A Systematic Review of Community Opioid Overdose Prevention and Naloxone Distribution Programs

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Community-based opioid overdose prevention programs (OOPPs) that include the distribution of naloxone have increased in response to alarmingly high overdose rates in recent years. This systematic review describes the current state of the literature on OOPPs, with particular focus on the effectiveness of these programs. We used systematic search criteria to identify relevant articles, which we abstracted and assigned a quality assessment score. Nineteen articles evaluating OOPPs met the search criteria for this systematic review. Principal findings included participant demographics, the number of naloxone administrations, percentage of survival in overdose victims receiving naloxone, post–naloxone administration outcome measures, OOPP characteristics, changes in knowledge pertaining to overdose responses, and barriers to naloxone administration during overdose responses. The current evidence from nonrandomized studies suggests that bystanders (mostly opioid users) can and will use naloxone to reverse opioid overdoses when properly trained, and that this training can be done successfully through OOPPs.

Key Words: naloxone, opioid overdose, overdose prevention, substance abuse services

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Unintentional poisoning, primarily due to drug overdose, is now the leading cause of injury-related death among Americans aged 25 to 64 years, having surpassed motor vehicle accidents in 2009 (Centers for Disease Control and Prevention, 2013). Every day in the United States, 100 people die of drug overdose (Centers for Disease Control and Prevention, 2011), and approximately 45 of those drug overdose fatalities involve prescription painkillers (Jones et al., 2014). Patients who overdose are in a life-threatening situation that requires an immediate medical intervention. Naloxone, a Food and Drug Administration–approved medication with well-established efficacy and safety, reverses opioid overdose and prevents fatalities (Buajordet et al., 2004; Clarke et al., 2005; Dahan et al., 2010; Boyer, 2012). In 1996, community-based programs, often referred to as opioid overdose prevention programs (OOPPs), began naloxone distribution directly to patients at high risk for overdose (Sporer and Kral, 2007; Wheeler et al., 2012). Although bystander administration of naloxone by nonmedical persons is considered an off-label use of the medication, some states have passed legislation protecting prescribing physicians and bystander administrators from civil and/or medical liability (Sporer and Kral, 2007; Davis et al., 2013). There are now more than 188 community-run programs operating across the United States in various service venues, including needle exchange programs, detention centers, community clinics, and drug-treatment facilities (Wheeler et al., 2012). Opioid overdose prevention programs provide training to bystanders in 2 key areas: (1) how to identify the symptoms of an opioid overdose and (2) how to respond, including administration of naloxone (Enteen et al., 2010).

Because of the novelty of OOPPs, published information on them is limited. There are no published systematic literature reviews describing OOPPs or assessing their outcomes. This article reviews characteristics and outcomes of OOPPs as described in the current peer-reviewed literature. The review describes demographic and clinical characteristics of OOPP participants, describes OOPP curriculums and addresses the following questions: (1) Do OOPPs with naloxone distribution reduce fatal and nonfatal overdose rates among participants? (2) Are OOPPs effective at increasing nonmedical bystander knowledge of prevention, risk factors, and recognition of opioid overdose? (3) Do nonmedical bystanders trained at OOPPs respond correctly to witnessed opioid overdoses?

METHODS

We searched PubMed, MEDLINE, and PsychINFO online databases using the Boolean search query: (opioid OR opiate) AND overdose AND prevention, limited to English language. This query yielded 360 unique citations, which were imported into an electronic database (EndNote X5; Thomson Reuters, Philadelphia, Pennsylvania). The following prespecified inclusion and exclusion criteria were used to determine article relevance. We included original, peer-reviewed articles evaluating community OOPPs that reported a training outcome and/or a report of overdose reversal rate, overdose fatalities, or another measure of overdose rate among program participants. Articles could include a single program or a small group of affiliated regional programs. Articles were excluded if OOPPs did not incorporate training on the use of

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naloxone and naloxone distribution as part of their program. Articles based on conglomerate data were excluded because of the inability to extract program-specific information. Finally, program evaluations that focused exclusively on health care personnel knowledge or training were excluded.

A.K.C. and C.M.W. used the specified inclusion and exclusion criteria to independently screen titles and abstracts for potential inclusion, identifying 33 articles for full-text review. If it was unclear from the title and abstract whether the article met inclusion and exclusion criteria, we included it for full-text review. Articles selected by either reviewer underwent full-text review. In addition, A.K.C. manually reviewed citations from key articles, generating 5 additional articles for inclusion in full-text review. Thirty-eight articles were reviewed in full-text form independently by C.M.W. and A.K.C. to identify final articles for abstraction. When the reviewers reached different decisions, E.L.W. acted as the final arbitrator for inclusion or exclusion of a study. Nineteen articles fit inclusion and exclusion criteria and were included in this study. Seventeen were excluded from further analysis on the basis of our hierarchy of inclusion and exclusion criteria: 11 did not evaluate a community OOPP (Darke and Hall, 1997; Seal et al., 2001; Oldham and Wright, 2003; Wright et al., 2006; Thurmond and Bowman, 2007; Lenton et al., 2009a,b; Neira-León et al., 2011; Beletsky et al., 2012; Leece and Orkin, 2013; Jones et al., 2014), 2 did not report a training outcome and/or measure of overdose rate among program participants (Markham Piper et al., 2008; Strang et al., 2008b), 1 did not include training on the use of naloxone and naloxone distribution as part of its program (Branagan and Grogan, 2006), 2 were based on conglomerate data (Bowman et al., 2008; Green et al., 2008), and 1 focused exclusively on health care personnel knowledge or training (Mayet et al., 2011). Two additional articles (Worthington et al., 2006; Heller and Stancliff, 2007) were excluded because they used samples duplicated in whole or part from other included studies. When articles contained duplicate or partly duplicate samples, we included the article that contained results most relevant to this review; if all articles contained relevant results, we chose the article that included the largest sample population.

A quality appraisal was performed on all studies included in the review. Table 1 lists areas addressed in the quality appraisal, which was adapted from a preexisting quality assessment scale (Jinks et al., 2011). A.K.C. and C.M.W. independently scored each article and then reconciled differences in scoring through joint review and discussion. E.L.W. acted as final arbitrator for unresolved differences in scoring. Scores for attrition rate were awarded incrementally with 0.5 points given for discussion of attrition rates and an additional 0.5 points for having a follow-up rate greater than 50%.

RESULTS

State of the Current Literature

Of 19 published studies, 14 were cohort studies that included baseline and follow-up results based on some form of questionnaire administered at separate time points (Galea et al., 2006; Markham Piper et al., 2008; Strang et al., 2008a; Doe-Simkins et al., 2009; Lopez Gaston et al., 2009; Tobin

TABLE 1. Quality Ratings of Reviewed Articles

Authors (Publication Year)	Research Questions/Objectives/Hypothesis Are Clear and Appropriate	Clear Overview of Intervention Is Given With Use of Appropriate Outcome Measures	Sample Size Is Given	Randomization Method Used in Sample Selection*	Attrition Rate Is Recorded and Discussed	Data Analysis Is Adequately Described and Rigorous	Outcomes Are Clearly Described	Ethical Issues Are Suitably Addressed	Total Score
Bennett et al. (2011)	1	1	1	0	0.5	0.5	1	0	5
Bennett and Holloway (2012)	1	1	1	0	0	1	1	1	6
Dettmer et al. (2001)	0	1	1	0	0.5	0.5	1	0	4
Doe-Simkins et al. (2009)	0	1	1	0	1	1	1	0	5
Enteen et al. (2010)	1	1	1	0	0.5	1	1	0.5	6
Galea et al. (2006)	1	1	1	0	1	1	1	1	7
Lopez Gaston et al. (2009)	1	1	1	0	1	1	1	1	7
Lankenau et al. (2013)	1	1	1	1*	NA	1	0.5	1	6.5
Leece et al. (2013)	1	1	1	0	0	0.5	1	0.5	5
Markham Piper et al. (2008)	1	1	1	0	0.5	1	1	1	6.5
Maxwell et al. (2006)	0.5	1	0.5	0	0	0	1	1	4
McAuley et al. (2010)	1	1	1	0	1	1	1	1	7
Sherman et al. (2008)	1	1	1	1*	NA	1	1	1	7
Strang et al. (2008a)	1	1	1	0	1	1	1	1	7
Tobin et al. (2009)	1	1	1	0	0.5	1	1	1	6.5
Wagner et al. (2010)	1	1	1	0	1	1	1	1	7
Walley et al. (2013a)	1	1	1	0	1.0	1	1	1	7
Walley et al. (2013b)	1	1	1	0	0.5	1	1	1	6.5
Yokell et al. (2011)	0.5	1	1	0	0.5	0	1	1	5

*Randomization was a criterion for nonqualitative studies; for qualitative studies, the alternative criterion was "recruitment of participants is adequately described." Lankenau et al. (2013) and Sherman et al. (2008) are qualitative studies.

NA, not applicable.

et al., 2009; Enteen et al., 2010; McAuley et al., 2010; Wagner et al., 2010; Bennett et al., 2011; Yokell et al., 2011; Bennett and Holloway, 2012; Walley et al., 2013a,b). Three studies were primarily descriptive but included outcome information based on spontaneous self-report of OOPP participants (Dettmer et al., 2001; Maxwell et al., 2006; Leece et al., 2013). Two studies were qualitative and did not include follow-up (Sherman et al., 2008; Lankenau et al., 2013). There were no randomized studies. Study quality scores ranged from 4 to 7 (mean = 6.1, median = 6.5, and mode = 7) out of a possible 8 (Table 1). Most studies scored 0 for randomization and attrition, whereas all studies scored 1 for overview of intervention and outcome measures. Eighteen of 19 studies received full scores for sample size and clearly described outcomes. The overall descriptive quality of the included studies, none of which were randomized and most of which had low rates of follow-up, was fair.

Demographics and Clinical Characteristics of Participants

Fifteen studies included a total of 9165 self- or purposively selected OOPP participants (Table 2). Four articles were not included in the calculation of sample size; 3 were excluded (Doe-Simkins et al., 2009; Lopez Gaston et al., 2009; Walley et al., 2013a) because these studies included overlapping OOPP sites, and 1 was excluded because it did not report an exact sample size (Maxwell et al., 2006). The mean age of participants was 37.4 years (based on 1615 participants from 7 studies); most participants were men (68.3%, based on 4149 participants from 12 studies) and white (61.4%, based on 3366 participants from 7 studies). Only one study reported serving primarily African American participants (Tobin et al., 2009).

Nearly half of OOPP participants reported experiencing an overdose during their lifetime (49.6%, based on 2036 participants from 9 studies). Across 8 studies, 79.2% of study participants reported witnessing an overdose during their lifetime. Doe-Simkins et al. (2009) reported that the median number of lifetime witnessed overdoses was 5, and Sherman et al. (2008) reported that participants witnessed a median of 6 overdoses in their lifetime. Two studies reported that nearly one third of participants witnessed at least 1 fatal overdose. The primary self-reported drug used before the overdose was heroin. Contrary to other studies, Bennett et al. (2011) reported high rates of overdose on both heroin (92.0%) and other opioids (93.4%).

OOPP Curriculum

The primary components of reported OOPPs' curricula included (1) recognizing overdose, (2) preventing overdose, (3) risk factors for overdose, (4) appropriate response to overdose, and (5) administration of naloxone (Table 2). Interestingly, only 1 study provided an explicit definition of overdose (Markham Piper et al., 2008), although 15 studies reported including recognition of overdose symptoms as part of their OOPP curriculum. Fourteen articles reported inclusion of overdose prevention in their curriculum and 12 explicitly reviewed factors that could increase the risk of overdose, such as mixing drugs, using drugs alone, periods of abstinence that contribute to alterations in tolerance, and drug purity. Sixteen articles reported an OOPP curriculum that included appropriate responses to overdose events, such as contacting emergency medical personnel, instructions on rescue breathing/cardiopulmonary resuscitation (CPR), placing the person in the recovery position, and staying with the victim. All 19 articles also included naloxone administration as part of their curriculums. Fifteen articles reported providing training on needle-based naloxone administration, with some programs providing additional features such as the opportunity to practice injection techniques using oranges (Bennett and Holloway, 2012). Three articles reported on programs that offered nasal naloxone, all of which were affiliated with the OOPP in Massachusetts and all of which provided the opportunity for participants to assemble the naloxone with the atomization device and demonstrate naloxone administration (Doe-Simkins et al., 2009; Walley et al., 2013a,b).

Opioid overdose prevention program training sessions varied among programs from 10 minutes to 1 hour in length. Most articles did not specify the qualifications of individuals who conducted the training sessions or the size of the sessions. Because laws for prescribing naloxone vary by state, physician involvement varied across the programs. Rhode Island's pilot program participants completed the training curriculum, then the program staff notified the program physician by phone and the program staff distributed the prescribed naloxone (Yokell et al., 2011). The SKOOP program in New York City required participants to briefly meet with a physician for a targeted medical history before receiving a naloxone kit (Galea et al., 2006; Markham Piper et al., 2008). Some articles did not discuss physician involvement or stated that providers prescribed and dispensed naloxone but did not give specific details.

Do OOPPs, With Naloxone Distribution, Reduce Fatal and Nonfatal Overdose Rates Among Participants?

Naloxone was used successfully by participants in all but one reviewed study, for a total of 1949 reported naloxone administrations across 18 programs. Eleven studies reported 100% survival rate post–naloxone administration; the remaining articles reported a range of 83% to 96% survival. In 2 articles that observed lower rates of survival, this finding was confounded by a greater number of unknown overdose outcomes (Markham Piper et al., 2008; Enteen et al., 2010). Contrary to other studies, Lopez Gaston et al. (2009) found that naloxone was not used in any of the witnessed overdose cases for which data were available. Two articles attempted to address whether OOPPs reduced opioid overdose mortality at a population level. Using an interrupted time series analysis, Walley et al. (2013b) found that areas in Massachusetts with higher levels of enrollment in OOPPs had lower rates of opioid-related overdose death after controlling for other factors. Maxwell et al. (2006) suggest that the Chicago Recovery Alliance OOPP may have been associated with an observed decrease in heroin overdose deaths in Chicago. They argue that the trend toward decreasing deaths began in the same year that the OOPP was instituted and has continued since then. However, they provide no detailed analysis to test this hypothesis.

Naloxone administrations were not successful in 12 known situations (Maxwell et al., 2006; Enteen et al., 2010; Bennett et al., 2011; Bennett and Holloway, 2012; Walley et al.,

TABLE 2. Articles Included in Review

Authors (Year)	Program Name	Program Site (Location)	Sample Size	Time Frame	Outcomes: Num Nal Admin/Num Indiv Used Nal/ Num Witnessed Overdoses	Outcomes: % Survived After Nal/ Change in Knowledge	Outcomes: % Follow Up/ Sources of Outcome Data	Training Content (Duration/Setting)
Bennett et al. (2011)	Prevention Point Pittsburg	Syringe exchange program (Pittsburgh, Pennsylvania)	426	July 2005-December 2008	249/89/NR	96%/NR	33%/ nal refill form	Overdose prevention Risk factors for overdose Recognize overdose Activate EMS Rescue breathing Needle-based nal admin (25 min/provided by staff or volunteers)
Bennett and Holloway (2012)	Take Home Naloxone Demonstration Project	Multiple sites including community settings and prison sites (Wales)	525	September 2009-September 2010	28/NR/NR	96%/ Stat sig increased knowledge of risk factors; Confidence with nal admin increased from 67% to 92%; Mouth to mouth resuscitation increased from 69% to 88%	5%/pre- and posttraining and nal refill form	Overdose prevention Risk factors for overdose Recognize overdose Activate EMS CPR Needle-based nal admin First aid (1 hr/group with 1-3 trainers)
Dettmer et al. (2001)	NR	Mobile services for drug users (Berlin, Germany) and local drug service locations (Jersey, United Kingdom)	Berlin = 124; Jersey = 101	January 1999-April 2000; October 1998-February 2000	Berlin: 29/22/NR; Jersey: 5/NR/NR	100% in both locations/NR	33% (Berlin) and NR (Jersey)/ spontaneous self-report (Berlin) and NR (Jersey)	Emergency resuscitation Needle-based nal admin (NR)
Doe-Simkins et al. (2009)	Boston Public Health Commission Naloxone Distribution Program	Syringe exchange program (Boston, Massachusetts)	385	September 2006-December 2007	74/50/NR	100%/NR	72%/nal refill form	Overdose prevention Intranasal nal admin (15 min/NR)
Enteen et al. (2010)	Drug Overdose Prevention and Education Project	Syringe exchange programs, reentry programs, opioid substitution clinics, pain management clinics, and single room occupancy hotels (San Francisco, California)	1942	September 2003-December 2009	399/310/NR	89%/75% of participants who used nal also used complementary overdose prevention strategies	24%/nal refill form	Overdose prevention Risk factors for overdose Recognize overdose Activate EMS Rescue breathing Nal admin Mechanism of overdose Aftercare (10-30 min/NR)
Galea et al. (2006)	Overdose Prevention and Reversal Program	Syringe exchange program (New York, New York)	25	June 2004-January 2005	10/NR/26	100%/increase for 58% to 82% of respondents called ambulance for last witnessed overdose at FU	88%/baseline and 3-mo FU survey	Recognize overdose Activate EMS Rescue breathing Needle-based nal admin (1 hr/small group or indiv plus indiv meeting with physician)

(*Continues*)

TABLE 2. Articles Included in Review (*Continued*)

Authors (Year)	Program Name	Program Site (Location)	Sample Size	Time Frame	Outcomes: Num Nal Admin/Num Indiv Used Nal/ Num Witnessed Overdoses	Outcomes: % Survived After Nal/ Change in Knowledge	Outcomes: % Follow Up/ Sources of Outcome Data	Training Content (Duration/Setting)
Lopez Gaston et al. (2009)*	NR	Detox center and community drug treatment teams (Birmingham and London, England)	70	January 2006-January 2007	0/NR/16	NA/stat sig mean increase from baseline to 6 mo FU in knowledge of overdose signs and in knowledge of actions to take in an overdose event	82.8% at 3 mo and 65% at 6 mo/pre- and posttraining survey and FU surveys at 3 and 6 mo	Overdose prevention Risk factors for overdose Recognize overdose Activate EMS Recovery position Needle-based nal admin (30 min/group of 3-10 or indiv)
Lankenau et al. (2013)	Homeless Healthcare Los Angeles and Common Ground Westside	Community health care programs, including syringe exchange (Los Angeles, California)	30	2010-2011	15/NR/30	100%/NR	NA/interview containing closed- and open-ended questions	Recognize overdose Activate EMS Rescue breathing CPR Needle-based nal admin (NR/NR)
Leece et al. (2013)	Prevent Overdose in Toronto	Syringe exchange program and partner sites (Toronto, Ontario)	209	August 2011- April 2012	17/NR/NR	100%/NR	NR/spontaneous self-report	Overdose prevention Recognize overdose Activate EMS Chest compressions Needle-based nal admin Aftercare Nal kit care and logistics (20 min/indiv or small group by RN or counselor)
Maxwell et al. (2006)	Chicago Recovery Alliance	Multiple sites targeting active injection drug users (Chicago, Illinois)	NR (approx 3500 multidose vials of naloxone provided)	January 2001-NR	319/NR/NR	99%/anecdotal reports of increased self-efficacy and personal concern for health after being involved in OOPP	NR/spontaneous self-report	Pharmacology of opioids and nal Opioid neurophysiology Overdose prevention Risk factors for overdose Recognize overdose Rescue breathing Prevention of choking and aspiration Needle-based nal admin Aftercare (NR/NR)
McAuley et al. (2010)	Lanarkshire Naloxone Pilot	Ambulance service users (Scotland)	19	NR	2/NR/3	100%/knowledge scores improved from mean of 7.03 at baseline (n = 33) to 10.54 at 2 mo (n = 13) and 10.33 at 6 mo (n = 6); confidence scores improved from mean of 19.63 at baseline (n = 19) to 28.00 at 2 mo (n = 12) and 29.60 at 6 mo (n = 5)	89% at 2 and 6 mo/ Survey at baseline, 2 mo and 6 mo FU	Activate EMS BLS Needle-based nal admin "Educational and practical skills" (NR/NR)

(*Continues*)

TABLE 2. Articles Included in Review (*Continued*)

Authors (Year)	Program Name	Program Site (Location)	Sample Size	Time Frame	Outcomes: Num Nal Admin/Num Indiv Used Nal/ Num Witnessed Overdoses	Outcomes: % Survived After Nal/ Change in Knowledge	Outcomes: % Follow Up/ Sources of Outcome Data	Training Content (Duration/Setting)
Markham Piper et al. (2008)	Skills and Knowledge on Overdose Prevention	Syringe exchange and harm reduction sites (New York, New York)	122	March 2005-December 2005	82/50/NR	83%/NR	NR/nal refill form	Overdose prevention Risk factors for overdose Recognize overdose Activate EMS Rescue breathing Needle-based nal admin Cooperation with police and medical staff Sharing education about nal and overdose with drug-using partners (10-30 min/ indiv, pair, or group of 5-15 people by staff and volunteers plus 1-2 min with physician)
Sherman et al. (2008)	Chicago Recovery Alliance	Syringe exchange program (Chicago, Illinois)	31	3 mo in 2004	18/NR/NR	100%/subjective reports of increased sense of ability to help peers and comfort level with nal admin	NA/qualitative interviews	Overdose prevention Recognize overdose Rescue breathing Prevention of choking and aspiration Needle-based nal admin (30 min/indiv or small group)
Strang et al. (2008a)	NR	20 drug treatment facilities (England)	239	2005-2006	10/10/18	100%/knowledge composite scores increased stat sig from 16.7 pretraining to 21.4 posttraining	78%/pre- and posttraining survey and 3-mo FU survey	Risk factors for overdose Recognize overdose Nal admin Actions to be taken during overdose (NR/NR)
Tobin et al. (2009)	Staying Alive Program	Syringe exchange programs (Baltimore, Maryland)	250	October 2004-April 2005	22/19/51	100%/knowledge of risk factors for OD did not change; knowledge about naloxone improved for 46% of sample	34%/6-mo FU assessment	Overdose prevention Risk factors for overdose Recognize overdose Rescue breathing Recovery position Needle-based nal admin (1 hr/NR)
Wagner et al. (2010)	Homeless Health Care Los Angeles Center for Harm Reduction, Skid Row	Community health care program including syringe exchange (Los Angeles, California)	66	September 2006-January 2008	28/NR/35	NR/stat sig increase in overall knowledge index from a baseline mean of 77% to 3-mo mean of 91%	71%/nal refill form and 3-mo FU interview	Overdose prevention Risk factors for overdose Recognize overdose Activate EMS Rescue breathing Recovery position Needle-based nal admin Mechanisms of opioid overdose (1 hr/indiv or group of 2-6 people, training by 2 trainers, brief meeting with physician)

(*Continues*)

TABLE 2. Articles Included in Review (*Continued*)

					Outcomes			
Authors (Year)	**Program Name**	**Program Site (Location)**	**Sample Size**	**Time Frame**	**Num Nal Admin/Num Indiv Used Nal/ Num Witnessed Overdoses**	**% Survived After Nal/ Change in Knowledge**	**% Follow Up/ Sources of Outcome Data**	**Training Content (Duration/Setting)**
Walley et al. (2013a)	MA Opioid Overdose Prevention Pilot Program	Addiction treatment programs, HIV prevention programs, syringe exchanges, emergency departments and homeless shelters (MA)	1553	September 2008-December 2010	92/62/NR	100%/NR	51%/nal refill form	Overdose prevention Risk factors for overdose Recognize overdose Activate EMS Rescue breathing Intranasal nal admin (5-60 min/indiv or group trainings by public health workers)
Walley et al. (2013b)	MA Overdose Education and Naloxone Distribution Program	HIV education centers, syringe exchanges, substance abuse treatment programs, emergency and primary health care centers, and community meetings (MA)	4857	September 2006-December 2009	545/NR/NR	98%†/NR	11%/nal refill form	Overdose prevention Risk factors for overdose Recognize overdose Activate EMS Rescue breathing Intranasal nal admin (10-60 min/indiv or group by OOPP trainers)
Yokell et al. (2011)	Preventing Overdose and Naloxone Intervention	Syringe exchange, HIV education center, substance abuse treatment programs, and homeless shelters (RI)	120	2006-NR	5/5/NR	100%/NR	8%/nal refill form and 3-mo FU survey	Overdose prevention Risk factors for overdose Response to overdose Nal admin (NR/training by research assistant)

*Six-month follow-up of a subset of participants from Strang et al. (2008).

†Naloxone was 98% effective, but the 2 individuals for whom it was not effective were subsequently treated by EMS and survived; therefore survival rate was 100%.

Admin, administrations; approx, approximately; BLS, basic life support; CPR, cardiopulmonary resuscitation; detox, detoxification; EMS, emergency medical services; FU, follow-up; indiv, individuals; MA, Massachusetts; NA, not applicable; nal, naloxone; NR, not reported; num, number; OD, overdose; OOPP, opioid overdose prevention program; stat sig, statistically significant; RI, Rhode Island; RN, registered nurse.

2013b). For 3 unsuccessful administrations, victims received emergency care and survived (Walley et al., 2013b), whereas in the 9 other unsuccessful administrations, the victims died. The cause of death was not reported for these individuals, and in one article, the authors speculated that witnesses may have arrived too late (Enteen et al., 2010).

Nine articles reported adverse outcomes associated with the use of naloxone. The only common physiologic adverse event reported was vomiting or other symptoms of precipitated withdrawal (109 instances). Rare but serious adverse events included 4 reported seizures (Maxwell et al., 2006; Enteen et al., 2010). In one situation where a seizure was reported, it was noted that the patient had a history of concurrent alprazolam use (Maxwell et al., 2006). Other nonphysiological adverse events included 4 arrests (Enteen et al., 2010; Wagner et al., 2010) and reports of problems with police, first responders, shelters, or treatment programs due to possession of naloxone (Galea et al., 2006; Markham Piper et al., 2008; Doe-Simkins et al., 2009; Enteen et al., 2010; Wagner et al., 2010; Lankenau et al., 2013). In one program using nasally administered naloxone, during 4 overdoses, the mucosal atomization adapter could not be connected to the naloxone syringe (Doe-Simkins et al., 2009).

Are OOPPs Effective at Increasing Nonmedical Bystander Knowledge of Prevention, Risk Factors, and Recognition of Opioid Overdose?

Eight articles reported pre- and posttraining measures of change in knowledge about opioid overdose. In a study of 525 Welsh opioid users, Bennett and Holloway (2012) reported statistically significant increases in knowledge of overdose risk factors, signs and symptoms of an overdose, appropriate responses to an overdose, and the use of naloxone in overdose events immediately after an OOPP training. However, these participants were not retested after an extended period of time, nor were these results linked with information from individuals who reported later witnessing or experiencing an overdose. Tobin et al. (2009) reported, in a population of injection drug users (IDU), only limited change in knowledge 6 months after OOPP trainings. Knowledge of risk factors for overdose was high both pre- and posttraining, whereas posttraining knowledge about naloxone improved on some questions but declined on others. Among 239 British opioid users, Strang et al. (2008a) noted statistically significant improvements in knowledge of risk factors for overdose, overdose signs, appropriate responses to overdose, and use of naloxone immediately after an OOPP training. Three months after the initial training, 78% of participants demonstrated retention of overdose knowledge. In a subset of approximately 30% of the original cohort of Strang et al. (2008a), knowledge of overdose signs and response to overdose situations was still retained at the 6-month follow-up (Lopez Gaston et al., 2009). The 3-month follow-up sample of Wagner et al. (2010), 47 of an original 69 IDUs in Los Angeles who participated in an OOPP training, demonstrated a statistically significant increase on their overall knowledge score, which included questions on overdose risks, recognition of overdose, and naloxone use. McAuley et al. (2010) reported retention in cumulative knowledge scores regarding overdose risk factors at 2 and 6 months in 19 Scottish drug users; however, the small sample size precluded determination of whether this change was statistically significant. In a qualitative study of 31 Chicago IDUs who had completed OOPP training, Sherman et al. (2008) found that they possessed extensive knowledge regarding overdoses. Their subjective reports also demonstrated increased confidence and comfort with naloxone administration after training. Among those who had administered naloxone, individuals reported initial apprehension replaced by a sense of comfort and achievement after witnessing a successful reversal (Sherman et al., 2008). Finally, Maxwell et al. (2006) noted anecdotal knowledge increase in overdose risks and signs of overdose.

Do Nonmedical Bystanders Trained at OOPPs Respond Correctly to Witnessed Opioid Overdoses?

Eleven articles reported on other strategies besides naloxone administration to respond to an overdose. Among these studies, 23% to 66% participants reported using rescue breathing or CPR (Markham Piper et al., 2008; Tobin et al., 2009; Enteen et al., 2010; Wagner et al., 2010; Bennett et al., 2011; Lankenau et al., 2013), 9% to 31% reported using a sternal rub to try to arouse the victim (Tobin et al., 2009; Enteen et al., 2010; Wagner et al., 2010; Bennett et al., 2011; Lankenau et al., 2013), and 22% to 72% placed the victim in the recovery position (Markham Piper et al., 2008; Lopez Gaston et al., 2009). Participants also reported using nonrecommended strategies in response to overdoses, such as using ice or cold water to try to revive the victim (Markham Piper et al., 2008; Tobin et al., 2009; Wagner et al., 2010; Lankenau et al., 2013), shaking or hitting the victim (Wagner et al., 2010; Lankenau et al., 2013), or injecting salt or other drugs (Tobin et al., 2009). Overall, participants used both OOPP-recommended and nonrecommended strategies to deal with overdose (Sherman et al., 2008; Lankenau et al., 2013). Two large studies, collecting follow-up data only from patients who requested a naloxone refill, reported that at least 75% of returning participants who used naloxone concurrently used at least one other appropriate overdose response strategy (Doe-Simkins et al., 2009; Enteen et al., 2010). A smaller study, with a higher follow-up rate, reported that about half of trained participants used only OOPP-recommended strategies, whereas the other half used both recommended and nonrecommended strategies (Wagner et al., 2010). There was some evidence that training is associated with an increased use of appropriate overdose strategies. In 3 studies (total $n = 66$) that compared reported responses to actual overdoses before training and 3 to 6 months after training, there was a consistent increase in reported use of sternal rubs, rescue breathing, remaining with the victim until help arrived, and placing the victim in the recovery position (Galea et al., 2006; Tobin et al., 2009; Wagner et al., 2010) and a decrease in use of inappropriate responses such as shouting at the victim, using ice or cold water, walking the victim, or injecting the victim with salt or other drugs (Galea et al., 2006; Tobin et al., 2009). Bennett and Holloway (2012) compared an OOPP-trained group ($n = 28$) with a nontrained comparison group ($n = 38$) and found that the OOPP-trained individuals were more likely to place the victim in the recovery position

and call an ambulance but less likely to use CPR. The authors speculated that the decreased use of CPR was because of less perceived need for CPR, given the efficacy of naloxone.

Alerting emergency medical services (EMS) is an OOPP-recommended action that is of particular significance because naloxone has a short duration of action and individuals may experience medical complications related to recurring inadequate respiration. In addition, notification of EMS may simultaneously alert police to respond to the scene. The reported range of EMS notification varied from 29% to 100% among 9 studies that reported posttraining EMS notification, with 6 studies reporting a rate of less than 50%. Two qualitative studies identified fear of police involvement as one of the main reasons that participants did not alert EMS (Sherman et al., 2008; Lankenau et al., 2013). Lankenau et al. (2013) noted that participants were more comfortable notifying EMS if they were in a public location and if naloxone was not available. Furthermore, in this study, participants never called EMS when naloxone was administered in a private location. Bennett et al. (2011) reported that 71% of participants who did not notify EMS cited the reason as fear of police involvement, whereas only 22% cited the reason as perceiving medical assistance as unnecessary. Conversely, Tobin et al. (2009) reported that only 16% of those who did not call 911 reported fear as the reason and 84% reported that medical assistance was not needed. Of note, 2 studies reported actual harassment of participants by EMS (Sherman et al., 2008; Enteen et al., 2010). In qualitative interviews, most participants who called EMS reported receiving positive feedback for their use of naloxone. There were 4 reported positive interactions with police accompanying EMS (Sherman et al., 2008). Five studies compared rates of EMS notification pre- and posttraining: 2 reported a decrease in rates of notification (Tobin et al., 2009; Bennett et al., 2011), 2 reported an increase (Galea et al., 2006; Bennett and Holloway, 2012), and 1 reported no change (Wagner et al., 2010).

DISCUSSION

The current literature suggests that nonmedical bystanders trained by OOPPs are able to administer naloxone effectively and use additional recommended and nonrecommended strategies in response to an overdose. Evidence suggests that OOPPs may increase knowledge of prevention and risk factors for overdose, but the methodological rigor of these studies limits confidence in this finding. Currently published articles are of fair quality, as evidenced by the quality appraisal scores. None of the 17 quantitative studies used randomization, and all studies relied on participant self-reports. The lack of randomized controlled trials of OOPPs limits any conclusions that can be reached about their overall effectiveness, whereas the well-established efficacy of naloxone in reversing opioid overdose (Boyer, 2012) creates an ethical challenge that makes future randomized efficacy trials of OOPP unlikely. Effectiveness trials randomized by treatment program remain a viable option for study. The generalizability of reviewed OOPP studies is further limited because systematic prospective methods were infrequently used to follow up with OOPP participants and when these methods were used, the follow-up period was short (6 months) or the sample size was small (<75 persons). Many of these studies reported findings from pilot programs that collected follow-up data only from participants returning for naloxone refills or other standard clinical services. Four of the studies made no systematic attempt to follow up with participants and 10 studies followed up with less than half of the participants. The high rate of attrition observed in these studies could have resulted in under- or overreporting of outcomes, particularly given that many studies collected follow-up data only on patients who requested naloxone refills. Finally, the methodological and measurement differences across studies make it challenging to synthesize the results and ultimately determine the effectiveness of OOPPs. The development of a standardized OOPP evaluation and outcome tool would allow consistent measurement across studies, enhancing the empirical evidence regarding the effectiveness of OOPPs.

In the current review, heroin was identified as the drug most frequently reported used before the overdose. This finding does not reflect national data from the United States and may be attributable to the high number of OOPPs delivering services in conjunction with needle exchange programs. According to the National Vital Statistics System, the leading cause of drug overdoses is opioid analgesics, not heroin (Paulozzi, 2012). Needle exchange programs are an excellent strategy to reach intravenous drug users and illicit drug users who are not likely to be receiving services from the addiction treatment specialty system. However, non-IDUs and patients across various health care settings, including substance abuse treatment centers, pain clinics, dental offices, emergency departments, and primary care clinics, may be at high risk for overdose.

The demographic characteristics of OOPP participants in the reviewed studies may not accurately represent all persons at high risk of overdose death on the basis of epidemiological studies. For example, most program participants were men (71.4%) and whereas men are at an increased risk for drug overdose deaths compared with women (Paulozzi, 2012), more than half of the estimated 2.4 million Americans initiating prescription drugs nonmedically in the past year were women (Substance Abuse and Mental Health Services Administration, 2011). Research examining sex-specific needs in OOPPs and clinical consideration of how to improve OOPP participation by individuals misusing prescription opioids may be warranted.

Program curricula were fairly standard across studies, but there was no indication of whether curricula were manualized or empirically tested. Although most studies did not include specific details of their curriculum, they usually did note that their curriculum addressed how to recognize overdose, risk factors for overdose, and how to appropriately respond to overdose events. It is difficult to assess the effectiveness of these educational programs because of the lack of systematic measures and consistent follow-up. Two studies demonstrated improvement in knowledge immediately after OOPP training, but this is of limited value in determining retention of knowledge over time. The 5 studies that provided 3- or 6-month follow-up showed some improvement in at least some areas of OOPP knowledge, but the results also suggest that studies may have observed ceiling effects in their measurement instruments, which make it difficult to accurately measure

absolute increase in knowledge. A standardized approach to assessing changes in knowledge, assessing retention in knowledge over time, and achieving higher follow-up rates would provide stronger support regarding the efficacy of OOPPs at increasing nonmedical bystander knowledge of prevention, risk factors, and recognition of overdose.

One convincing indication that a participant has acquired OOPP knowledge is through the demonstration of that knowledge. In this case, positive outcomes in actual overdose situations may indicate effective OOPP training even without more methodologically rigorous follow-up testing. By this measure, we can conclude that at least some trained individuals retained and made use of their OOPP training by reversing opioid overdoses that they subsequently witnessed. Including only the reviewed studies, nearly 2000 overdoses were reversed by lay bystanders who had received OOPP training. All but 1 of 19 articles indicated that participants used and refilled their naloxone prescriptions at an appropriate rate, again suggesting that across different locations in the United States and Great Britain, current OOPP trainings consistently provide sufficient knowledge for individuals to effectively administer naloxone. Because most individuals who overdose recover even without medical attention (Darke et al., 2007), it is not possible simply to equate use of naloxone with reductions in overall mortality from overdose. However, Walley et al. (2013b) provide evidence that a comprehensive OOPP may actually reduce population mortality rates from opioid overdose. Further studies of this type would better illustrate the public health impact of OOPPs in reducing the morbidity and mortality associated with the opioid overdose epidemic.

The current evidence suggests that individuals who use naloxone effectively also use both appropriate and inappropriate additional strategies in response to overdose. The high variation in rates of use suggests that different training programs may be more or less effectively reinforcing other lifesaving measures. Although several articles suggest that training improved the use of sternal rubs, rescue breathing, and use of the recovery position, it is discouraging that, in the most methodologically sound articles, the same individuals who were able to correctly administer naloxone used other appropriate overdose response strategies less than half the time. In addition, ineffective and potentially harmful strategies, such as pouring ice or cold water on the victim, continued to be used after training.

Our review confirmed that most OOPP participants do not call EMS when they witness an overdose. This finding is consistent with observational research conducted before the availability of bystander-administered naloxone, which showed that individuals who witnessed an overdose rarely contacted EMS (Tobin et al., 2005). Rates of EMS notification in our review were similar to the use rates of other appropriate overdose strategies such as rescue breathing. Several articles provided more detailed analysis of EMS use, suggesting that (1) participants fear negative consequences if they call for assistance and (2) although there were a few cases of EMS harassment, most individuals who contacted EMS reported positive experiences. Trainings that directly addressed these 2 factors might improve rates of EMS notification. Future research may investigate whether laws that provide civil and/or criminal protection for bystanders who call EMS in response to an overdose result in increased notification of EMS by OOPP participants.

Our systematic review is subject to several limitations. Our review has a narrow focus and included a limited number of the total articles published on OOPPs. Because this review focused on OOPP outcomes, descriptive articles were excluded. The review included only peer-reviewed articles that were published in English and therefore may have missed important international differences in OOPPs. There are more than 188 OOPPs operating in the United States alone, but only a few have published peer-reviewed assessments or evaluations; therefore, our report of the number of overdoses reversed is about an order of magnitude lower than that found in a more comprehensive recent survey of OOPPs nationwide (Wheeler et al., 2012). The survey by Wheeler et al. (2012) and others that included multiple OOPPs within one publication were not included in this review because the data could not be disaggregated at the program level.

Our review was not able to determine the effectiveness of OOPPs in reducing fatal and nonfatal overdoses because of the methodological limitations of the studies. However OOPP participation is associated with overdose reversals, increased knowledge and ability to respond appropriately in an overdose situation, and the ability of nonmedical bystanders to safely administer naloxone. Although participation in OOPPs may not increase EMS notification, some participants do use other appropriate strategies, including rescue breathing and placing victims in the recovery position. Although naloxone is a life-saving medication, other strategies are essential to *prevent* the occurrence of an overdose and it is necessary to provide response strategies if a naloxone kit is not readily available and/or there are any problems contacting EMS. Given that OOPPs provide training on overdose risk factors, prospective large-scale longitudinal studies are needed to determine whether participation is associated with a decreased risk of fatal and nonfatal overdose. Testing the effectiveness of training requires a more standardized approach to evaluation, including tools to accurately measure change in knowledge, demonstration of achieved knowledge, and more careful follow-up. Opioid overdose prevention programs have the potential to reduce opioid overdose morbidity and mortality, but their effectiveness is currently unknown. Well-designed studies are needed to evaluate the extent to which OOPPs reduce drug-related morbidity and mortality, examine strategies to implement OOPPs into existing clinical practices, and determine the population-level benefit of OOPPs.

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