and providers (performance bias) Subjective outcomes	Low risk	Blinding of participants and providers, and it is unlikely that the blinding could have been broken
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding. Blinding of key study participants and personnel is attempted, but it is likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgement of low or high risk
5. Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding. Blinding of outcome assessment is ensured, and it is unlikely that the blinding could have been broken
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding. Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgement of low or high risk
6. Blinding of outcome assessor (detection bias) Subjective outcomes	Low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding. Blinding of outcome assessment is ensured, and it is unlikely that the blinding could have been broken
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding. Blinding of outcome assessment, but it is likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgement of low or high risk

Item	Judgement	Description
7. Incomplete outcome data (attrition bias) For all outcomes except retention in treatment or dropout	Low risk	No missing outcome data. Reasons for missing outcome data are unlikely to be related to the true outcome (for survival data, censoring unlikely to be introducing bias). Missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups. For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is not enough to have a clinically relevant impact on the intervention effect estimate. For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes is not enough to have a clinically relevant impact on observed effect size. Missing data have been imputed using appropriate methods. All randomised patients are reported/analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat)
	High risk	The reason for missing outcome data is likely to be related to the true outcome, with either imbalance in numbers or reasons for missing data across intervention groups. For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is enough to induce clinically relevant bias in an intervention effect estimate. For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes is enough to induce clinically relevant bias in observed effect size. 'As-treated' analysis is done with substantial departure of the intervention received from that assigned at randomisation
	Unclear risk	Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided, number of dropouts not reported for each group)
8. Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way. The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk	Not all of the study's pre-specified primary outcomes have been reported. One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified. One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect). One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis. The study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear risk	Insufficient information to permit judgement of low or high risk

Annex 6

Criteria for risk of bias assessment: case–control studies

Selection

1) Adequate definition of the cases
   a) yes, with independent validation
   b) yes, e.g. record linkage or based on self-reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases
   b) potential for selection biases or not stated

3) Selection of controls
   a) community controls
   b) hospital controls
   c) no description

4) Definition of controls
   a) no history of disease (end point)
   b) no description of source

Comparability

5) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for the most important factor
   b) study controls for any additional factor
   c) no control or adjustment for potential confounders

Exposure

6) Ascertainment of exposure
   a) secure record (e.g. surgical records)
   b) structured interview where blind to case/control status
   c) interview not blinded to case/control status
   d) written self-report or medical record only
   e) no description

7) Same method of ascertainment for cases and controls
   a) yes
   b) no

8) Non-response rate
   a) same rate for both groups
   b) non-respondents described
   c) rate different and no designation

Criteria for risk of bias assessment: cohort studies

Selection

1) Representativeness of the exposed cohort:
   a) truly representative of the average in the community
   b) somewhat representative of the average in the community
   c) selected group of patients
   d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort
   a) drawn from the same community as the exposed cohort
   b) drawn from a different source
   c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure
   a) secure record
   b) structured interview
   c) written self-report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for the most important factor
   b) study controls for any additional factor

Outcome

1) Assessment of outcome
   a) independent blind assessment
   b) record linkage
   c) self-report
   d) no description

2) Was follow-up long enough for outcomes to occur?
   a) yes
   b) no

3) Adequacy of follow-up of cohorts
   a) complete follow-up — all subjects accounted for
   b) subjects lost to follow-up unlikely to introduce bias — small number lost (< 10 % or a description provided of those lost)
   c) no statement

Criteria for risk of bias assessment: interrupted time series

Clearly defined point in time when the intervention occurred.

a) Intervention occurred at a clearly defined point in time
b) NOT CLEAR because it is not reported in the paper
c) Intervention did not occur at a clearly defined point in time

At least three data points before, and three after, the intervention.

a) Three or more data points before and three or more data points recorded after the intervention
b) NOT CLEAR because it is not reported in the paper
c) Fewer than three data points recorded before, and three data points after, the intervention

Protection against secular changes (the intervention is independent of other changes).

a) Intervention occurred independently of other changes over time
b) NOT CLEAR because it is not reported in the paper
c) Intervention was not independent of other changes over time

Protection against detection bias (intervention is unlikely to affect data collection)

a) Intervention is unlikely to affect data collection (e.g. sources and methods of data collection were the same before and after the intervention)
b) NOT CLEAR because it is not reported in the paper
c) Intervention is likely to affect data collection (e.g. any change in source or method of data collection before vs. after the intervention)

Blinded assessment of primary outcome(s)

a) Explicit statement of authors that the primary outcome variables were assessed blindly OR the outcome variables are objective, e.g. length of hospital stay, drug levels as assessed by a standardised test
b) NOT CLEAR if not specified
c) Outcomes were not assessed blindly

Completeness of data set

a) Data set covers 80–100 % of total number of participants or episodes of care in the study
b) NOT CLEAR if not specified
c) Data set covers less than 80 % of the total number of participants or episodes of care in the study

TD-AU-14-009-EN-N

Acknowledgements

We would like to thank John Strang and Rebecca McDonald, King's College London, and Nick Welsh, public health physician and consultant in substance use (Cambodia and Australia), for peer reviewing the paper. Authors: Silvia Minozzi, Laura Amato and Marina Davoli, Cochrane Drugs and Alcohol Group.

EMCDDA project team: Marica Ferri, Lucas Wiessing, Isabelle Giraudon and Roland Simon.

About the EMCDDA

The European Monitoring Centre for Drugs and Drug Addiction is the hub of drug-related information in Europe. Its mission is to provide the European Union and its Member States with 'factual, objective, reliable and comparable information' on drugs and drug addiction and their consequences. Established in 1993, it opened its doors in Lisbon in 1995, and is one of the European Union's decentralised agencies. The Centre offers policymakers the evidence base they need for drawing up drug laws and strategies. It also helps professionals and researchers pinpoint best practice and new areas for analysis.

Related EMCDDA publications and web information

- *Mortality related to drug use in Europe: public health implications*, Selected issue, 2011
- Best practice portal
- *Preventing overdose deaths,* Perspectives on Drugs

These and all other EMCDDA publications are available from emcdda.europa.eu/publications

Luxembourg: Publications Office of the European Union
doi: 10.2810/396726 | ISBN 978-92-9168-756-5

This publication is available only in electronic format.

EMCDDA, Praça Europa 1, Cais do Sodré, 1249-289 Lisbon, Portugal
Tel. (351) 211 21 02 00 | info@emcdda.europa.eu
emcdda.europa.eu | twitter.com/emcdda | facebook.com/emcdda

Publications Office