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A Review of Opioid Overdose Prevention and Naloxone Prescribing: Implications for Translating Community Programming into Clinical Practice

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Abstract

Background—As physicians have increased opioid prescribing, overdose deaths from pharmaceutical opioids have substantially increased in the United States. Naloxone hydrochloride (naloxone), an opioid antagonist, is the standard of care for treatment of opioid induced respiratory depression. Since 1996, community-based programs have offered overdose prevention education and distributed naloxone for bystander administration to people who use opioids, particularly heroin. There is growing interest in translating overdose education and naloxone distribution (OEND) into conventional medical settings for patients who are prescribed pharmaceutical opioids. For this review, we summarized and classified existing publications on overdose education and naloxone distribution to identify evidence of effectiveness and opportunities for translation into conventional medical settings.

Methods—For this review, we searched English language PubMed for articles on naloxone based on primary data collection from humans, including feasibility studies, program evaluations,

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AUTHOR CONTRIBUTIONS

SR Mueller, IA Binswanger, and AY Walley conceived of the review. SR Mueller, IA Binswanger, AY Walley and JM Glanz formulated the methods for the review. SR Mueller conducted the search of the literature. SR Mueller, IA Binswanger, AY Walley and SL Calcaterra reviewed the articles. All authors interpreted the review findings. SR Mueller drafted the manuscript. All authors reviewed and provided critical revisions to the manuscript. All authors give final approval for publication.

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surveys, qualitative studies and studies comparing the effectiveness of different routes of naloxone administration. We also included cost-effectiveness studies.

Results—We identified 41 articles that represented 5 categories: evaluations of OEND programs, effects of OEND programs on experiences and attitudes of participants, willingness of medical providers to prescribe naloxone, comparisons of different routes of naloxone administration, and the cost-effectiveness of naloxone.

Conclusions—Existing research suggests that people who are at risk for overdose and other bystanders are willing and able to be trained to prevent overdoses and administer naloxone. Counseling patients about the risks of opioid overdose and prescribing naloxone is an emerging clinical practice which may reduce fatalities from overdose while enhancing the safe prescribing of opioids.

Keywords

overdose; opioids; prevention; primary care

INTRODUCTION

Unintentional poisoning represents a significant, growing problem in the United States.[1–5] Drug poisoning fatalities now exceed deaths from motor vehicle crashes.[6] In 2010, opioid poisonings accounted for over 16,000 deaths.[7] Unintentional poisoning from pharmaceutical opioids has become an epidemic in the last decade, in part due to increasing opioid analgesic availability.[8] Overdose education and provision of naloxone is one approach to address this epidemic.

Naloxone is a short-acting opioid antagonist used by medical practitioners to reverse opioid overdose since 1971. In the United States, it is approved by the Food and Drug Administration (FDA) for prescription use.[9] Naloxone antagonizes opioid effects by displacing opioid agonists from opioid receptors in the central nervous system, reversing respiratory depression. Naloxone can be administered intranasally (IN), intramuscularly (IM), intravenously (IV), or subcutaneously and is effective against all opioid agonists, including morphine, heroin, oxycodone, and methadone. To reverse long-acting opioids, the dose may need to be repeated. The major adverse effect of naloxone in opioid-dependent patients is precipitated opioid withdrawal. This effect results from the rapid displacement of opioid agonist from the opioid receptor, the same mechanism by which naloxone also reverses respiratory depression. Naloxone has no psychoactive properties, is not a scheduled drug, and has no abuse potential.[10]

Community-based and public health organizations have developed overdose education and naloxone distribution (OEND) programs to prevent opioid overdose fatalities among people who use heroin, and, more recently, among people who use pharmaceutical opioids. In a survey of OEND programs completed in 2010,188 programs located in 15 states and the District of Colombia provided take-home naloxone to people who used opioids.[11] From 1996 to 2010, these programs had trained and distributed naloxone to over 50,000 persons and received reports of over 10,000 overdose reversals.[11] Prevention strategies employed by

these OEND programs may be applicable to the prevention of pharmaceutical opioid overdose deaths in primary care and specialty medical practices.

Provision of naloxone as a part of a strategy to address opioid overdose has been endorsed by several US Federal agencies.[12] In 2013, the Substance Abuse and Mental Health Services Administration released the Opioid Overdose Prevention Toolkit to provide communities and local governments information to develop policies to prevent opioid related deaths.[13] Scotland and Wales recently developed national naloxone distribution programs.[14] In early 2014, Norway began offering naloxone for the first time in intranasal form.[15] Other countries to allow for the distribution of naloxone include Sweden,[16] England,[17] Germany,[18] Italy,[19] Canada,[20] and Australia.[21]

Conventional medical settings, such as primary care, pain clinics, emergency departments, and addiction treatment centers are potential venues for overdose education and naloxone prescription. These sites provide opioid prescriptions or medications and patients may present to these sites with complications from opioid use. Our aim was to review and classify existing publications on OEND and naloxone in community-based settings. We sought to identify evidence of effectiveness and opportunities for translation of these practices into conventional medical settings.

METHODS

Search Strategy and Article Selection

One author searched English language PubMed for peer-reviewed, original research articles through May 2014 using the following Medical Subject Heading (MeSH) terms: *naloxone, drug overdose*. This search yielded 254 articles. Two authors reviewed the abstracts of the 254 articles and excluded 221 articles because they were non-human studies, studies that did not focus on pre hospital-based administration of naloxone, efficacy studies in controlled settings, commentaries and perspectives, medical news articles, and policy or legal reviews. Based on the aim of our review to inform OEND programming in conventional medical settings, we included original peer-reviewed articles that involved primary data collection from patients or medical providers about OEND programs, including feasibility studies and program evaluations (if they included data collected from participants), surveys and qualitative studies of attitudes towards take-home naloxone, and studies comparing the effectiveness of different routes of naloxone administration in pre- and non-hospital settings. We also included cost-effectiveness studies. We also consulted national content experts and 3 of the authors searched the reference lists of the included articles, producing 7 additional articles which met inclusion criteria. A final consensus was reached by these 3 authors on the 41 articles included in this review. For reporting purposes, we then classified the articles into 5 major topic areas. A PRISMA diagram (Figure 1) summarizes articles that were included in our initial search and were excluded based on our article selection criteria.[22]

Article Abstraction

Two of the authors reviewed each article and recorded the location, the number of participants, the population, the study design, the questions addressed by the article, and a

summary of key findings. Given the early stage of research in this area and the heterogeneous methods and outcomes employed, we chose not to apply systematic methods, such as meta-analysis, to summarize outcomes.

RESULTS

We identified 41 articles that met our inclusion criteria (Table 1). After reviewing articles that met inclusion criteria, we categorized the articles into 5 topical categories. Nineteen articles evaluated overdose prevention programs. These studies were largely observational in nature and included evaluations of programming. They also included 4 prospective cohort studies which followed participants over time.[18, 23–25] The next set of articles (n=11) evaluated the effects of OEND programs on the experiences and attitudes of participants. These included qualitative (n=4) and survey (n=7) studies. Four articles described willingness of medical providers to prescribe naloxone. Five studies compared routes of naloxone administration in pre-hospital settings. In this category were 4 prospective studies, of which 2 were observed cohorts and 2 were randomized trials. Finally, two studies evaluated the cost-effectiveness of naloxone. The following results summarize our findings.

Evaluation of Overdose Education and Naloxone Distribution Programs

Community based organizations and a number of state public health departments began conducting and sponsoring OEND programs in 1996.[11] OEND programs typically make naloxone directly available to people who use opioids, outside of a medical setting, and include training on opioid overdose prevention, recognition, and response. The overdose response training includes seeking help from the emergency medical system, rescue breathing, administering naloxone, and staying with the victim until recovery or help arrives.

The articles representing program evaluations of OEND programs in Table 1 suggests that mortality from overdose can be prevented by providing overdose education and naloxone to a variety of participants, including people who used needle exchange programs and injected heroin,[18, 23, 26–36] people using pharmaceutical opioids,[37, 38] people who use opioids in treatment,[24, 25] and the family and friends of people who use drugs.[39, 40] These studies demonstrated that OEND trainings improved participants' knowledge of opioid overdoses and equipped them to administer naloxone safely and effectively when witnessing an overdose. One study suggested that participants reduced their frequency of injecting drugs and were more likely to enter treatment six months after naloxone training compared to baseline.[35] In Chicago, overdose deaths were reduced after the introduction of the OEND program.[33] An analysis that compared communities in Massachusetts with no OEND implementation to those with low implementation (1–100 people trained per 100,000 population) and high implementation (greater than 100 people trained per 100,000 population), demonstrated 27% and 46% reductions in opioid overdose mortality rates, respectively, after adjusting for community level demographic and substance use factors.[40]

Effects of OEND Programs on Experiences and Attitudes of Participants

A number of articles support the feasibility of OEND programs. One concern that may inhibit naloxone prescribing is that potential bystanders or witnesses may not wish to

intervene in response to an overdose. Several studies confirm that witnesses are willing to take action to revive victims.[19, 41–44] One study of people who use heroin showed that nearly every participant was willing to administer naloxone and perform rescue breathing if they had been trained.[45] The majority of participants from a needle exchange program who used heroin (92 percent) in an Australian study also reported a willingness to participate in an OEND program. Other studies assessed the willingness of participants to have naloxone used on them in an overdose event, with most participants responding that they would want naloxone to be administered to them in an overdose.[46]

Because naloxone must be administered by a bystander, concerns that lay bystanders cannot accurately identify an opioid overdose and properly administer naloxone have been raised.[47] Several studies suggest that bystanders, including people who use opioids, are capable of recognizing an opioid overdose and administering naloxone.[48, 49] In addition to targeting people who use opioids, some OEND programs focus on educating family members and/or bystanders who may witness an opioid overdose.[50] An evaluation of six OEND programs concluded that trained participants were more likely to recognize overdose scenarios and identify when naloxone administration was indicated compared to those who had not received training.[49] Trained respondents scored similarly to medical experts in accurately recognizing overdose scenarios and identifying instances when naloxone was indicated.[49] In a prospective study of overdose training and naloxone provision in 239 people who use opioids, participants had significant improvements in their knowledge of the risk factors for overdose, characteristics of an overdose, and the appropriate actions to reverse a potentially fatal overdose.[24] In Massachusetts, where a state sponsored OEND program has been in existence since 2007, methadone maintenance and medically supervised withdrawal (inpatient detoxification) patients have been successfully trained in overdose prevention, equipped with naloxone rescue kits, and rescued people in the community.[37] One study investigated the ability of participants to accurately share information about overdose prevention and naloxone administration with their peers and family, finding that they were able to successfully diffuse information from the program to others.[51]

Naloxone may be particularly beneficial in populations that may avoid or delay calling for emergency services (e.g. 911) when they witness an overdose due to fear of arrest for heroin or opioid analgesic possession, a pre-existing warrant, or because they are afraid of jeopardizing their housing.[45, 52] While overdose education typically includes instruction on calling emergency services, trained bystanders may feel more capable to handle an overdose without help from paramedics or medical personnel. A survey of prospective OEND trainees in Baltimore reported that fewer subjects would call for help after naloxone training.[53] These concerns may be reduced through legislation and collaboration with law enforcement to shield bystanders from legal consequences when calling 911 or administering naloxone.[35]

Medical Providers Willingness to Prescribe Naloxone

Prescribers in general medical practice have limited experience regarding naloxone for take-home use and potential misconceptions about naloxone. In one study of 571 physicians conducted from 2002 to 2003, 23% of those surveyed were aware of the option of prescribing take-home naloxone as an intervention to prevent the development of overdose

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