Original Article

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Naloxone Effectiveness

A Systematic Review

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Abstract

Purpose: Opioid abuse and overdose is a public health concern as it relates to increased morbidity and mortality. This systematic review focuses on the application of take-home naloxone programs and its association with decreased mortality among those who abuse opioids. Take-home naloxone programs consist of distributed naloxone kits and corresponding education of overdose recognition. The purpose of this systematic review was to determine if programs that supply take-home naloxone are effective in preventing fatal overdoses among those who abuse opioids.

Methods: A systematic search was conducted in Academic Search Complete, CINHAL, MEDLINE, PsychINFO, and SocINDEX. The key words searched were ''programs,'' ''take-home kits,'' ''Narcan,'' ''Naloxone,'' and ''mortality.'' On the basis of the predefined inclusion and exclusion criteria, nine studies were found for inclusion.

Results: Study results were then synthesized, qualitatively, and within the current research, there is overwhelming support of take-home naloxone programs being effective in preventing fatal opioid overdoses. A significant limitation of this systematic review is the lack of randomized controlled trials as it is viewed as unethical withholding a known lifesaving medication from an at-risk population.

Practice Implications: On the basis of the most current evidence, there is overwhelming support of take-home naloxone programs associated with decreased mortality among those who abuse opioids. As a result, there is an implication for a practice change that take-home naloxone programs should be more widely implemented throughout communities as a method of decreasing mortality associated with opioid overdoses. It is recommended that further research is done examining the cost-effectiveness of these programs.

Keywords: Mortality, Naloxone, Narcan, Programs, Take-Home Kits

INTRODUCTION

Opioid abuse is on the rise in the United States and has become a national crisis. The opioid epidemic traverses all genders, races, age groups, and socioeconomic classes, and increasing mortality rates are associated with this epidemic. In 2014, there were 47,055 drug overdose deaths recorded in the United States, and of these, 28,647 had opioids involved (Rudd, Seth, David, & Scholl, 2016). According to the Office of National Drug Control Policy (2017), there was an increase of 5,000 deaths in 2015 compared with 2014 from overdoses involving opioids. Opioid overdose is characterized by life-threatening respiratory and central nervous system depression and, if left untreated, may lead to irreversible hypoxic brain injury and death, increasing morbidity and mortality rates (Morrone, 2016). Naloxone, an opioid antagonist, is an effective method, if used in a timely manner, to reverse the action of opioids and is becoming increasingly available to the public. Naloxone take-home kits (THKs) are becoming available to the public and laypersons, and there are more programs being established providing these kits as well as corresponding education on proper use and signs of opioid overdose (McDonald & Strang, 2016). McDonald, Campbell, and Strang (2017) reported that naloxone THKs were being distributed in the early 1990s as a harm reduction strategy in syringe exchange clinics mostly for heroin users in Italy. The research done by McDonald et al. describes how the original THKs have grown into programs that place naloxone in the hands of users, caregivers, laypersons, and emergency personnel for opioid overdose administration. Naloxone THKs have evolved from harm reduction strategies into many community-based programs in the United States, as well as many other countries, to decrease mortality in the growing number of opioid overdoses (McDonald et al., 2017).

RESEARCH PURPOSE

Because of the overwhelming statistics relayed above in regard to the opioid epidemic and opioid-related deaths (ORDs), a systematic review was undertaken to examine the effectiveness of THKs and their effect in reducing mortality. The aim of this systematic review was to determine if programs that supply take-home naloxone (THN) are effective in preventing fatal overdoses

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among those who abuse opioids. The specific research question being sought to answer is: Are THN programs effective in preventing fatal overdoses among those who abuse opioids?

METHODS

A comprehensive literature review was conducted through Academic Search Complete, CINHAL, MEDLINE, PsycINFO, and SocINDEX. Key words used were "programs or take-home kits," "Narcan or Naloxone," and "mortality." The initial search yielded 118 articles that were reduced to 68 once all duplicates were removed. Exclusion criteria consisted of articles that contained studies with buprenorphine, emergency room naloxone administration, and/or methadone; reporting of only educational programs for opioids not specific to Narcan or naloxone; or where statistical data of opioid use or epidemic are not related to reduced mortality. Inclusion criteria were identified as articles limited to those written in the English language, articles from 2014 to present with exceptions of hallmark studies, and studies that included results of decreased opioid-related mortalities due to THN programs. The search was conducted again 14 weeks later to ascertain if any new studies were published that would be considered for inclusion and obtaining data saturation. The secondary search yielded 125 articles; with duplicates removed, there were 73 remaining, five of which were new for review. All of the five additional studies were excluded based on the above inclusion/exclusion criteria, culminating in the nine studies that have been included and utilized for this systematic review.

RESULTS

The first reference applicable to our research question and purpose was a systematic review conducted by McDonald and Strang in 2016. The authors of this systematic review included 22 observational studies gleaned from PubMed, MEDLINE, and PsycINFO. The authors applied the Bradford Hill criteria when evaluating the data from each individual study. The Bradford Hill evaluation consists of nine criteria in which to evaluate causality when only correlational data exist (McDonald & Strang, 2016). The following nine criteria are as follows: strength of association, consistency, specificity, temporality, dose–response relationship, plausibility, coherence, experimental evidence, and analogy. The authors also included additional five criteria for feasibility as recommended by the World Health Organization. Among the studies included, the sample sizes ranged from 24 to 2,912, globally including the United States, Canada, the United Kingdom, and Germany. In synthesizing McDonald and Strang's results, emerging pertinent findings are that there is a strong association between THN programs and decreased mortality as seen by confidence intervals of 95.5 and 97.1 in terms of upper and lower estimates of successful opioid survivals (McDonald & Strang, 2016). Another important finding, as seen through the Bradford Hill criteria, is the specificity for naloxone regarding opioid-only reversal (McDonald & Strang, 2016). Naloxone is the antagonist to opioid-induced overdoses and will have no effect if utilized for other drug overdoses, strengthening its utilization in take-home programs (McDonald & Strang, 2016). In one study cited within the review, by Walley and colleagues (2013), communities were compared that implemented THKs versus no THKs and their findings indicate decreased overdose deaths in communities with THKs. One of the strongest limitations of this review is not having any studies to include that involve randomization. It can be viewed as unethical to withhold naloxone, a known lifesaving medication for those experiencing opioid overdose.

The second systematic review for inclusion is "Preventing Fatal Overdoses: A Systematic Review of the Effectiveness of Take-Home Naloxone" as seen in the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2015). This review included 21 studies ranging in study design in which the authors searched PubMed, EMBASE, Central, CINAHL, Web of Science, and CDAG register. In conclusion, the authors were able to determine that evidence suggests that THN programs are associated with decreased mortality (EMCDDA, 2015). This conclusion is supported via lower rates of opioid overdose in communities that have THN programs in effect when compared with communities without programs in place (EMCDDA, 2015). It is important to note the authors' conclusion that THN programs are effective when correlated with layperson training and education in use of naloxone and identification of opioid overdose (EMCDDA, 2015).

Furthermore, 19 of the studies encompassed in the review by the EMCDDA, as referenced above, were cited in "A Systematic Review of Community Opioid Overdose Prevention and Naloxone Distribution Programs" (Clark, Wilder, & Winstanley, 2014). The databases searched included PubMed, MEDLINE, and PsychINFO. The studies included cohort, descriptive, and qualitative studies. The outcomes of those who participated in the opioid overdose prevention programs (OOPPs) showed high survival rates after administration of naloxone in all of the studies, with 11 being at 100%, and the remaining were reported from 83% to 96% (Clark et al., 2014). OOPPs supply participants with THN in addition to knowledge of how to administer as well as risk factors for overdose and how to recognize, prevent, and respond to an overdose. The conclusions of this review were that increased knowledge and training gained from OOPPs for bystanders are effective in reducing mortality (Clark et al., 2014). The limitations for this study include the lack of randomized controlled trials, the fact that many of the study findings were from pilot programs, and the lack of follow-up with participants.

Although the purpose of this fourth systematic review, "Combating Opioid Overdose With Public Access to Naloxone," is different from the others identified, its results were supportive of overdose education programs and naloxone distribution (Mitchell & Higgins, 2016). There were 38 articles included for review from the following databases—CINAHL Complete, MEDLINE Complete, PubMED, and Psychology and Behavioral Sciences Collection—and were included based on inclusion/exclusion criteria not related to study design. The authors identified six themes from the emerging research studies: global trends, U.S. overdose education programs with naloxone distribution, barrier to naloxone distribution, political opposition and support, financial impact, and recommendations.

The authors cite successful opioid-drug overdose prevention programs within California, Massachusetts, Pennsylvania, and New York, specifically San Francisco, which had a reported 89% success rate with naloxone (Mitchell & Higgins, 2016). This review not only looked at the effect of opioid prevention programs distributing naloxone but also examined the financial aspect of these programs, which is seemingly found to be cost effective even in conservative estimates (Mitchell & Higgins, 2016). The effectiveness of naloxone related to its outpatient use in suspected overdoses has gained enough medical and political support that, at the time of this review, fast-track intranasal Narcan was approved for distribution by the Food and Drug Administration (FDA) and is now looking into over-the-counter access (Mitchell & Higgins, 2016). A limitation of this review is the lack of strong evidence in support of THN programs as randomized controlled trials are not considered ethical. As a result of this limitation, there is a diminished proven effect and a noted strength of this novel intervention in combating the opioid epidemic both nationally and globally.

One hallmark study conducted by Bennett and Holloway (2012) has a repeated measure design that included 521 opioid abusers and four nonopioid abusers. Participants were tested before and after training regarding THKs, and follow-up was through refill requests. The sample population consisted of 362 participants from five community sites and 163 from three different prisons within Wales. This study aimed to measure four outcomes, knowledge changes regarding the use of naloxone in opioid overdoses, and changes in confidence and willingness in implementing the use of this new knowledge (Bennett & Holloway, 2012). The final two outcomes the authors wanted to examine were how overdoses were managed with the use of naloxone versus how overdoses were managed without the use of naloxone (Bennett & Holloway, 2012). The researchers obtained approval via the University of Glamorgan Ethics Committee and the Welsh Government. Informed consent was obtained from all participants, and confidentiality was provided via anonymized data. Through their results, the researchers were able to synthesize and determine that naloxone training and THKs are effective in preventing opioid-related overdoses (Bennett & Holloway, 2012). The results of this study were utilized as the catalyst for the initiation of the THN project throughout Wales. Within their research, in all but one case in which naloxone was used, all victims were saved (Bennett & Holloway, 2012). A limitation of this study is that it was intended to be a quasi-experimental design, adding to the design's rigor. However, this was not feasible to have an equal control and experimental groups as it would be unethical to withhold naloxone from future agencies that wanted to distribute naloxone to at-risk clients. In addition, the authors cite a threat to validity in their inability to control for differences within the pretest groups (Bennett & Holloway, 2012). One final limitation to note is that recall bias may exhibit an effect due to the retrospective design of the study. Overall, the results of this study showed rigor and validity being that the country of Wales utilized these results as the reason to implement THN programs nationwide.

Another hallmark study for inclusion is "Opioid Overdose Rates and Implementation of Overdose Education and Nasal Naloxone Distribution in Massachusetts: Interrupted Time Series Analysis" by Walley et al. (2013). Data were collected from 2002 to 2009 of 19 communities comparing the implementation of overdose education and nasal naloxone distribution (OEND) programs with high and low implementation with those with no implementation. The programs included education of minimization of overdose risks, assessment of unresponsiveness, administration of naloxone, and seeking help after placing individuals in a recovery position (Walley et al., 2013). Information was collected from death certificates and hospital discharge codes to determine overdose rates by community. The results of the 19 communities studied were 2,912 individuals enrolled in the OEND programs, and 327 rescue attempts were made at a 98% success rate (Walley et al., 2013). The conclusions indicate that those communities with both high and low implementations of OEND programs had a decrease in opioid deaths as compared with those without program implementation. One strength was the use of the interrupted time series study method. Limitations identified are as follows: the true population of opioid users due to possible misclassification of opioid deaths and emergency room coding, inaccurate indication of trends within communities due to clustered overdose events, nonvalidated data among other populations, and, due to self-report, the underreporting of overdose rescue attempts (Walley et al., 2013). This study did provide valuable information and outcomes that show a positive correlation between OEND programs and decreased mortality with opioid overdoses. Further studies should be conducted to further validate these data.

A seventh study for inclusion by Bird, McAuley, Perry, and Hunter examined the effectiveness of Scotland's National Naloxone Program (NNP) in relation to ORDs as a pre–post design (Bird et al., 2016). Main aims that the researchers sought to examine were fourfold: summarize the power of Scotland's NNP as a before/after evaluation as determined by primary and secondary outcomes, appraise the evidence for the NNP's effectiveness, assess for causality via Bradford Hill's criteria, and estimate the cost-effectiveness of the NNP in terms of quality-adjusted life years as a gain of 1–10 years (Bird et al., 2016). The primary outcome measured, effectiveness of the NNP, was the percentage of ORDs within 4 weeks of prison release. The secondary outcome measured consists of the primary outcome in addition to ORDs with a 4-week hospital discharge. Both primary and secondary outcomes were evaluated before and after 3-year periods. Statistical power was determined for a sample size at 80% based on evaluation periods of 5 years before the NNP and 3 years after the NNP, with an expectation of 30% and 20% reduction in ORDs, respectively, to the primary and secondary outcomes (Bird et al., 2016). The authors clearly delineate the definition of prison release and hospital discharge as well as the process of determining ORDs. Through evaluation, a 95% confidence interval was determined for ORDs in relation to prison release

and prison release/hospital discharge as 36% and 22% reduction, respectively (Bird et al., 2016). Furthermore, the evaluation of the Bradford Hill's criteria for causality was met in terms of strength, consistency, specificity, analogy, biological gradient, and plausibility, and partially met were temporality, coherence, and experiment (Bird et al., 2016). Through this, the researchers were able to determine that the decrease in ORDs during this period was associated with the initiation of the NNP. Limitations exist within the study; one poignant limitation is that THN is not typically used by the person acquiring it, in such that the beneficiaries of the program are not individually identifiable (Bird et al., 2016). Overall, the conclusions of this study are in support of the effectiveness of Scotland's NNP in reducing mortality, cost-effectiveness, and may be beneficial for implementation in other countries. Further long-term studies should be completed to strengthen the conclusions of this study.

The only randomized controlled study found for inclusion was on the effectiveness of naloxone in the reduction of opioid overdose deaths, the pilot N-ALIVE study conducted in Scotland and England (Parmar, Strang, Choo, Meade, & Bird, 2017). According to Parmar et al. (2017), prisoners with a history of heroin use are at a higher risk for overdose after prison release within the first 4 weeks, as also reported in the work of Bird et al. (2016). The pilot trial was designed to investigate if overdose deaths decreased by providing naloxone-on-release (NOR). The participants were randomized into an NOR group and a control group that did not receive naloxone. The goal was to decrease drug-related deaths within the first 4 weeks by 30% and by 20% in Weeks 5–12. There were 1,685 participants randomized between May 28, 2012, and December 8, 2014. The pilot trial was stopped on December 8, 2014, after analysis revealed that ex-prisoners in the NOR group were more likely (3:1 ratio) to administer the naloxone to someone else experiencing an overdose (Parmar et al., 2017). This made it difficult to assess the effectiveness of the naloxone on the participants, which made it impossible to capture accurate data for the pilot trial (Parmar et al., 2017). Because of this conclusion, the main trial was not able to move forward. There was, however, a 3.5% decrease in mortality due to opioid overdose within the first 4 weeks after prison release (Parmar et al., 2017). At the close of the pilot trial, all of the participants in the control group were given NOR. This study had a similar limitation to other studies in that it was difficult to obtain accurate follow-up data because they were self-reported. It was difficult to ensure the naloxone was used only on the participants and not on others experiencing overdose. The study did find positive enrollment and, participants felt safer in their heroin use with naloxone (Parmar et al., 2017). There was no information to indicate that provision of naloxone encouraged the use of heroin. Further studies are needed to be done using a different design method to better establish if NOR decreases mortality from opioid overdose after prison release as this population is at a high risk for overdose.

Finally, one meta-analysis, "Exploring the Life-Saving Potential of Naloxone: A Systematic Review and Descriptive Meta-Analysis of Take Home Naloxone (THN) Programmes for Opioid Users," was included within this systematic review (McAuley, Aucott, & Matheson, 2015). Within this systematic review and meta-analysis, four of the above studies were utilized for this particular systematic review (Bennett & Holloway, 2012; Clark et al., 2014; EMCDDA, 2015; Walley et al., 2013). This study by McAuley et al. (2015) systematically examined the existing literature on THN programs, which was determined that there are now sufficient preexisting data to perform a meta-analysis for extrapolation to populations worldwide. The researchers were able to identify 25 applicable studies related to THN programs, of which nine were eligible for a meta-analysis. The researchers were then able to calculate a proportion of use, which is needed for public health planners when determining resource allocation in regard to people who use drugs. Conclusions reached by the researchers were that there is strong evidence in support of THN programs due to the number of successful reversals, which can be theorized as reduced mortality, in addition to minimally noted adverse effects from naloxone administration (McAuley et al., 2015). Furthermore, if the entire population of those who use drugs had access to naloxone and associated training programs, one can consider this as the maximum potential lives saved and thus decreased mortality (McAuley et al., 2015). One limitation of this descriptive meta-analysis and systematic review is that it is noted to have a lack of randomized controlled trials partly due to ethical concerns. However, suggestions are made for future studies to be conducted as fixed time series studies to determine calculable follow-up rates for the effectiveness of THKs and decreased mortality (McAuley et al., 2015).

SUMMARY OF FINDINGS

Although the evidence favors the use of naloxone in THKs as associated with the reduction of opioid overdose mortality, there are some limitations noted. One overarching limitation theme of this systematic review is the lack of research studies that utilize randomization and/or randomized controlled trials. Randomization can be viewed as unethical in withholding naloxone, a lifesaving medication, among this population who are at risk for overdose. There was one randomized controlled pilot study included, which had to be ceased because of most naloxone administration being used on other people rather than the person it was dispensed to (Parmar et al., 2017). Most of the studies included in this review were systematic reviews, with one being a meta-analysis, which showed high levels of evidence. The remaining studies for inclusion either were hallmark studies within this field or ranged in level of evidence with grades of I (B/C; "Grading Guide," n.d.). Because of the difficulty of conducting randomized controlled trials, these systematic reviews consist of lower-grade evidence studies throughout. Although these systematic reviews included within this review do not contain randomized controlled trials, many are studies used for population-based interventions. Data collection throughout most of the included studies utilizes self-report collection methods to obtain mortality statistics, thus placing a threat to validity and reports of true mortality

statistics. There needs to be a better data collection following designated periods, such as 3-, 6-, or 12-month follow-up, when determining patient outcomes as a result of THKs. Naloxone is known to reverse the effects of opioids in an overdose, and studies show evidence that communities with THN programs have decreased mortality from ORDs as compared with communities without these programs.

DISCUSSION

In conclusion, the aim of this systematic review was to answer the following research question: Are THN programs effective in preventing fatal overdoses among those who abuse opioids? Despite limited and lower levels of evidence within the available research, the current evidence is overwhelmingly in support of THN programs as being effective in preventing fatal overdoses among those who abuse opioids. In synthesizing the above results of this systematic review, the effectiveness of these naloxone THKs, as a product used in preventing fatal overdoses, can be viewed as decreased mortality rates, increased successful opioid reversals due to use of naloxone, or increased survival rates. Furthermore, the authors recommend a practice change that THKs be more widely available for implementation throughout communities as a method in decreasing mortality rates associated with opioid overdose. In addition, it is recommended that further studies be conducted consisting of systematic reviews and meta-analyses examining the cost-effectiveness of THN programs for implementation of widespread use at the population level, as it is already determined to be an effective lifesaving method. Within this current systematic review, some of the included studies examined the cost-effectiveness of these programs, but more evidence is needed before making population level changes.

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