

CADTH RAPID RESPONSE REPORT:  
SUMMARY WITH CRITICAL APPRAISAL

# Intranasal and Intramuscular Naloxone for Opioid Overdose in the Pre-Hospital Setting: A Review of Comparative Clinical and Cost-Effectiveness, and Guidelines

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**Authors:** Kwakye Peprah, Nina Frey

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## Context and Policy Issues

The number of opioid overdose cases is increasing in Canada. A joint report by the Canadian Institute for Health Information (CIHI) and the Canadian Centre on Substance Abuse found that between 2007-2008 and 2014-2015, the rate of hospitalizations due to opioid poisoning in Canada increased by more than 30%.<sup>1</sup> A report by the Canadian Community Epidemiology Network on Drug Use (CCENDU) identified that fentanyl-related deaths (fentanyl-implicated or fentanyl-detected deaths<sup>a</sup>) have increased by as much as 20 times in some of Canada's largest provinces in the past five years.<sup>2</sup> Data from the Office of the Chief Coroner for Ontario show that the number of deaths due to opioid toxicity (including codeine, fentanyl, hydromorphone, methadone, morphine, oxycodone) increased from 206 in 2004 to 624 in 2014.<sup>3</sup> In the first ten months of 2016, 914 people died of illicit drug overdose in BC, and fentanyl was detected in 60% of these fatalities.<sup>4</sup> In Alberta, 343 individuals died from an apparent drug overdose related to fentanyl in 2016.<sup>5</sup> Currently, there are no national-level data available for prescription opioid-related mortality in Canada.<sup>6</sup>

Naloxone is a drug that can temporarily reverse opioid overdose. Naloxone is a competitive opioid antagonist with rapid onset and very short duration of action due to its high lipid solubility which promotes rapid entry and high concentrations in the brain.<sup>7-9</sup> Naloxone is also rapidly eliminated with a terminal elimination half-life of 64 to 90 minutes.<sup>9,10</sup> The pharmacokinetics of naloxone are described as linear (dose-proportional) which means that naloxone levels in the brain parallel levels in blood or plasma, so close correlation of blood or plasma concentrations and pharmacological activity is expected.<sup>9</sup> Naloxone is extensively metabolized after oral administration due to high first pass metabolism and for this reason it cannot be given by the oral route.<sup>9</sup>

Once administered, naloxone displaces the opiate at the  $\mu_2$  receptors rapidly and effectively reversing potentially fatal opiate effects, such as respiratory depression, within a few minutes.<sup>11</sup> This temporary reversal of opioid overdose allows time to seek emergency help.<sup>12</sup> Naloxone has been used to reverse the effects of a wide range of natural, semisynthetic, and synthetic opioids in both pre-hospital (community) and hospital settings.<sup>11</sup> It has no potential for abuse or overdose nor does it have any pharmacological activity in the absence of opioids or other opioid antagonists.<sup>13-15</sup> It is considered safe over a wide dose range up to 10 mg.<sup>7,16</sup> A repeat dose of naloxone can be given 5 minutes after the first dose, if the person is not awakening or breathing well enough (10 or more breaths per minute).<sup>17</sup> It is recommended that one still seek emergency medical assistance even if naloxone is administered.<sup>18,19</sup> Given that the naloxone is a short acting drug, the effects of naloxone are temporary. Hence, the

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<sup>a</sup> "Fentanyl-implicated deaths" refers to deaths where fentanyl was a cause or contributing cause of the death. "Fentanyl-detected deaths" refers to deaths where fentanyl was detected in the body irrespective of cause.<sup>2</sup>

individual may again experience sedation and respiratory depression after the effect of naloxone wears off, and further repeat dose of naloxone, and emergency medical assistance may be required.<sup>17</sup> Given that opioids vary in their duration of action, metabolism, and degree of affinity to mu-receptor, the effectiveness of naloxone, and need for repeated dose may depend on these factors.<sup>20</sup> Naloxone only reverses overdose of opioids, and is not effective for overdose of other drugs like cocaine.<sup>21</sup>

Naloxone has been approved for use in Canada for more than 40 years.<sup>21</sup> It is also on the World Health Organization's List of Essential Medicines.<sup>21</sup> In March 2016, Health Canada amended its prescription drug list to allow non-prescription use of naloxone for emergency use for opioid overdose outside hospital settings.<sup>22</sup>

There are several injectable (generic) formulations of naloxone available in Canada. The injectable formulations (for intramuscular, intravenous, or subcutaneous use) are available in 0.4mg/ml and 1mg/ml strengths.<sup>23</sup> Although not approved by Health Canada or the FDA, the practice of using an atomization device to deliver the injectable formulation through the nasal route has also been reported and studied.<sup>20,24</sup> In October 2016, Health Canada approved a nasal spray formulation of naloxone, Naloxone Hydrochloride Nasal Spray (also known as Narcan Nasal Spray<sup>b</sup> in the United States). This is a needleless device that delivers a fixed intranasal (IN) dose of naloxone.<sup>18,26</sup> It is available in 2 mg/0.1ml and 4mg/0.1ml strengths.<sup>23</sup> The typical shelf life of naloxone products is 18 months to 24 months.<sup>27</sup> See Appendix 1 for a list of naloxone products available in Canada.

Given the increase in opioid related overdose and deaths in Canada, there have been efforts made to increase the availability of naloxone. As of March 2016, seven of the 13 provinces and territories in Canada had established take-home naloxone programs, and there were more than 500 sites across Canada where take home naloxone kits are distributed.<sup>8</sup> These programs are usually managed and funded by health departments and/or not-for-profit groups, and distributed or administered through hospitals, clinics, pharmacies, prisons, community health centers, needle exchange programs, or first responders.<sup>28</sup>

In Canada, the approximate cost of a take-home naloxone kit is \$35, and generally contains two one-ml single dose ampoules of naloxone (0.4 mg/ml solution) for intramuscular injection, and other kit components such as syringes, needles, gloves, ampoule breakers etc.<sup>8</sup> However the cost of the Naloxone Hydrochloride Nasal Spray has been reported to be \$125 per two doses (i.e. almost 6 times more expensive than the naloxone kits with injectable formulation).<sup>29</sup> Additionally, an auto-injector formulation of naloxone, Evzio is also available in the US, but it is not yet approved in Canada.<sup>30</sup> The cost of the auto-injector formulation is reported to be USD\$ 4500.<sup>31</sup> Table 1 provides an overview of naloxone formulations available in Canada.

<sup>b</sup> Naloxone was first marketed as Narcan<sup>®</sup> injection for intravenous (IV), intramuscular (IM), and subcutaneous (SC) administration. However, Narcan injection has been discontinued and is no longer marketed in United States or Canada.<sup>23,25</sup> Only generic formulations of injectable naloxone are available.

**Table 1: Overview of naloxone formulations available in Canada.** <sup>8,20,23,24,26</sup>

Formulations	Available strengths	Route of delivery	Approximate Cost	Other Notes
Injectable naloxone (generics)	0.4 mg / ml 1 mg / ml	Intramuscular, Subcutaneous, Intravenous	\$35 (Cost for take home naloxone kits, including 2 doses of naloxone and other kit components such as needles, gloves, syringes etc.)	Assembly required
		Intranasal, using a atomization device <i>This delivery method is not approved by Health Canada</i>	<i>unknown</i>	Assembly required Needless delivery
Naloxone Hydrochloride Nasal Spray (brand)	2 mg / 0.1ml 4 mg / 0.1ml	Intranasal	\$ 125 per two doses	No Assembly required Needless delivery

Naloxone is a life-saving drug. However, there are different formulations and delivery mechanisms for naloxone available in Canada, with substantial differences in their costs, and uncertainty around the additional benefit associated with the additional cost. An assessment is required to assist decision-makers in determining the most suitable formulation of naloxone for the treatment of opioid poisoning. The purpose of this review is to provide evidence on the comparative clinical effectiveness and cost effectiveness of the various formulations and delivery mechanisms of naloxone for the treatment of opioid poisoning. Clinical practice guidelines will also be examined

## Research Questions

1. What is the comparative clinical effectiveness of Naloxone Hydrochloride Nasal Spray versus intramuscular naloxone?
2. What is the comparative clinical effectiveness of Naloxone Hydrochloride Nasal Spray versus naloxone administered intranasally using a mucosal atomizer?
3. What is the comparative clinical effectiveness of naloxone administered intranasally using a mucosal atomizer versus intramuscular naloxone?
4. What is the cost-effectiveness of Naloxone Hydrochloride Nasal Spray, naloxone administered intranasally using a mucosal atomizer or intramuscular naloxone?
5. What are the evidence-based guidelines associated with the use of naloxone in the treatment of opioid overdose in the pre-hospital setting?

## Key Findings

No clinical studies on Naloxone Hydrochloride Nasal Spray (device pre-filled with naloxone) were identified.

The literature search identified two studies comparing intramuscular naloxone with naloxone administered intranasally using an atomization device. The two unblinded randomized controlled trials reported that treatment with intramuscular naloxone resulted in a higher proportion of patients who achieved adequate response, and, at least, a nominally faster mean time to achieve adequate response compared with naloxone administered intranasally using a mucosal atomizer. Both studies found that the proportion of patients who required rescue naloxone after the initial dose was significantly lower with intramuscular naloxone than with naloxone administered intranasally using a mucosal atomizer. In both studies, the incidence of adverse events was similar for naloxone administered intranasally using a mucosal atomizer and intramuscular naloxone. Common adverse events were mild agitation and/or violence; nausea and/or vomiting; and headache.

The 2015 American Heart Association Guidelines Update recommends intramuscular or intranasal naloxone as first aid treatment of patients with known or suspected opioid overdose. It also recommends that persons at risk for opioid overdose or those living with or in frequent contact with such persons be given opioid overdose response education, either alone or in combination with naloxone distribution and training.

The literature search did not identify any studies which evaluated the cost-effectiveness of Naloxone Hydrochloride Nasal Spray, naloxone administered intranasally using a mucosal atomizer, or intramuscular naloxone.

## Methods

### Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD), Canadian and major international health technology agencies, as well as a focused Internet search. For research questions 1 to 3, no limits were used to limit retrieval. For research question 4, a methodological filter was applied to limit retrieval to economic studies. For research question 5, a methodological filter was applied to limit retrieval to guidelines. The search was also limited to English language documents published between January 1, 2005 and February 9, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 2.

**Table 2: Selection Criteria**

<b>Population</b>	<p>Patients (of any age) suspected of opioid overdose in the pre-hospital setting</p> <ul style="list-style-type: none"> <li>Subgroups of interest: pediatric (<math>\leq 18</math> years of age) and adult (<math>&gt; 18</math> years of age) populations, pregnant and lactating, geriatric</li> </ul>
<b>Intervention</b>	<p><b>Questions 1 and 2:</b></p> <ul style="list-style-type: none"> <li>Naloxone Hydrochloride Nasal Spray</li> </ul> <p><b>Question 3:</b></p> <ul style="list-style-type: none"> <li>Naloxone administered intranasally using a mucosal atomizer (i.e., kit with naloxone, luer-lock syringe barrel, and mucosal atomizer device)</li> </ul> <p><b>Question 4:</b></p> <ul style="list-style-type: none"> <li>Naloxone Hydrochloride Nasal Spray, naloxone administered intranasally using a mucosal atomizer, or intramuscular naloxone</li> </ul> <p><b>Question 5:</b></p> <ul style="list-style-type: none"> <li>Naloxone (any dose or route of administration)</li> </ul>
<b>Comparator</b>	<p><b>Questions 1 and 3:</b></p> <ul style="list-style-type: none"> <li>Intramuscular naloxone <sup>a</sup></li> </ul> <p><b>Question 2:</b></p> <ul style="list-style-type: none"> <li>Naloxone administered intranasally using a mucosal atomizer</li> </ul> <p><b>Question 4:</b></p> <ul style="list-style-type: none"> <li>Any of the following alternative modes of naloxone administration (i.e., Naloxone Hydrochloride Nasal Spray, naloxone administered intranasally using a mucosal atomizer, intramuscular naloxone)</li> </ul> <p><b>Question 5:</b></p> <ul style="list-style-type: none"> <li>No comparator required</li> </ul>
<b>Outcomes</b>	<p><b>Questions 1 and 3:</b></p> <ul style="list-style-type: none"> <li><u>Clinical effectiveness</u>: (e.g., proportion of patients with an adequate response within 10 minutes of administration, change in level of consciousness, time to adequate response, hospitalization, requirement for rescue naloxone due to inadequate primary response, vital signs, arterial blood oxygen saturation);</li> <li><u>Harms</u>: (e.g., drug-related adverse events; frequency of adverse events, opioid withdrawal effects, including acute opioid withdrawal syndrome, length and severity of withdrawal, length of hospital stay; cardiovascular side-effects; administration-related adverse events such as needle site reactions and needle stick injury; study-related side-effects [e.g., agitation]; and rebound opioid toxicity)</li> </ul> <p><b>Question 4:</b></p> <ul style="list-style-type: none"> <li>Cost-effectiveness outcomes (e.g., cost per benefit or clinical outcome, cost per quality adjusted life year)</li> </ul> <p><b>Question 5:</b></p> <ul style="list-style-type: none"> <li>Evidence-based guideline recommendations regarding the appropriate use of naloxone (including route of administration, dosing) in the pre-hospital setting</li> </ul>
<b>Study Designs</b>	<p><b>Questions 1 and 3:</b></p> <ul style="list-style-type: none"> <li>Health technology assessments; systematic reviews/meta-analyses; randomized controlled trials; non-randomized studies;</li> </ul> <p><b>Question 4:</b></p> <ul style="list-style-type: none"> <li>Economic evaluations; and</li> </ul> <p><b>Question 5:</b></p> <ul style="list-style-type: none"> <li>Evidence-based guidelines</li> </ul>

<sup>a</sup> Excluding Evzio auto-injector

### Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 2, they were duplicate publications, or were published prior to 2005.

## Critical Appraisal of Individual Studies

The included randomized studies were critically appraised using the Downs and Black checklist for measuring study quality. The included guideline was appraised using the AGREE II instrument.<sup>32</sup> Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were narratively described narratively.

## Summary of Evidence

### Quantity of Research Available

A total of 567 citations were identified in the literature search. Following screening of titles and abstracts, 537 citations were excluded and 30 potentially relevant reports from the electronic search were retrieved for full-text review. The grey literature search identified no potentially relevant publications. Of the 30 potentially relevant articles, 27 publications were excluded for various reasons, while three publications including one guideline, met the inclusion criteria and were included in this report. Appendix 2 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 7.

## Summary of Study Characteristics

### *Randomized controlled trials*

A summary of the main study characteristics of the two clinical trials<sup>24,33</sup> that met the inclusion criteria of this review is reported below with additional details provided in Appendix 3.

### *Study Design*

The studies by Kerr et al.<sup>24</sup> and Kelly et al.<sup>33</sup> were both prospective, randomized, unblinded trials. In both studies, data were collected by paramedics of ambulance services who randomly assigned patients with suspected opioid overdoses to receive naloxone administered intranasally using a mucosal atomizer or intramuscular naloxone treatment. In both studies,<sup>24,33</sup> allocation was randomized using a concealed system, with the treatment protocol contained in a sealed envelope that was opened after patient eligibility was determined.

### *Country of Origin*

Both studies<sup>24,33</sup> were conducted in Australia. The trial by Kerr et al.<sup>24</sup> was conducted in a metropolitan area from 1 August 2006 to 31 January 2008, while Kelly et al.<sup>33</sup> conducted their study in rural and metropolitan areas from 5 January 2002 and 19 December 2003.

### *Patient Population*

Kerr et al.<sup>24</sup> included 172 patients and Kelly et al.<sup>33</sup> included 155 patients in their respective studies. Participants in the two trials<sup>24,33</sup> were patients suspected of opiate overdose who had fewer than 10 respirations per minute and were unarousable. In the study by Kerr et al.,<sup>24</sup> a Glasgow Coma Score (GCS)  $\leq 12$  and requiring pre-hospital treatment for suspected opioid overdose was another inclusion criterion. The type of opioid was not reported in either study. Determinants of suspected opioid overdose included altered conscious state, pinpoint pupils, and respiratory depression

(respirations < 10). The patients were predominantly male and had a median age ranging from 28 to 29 years. In each of the studies,<sup>24,33</sup> patients were not eligible for enrolment if they had major facial trauma, blocked nasal passages, or epistaxis.

### *Interventions and Comparators*

Both Kerr et al.<sup>24</sup> and Kelly et al.<sup>33</sup> compared naloxone administered intranasally to naloxone given by the intramuscular route. Each patient in both studies was treated with a 2 mg dose of naloxone. In each of the studies,<sup>24,33</sup> patients assigned to intramuscular administration were treated with 2 mg in 5mL naloxone injectable solution according to standard procedure (n=89 and n=71 in Kerr et al.<sup>24</sup> and Kelly et al.<sup>33</sup>, respectively). For intranasal administration, patients (n=83) in the study by Kerr et al.<sup>24</sup> received 1 mg of naloxone in 0.5mL solution in each nostril while patients (n=84) in the study by Kelly et al.<sup>33</sup> received 1 mg of naloxone in 2.5mL solution in each nostril. The naloxone preparation used by Kerr et al.<sup>24</sup> was a 2 mg/mL naloxone solution, specifically manufactured for the study. Kelly et al.,<sup>33</sup> used an injectable naloxone preparation containing 2 mg naloxone in 5mL solution. In both studies,<sup>24,33</sup> a mucosal atomization device was used to deliver intranasal naloxone. All patients were eligible for a rescue dose of intramuscular naloxone (0.8 mg) if they did not respond within 8 to 10 minutes of the initial dose.

In both studies,<sup>24,33</sup> patients were given standard supportive care, including airway and breathing support as needed until they recovered or were transported to the hospital for further management.

### *Outcomes*

The proportion of patients with an adequate response within 10 minutes of naloxone administration was the primary outcome of interest in the trial by Kerr et al.,<sup>24</sup>. Kelly et al.<sup>33</sup> had the response time as the primary outcome measure. Response was defined as effective and spontaneous respirations at a rate  $\geq 10$  respirations per minute in both studies. A GCS score  $\geq 13$  was an alternative measure of response in the study by Kerr et al.,<sup>24</sup>. Response time was defined as the time to regain a respiratory rate greater than 10 respirations per minute.

Kerr et al.,<sup>24</sup> reported time to adequate response, the requirement for rescue naloxone, hospitalization, and frequency of adverse events as secondary outcomes. Secondary outcomes in the study by Kelly et al.<sup>33</sup> were the proportion of patients with a respiratory rate greater than 10 respirations per minute at 8 minutes, GCS score greater than 11 at 8 minutes, or requiring rescue naloxone, and the rate of adverse events. Another secondary outcome in the study by Kelly et al.<sup>33</sup> was the proportion of patients for whom initial intranasal naloxone alone was sufficient treatment.

### *Guidelines*

Part 10.3 of the 2015 American Heart Association Guidelines Update<sup>19</sup> for cardiopulmonary resuscitation and emergency cardiovascular care discusses administration of naloxone in opioid-associated resuscitation emergencies, including first aid in pre-hospital context. A summary of the characteristics of the guideline<sup>19</sup> is reported in Table 3 of Appendix 3.

## Summary of Critical Appraisal

### *Randomized Controlled Trials*

Both Kerr et al.<sup>24</sup> and Kelly et al.,<sup>33</sup> clearly described the objectives of the study, as well as the interventions and main outcomes of interest. Although both studies were randomized controlled trials with allocation processes intended to minimize selection bias, there was a high potential for bias because they were unblinded studies. However, it would be challenging to achieve adequate blinding for intramuscular and intranasal routes of administration which are distinct, particularly in an emergency situation.. Investigators in each trial made a sample size determination to ensure that the studies were sufficiently powered to detect significant differences in outcomes between the intranasal and intramuscular routes of administering naloxone. However, Kelly et al.,<sup>33</sup> reported that their study had a low power to detect significant differences in secondary outcomes such as the need for rescue naloxone. In each of the studies,<sup>24,33</sup> statistical analysis was robust, and the main findings were clearly reported with 95% CI, thereby providing estimates of random variability for the reported outcomes. However, the data for the studies<sup>24,33</sup> were extracted from patients' case records prepared by paramedics. Thus, because investigators did not have firsthand access to the patients, they could not ascertain the accuracy and completeness of the data. Assessment of consciousness in both studies<sup>24,33</sup> was done using the GCS. Although the GCS scale is widely used as an outcome measure of consciousness in patients with traumatic brain injury,<sup>34,35</sup> its validity in patients with opioid intoxication is unclear. It has been reported in literature that the GCS scale does not determine the degree of improvement or worsening in opioid-intoxicated patient following naloxone intervention.<sup>34</sup> The authors of both studies<sup>24,33</sup> acknowledged a grant support but stated that there was no conflict of interest. Details of the critical appraisal of the individual studies are provided in Appendix 4.

### *Guidelines*

The scope and purposed of the guideline were clearly defined, and its development followed a rigorous process involving 250 reviewers from 39 countries, who addressed 439 PICO (population, intervention, comparator, outcome) questions by systematic reviews and evidence evaluation. Methodological details such as the search strategies and study selection process were not clearly reported. A public consultation was conducted to solicit feedback from relevant stakeholders. Table 4 in the appendix provides further details of the appraisal of the guidelines.<sup>19</sup>

## Summary of Findings

### *What is the comparative clinical effectiveness of Naloxone Hydrochloride Nasal Spray versus intramuscular naloxone?*

The literature search for this review did not identify any studies that evaluated the comparative clinical effectiveness of Naloxone Hydrochloride Nasal Spray versus intramuscular naloxone.

### *What is the comparative clinical effectiveness of Naloxone Hydrochloride Nasal Spray versus naloxone administered intranasally using a mucosal atomizer?*

The literature search for this review did not identify any studies that evaluated the comparative clinical effectiveness of Naloxone Hydrochloride Nasal Spray versus naloxone administered intranasally using a mucosal atomizer.

*What is the comparative clinical effectiveness of naloxone administered intranasally using a mucosal atomizer versus intramuscular naloxone?*

Two unblinded randomized controlled trials<sup>24,33</sup> were identified to answer this question. Further details about the main findings of these studies<sup>24,33</sup> have been provided in Table 6 of Appendix 5.

**Proportion of patients with adequate response (>10 breaths within 8 to 10 minutes)**

Kerr et al.<sup>24</sup> defined response as effective and spontaneous respirations at a rate  $\geq 10$  per minute and/or GCS  $\geq 13$ . They found that the proportion of patients with an adequate response within 10 minutes after the initial dose was higher among patients who were treated with intramuscular injection (77.5%) than in patients treated intranasally (72.3%). However, the difference, 5.2% (95% confidence interval [CI] - 18.2% to 7.7%), was not statistically significant.

Although Kelly et al.<sup>33</sup> reported a similar trend, they found that a significantly higher proportion of patients who received intramuscular naloxone achieved spontaneous respirations than patients who received intranasal naloxone (82% versus 63%;  $P = 0.0163$ , log rank). It should be noted that Kerr et al.<sup>24</sup> assessed adequate response within 10 minutes of initial dose while Kelly et al.<sup>33</sup> did the assessment at 8 minutes. It is unknown whether the difference in time contributed to the difference in the level of statistical significance.

Kelly et al.<sup>33</sup> also reported on the proportion of patients with a GCS score greater than 11 at 8 minutes as a stand-alone outcome. Although the proportion of patients who achieved GCS score greater than 11 at 8 minutes was higher with intramuscular naloxone than with intranasal naloxone, the difference was not statistically significant (72% versus 57%;  $P = 0.0829$ ).

**Time to adequate response**

The studies by both Kerr et al.,<sup>24</sup> and Kelly et al.<sup>33</sup> demonstrated that time to regain greater than 10 breaths per minute was, at least numerically faster with intramuscular naloxone than with intranasal naloxone, but the difference was not always statistically significant. In the study by Kerr et al.,<sup>24</sup> the mean time to achieve adequate response was similar with intramuscular and intranasal naloxone (8.0 minutes versus 7.9 minutes). Multivariate analysis showed that the difference was not statistically significant (Odds ratio [OR] = 0.84; 95% CI: 0.6 to 1.2;  $P = 0.29$ ). However, Kelly et al.<sup>33</sup> found a statistically significantly faster mean time to adequate response with intramuscular naloxone than intranasal naloxone (6 minutes versus 8 minutes;  $P = 0.006$ , log rank).

**Requirement for supplementary naloxone**

Kerr et al.<sup>24</sup> reported that the need for rescue naloxone due to inadequate response to initial dose was significantly higher among patients treated with intranasal naloxone than those treated with intramuscular naloxone (18.1% versus 4.5%; 95% CI: 4.2, to 22.9). However, hospitalization was similar between the two groups with 24 (28.9%) patients in the intranasal group and 23 (25.8%) in the intramuscular group being hospitalized for further management. The trend was similar in the study by Kelly et al.<sup>33</sup> in which 26% of patients treated intranasally required rescue naloxone compared with 13% of patients in the intramuscular group. However, the difference was not

statistically significant ( $P = 0.0558$ ). Hospitalization rate was not reported in this study.<sup>33</sup>

Kelly et al.<sup>33</sup> also reported the proportion of patients for whom intranasal naloxone alone was sufficient treatment as a stand-alone outcome, reporting that 62 (74%) patients treated with intranasal naloxone showed adequate response and did not require additional therapy.

### Adverse events

The common adverse events reported in the two included studies<sup>24,33</sup> were agitation and/or violence; nausea and/or vomiting; and headache. Kelly et al.<sup>33</sup> also reported the incidence of tremor and sweating. Kerr et al.<sup>24</sup> reported that adverse events occurred in 19.3% of patients treated intranasally and in 19.1% of patients treated intramuscularly. Kelly et al.<sup>33</sup> found adverse events in 12% of patients treated intranasally and 21% of patients treated intramuscularly. Overall, the difference was not statistically significant in either study. However, Kelly et al.<sup>33</sup> reported that agitation/irritation occurred at a significantly higher rate in patients who received intramuscular naloxone than those who were treated intranasally (13% versus 2%;  $P = 0.0278$ ). In both studies,<sup>24,33</sup> The adverse events were minor, in general. However, Kerr et al.<sup>24</sup> reported that a patient in the intramuscular group had a grand mal epileptic seizure for which he was given intravenous diazepam and transferred to a hospital for further management.

### *What is the cost-effectiveness of naloxone administered intranasally or intramuscularly?*

The literature search for this review did not identify any studies that evaluated the cost-effectiveness of naloxone administered intranasally or intramuscularly.

### *What are the evidence-based guidelines associated with the use of naloxone in the treatment of opioid overdose in the pre-hospital setting?*

In view of the demonstrated safety and effectiveness of naloxone, Part 10.3 of the 2015 American Heart Association Guidelines Update<sup>19</sup> recommends that lay rescuers and healthcare providers administer naloxone intramuscularly or intranasally as first aid to patients with known or suspected opioid overdose. The Guidelines Update also recommends opioid overdose response education, either alone or coupled with naloxone distribution and training, to persons at risk for opioid overdose or those living with or in frequent contact with such persons. Table 7 in Appendix 5 has further details about the recommendations from the guidelines.<sup>19</sup>

### Limitations

For comparative effectiveness, the literature search found two unblinded randomized controlled trials<sup>24,33</sup> conducted in Australia which met the inclusion criteria for this review. These studies had information to answer one of the three research questions on comparative effectiveness. The author-list and the similarity in study designs and methodologies of the two studies<sup>24,33</sup> suggest that the same research group conducted both studies. Thus, there is a limitation in the amount of literature and the study design and interpretation of findings are restricted to the perspectives of one research group.

Although the included studies<sup>24,33</sup> were designed to assess the comparative effectiveness of intranasal naloxone and intramuscular naloxone in patients with suspected heroin overdose, there was no mechanism in place to confirm that the patients who were included had taken heroin in overdose. Further, the investigators in both trials<sup>24,33</sup> did not do the firsthand data collection, there were no measures in place to ensure all eligible patients were enrolled during the study period, and the analysis did not control for the opioid load. Therefore, it is unclear if the findings can be replicated in a variety of opioid intoxication situations.

Naloxone administered intranasally using a mucosal atomizer was administered in a volume of 2.5 mL in each nostril in the study by Kelly et al.<sup>33</sup> and 0.5 mL in each nostril in the study by Kerr et al.<sup>24</sup> However, it has been reported that the optimal volume for intranasal delivery is 0.1 mL to 0.15 mL.<sup>10</sup> Thus, the findings of these studies may not be generalizable to other administration volumes, in particular the smaller volume (0.1 mL) of the Naloxone Hydrochloride Nasal Spray.

## Conclusions and Implications for Decision or Policy Making

Naloxone has been used to reverse opioid overdose for more than four decades.<sup>21</sup> Health Canada has approved two different formulations of naloxone; injectable naloxone for intramuscular administration (available as generics), and Naloxone Hydrochloride Nasal Spray, a needleless device that delivers a fixed intranasal dose of naloxone.<sup>18,23,26</sup> Although not approved by Health Canada or the FDA, the practice of using an atomization device to deliver the injectable formulation through the nasal route has also been reported and studied.<sup>20,24,33</sup>

The literature search identified two studies comparing intramuscular naloxone with intranasal naloxone using an atomization device. No studies were identified evaluating the clinical effectiveness of Naloxone Hydrochloride Nasal Spray. The two unblinded randomized control trials<sup>24,33</sup> found that the proportion of suspected opioid-overdosed patients with an adequate response after an initial dose of naloxone range from was 77.5% to 82.0% with intramuscular treatment and 63% to 72.3% in with intranasal treatment. Both Kerr et al.<sup>24</sup> and Kelly et al.<sup>33</sup> reported that adequate response was achieved faster with intramuscular naloxone than with intranasal naloxone. The statistical significance in the differences in response between the intramuscular and intranasal routes was inconclusive in both comparisons. Kerr et al.<sup>24</sup> found no significant difference in any of the measures while Kelly et al.<sup>33</sup> showed that the difference was statistically significant for intramuscular naloxone in both cases. Treatment with intranasal naloxone resulted in significantly higher requirement for rescue naloxone in both studies.<sup>24,33</sup> Common adverse events included agitation and/or violence; nausea and/or vomiting; and headache. In general, they were mild and similar between treatment groups. However, Kerr et al.<sup>24</sup> reported that a patient in the intramuscular group had a grand mal epileptic seizure for which he was given intravenous diazepam and transferred to a hospital for further management.

A concern pertaining to off-label use of injectable naloxone solution administered IN through the use of an atomization device is the larger volume of less concentrated naloxone solution that is given.<sup>10</sup> It is possible that larger volumes of naloxone may drain into the throat and be swallowed, thereby limiting the effectiveness. Naloxone delivered intranasally using an atomizer was administered in a volume of 2.5 mL in the study by Kelly et al.<sup>33</sup> and 0.5 mL in the study by Kerr et al.<sup>24</sup> However, it has been

reported that the optimal volume for intranasal delivery is 0.1 mL to 0.15 mL.<sup>10</sup> Thus, the findings of these studies may not be generalizable to other administration volumes, in particular the smaller volume (0.1 mL) of the Naloxone Hydrochloride Nasal Spray. There are no peer-reviewed, published studies that describe the pharmacokinetic properties of intranasal naloxone dosed with an improvised atomization device.<sup>36</sup>

Another consideration is the also the effectiveness of the atomization device that are used to deliver the injectable naloxone intranasally. For example, Health Canada recently issued an advisory that the manufacturer of “MAD Nasal Intranasal Mucosal Atomization Device” has recalled certain lots of the device because it may not be able to deliver a fully atomized (fine) spray of medication, reducing the effectiveness of medication delivered using the atomizer.<sup>37</sup> Additionally, the use of an atomization device to deliver intranasal naloxone is not approved by Health Canada, hence, the effectiveness of such mechanism, and of specific atomization devices cannot be confirmed.

No evidence comparing Naloxone Hydrochloride Nasal Spray to intramuscular naloxone or naloxone administered intranasally using a mucosal atomizer device was identified. The approval of Naloxone Hydrochloride Nasal Spray by Health Canada and the US FDA was based on one phase 1, open-label, randomized, 5-way crossover trial (See Appendix 6) in healthy human volunteers.<sup>36</sup> Based on the study, all the intranasal doses studied (2 mg, 4 mg, and 8 mg) appeared to have a similar time to onset of action as a 0.4 mg IM dose. In terms of approximate dose equivalency (based on a relative bioavailability of IN to IM of 50%), 2 mg and 4 mg of IN naloxone would provide similar plasma concentrations as 1 mg and 2 mg of IM naloxone, respectively. Duration of action was not reported so it was not possible to assess the need for repeat doses of naloxone based on IN versus IM administration or on the initial dose administered. It must be noted that even when taking the 50% relative bioavailability of Naloxone Hydrochloride Nasal Spray to IM naloxone into consideration, a single 4 mg/0.1 mL dose of Naloxone Hydrochloride Nasal Spray delivers almost a five times higher dose of naloxone compared to a single 0.4 mg/mL dose of IM naloxone. The added value of the increased dose delivered by Naloxone Hydrochloride Nasal Spray is unknown.

The new formulation, Naloxone Hydrochloride Nasal Spray, could be more convenient for bystanders as it could potentially decrease the risks associated with the use of needle sticks such as exposure to blood-borne virus.<sup>16,20</sup> However, the effectiveness of intranasal delivery may be limited in individuals with nasal abnormalities.<sup>18,20</sup> Additionally, the cost of Naloxone Hydrochloride Nasal Spray is approximately 4 times higher than a take-home naloxone kit that contains naloxone and other kit components such as syringes, gloves, masks etc.

Overall, the clinical trials comparing intramuscular naloxone with naloxone administered intranasally using a mucosal atomizer<sup>24,33</sup> show that intramuscular naloxone tended to have, at least, a nominally higher efficacy than intranasal naloxone in terms of higher proportion of patients who achieved adequate response, faster time to adequate response, and fewer patients needing rescue naloxone. The incidence of adverse events was similar for intranasal and intramuscular naloxone,

and adverse events were mild, in general. No evidence was identified regarding the effectiveness of Naloxone Hydrochloride Nasal Spray.

Part 10.3 of the 2015 American Heart Association Guidelines Update recommends either intramuscular or intranasal naloxone administration by lay rescuers and healthcare providers as first aid treatment of patients with known or suspected opioid overdose. The Guidelines Update<sup>19</sup> also recommends opioid overdose response education, either alone or coupled with naloxone distribution and training, to persons at risk for opioid overdose or those living with or in frequent contact with such persons.

The literature search did not identify any studies which evaluated the cost-effectiveness of Naloxone Hydrochloride Nasal Spray, naloxone administered intranasally using a mucosal atomizer, or intramuscular naloxone.

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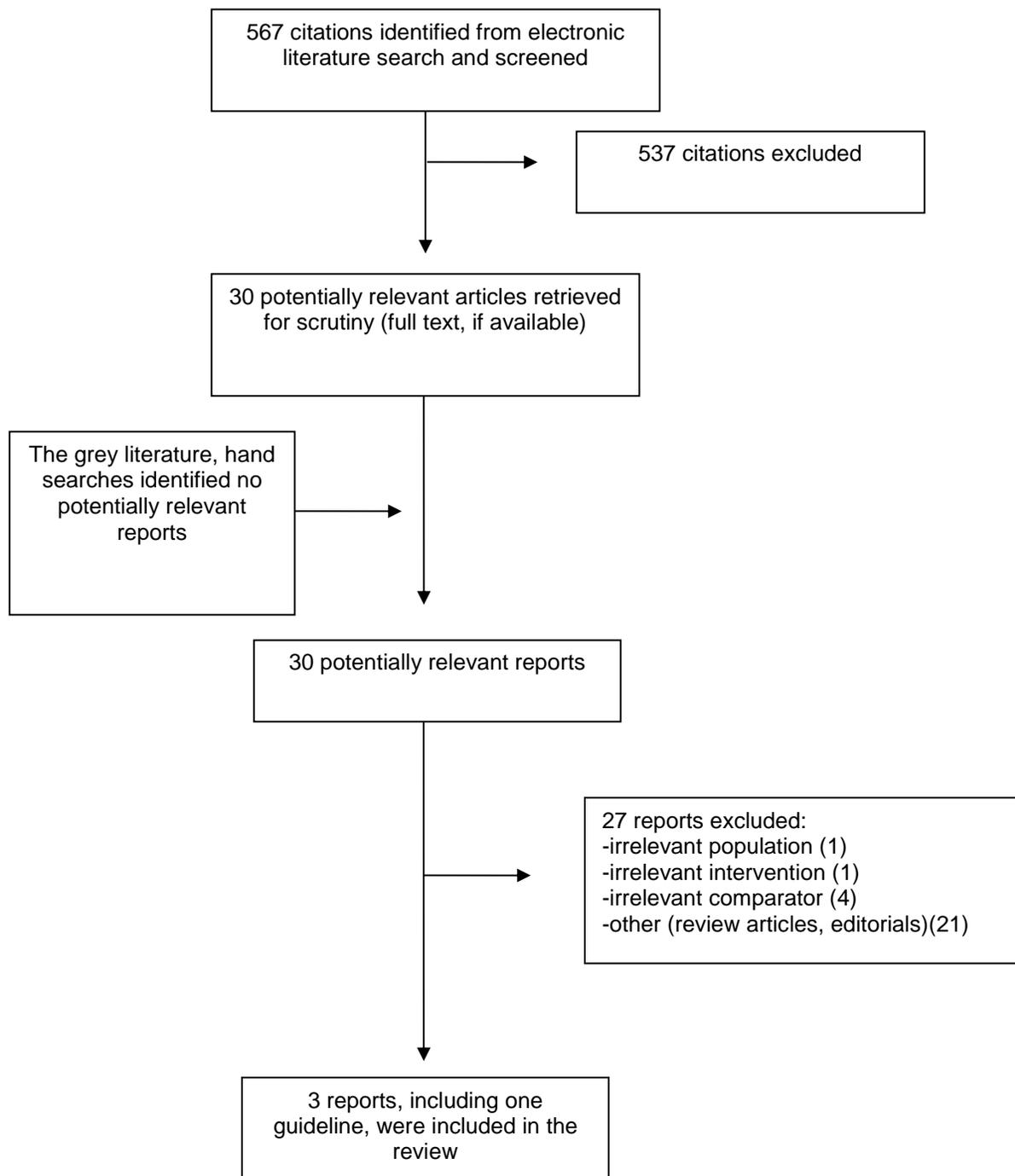
## Appendix 1: List of naloxone products approved for sale in Canada<sup>c</sup>

**Table 1: List of naloxone products approved for sale in Canada**

Product	Company	Strength
Route of Administration: Intramuscular, Intravenous, Subcutaneous		
Naloxone Hydrochloride Injection, USP	Mylan Pharmaceuticals ULC	0.4 mg/ml
Injectable Naloxone Hydrochloride	Omega Laboratories Ltd	0.4 mg/ml
Naloxone Hydrochloride Injection	Omega Laboratories Ltd	0.4 mg/ml <i>(in 1ml &amp; 10ml vials)</i>
Naloxone Hydrochloride Injection	Omega Laboratories Ltd	1.0 mg/ml <i>(in 2ml vials)</i>
Naloxone HCL Injection 0.4mg/ml USP	Sandoz Canada Incorporated	0.4 mg/ml
Naloxone HCL Injection 1mg/ml USP	Sandoz Canada Incorporated	1.0 mg/ml
Naloxone Hydrochloride Injection SDZ Preservative Free	Sandoz Canada Incorporated	0.4 mg/ml <i>(in single use 1ml ampoule)</i>
S.O.S. Naloxone Hydrochloride Injection	Sandoz Canada Incorporated	1.0 mg/ml
S.O.S. Naloxone Hydrochloride Injection	Sandoz Canada Incorporated	0.4 mg/ml
Naloxone Hydrochloride Injection USP	Teligent OU	0.4 mg/ml
Naloxone Injectable	Teligent OU	0.4 mg/ml
Route of Administration: Nasal		
Naloxone Hydrochloride Nasal Spray	Adapt Pharma	2 mg/0.1 ml
Naloxone Hydrochloride Nasal Spray	Adapt Pharma	4 mg/0.1 ml

<sup>c</sup> Information extracted from the Health Canada Drug Product Database (February 10, 2017) <sup>23</sup>

## Appendix 2: Selection of Included Studies



## Appendix 3: Characteristics of Included Publications

Table 2: Characteristics of Included Publications

Author, Publication Date, Country	Study Design	Population	Intervention	Comparator(s)	Outcomes
Kelly 2005 <sup>33</sup> Australia	Prospective, randomized, unblinded RCT	155 patients who required pre-hospital treatment for suspected opiate overdose. They were mostly male (70% and 73% in the IN and IM groups, respectively) with median (range) age of 28 (13 to 52) years in the IN group and 30 (16 to 57) years in the IM group.	2 mg IN naloxone (in the form of 2mg/5mL injectable preparation administered by a mucosal atomization device; 1 mg (2.5 ml) in each nostril [n=84])	2mg IM naloxone (in the form of 2 mg/5 mL injectable preparation administered by standard IM procedure [n=71])	<u>Primary:</u> Mean time to regain spontaneous respiration rate (defined as >10 breaths/min) <u>Secondary:</u> Proportion of patients with a respiratory rate greater than 10 breaths per minute at 8 min, with Glasgow Coma Scale (GCS) score of >11 at 8 min, and requiring rescue naloxone, for whom IN naloxone alone was sufficient treatment Rate of adverse events
Kerr, 2009 <sup>24</sup> Australia	Prospective, randomized, unblinded RCT	172 patients who were treated for suspected opiate overdose in the pre-hospital setting. They were mostly male (77.1% and 70.8% in the IN and IM groups, respectively) with mean ages of 30.6 years and 31.8 years in the IN and IM groups, respectively. Median age was 29 years.	2 mg IN naloxone (in the form of 2mg/mL injectable preparation administered by a mucosal atomization device; 1 mg (0.5 ml) in each nostril [n=83])	2mg IM naloxone (in the form of 2 mg/5 mL injectable preparation administered by standard IM procedure [n=89])	<u>Primary:</u> Proportion of patients who responded within 10 minutes <u>Secondary:</u> time to adequate response and the requirement for supplementary naloxone

IM = intramuscular; IN = intranasal; RCT = randomized controlled trial

**Table 3: Characteristics of Included Guidelines**

Objectives			Methodology			
Intended users/ Target population	Intervention and Practice Considered	Major Outcomes Considered	Evidence collection, Selection and Synthesis	Evidence Quality and Strength	Recommendations development and Evaluation	Guideline Validation
<b>Lavonas, 2015<sup>19</sup> – American Heart Association Guidelines Update</b>						
Clinicians and lay rescuers <sup>a</sup> /cardiac arrest patients and all with suspected opioid toxicity	Recommendations to address cardiac arrest in situations that require special treatments or procedures other than those provided during BLS and ACLS.	Effective management of resuscitation in several critical situations, including cardiac or respiratory arrest associated with opioid overdose.	The evidence for recommendations in the Guidelines Update was based on extensive systematic reviews done by ILCOR, with publications by international CoSTR in 2010 and 2015.	Study methodologies and the 5 core GRADE domains of risk of bias, inconsistency, indirectness, imprecision, and other considerations were used to rate the quality of evidence. LOEs were defined as: <b><u>Level A</u></b> High-quality evidence from more than 1 RCTs Meta-analysis of high-quality RCTs One or more RCTs corroborated by high-quality registry studies <b><u>Level B-R</u></b> Moderate quality evidence from 1 or more RCTs Meta-analysis of moderate quality RCTs <b><u>Level B-NR</u></b> Moderate quality evidence from 1 or more well-designed well-	Treatment recommendations were informed by the ILCOR recommendations and created using GRADE-evaluated evidence, with consensus, where possible. CORs were defined in terms of benefits and risks as follows: <b><u>Class I (Strong)</u></b> Benefit >>> Risk  <b><u>Class IIa (Moderate)</u></b> Benefit >> Risk  <b><u>Class IIb (Weak)</u></b> Benefit ≥ Risk  <b><u>Class III: No Benefit (Moderate)</u></b> Benefit = Risk  <b><u>Class III: Harm (Strong)</u></b> Risk > Benefit	Tools validated by experts in methodology were used in developing the recommendations to ensure that the AHA COR and LOE framework and the ILCOR GRADE evidence review were consistently applied

**Table 3: Characteristics of Included Guidelines**

Objectives			Methodology			
Intended users/ Target population	Intervention and Practice Considered	Major Outcomes Considered	Evidence collection, Selection and Synthesis	Evidence Quality and Strength	Recommendations development and Evaluation	Guideline Validation
				executed non-randomized studies, observational studies, or registry studies Meta-analysis of such studies <u><b>Level C-LD</b></u> Randomized or nonrandomized observational or registry studies with limitations of design or execution Meta-analysis of such studies Physiological or mechanistic studies in human subjects <u><b>Level C-EO</b></u> Consensus of expert opinion based on clinical experience		
a As it relates to Part 10.3: Cardiac or respiratory arrest associated with opioid overdose						

ACLS = advanced cardiovascular life support; AHA = American Heart Association; BLS = basic life support; CoSTR = Consensus on Science With Treatment Recommendations; COR = classes of recommendation; ECC = Emergency Cardiovascular Care; GRADE = Grading of Recommendations Assessment, Development and Evaluation; ILCOR = International Liaison Committee on Resuscitation; LOE = levels of evidence

## Appendix 4: Critical Appraisal of Included Publications

**Table 4: Strengths and Limitations of Randomized Controlled Trials using Downs and Black Checklist<sup>38</sup>**

Strengths	Limitations
Kelly 2005 <sup>33</sup>	
<ul style="list-style-type: none"> <li>• The objectives of the study, as well as the interventions and main outcomes of interest were clearly described.</li> <li>• The main finding were clearly reported with 95% CI, thereby providing estimates of random variability for the reported outcomes</li> <li>• Patients were randomly assigned to receive 2 mg of naloxone either by the nasal or intramuscular route, using a pre-specified number allocation protocol. Randomization minimized selection bias.</li> <li>• A sample size determination was made to ensure the study was sufficiently powered to detect a significant difference in the primary outcome (time to regain a respiratory rate greater than 10 per minute) between the two interventions.</li> <li>• The authors acknowledged a grant support from a foundation but stated that there was no conflict of interest.</li> </ul>	<ul style="list-style-type: none"> <li>• This it was an unblinded study; therefore, the potential for outcome bias is high.</li> <li>• The investigators did not do a firsthand collection of data for the study; therefore, it cannot be ruled out that eligible patients were missed since the accuracy of the data depended on the completeness of patients' case records (hand-written by paramedics) from which they were derived.</li> <li>• The study was not sufficiently powered to detect significant differences in secondary outcomes such as the requirement for rescue naloxone.</li> <li>• The validity of GCS scale as an outcome measure in the study population is unclear. It has been reported in literature that the GCS scale does not determine the degree of improvement or worsening in opioid-intoxicated patient following the intervention.<sup>34</sup> Therefore, the AVPU scale would be a more appropriate outcome measure.<sup>34</sup></li> <li>• It is unknown if the results can be replicated in patients different levels of intoxications since the analysis could not control for the opioid load.</li> </ul>
Kerr, 2009 <sup>24</sup>	
<ul style="list-style-type: none"> <li>• The objectives of the study, as well as the interventions and main outcomes of interest were clearly described</li> <li>• The main finding were clearly reported with 95% CI, thereby providing estimates of random variability for the reported outcomes</li> <li>• A block randomization process was used to achieve even distribution of allocations and minimize selection bias.</li> <li>• The study had sufficient power to detect significant differences in outcomes between the two interventions.</li> <li>• Data entries for the study were checked for accuracy by an independent blinded research assistant, with a third researcher arbitrating cases of data discrepancy.</li> <li>• Statistical analysis was robust, and included regression analyses using age, gender, and concomitant alcohol and/or drug use as correlates.</li> <li>• The authors declared no conflict of interest.</li> </ul>	<ul style="list-style-type: none"> <li>• This was an unblinded study; therefore, the potential for outcome bias is high.</li> <li>• The investigators did not do a firsthand collection of data for the study; and there were no measures in place to ensure all eligible patients during the study period were enrolled.</li> <li>• Although the study was designed to assess the comparative effectiveness of intranasal naloxone and intramuscular naloxone in suspected heroin overdose, there was no mechanism in place to confirm the heroin overdose and the analysis could not control for the opioid load. Therefore, it is unclear if the findings apply to all variety of opioid-intoxications.</li> </ul>

Table 5: Strengths and Limitations of Guidelines<sup>38</sup>

Strengths	Limitations
Lavonas, 2015 <sup>19</sup> – American Heart Association Guidelines Update	
<ul style="list-style-type: none"> <li>• The objectives, targeted users and population to whom it was meant to apply were well-described. Topics for systematic review were prioritized based on clinical significance and availability of new evidence</li> <li>• Members of ILCOR and the AHA ECC staff collaborated with consultants to develop the SEERS website to facilitate the structured and consistent evidence review process for the guidelines.</li> <li>• All draft recommendations, as well as the ILCOR draft consensus on science statements and treatment recommendations and the CoSTR drafts were posted to allow public comment, including conflict of interest disclosures.</li> <li>• The recommendations were reached by consensus, where possible, using the AHA COR and LOE process. The quality of evidence was evaluated using the GRADE process for evidence evaluation, which is a validated and widely used tool.</li> <li>• In place of cyclical procedure for updating the guidelines, a continuous evidence evaluation and guidelines update process has been instituted using online publication.</li> <li>• The recommendations are specific and clear, with options for managing a variety of conditions.</li> </ul>	<ul style="list-style-type: none"> <li>• Criteria for evidence selection and procedure for updating the guideline were not available for assessment. However, with 250 reviewers from 39 countries addressing 439 PICO questions by systematic reviews and evidence evaluation, using well validated tools, it is unlikely that this is a source of quality concern</li> </ul>

AHA = American Heart Association; COR = Classes of Recommendation; CoSTR = Consensus on Science with Treatment Recommendations; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; ILCOR = International Liaison Committee on Resuscitation; LOE = Levels of Evidence; PICO = population, intervention, comparator, outcome; SEERS = Systematic Evidence Evaluation and Review System

## Appendix 5: Main Study Findings and Author’s Conclusions

Table 6: Summary of Findings of Included Studies

Main Study Findings	Author’s Conclusion
Kelly 2005 <sup>33</sup>	
<p><u>Mean time to regain &gt;10 breaths per minute</u>            Patients who received intramuscular naloxone responded faster (mean time 6 minutes, 95% CI: 5, 7) than those treated with intranasal naloxone (mean time 8 minutes, 95% CI: 7, 8). The difference was statistically significant (<math>P = 0.006</math>, log rank).</p> <p><u>Proportion of patients with &gt;10 breaths per minute at 8 minutes</u>            The IM intervention resulted in significantly (<math>P = 0.0163</math>, log rank) more patients with spontaneous respirations within 8 minutes (82%) than patients who received the intranasal intervention (63%). The OR (95% CI, was 2.6 (1.2, 5.5) in favor of intramuscular naloxone.</p> <p><u>Proportion of patients with GCS score of &gt;11 at 8 min</u>            A greater proportion of patients treated with intramuscular naloxone (72%) had GCS score greater than 11 at 8 minutes compared with those treated with intranasal naloxone (57%). However, the difference did not reach the level of statistical significance (<math>P = 0.0829</math>; OR = 1.9; 95% CI: 0.98, 3.7). The time to GCS score greater than 11 was also not significantly different (<math>P = 0.376</math>, log rank) between the two interventions.</p> <p><u>Proportion of patients requiring rescue naloxone</u>            Intramuscular administration of naloxone resulted in a trend towards a lower requirement for rescue naloxone than intranasal administration. However, the difference was not statistically significant (13% versus 26%; <math>P = 0.0558</math>; OR = 2.4; 95% CI, 1.0–5.7)</p> <p><u>Proportion of patients for whom intranasal naloxone alone was sufficient treatment</u>            Sixty-two (74%) patients treated with intranasal naloxone showed adequate response and did not require additional therapy. The proportion of patients for whom intramuscular naloxone alone was sufficient treatment was no specified</p> <p><u>Rate of adverse events</u>            Adverse events were minor in both groups. Reported AEs were agitation and/or irritation, nausea and/or vomiting, headache, tremor, and sweating. Although treatment with intramuscular naloxone tended to have a higher incidence of AEs than the intranasal naloxone, the difference, in general, was not statistically significant (21% versus 12%, <math>P = 0.1818</math>). However, agitation/irritation occurred at a significantly higher rate in patients who received intramuscular naloxone than those who were treated intranasally (13% versus 2%; <math>P = 0.0278</math>).</p>	<p>“IN (<i>intranasal</i>) naloxone is effective in treating opiate-induced respiratory depression, but is not as effective as IM (<i>intramuscular</i>) naloxone. IN delivery of naloxone could reduce the risk of needlestick injury to ambulance officers and, being relatively safe to make more widely available, could increase access to life-saving treatment in the community.”<sup>33</sup> page 24</p>

**Table 6: Summary of Findings of Included Studies**

Main Study Findings	Author's Conclusion
<b>Kerr, 2009<sup>24</sup></b>	
<p><u>Proportion of patients who responded within 10 minutes</u> Sixty (72.3%) in the intranasal group and 69 (77.5%) in the intramuscular group achieved an adequate response within 10 minutes from initial naloxone treatment, without the need for a rescue dose. The difference was 5.2% (95% CI -18.2, 7.7%) in favor of intramuscular naloxone. The OR (95% CI) from multivariate analysis was 0.7(0.3, 1.5)</p> <p><u>Time to adequate response</u> The mean response time was similar between the two groups, with 8.0 minutes in the intranasal group and 7.9 minutes in the intramuscular group, HR 0.8 (95% CI: 0.6, 1.2). Multivariate analysis showed that the difference was not statistically significant (OR =0.84, 95% CI: 0.6, 1.2; P = 0.29)</p> <p><u>Requirement for supplementary naloxone</u> The need for rescue naloxone for inadequate response was higher in the intranasal group (18.1%) than in the intramuscular group (4.5%). The statistically significance of the difference (13.6%; 95% CI: 4.2, 22.9) remained, even after multivariate analysis controlling for age, gender and suspected concomitant alcohol and/or drugs (OR = 4.8, 95% CI: 1.4, 16.3; P = 0.01). Hospitalization was similar between the two groups with 24 (28.9%) patients in the intranasal group and 23 (25.8%) in the intramuscular group being hospitalized.</p> <p><u>Adverse events</u> Adverse events were reported in 16 (19.3%) patients in the intranasal group and 17 (19.1%) patients in the intramuscular group. The difference was not statistically significant (0.2% 95% CI: -11.6, 11.9). Adverse events were generally minor and included agitation and/or violence; nausea and/or vomiting; and headache. However, a patient in the intramuscular group had a grand mal epileptic seizure for which he was given i.v. diazepam, and was transferred to a hospital for further management.</p>	<p>“Concentrated intranasal naloxone reversed heroin overdose successfully in 82% of patients. Time to adequate response was the same for both routes, suggesting that the i.n. route of administration is of similar effectiveness to the i.m. route as a first-line treatment for heroin overdose.”<sup>24</sup> page 2067</p>

AE = adverse event; CI = confidence interval; GCS = Glasgow Coma Scale; HR = hazard ratio; i.m. = intramuscular; i.n. = intranasal; OR = odds ratio; i.v. = intravenous

**Table 7: Recommendations from Guidelines**

Recommendation	Class of recommendation, Level of evidence
Lavonas, 2015 <sup>19</sup> – American Heart Association Guidelines Update– Part 10.3	
Recommendation for First Aid and Basic Life Support by Non–Healthcare Provider	
It is reasonable to provide opioid overdose response education, either alone or coupled with naloxone distribution and training, to persons at risk for opioid overdose (or those living with or in frequent contact with such persons).	Class IIa, LOE C-LD
It is reasonable to base this training on first aid and non-healthcare provider BLS recommendations rather than on more advanced practices intended for healthcare providers.	Class IIa, LOE C-EO
Empiric administration of IM or IN naloxone to all unresponsive victims of possible opioid-associated life-threatening emergency may be reasonable as an adjunct to standard first aid and non- healthcare provider BLS protocols. Standard resuscitation procedures, including EMS activation, should not be delayed for naloxone administration	Class IIb, LOE C-EO
Victims who respond to naloxone administration should access advanced healthcare services.	Class I, LOE C-EO
Recommendation for Basic Life Support by Healthcare Provider	
Respiratory Arrest	
For patients with known or suspected opioid overdose who have a definite pulse but no normal breathing or only gasping (i.e., a respiratory arrest), in addition to providing standard BLS care, it is reasonable for appropriately trained BLS healthcare providers to administer IM or IN naloxone.	Class IIa, LOE C-LD
Cardiac Arrest	
Patients with no definite pulse may be in cardiac arrest or may have an undetected weak or slow pulse. These patients should be managed as cardiac arrest patients. Standard resuscitative measures should take priority over naloxone administration, with a focus on high-quality CPR	Class I, LOE C-EO
It may be reasonable to administer IM or IN naloxone based on the possibility that the patient is not in cardiac arrest	(Class IIb, LOE C-EO)
Responders should not delay access to more-advanced medical services while awaiting the patient’s response to naloxone or other interventions.	Class I, LOE C-EO
Unless the patient refuses further care, victims who respond to naloxone administration should access advanced healthcare services.	Class I, LOE C-EO

BLS = basic life support; CPR = compressions plus ventilation; EO = expert opinion; EMS = emergency medical service; IM = intramuscular; IN = intranasal; LOE = level of evidence; LD

## Appendix 6: Other Considerations

### Pharmacokinetic study of Naloxone Hydrochloride Nasal Spray

No clinical studies on Naloxone Hydrochloride Nasal Spray (device with naloxone) were identified in the clinical review. A pivotal pharmacokinetic (PK) study served as the basis for the approval of Naloxone Hydrochloride Nasal Spray by Health Canada and the US Food and Drug Administration (FDA).<sup>16,39</sup>

The pivotal PK trial (*Naloxone-Phase 1a-002; NCT 02572089*), was a phase 1, open-label, randomized, 5-period, 5-treatment, 5-sequence crossover trial in 30 (28 completed) healthy human male and female volunteers.<sup>36</sup> The study evaluated Naloxone Hydrochloride Nasal Spray (2 mg or 4 mg doses given as 1 or 2 sprays of 20 mg/mL or 4 mg and 8 mg doses given as 1 or 2 sprays of 40 mg/mL) compared to intramuscular (IM) naloxone (0.4 mg dose given as 0.4 mg/mL).<sup>36</sup> Each Naloxone Hydrochloride Nasal Spray was equivalent to a volume of 0.1 mL. A parallel usability study tested ease of use of the device by lay people in a simulated overdose.<sup>36</sup> A brief overview is of the PK study is provided.

Following Naloxone Hydrochloride Nasal Spray administration, naloxone plasma concentrations were detectable at 2.5 minutes, which is consistent with rapid systemic absorption. Median T<sub>max</sub> values (time to reach the maximum plasma concentration) ranged from 0.3 to 0.5 hours after Naloxone Hydrochloride Nasal Spray compared to 0.4 hours after IM. The C<sub>max</sub> (peak plasma concentration) and AUC (area under the plasma concentration-time curve, used to estimate bioequivalence of drugs) after the Naloxone Hydrochloride Nasal Spray doses of naloxone appeared to increase in a dose-proportional manner from 2 mg to 8 mg. The terminal elimination half-lives for Naloxone Hydrochloride Nasal Spray (2 hours) and naloxone IM (1.3 hours) were also similar. Both Naloxone Hydrochloride Nasal Spray and IM naloxone were well tolerated and there were no safety differences related to route of administration. Few nasal mucosa adverse events were reported after Naloxone Hydrochloride Nasal Spray administration.

The geometric mean ratios of dose-corrected C<sub>max</sub> for the Naloxone Hydrochloride Nasal Spray doses vs. IM ranged from 55.1% to 70.8% whereas dose-corrected AUC for the Naloxone Hydrochloride Nasal Spray doses vs. IM ranged from 43.9% to 53.5%. These results clearly show that the intranasal route is not bioequivalent to the IM route for naloxone. Rather, the relative bioavailability of Naloxone Hydrochloride Nasal Spray compared to IM is approximately 50% which means that twice the amount of Naloxone Hydrochloride Nasal Spray is required to achieve the same plasma concentrations as naloxone IM. Therefore, based on the pivotal PK study, the approximate dose equivalency would be 2 mg and 4 mg of Naloxone Hydrochloride Nasal Spray provides similar plasma concentrations as 1 mg and 2 mg of IM naloxone, respectively. Hence, a single 4 mg/0.1 mL dose of Naloxone Hydrochloride Nasal Spray delivers almost a five times higher dose of naloxone compared to a single 0.4 mg/mL dose of IM naloxone. The added value of the higher dose delivered by Naloxone Hydrochloride Nasal Spray is uncertain.

Time to onset of effect also appears likely to be similar for the Naloxone Hydrochloride Nasal Spray and IM routes based on the similarity of the T<sub>max</sub> values for naloxone, which were all within 0.3 to 0.5 hours.<sup>36</sup> Interpretation of the results for

time to onset of action is complicated by not knowing the lowest effective dose or minimum therapeutic concentration of naloxone. The efficacy of naloxone in reversing opioid overdose is dependent upon the type, quantity, and PK characteristics of the opioid ingested and their relative affinities for opiate receptors.<sup>39</sup> The US FDA rationalized that the first few minutes after naloxone administration are of particular importance because if the overdose has led to apnea, time is of the essence if the brain is to be spared permanent hypoxic injury.<sup>39</sup> As a result, in addition to C<sub>max</sub> and T<sub>max</sub>, it is necessary to demonstrate that the naloxone levels after Naloxone Hydrochloride Nasal Spray are comparable to the approved route (IM) during the first minutes after dosing.<sup>39</sup> The US FDA examined the rate of absorption and plasma concentrations of naloxone from the five treatment arms in the pivotal study over the first hour post-dose and concluded that Naloxone Hydrochloride Nasal Spray levels rise as early as naloxone IM and peak higher (i.e., 4 mg Naloxone Hydrochloride Nasal Spray provides naloxone concentrations that are 3.5- to 6-fold higher than 0.4 mg IM).<sup>39</sup> In the pivotal PK study, if one assumes the threshold for efficacy is reached with the IM dose (0.4 mg), then all the Naloxone Hydrochloride Nasal Spray doses (2 mg, 4 mg, and 8 mg) appear to have a similar time to onset of action as the IM dose.

Duration of action (i.e., time spent above the minimum therapeutic concentration) was not reported in the pivotal PK study. Although the time to onset of action was similar between Naloxone Hydrochloride Nasal Spray doses, the duration of action appears to be longer as the dose of Naloxone Hydrochloride Nasal Spray increases. Duration of action is a key consideration because due to the rapid elimination and short half-life of naloxone, plasma concentrations can quickly fall below the minimum therapeutic concentration and the effect of naloxone wears off. As a result, rebound or re-emergence of respiratory depression and other overdose symptoms can occur while the opioid is still present, especially if it has a longer half-life than naloxone.<sup>16</sup> For this reason, multiple doses of naloxone may be required.<sup>16</sup>

The human factors and usability study (N=116) included adolescents (12 to 17 years of age) and adults who were evaluated on critical tasks for administration of the IN naloxone drug product.<sup>36</sup> More than 90% of study participants successfully performed the critical tasks using 1 or 2 devices.<sup>36</sup> It was concluded that the IN product could be used by first responders and the lay public.<sup>36</sup>

The Health Canada-approved dosing recommendations for the Naloxone Hydrochloride Nasal Spray state that the lowest available strength (2 mg) should be used as the initial dose and if the patient does not respond within 2-3 minutes, additional doses (2 mg or 4 mg) up to a maximum of 10 mg should be administered.<sup>18</sup> Based on a relative bioavailability of 50%, an initial 2 mg Naloxone Hydrochloride Nasal Spray dose would be considered equivalent to 1 mg IM dose and a 4 mg Naloxone Hydrochloride Nasal Spray dose would be equivalent to 2 mg IM dose, which corresponds with the maximum recommended initial dose in adult clinical guidelines.<sup>16</sup> While there is a risk that high levels of naloxone could trigger an Acute Opioid Withdrawal Syndrome (AOWS), this is not life-threatening but could pose a danger to bystanders or caregivers due to sudden aggression reactions by the patient. Health Canada did not consider that the higher levels of naloxone resulting from a 4 mg dose would be a concern with regard to AOWS.<sup>16</sup> The US FDA rationalized that doses of naloxone are administered in an incremental manner and by doing so it may be possible to avoid precipitating an AOWS in opioid-tolerant

patients.<sup>16</sup> Both Health Canada and the US FDA acknowledge that while there may be risks associated with naloxone, they are well known, and that any dose of naloxone should be used in an overdose situation as any risk is outweighed by the benefits of life-saving treatment.<sup>16,39</sup>

### Intranasal versus intramuscular route of delivery

Various factors can compromise intranasal absorption which include epistaxis, nasal mucus, trauma, septal abnormalities, and other intranasal pathology.<sup>20</sup> The Naloxone Hydrochloride Nasal Spray Product Monograph states as a general warning that the effectiveness of naloxone (IN) has not been assessed in people with intranasal conditions such as abnormal nasal anatomy, nasal symptoms (i.e., blocked and/or runny nose, nasal polyps, etc.) or in people having a product sprayed into the nasal cavity prior to naloxone administration.<sup>18</sup> It is not known if these conditions affect naloxone's effectiveness when administered by the intranasal route.<sup>18</sup> As such, it is important to keep in mind that the study conditions for Naloxone Hydrochloride Nasal Spray were very tightly controlled so as to remove any sources of variability that were not specifically related to the drug products being tested.

Various factors can also affect absorption of an injectable product, as although it is generally assumed that 100% of the dose is administered by injection, absorption rates for IM (or subcutaneous) injections can vary due to dependence on blood flow to the injection site, rate of blood flow away from the site, and amount of muscle and adipose tissue present.<sup>20</sup> As a result, it must be recognized that for both the IN and IM routes, there are potential sources of variability that could affect absorption and subsequently the efficacy of naloxone.

### Other

The efficacy of naloxone in reversing opioid overdose is dependent upon the type, quantity, and PK characteristics of the opioid ingested and their relative affinities for opiate receptors.<sup>39</sup>

## Appendix 7: Additional References of Potential Interest

An abridged version of the 2015 AHA Guideline Update<sup>19</sup> with an emergency algorithm for bystanders to provide care in opioid-associated life-threatening emergency situations in out-of-hospital settings

- Drennan IR, Orkin AM. OPIOID CRISIS. Prehospital naloxone administration for opioid-related emergencies. *J Emerg Med Serv JEMS*. 2016 Mar;41(3):36-9.

Comparison of intranasal and intravenous naloxone in opioid overdose

- Sabzghabaee AM, Eizadi-Mood N, Yaraghi A, Zandifar S. Naloxone therapy in opioid overdose patients: intranasal or intravenous? A randomized clinical trial. *Arch*. 2014 May 12; *Med. Sci.* 10(2):309-14.
- Robertson TM, Hendey GW, Stroh G, Shalit M. Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose. *Prehosp Emerg Care*. 2009;13:512–515. doi: 10.1080/10903120903144866.
- Barton ED, Colwell CB, Wolfe T, Fosnocht D, Gravitz C, Bryan T, Dunn W, Benson J, Bailey J. Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. *J Emerg Med*. 2005;29:265–271. doi: 10.1016/j.jemermed.2005.03.007.
- Loimer N, Hofmann P, Chaudhry HR. Nasal administration of naloxone is as effective as the intravenous route in opiate addicts. *Int J Addict*. 1994;29:819–827.

The following pharmacokinetic studies have been listed at ClinicalTrials.gov. As at February 27<sup>th</sup>, 2017 they were classified as completed but they did not have any published data.

- NCT02598856 – Bioavailability of nasal naloxone and injected naloxone compared (OPI-15-002)
- NCT02307721– Pharmacokinetics and pharmacodynamics of a new formulation of nasal naloxone for prehospital use (OPI-14-001)
- NCT02572089 – Pharmacokinetic evaluation of intranasal and intramuscular naloxone in healthy volunteers
- NCT02158117 – Bioavailability of a new formulation of nasal naloxone for prehospital use
- NCT01939444 – A pilot study of the bioavailability of nasal naloxone