Examining the effectiveness of naloxone on opioid related overdose: A structured review

Rachel Lee[1] and Nicole Ripley[1]
[1]Interdisciplinary School of Health Sciences – University of Ottawa

Abstract

Opioids are a psychoactive group of drugs that are used by approximately 35 million people worldwide, and account for majority of the 190 900 drug related deaths that occur annually. Globally, there has been an increase in the usage of both synthetic and natural opioids, resulting in a higher number of deaths due to opioid overdose. Naloxone, however, is an opioid antagonist that can be used to stop or reverse the effects of these potentially fatal drugs by increasing respiration, thus aiding in the avoidance of death. This review, therefore, aims to assess the relationship between the usage of Naloxone and mortality rates due to opioid overdose among opioid users. PubMed and Scopus databases were used to gather literature using the following key words: ("Naloxone" AND "overdose" AND "mortality rate"). Articles were then included if they met the following criteria: written in English, published within the past 15 years, including humans only, and cohort studies, case-controls or systematic reviews. The reference lists were also reviewed, and taken into consideration for the selection process. Titles and abstracts of articles that met the inclusion criteria were then examined to determine relevance with regards to the scientific question. Finally, each article was read in full to obtain the total number of articles to be included in the structured review. A total of 7 articles met the criteria and were used in the final structured review. These studies indicate a positive association between the usage of Naloxone and decreased mortality rates due to opioid overdose, demonstrating that Naloxone is effective in reversing the effects of opioid overdose. Future research should compare mortality rates before and after the greater implementation of Naloxone treatments to determine if there has been a significant decrease in the number of deaths.

Background

- **Global increase** in the usage of both synthetic and natural opioids, resulting in a higher number of opioid related deaths (ORDs)[1], with men being the primary victims[2]
- **Opioid related overdose (ORO)** leads to respiratory depression (decreased oxygen levels in the body) → Death can result in 1-3 hours[3]
- **Naloxone**, acts as an opioid antagonist that can stop or reverse the effects of these potentially fatal drugs by increasing respiration
- Naloxone's high-affinity for opioid receptors leads to the displacement of bound opioids and inhibits additional binding of opioids for 20 to 90 minutes[4]
- **Standard dosage**: 2mg of naloxone intravenously or intramuscularly or 4 mg via an endotracheal tube – repeat if necessary[4]
- As of **March 2016**, naloxone (both nasal spray and injection) has been readily available to Canadians[5]

Figure 1: Naloxone injection kit

Research Question

This review aims to assess the relationship between the use of Naloxone and mortality rates due to opioid overdose among non-medical opioid users.

Methods

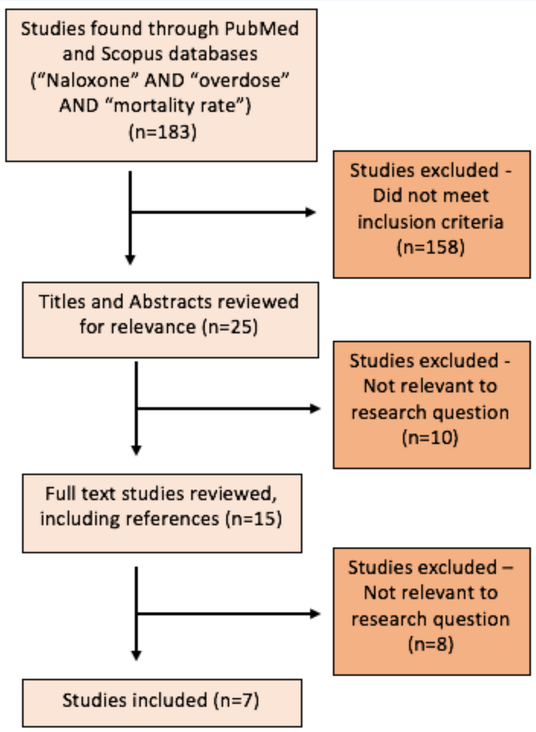

Figure 2: Flowchart outlining search process for relevant studies for structured review.

Table 1: Inclusion and Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Outcome	○Overdose	○Cancer ○Chronic pain ○HIV
Study Subject	○Humans only	○Non-human animals ○Tissue cultures, etc.
Study Type	○Cohort ○Case-control ○Systematic reviews	○Randomized Control Trials ○ Opinion pieces ○Letter to the editor, etc.
Population	○Opioid users	○Non-opioid users
Publication Date	○2002-2017	○Prior to 2002
Language	○Written in English	○Languages other than English

Appraisal: A modified version of the Critical Appraisal Skills Program (CASP) was used in order to evaluate the quality of the studies. A kappa score of 0.82 was obtained between the two judges, demonstrating an almost perfect agreement.

Results

Study	Design	Population	Key Findings	CASP
McAuley, Aucott & Matheson (2015)[6]	Systematic Review	n = 9 studies	○ 35 000 – 183 000 ORDs can be avoided every 3 months ○ Significant relationship between number of cities that implement naloxone treatment and number of lives saved ○ Suggest increase in distribution and usage of naloxone	**81%**
Clark, Wilder, Winstanley (2014)[2]	Systematic Review	n = 19 studies	○ Success rates of naloxone treatment is 83 – 100% ○ Failure of treatment may be due to late intervention	**94%**
Albert, Brason, Sanford, Dasgupta, Graham, Lovette (2011)[7]	Cohort	Community-based prevention program (Wilkes County, NC)	○ ORDs decreased from 43 to 29 per 100 000 persons within a span of 2 years after program implementation ○ No deaths or poisoning attributed to naloxone administration ○ No increase in overdose or ORDs after implementation	**68%**
Vike, Sloane, Smith, Chan (2003)[4]	Cohort	n = 556 427 (emergency medical responses)	○ 998 patients treated with naloxone, no reported deaths ○ 601 ORDs → patients not treated with naloxone ○ No further medical care needed after naloxone administration	**68%**
Bird, McAuley, Perry & Hunter (2015)[8]	Cohort	n = 12 000 kits provided, n = 15 prisons	○ Use of naloxone prevented 42 ORDs (95% CI) ○ Increased QALY by 6.1 years per person ○ Decreased ORDs by 36% (from 9.8% to 6.3%)	**89%**
Sherman, Gann, Scott, Carlberg, Bigg, Heimer (2008)[9]	Cohort	n = 31 persons (Chicago Recovery Alliance)	○ Majority male, median age 38 ○ 18 treated with naloxone, 100% success rate ○ 13 cases treated with other methods	**84%**
Schumann, Erickson, Thompson, Zautcke, Scott (2008)[10]	Cohort	n = 55 ER visits	○ 80% treated with naloxone, followed by hospital release ○ 342 additional death certificates examined, 6.9% of which were untreated ORDs ○ Mortality rates call for greater implementation of out-patient naloxone programs	**82%**

Discussion

Summary of Findings

- No reported deaths due to Naloxone administration
- Doses for 20x the estimated number of users need to be made available[6]
- ORO and ORD rates have not increased since the implementation of naloxone programs[7]
- Does not need to be administered by an HCP or in a medical setting
- More effective than the current practices[9]

Limitations

- ORO is subjective
- Examined different populations
- Lack of statistical analysis
- No comparison to gold-standard
- Confounders: sex, age, socio-economic status
- New intervention

Strengths

- Consistent results
- Examined different populations
- Used multiple methods to retrieve articles

Conclusion

- Naloxone treatment **decreases mortality rates** due to ORDs among non-medical opioid users
- **Future directions**: Focus on Canadian population, More statistical analysis comparing naloxone with current gold-standard treatment, Compare mortality rates before and after implementation of intervention
- Implement laws/policies that **facilitate access** to naloxone

Acknowledgments

This opportunity was made possible by Dr. Raywat Deonandan and the Canadian Society for Epidemiology and Biostatistics – University of Ottawa.

References

1. United Nations Office on Drugs and Crime. Market analysis of synthetic drugs 2017. https://www.unodc.org/wdr2017/field/Booklet_4_ATSNPS.pdf. Published June 22, 2017. Accessed November 3, 2017.
2. Clark AK, Wilder CM, Winstanley EL. A systematic review of community opioid overdose prevention and naloxone distribution programs. *J Addict Med*. 2014;8(3):153-163.
3. Hawk KF, Vaca FE, D'Onofrio G. Reducing Fatal Opioid Overdose: Prevention, Treatment and Harm Reduction Strategies. *Yale J Biol Med*. 2015;88(3):235-245.
4. Vike GM, Sloane C, Smith AM, Chan TC. Assessment for deaths in out-of-hospital heroin overdose patients treated with naloxone who refuse transport. *Acad Emerg Med*. 2003;10(8):893-896.
5. Frequently Asked Questions: Access to naloxone in Canada (including NARCAN™ Nasal Spray). Government of Canada. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/narcan-nasal-spray-frequently-asked-questions.html. Updated June 30, 2017. Accessed Nov 20, 2017.
6. McAuley A, Aucott L, Matheson C. Exploring the life-saving potential of naloxone: A systematic review and descriptive meta-analysis of take home naloxone (THN) programmes for opioid users. *Int. J. Drug Policy*. 2015;26(12):1183-1188.
7. Albert S, Brason FW II, Sanford CK, Dasgupta N, Graham J, Lovette B. Project Lazarus: Community-based overdose prevention in rural North Carolina. *Pain Medicine*. 2011;12:S77-S85.
8. Bird AM, McAuley A, Perry S, Hunter C. Effectiveness of Scotland's National Naloxone Programme for reducing opioid-related deaths: a before (2006-10) versus after (2011-13) comparison. *Addiction*. 2016;111(5):883-891.
9. Sherman S, Gann D, Scott G, Carlberg S, Bigg D, Heimer R. A qualitative study of overdose responses among Chicago IDUs. *Harm Reduct. J*. 2008;5(1):2
10. Schumann H, Erickson T, Thompson TM, Zautcke JL, Scott J. Fentanyl epidemic in Chicago, Illinois and surrounding Cook County. *Clin. Toxicol*. 2008;46(6):501-506.