Does take-home naloxone fulfill the Bradford Hill criteria for effectiveness?
A systematic review

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Overview

1. Introduction: opioid overdose deaths and naloxone
2. Methods: identification of eligible studies
3. Results: evaluation using the Bradford Hill criteria
4. Limitations and strengths of this review
5. Conclusion
1 | Introduction

- Opioid use = int’l public health problem (UNODC/WHO 2013)
- Estimated 1.3 million problem opioid users in EU (EMCDDA 2015a)

- Take-home naloxone (THN) since 1996 (Bigg 2002; Strang et al 1996)
- 2014 WHO Guidelines
- Systematic reviews (Clark 2014; EMCDDA 2015)

Study aim:
- Apply established criteria to address: ‘Are THN programs effective at reducing opioid overdose deaths?’
2.1 | Systematic Search

Replication of search strategy by Clark et al. (2014):
1. MEDLINE, PsychINFO, and PubMed
   • January 1946 and June (3rd week) 2015
   • Boolean search query: (opioid OR opiate) AND overdose AND prevention
2. Grey literature
3. Hand-searching

Exclusion criteria:
• Reporting on naloxone/buprenorphine, case reports; not reporting on heroin or opioid users, not reporting on naloxone, not reporting on overdose, not reporting primary research data.

Inclusion criteria:
• Original quantitative (or mixed-method) studies of take-home naloxone programs that trained opioid users in overdose prevention AND reported on overdose outcomes
2.2 | Identification of Eligible Studies

1. **Electronic databases:** 1,397 records (150 Medline + 475 PubMed + 772 PsycInfo)

2. **Grey literature:** 0 records

3. **Hand-searching:** 5 records

**22 studies included in analysis:**
- 1x interrupted-time series analysis
- 16x pre-post studies
- 3x case-series
- 2x cross-sectional
- No randomization

Records identified through database searching \((n = 1,397)\)
- Duplicates \((n = 210)\) and non-English language articles \((n = 23)\) excluded

Studies screened for title or abstract \((n = 1,164)\)
- Irrelevant records excluded \((n = 1,021\) based on title; \(n = 107\) based on abstract)

Full papers retrieved \((n = 36)\)
- Excluded based on full paper \((n = 19)\)
  - Case study: \(n = 1\)
  - Not relevant: \(n = 8\)
  - Population: \(n = 2\)
  - Qualitative: \(n = 4\)
  - Review article: \(n = 4\)

Additional papers identified from hand-searching \((n = 5)\)

Included studies \((n = 22)\)
2.3 | Analysis: Bradford Hill Criteria

- British statistician Sir Austin Bradford Hill (1965)
- Designed to assess causality when only correlational data are available

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3.1 | Results: Bradford Hill Criteria

1) Strength of Association
   
   The stronger the association between the exposure to a treatment and the clinical outcome, the less likely it is influenced by an external variable.
   
   • 21/22 studies: THN → 2,278 OD reversals
   • 1/21 studies: 16 ODs witnessed, no naloxone on site

2) Temporality
   
   A cause-and-effect hypothesis can only find empirical support if the presumed cause precedes the effect in time.
   
   • 21/22 studies: THN preceded OD reversals
   • Interrupted time-series analysis (Walley et al 2013a)
3.2 | Results: Bradford Hill Criteria (cont’d)

3) Consistency

*The credibility of a finding increases if different investigators can replicate it across different locations and under different circumstances.*

- Replication in 15 different cities/states in CA, DE, UK, and US

4) Biological Plausibility

*There is stronger support for causality if there is a likely biological or pharmacological mechanism that can explain the association between exposure to treatment and the outcome.*

- Naloxone binds to the μ-opioid receptor
- 21/22 studies: pharmacological action $\rightarrow \geq 2,278$ OD reversals
3.3 | Results: Bradford Hill Criteria (cont’d)

5) Coherence

*Causality between exposures to an intervention and the observed findings is supported when the association is coherent with current knowledge of the disease. Vice versa, conflicting or lack of supporting evidence would count against coherence.*

• Declining OD mortality during AUS heroin drought
• 0/22 studies fulfill criterion

6) Specificity

*Causality can be established when one intervention leads to one specific outcome and when said outcome has only one cause.*

• 2/22 studies:
  o No effect in case of cocaine intoxication (Dettmer et al 2001)
  o Fatal case with non-opioids in system (Maxwell et al 2006)
3.4 | Results: Bradford Hill Criteria (cont’d)

7) Dose-response Relationship

*If a dose-response relationship can be observed for the cause-and-effect hypothesis, increased exposure to a treatment will proportionally impact the clinical outcome.*

• 1/22 studies assessed dose response (Walley et al 2013a)
  o 19 communities split into 3 groups by enrollment
  o Significant implementation-dose relation

8) Experimental Evidence

*If experimental manipulation of the exposure-outcome association impacts the outcome, (semi)experimental evidence is given. This delivers the strongest support for causation.*

• Experimental evidence: 0/22 studies
  • Quasi-experimental evidence: 1/22 studies (Walley et al 2013a)
3.5 | Results: Bradford Hill Criteria (cont’d)

9) Analogy
If a treatment similar to A leads to a clinical outcome similar to B, then this analogy counts as evidence in support of our hypothesis that A causes B.

• THN compared to emergency medications for family use (e.g. EpiPen, Buccolam)
• 0/22 studies provide empirical data

SUMMARY:

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Bradford Hill (1965): “[T]he fundamental question - is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?”

• Strong support of the causation hypothesis:
  o THN reduced fatal OD outcomes
  o Alternative explanations unlikely

• Low rate of adverse events: 1 death per 122 lives saved
• High-risk populations: detox (2/22) and methadone patients (1/22), homeless users (5/22), prison inmates (1/22)
4.2 | Discussion: Strengths & Limitations

• First application of Bradford Hill criteria to int’l evidence base on THN
• Findings support 2014 WHO Guidelines and previous systematic reviews

Limitations:
• Studies reported on heroin ODs → effectiveness for Rx opioids unclear
• Follow-up: 9/22 studies systematic; range 5%-100% → selection bias?
• 21/22 studies: self-report data

Despite methodological limitations:
• Robust finding: THN → reduction in OD deaths
• Consistent with grey literature: e.g. Scotland prison release data (ISD 2014)
5 | Conclusions

THN programs:

① Fulfill 7/9 Bradford Hill criteria for causation;
② Reduce heroin OD mortality;
③ Should be standard of care for community-based prevention of heroin OD deaths.
References (A-L)


Bigg D. Data on take home naloxone are unclear but not condemning. BMJ: British Medical Journal. 2002. 324(7338), 678.


EMCDDA. European Drug Report 2015. 2015. Lisbon: EMCDDA.


References (M-Z)


Thank you

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