TITLE: Naloxone for Respiratory Depression in Patients with Drug or Addiction Issues: A Review of the Evidence on Safety and Guidelines

DATE: 05 September 2012

CONTEXT AND POLICY ISSUES

Natural or synthetic opioids can be used therapeutically, recreationally, and children may be unintentionally exposed to them.¹ Opioid addiction and abuse is a major medical and social problem all around the world.¹² The opioids exert their biologic effects through interactions with multiple opioid receptors (µ, δ and κ). The µ-opioid receptor is attributed to respiratory depression - a main hazard of severe opioid overdose which is potentially fatal.¹³⁻⁵

Opioid antagonists are commonly used as rescue medications to reverse severe opioid-induced respiratory depression.⁴⁻⁵ Naloxone is a non-selective, short-acting opioid receptor antagonist which acts on the µ-, δ- and κ-opioid receptors.² It has been approved by Health Canada as an opioid antagonist since 1994.⁷ The most common use of naloxone is for the treatment of opioid overdose in both hospital and out-patient settings, and in rapid detoxification (being given intravenously [i.v.] when combined with other medications).² Other routes of administration include intramuscular, subcutaneous, intranasal and through an endotracheal tube.¹⁻⁸

The safety of naloxone is well established in patients and healthy volunteers over a wide dose range (0.4 to 10 mg). However, clinical studies have indicated that naloxone may be associated with serious adverse effects, such as pulmonary edema, cardiac arrhythmias, hypertension / hypotension, seizures, and violent behavior.²⁻⁸,⁹ In addition, continuous monitoring of naloxone is recommended due to its shorter duration of action.⁹

The purpose of this review is to assess the evidence of harms related to the use of naloxone in management of respiratory depression in patients with polypharmacy intoxication or opioid dependence. Evidence-based guidelines and recommendation for the dosing of naloxone in this population will also be discussed.

RESEARCH QUESTIONS

1. What is the evidence on safety of naloxone for treatment of respiratory depression in patients with polypharmacy intoxication or opioid dependence?

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2. What are the evidence-based guidelines for the use of naloxone to treat respiratory depression in patients with polypharmacy intoxication or opioid-dependence?

KEY MESSAGE

One evidence-based guideline recommends that the dosage of naloxone for reversing respiratory depression in patients with opioid dependence should be initiated at 2 mg i.v. and repeated every 3 minutes until the condition is completely reversed or until a maximum dose of 10 mg has been given. Continuous monitoring of the use of naloxone is recommended. Naloxone-related adverse events were not assessed in health technology assessments, systematic reviews, meta-analysis or randomized controlled trials published after 2002.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2012, Issue 7), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2002 and August 7, 2012.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with polypharmaceutical intoxication or opioid dependence being treated for respiratory depression</th>
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<tbody>
<tr>
<td>Intervention</td>
<td>Naloxone</td>
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<tr>
<td>Comparator</td>
<td>Usual care</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Safety: cardiac arrhythmia, seizures and other adverse events</td>
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<tr>
<td></td>
<td>Evidence-based Guidelines</td>
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<tr>
<td>Study Designs</td>
<td>Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and evidence-based guidelines.</td>
</tr>
</tbody>
</table>

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications, were abstracts/conference proceedings, were included in a selected systematic review, or were published prior to 2002.
Critical Appraisal of Individual Studies

The AGREE (Appraisal of Guidelines for Research and Evaluation) instrument was used to evaluate the quality of evidence-based guidelines. A numeric score was not calculated, instead a narrative summary of strengths and limitations was provided.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 272 citations. Upon screening titles and abstracts, 265 citations were excluded, and 7 potentially relevant articles were retrieved for full-text review. One additional report was identified from grey literature search. Of the 8 potentially relevant reports, 7 did not meet the inclusion criteria, and thus one publication was included in this review. The study selection process is outlined in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Appendix 1). One evidence-based guideline met the inclusion criteria. No health technology assessments, systematic reviews, meta-analyses or randomized controlled trials were identified.

Additional references of potential interest are provided in the appendix.

Summary of Study Characteristics

A work group of the American Psychiatric Association (APA) published an updated practice guideline (2nd edition) in 2006 to provide guidance to psychiatrists who care for adult patients with substance use disorders, including opioid dependence. Literature searches of systematic reviews, meta-analyses, randomized or non-randomized trials and case series were carried out from 1995 (the year an initial guideline was published) to February 2005 in multiple databases. Assessment of the quality and strength of the evidence and formulation of the recommendations were based on expert consensus. A coding system listed the levels of evidence used in formulating the recommendations: A, double-blind randomized clinical trial; B, randomized clinical trial but not double-blind; C, cohort or longitudinal study; D, case-control study; E, review with secondary data analysis; F, review; and G, other such as text books, expert opinion, case reports and other reports. The strength of the recommendations was categorized as: [I] recommended with substantial clinical confidence; [II] recommended with moderate clinical confidence; and [III] may be recommended on the basis of individual circumstances. The authors indicated that the guideline will be updated at regular intervals, although no further details such as the period of updating were provided.

Summary of Critical Appraisal

The guideline of the treatment for substance use disorders by APA clearly described the target users and patient populations to whom the guideline is meant to apply. Systematic methods were used to search for relevant evidence. The evidence was categorized according to a pre-designed coding system. The methods for formulating the recommendations are clearly described. However, there were no explicit connections between strength of evidence and strength of recommendations. The drafts of this guideline were externally reviewed by other organizations and professionals in the field. It stated that the development of this guideline was not financially supported by any commercial organization, even though some authors may have received income related to the discussed treatments.
Summary of Findings

In the APA guideline, the authors indicated that naloxone reverses respiratory depression as well as other manifestations of opioid overdose.

The main recommendations regarding the dosing regimen of naloxone along with the levels of evidence were as follows (APA guideline page 34, grade of evidence indicated in parentheses):

- “The dosing of naloxone varies depending on whether the patient is known to be opioid dependent as well as on the extent of respiratory depression.” (G)
- “[I]n patients with CNS but not respiratory depression, an initial dose of 0.05–0.4 mg i.v. is recommended. The lower dose is used for opioid-dependent individuals” (G)
- “For any person who presents with significant respiratory depression, the initial suggested dose is 2.0 mg i.v., regardless of the individual’s drug use history; a beneficial response should occur within 2 minutes. Repeated doses can be administered every 3 minutes until respiratory or CNS depression is completely reversed or until a maximum dose of 10 mg i.v. has been given. If no response is observed after administration of the 10 mg of naloxone, the diagnosis of opioid overdose should be reconsidered.” (G)
- “Further monitoring and infusion of additional naloxone are needed to continue antagonizing the effects of severe opioid overdose.” (D and G)

Limitations

Scarce data regarding the safety of naloxone in reversing respiratory depression related to polypharmacy intoxication or opioid dependence were identified in this review. The evidence of the safety of naloxone relative to usual care in the target population was absent in the past 10 years, while the available clinical studies were generally focusing on its clinical effectiveness. In addition, there was no data available for patients with polypharmacy intoxication. The only literature meeting the selection criteria was an evidence-based clinical practice guideline developed by APA in 2006. It provides recommendations on dosage of naloxone in managing opioid-related significant respiratory depression, though “significant” was not defined in the document. The quality and strength of the evidence were reported, yet it is unclear how the strength of evidence was connected to the strength of recommendations. The authors indicated that the guideline was updated at regular intervals; however a detailed updating plan was not provided. It is unknown when a new version will be available since publication of the current guideline six years ago.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

A conclusion regarding the safety of naloxone on polypharmacy intoxication-related or opioid-related respiratory depression cannot be made due to lack of evidence.

The current evidence-based guideline recommends that the dosage of naloxone for reversing respiratory depression in patients with opioid dependence should be initiated at 2.0 mg i.v. and repeated doses can be administered every 3 minutes until respiratory depression is completely reversed or until a maximum dose of 10 mg i.v. has been given. Continuous monitoring of the use of naloxone is needed in patients with severe opioid overdose who require additional naloxone.
Well-designed clinical studies comparing naloxone with usual care are required to evaluate the safety of naloxone in patients with respiratory depression induced by polypharmacy intoxication or opioid dependence. In addition, a newer version of the guideline may be able to provide more up-to-date guidance in clinical practice.

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REFERENCES


APPENDIX 1: Selection of Included Studies

272 citations identified from electronic literature search and screened

265 citations excluded

7 potentially relevant articles retrieved for scrutiny (full text, if available)

1 potentially relevant report retrieved from other sources (grey literature, hand search)

8 potentially relevant reports

7 reports excluded:
- irrelevant population (3)
- irrelevant comparator (1)
- irrelevant outcomes (1)
- irrelevant study design (2)

1 reports included in review
APPENDIX 2: Addition References of Potential Interest


Note: see Appendix 2 page 2-11 Altered LOC – Suspected Opioid Overdose Protocol