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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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Abbreviations

ACEP	American College of Emergency Physicians
AGREE II	Appraisal of Guidelines for Research and Evaluation, version II
AHRQ	Agency for Healthcare Research and Quality
CAD$	Canadian dollar
CADTH	Canadian Agency for Drugs and Technologies in Health
CRD	Centre for Reviews and Dissemination
ED	Emergency Department
EMS	Emergency Medical Services
GCS	Glasgow Coma Scale
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
ICER	Incremental cost-effectiveness
IM	Intramuscular
IN	Intranasal
NAEMSP	National Association of EMS Physicians
NASEMSO	National Association of State EMS Officials
QALY	Quality-adjusted life-year
RCT	Randomized controlled trial
SR	Systematic review
SSRE	Sufficient spontaneous respiratory effort
SUD	Substance use disorder
TDSB	Toronto District School Board
USPSTF	United States Preventive Services Task Force
WFNS	World Federation of Neurosurgical Societies

Context and Policy Issues

The number of opioid overdose cases is increasing in Canada. Although data showing current national-level trends of opioid toxicity-related morbidity and mortality were not identified for this Rapid Response report, the Canadian Institute for Health Information and the Canadian Centre on Substance Abuse have jointly reported that the rate of hospitalizations due to opioid poisoning in Canada increased by more than 30% between 2007-2008 and 2014-2015.[1] Also, data from the Office of the Chief Coroner for Ontario show that the number of opioid overdose-related deaths increased from 206 in 2004 to 624 in 2014.[2]

Naloxone, a drug that can temporarily reverse opioid overdose, is a competitive opioid receptor antagonist with a rapid onset and short duration of action.[3] It has been used to reverse the effects of a variety of natural, semisynthetic, and synthetic opioids in both pre-hospital (community) and hospital settings.[4] Some advantages of using naloxone as a reversal agent for opioid overdose include absence of potential for abuse, a wide dose range without a likelihood of overdose, and a lack of pharmacological activity in the absence of opioids or other opioid antagonists.[3,5-7]

Health Canada approved non-prescription use of naloxone for emergency reversal of opioid overdose in pre-hospital settings in March 2016,[8] and authorized the sale for Naloxone Hydrochloride Nasal Spray in Canada on July 5, 2017.[9] Naloxone Hydrochloride Nasal Spray is a needleless device that delivers a fixed intranasal dose of naloxone.[9] Other formulations of naloxone, including injectable for intramuscular, intravenous, or subcutaneous use, are available in Canada. Also, atomizer devices have been used in practice to deliver injectable naloxone solution intranasally.[10,11] Both intranasal and

intramuscular naloxone formulations are available for pre-hospital use, including by laypersons in the community.

In 2017, CADTH produced a Rapid Response report summarizing evidence on the comparative clinical effectiveness, cost effectiveness, and evidence-based recommendations for use of the various formulations and delivery mechanisms of naloxone for the treatment of opioid poisoning in pre-hospital settiongs. The evidence available then for that report was limited in number and quality. Therefore, the objective of this current Rapid Response report is to review any new evidence that may have become available since the 2017 report and update the evidence.

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

One economic evaluation using a decision-analytic model with inputs from the medical literature and sources specific to Toronto showed that a school-based naloxone program to reduce opioid overdose mortality is likely to be cost-effective if there are at least two overdoses every year. A major limitation of the cost-effectiveness analysis was that, in the absence of data on incidence of overdoses on Canadian schools, the authors assumed between one overdose and 50 overdoses every 10 years across the entire 112 schools in the Toronto District School Board system, the subject of the study, without providing an adequate rationale for the assumption.

Based on evidence of very low quality, one guideline makes a weak recommendation that favors intranasal naloxone over intramuscular naloxone for patients with confirmed or suspected opioid overdose in out-of-hospital settings. Considerations for the recommendation were comparable efficacy across the two routes of administration, as well as ease of use and reduced adverse events associated with the intranasal formulation, which promotes increased safety of emergency medical service practitioners and patients. The guideline suggests that the initial dose should be enough to achieve adequate respiratory function without triggering withdrawal symptoms, considering factors such as the opioids in use in the local area.

The literature search did not identify any evidence regarding the comparative effectiveness of Naloxone Hydrochloride Nasal Spray versus intramuscular naloxone or the intranasal administration of naloxone solution using a mucosal atomizer device. Also, no new evidence was identified comparing the clinical effectiveness of intranasal naloxone

delivered by mucosal atomizer versus intramuscular naloxone other than that reported in a previously published CADTH Rapid Response report.[1]

Methods

Literature Search Methods

This report is an update of a literature search strategy developed for a previous CADTH report. For the current report, a limited literature search was conducted on key resources, including Medline via Ovid, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. For research questions 1 -3 no filters were applied to limit the retrieval by study type. Search filters were applied to limit the retrieval to economic studies for research question 4 and guidelines for research question 5. The initial search was limited to English-language documents published between January 1, 2005 and February 9, 2017. For the current report, database searches were rerun on October 23, 2019 to capture any articles published since the initial search date. The search of major health technology agencies was also updated to include documents published since February 2017.

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 1.

Table 1: Selection Criteria

Population	Patients (of any age) suspected of opioid overdose in the pre-hospital setting -Subgroups of interest: pediatric (≤ 18 years of age) and adult (> 18 years of age) populations, pregnant and lactating, geriatric
Intervention	Questions 1 and 2: • Naloxone Hydrochloride Nasal Spray Question 3: • Naloxone administered intranasally using a mucosal atomizer (i.e., kit with naloxone, luer-lock syringe barrel, and mucosal atomizer device) Question 4: • Naloxone Hydrochloride Nasal Spray, naloxone administered intranasally using a mucosal atomizer, or intramuscular naloxone Question 5: • Naloxone (any dose or route of administration)
Comparator	Questions 1 and 3: • Intramuscular naloxone Question 2: • Naloxone administered intranasally using a mucosal atomizer Question 4: • Any of the following alternative modes of naloxone administration (i.e., Naloxone Hydrochloride Nasal Spray, naloxone administered intranasally using a mucosal atomizer, intramuscular naloxone); no comparator Question 5:

	• No comparator required
Outcomes	Questions 1-3: • Clinical effectiveness: (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); • Harms: (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 needle site reactions and needle stick injury; study-related side-effects [e.g., agitation]; and rebound opioid toxicity) Question 4: • Cost-effectiveness outcomes (e.g., cost per benefit or clinical outcome, cost per quality adjusted life year) Question 5: • Evidence-based guideline recommendations regarding the appropriate use of naloxone (including route of administration, dosing) in the pre-hospital setting
Study Designs	Health Technology Assessment/Systematic Reviews/Meta-Analyses, Randomized Controlled Trials, Economic Evaluations, Non-Randomized Studies, Evidence-based Guidelines.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, were published before 2017 (the year the first CADTH Rapid Response report[1] on the topic was produced), or if they did not provide new relevant information than that in the original Rapid Response report.[1]

Critical Appraisal of Individual Studies

The Drummond checklist[12] was used as a guide to appraise the included economic evaluation.[13] The tool consists of 35 items used to assess three broad areas of the economic evaluation: study design, data collection, and analysis and interpretation of results.

The included guidelines were appraised using the Appraisal of Guidelines for Research and Evaluation, version II (AGREE II) instrument.[14] The AGREE II instrument consists of six quality-related domains: scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, and editorial independence of guidelines, with a total of 23 items. The tool is widely used to assess the development and reporting of guidelines.

Summary of Evidence

Quantity of Research Available

The literature search identified a total of 223 citations. Following screening of titles and abstracts, 201 abstracts and titles were excluded, and 22 potentially relevant reports from the electronic search were retrieved for full-text review. The grey literature search did not identify any additional relevant publications. Of the 22 potentially relevant articles, 20 papers were excluded for various reasons, and two publications met the inclusion criteria

and were included in this report. These comprised one economic evaluation[13] and one evidence-based guideline.[15]

Appendix 1 presents the PRISMA flowchart of the study selection.

Summary of Study Characteristics

One economic evaluation[13] assessing the cost-effectiveness of a naloxone program in secondary school and one evidence-based guideline[15] on the administration of naloxone by Emergency Medical Services (EMS) practitioners for patients with confirmed or suspected opioid overdose outside hospital settings were included in this Rapid Response report. The cost-effectiveness study[13] was published in 2018 and the guideline[15] was published in 2019.

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Economic Evaluation

The cost-effectiveness study[13] used a decision-analytic model with inputs from the medical literature and Toronto-specific sources to assess the costs, benefits, and cost-effectiveness of a school-based naloxone program. Four scenarios for effectiveness of school-based programs were considered with mortality reduction estimates derived from the literature and ranging from a 15% to 97% reduction in mortality. Deterministic and probabilistic sensitivity analysis was performed with variation in all relevant inputs.

The number of overdoses per year in Toronto high schools was unknown. Therefore, the base case assumed and expressed the expected number of opioid overdoses per year in a parameter ranging from 0.1 (representing one overdose every 10 years across the entire school system) to five. Other key assumptions included transportation of all overdose patients by ambulance to the emergency department (ED), all fatalities occurred after hospital admission, all overdose survivors progress to have chronic substance use disorder (SUD), and SUD was associated with higher-than-average mortality, higher-than-average costs, and lower-than-average quality-of-life. Also, it was assumed that the start-up costs would be amortized over 10 years at a 2.15% rate, the naloxone kits would need to be replaced every two years, all staff would require retraining every three years, and an additional 10% of staff would need to be trained per year to account for retirements and staff turnover.

The authors used a societal perspective and a lifetime horizon for evaluating costs and benefits. Projections for the study were based on 112 high schools in the Toronto District School Board (TDSB). Costs were expressed in 2017 Canadian dollars, adjusted for inflation with future costs and health benefits discounted at 1.5%, when necessary.

Cost factors included acquisition of initial naloxone inventory, training teachers and staff to identify signs and symptoms of an opioid overdose, administer naloxone, and then call emergency services, maintenance costs (including costs to replace naloxone inventory and for ongoing training), and costs associated with medical care. Toronto-specific sources were used for cost items such as physician costs, salary of teachers and nurses, ambulance, ED and hospital costs, whenever available.

Guideline

The guideline[15] was developed by the Medical Directors Council of the National Association of State EMS Officials in collaboration with the National Association of EMS Physicians and the EMS Committee of the American College of Emergency Physicians. Evidence for the guideline[15] was derived from a systematic review[16] on prehospital administration of naloxone for opioid poisonings sponsored by Agency for Healthcare Research and Quality (AHRQ). The authors of the systematic review[16] evaluated the strength of evidence of included studies using criteria adapted from the Methods Guide for Effectiveness and Comparative Effectiveness Reviews[17] and the Procedure Manual of the United States Preventive Services Task Force (USPSTF).[18] A Technical Expert Panel of relevant stakeholders, including a patient advocate, reviewed, summarized, and assessed the strength of the evidence from the systematic review,[16] and developed the recommendations. The guideline development process was guided by the standards prescribed by Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[19]

The grading of recommendations was based on the strength of the evidence as determined by factors such as confidence in the estimate of effect following evaluation for bias, inconsistency, indirectness, imprecision, and possible confounders.[15] The evidence was ranked in quality from high certainty (i.e., signifying confidence that the true effect was close to the reported effect estimate) to very low certainty (i.e., denoting very little confidence in the effect estimate, and a likelihood that the actual effect was substantially different from the effect estimate). A moderate certainty grade was assigned where confidence in the effect estimate was moderate, and the true effect was likely to be close to the effect estimate, but with a possibility that it was substantially different. A low certainty grade indicated limited confidence in the effect estimate, an that the actual effect may be significantly different from the effect estimate. Other factors considered in making a recommendation included ease of use, ability to titrate doses, and safety.

Country of Origin

The economic evaluation[13] study was performed in Canada, whereas the guideline[15] was developed and intended for use in the United States of America.

Patient Population

The economic evaluation[13] was based on a total of 74,000 students from 112 high schools in the TDSB. It was estimated that half (50%) of the study population was male, and the student age was assumed to be 16 years (range: 13 to 18 years).

The target patient population in the guidelines[15] was patients with confirmed or suspected opioid overdose.

Interventions and Comparators

Naloxone kit was the intervention of interest in the cost-effectiveness study.[13] A specific route of naloxone administration was not described in the study. However, the cost of naloxone kit used in the analysis was referenced to a source[20] that reported about naloxone nasal spray without providing any details about the formulation, dose, or frequency of administration. Thus, it is reasonable to assume that the intranasal naloxone was the intervention under review in the cost-effectiveness analysis.

The guideline discussed the intravenous, intramuscular, subcutaneous, and intranasal routes of administration of naloxone by EMS practitioners to persons with suspected opioid overdose.

Outcomes

The economic evaluation[13] considered the effectiveness of the school-based naloxone in preventing mortality using incremental cost-effectiveness ratio (ICER) as a function of the number of overdoses per year across all 112 TDSB high schools. Cost-effectiveness was measured in incremental costs per quality-adjusted life-year (QALY) gained, with a willingness-to-pay threshold of $50,000 per QALY gained.[13]

The overarching goal of the guideline[15] was to reduce the high mortality rate associated with opioid overdoses. The outcomes of interest in the systematic review[16] that provided evidence to support the guideline[15] were resumption of sufficient spontaneous respiratory effort as assessed by Glasgow Coma Scale (GCS) and mean response time, as well as the proportion of patients requiring repeat (rescue) naloxone after the initial dose.[16]

The GCS is a validated neurological scale developed to provide a reliable and objective method of assessing the level of impairment in consciousness, using response to defined stimuli.[21-23] It is a widely used instrument employed by neurosurgeons and other disciplines for all types of injured person, and is used by the World Federation of Neurosurgical Societies (WFNS) in a scale for grading patients with a subarachnoid hemorrhage.[21] The GCS comprises 15 items in three domains: motor response, verbal response, and eye-opening. The possible score on the GCS range from 3 for totally unresponsive to 15 indicating fully responsive or alert.[24,25]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Economic Evaluation

The cost-effectiveness study [13] included in this report was critically appraised using the Drummond checklist[12] as a guide. A well-defined question sought to explore the cost-effectiveness of a naloxone program for opioid overdoses in high schools under the TDSB as against the status quo, using a societal perspective and a lifetime horizon for evaluating costs and benefits. The effectiveness of using naloxone for opioid overdoses in the community was inferred from the literature and the continued advocacy to make naloxone widely available to laypersons through pharmacies and public health departments as a measure to reduce deaths related to opioid poisoning. However, the method of delivering (a nasal spray, or mucosal atomizer) was not considered in the evaluation. Therefore, it is unknown if the conclusion will apply to the different intranasal naloxone formulations equally.

The analysis included both the capital costs and operating costs. The sources of all values were identified with most (e.g., physicians', nurses', and teachers' salaries, costs of initial acquisition and subsequent replace of naloxone, etc.) quoted or derived from official sources, while others were taken from the literature. The discount rate for future costs and health benefits was 1.5%, consistent with the 2017 Canadian Guidelines for the Economic Evaluation of Health Technologies,[26] and costs were adjusted for inflation using the Canadian Consumer Price Index, Historical Summary (1998 to 2017).[27] Therefore, the

values appeared credible and did not present concerns about reliability. Cost-effectiveness was measured in incremental costs per QALY with a benchmark of $50,000 per QALY gained.

The authors performed deterministic and probabilistic sensitivity analysis with variation of all reasonable inputs and compared four scenarios of potential incremental effectiveness of a school-based program to the status quo to ascertain the robustness of the results to uncertainty in the model parameters. The conclusions of the study reflected the resulting incremental cost-effectiveness ratio. However, there were no public reports of overdoses at Toronto or other Canadian schools, causing the investigators to assume that the number overdoses would vary from one to 50 every 10 years across the entire school system. The rationale for this assumption was not provided. Thus, the generalizability of the conclusions of the cost-effectiveness analysis in populations with different incidences of opioid overdoses is unknown.

Guideline

The included guideline[15] was based on evidence from a systematic review on the EMS administration of naloxone for opioid poisonings, sponsored by AHRQ.[16] The guideline[15] demonstrated strengths in four of the six domains in the AGREE II instrument,[14] with positive score for every item in the scope and purpose, stakeholder involvement, clarity of presentation, and editorial independence domains. Thus, important details, such as an explicit link between recommendations and supporting evidence, criteria for selecting evidence, the strengths and limitations of the body of evidence, and methods for formulating recommendations, were provided, Also, there were clear description for all six of the items in the rigour of development domain. Although the process for external peer-review was unclear, it is unlikely to significantly affect the recommendations of the guideline[15] given that it was developed through collaboration of multiple professional bodies and stakeholders. Furthermore, the lack of a clear procedure to update the guideline[15] is not a practical limitation in the short-term (at least), since the guideline was developed and published recently (2019).

The guideline[15] provides advice on how to use naloxone in case of opioid overdose. However, there was no clear information about facilitators and barriers to its application, monitoring criteria, and potential resource implications of applying the recommendations. Lack of these pieces of information in the guideline[15] may be a source of limitation to its applicability, especially for community use.

Summary of Findings

Clinical effectiveness of Naloxone Hydrochloride Nasal Spray versus intramuscular naloxone

No relevant evidence regarding the clinical effectiveness of Naloxone Hydrochloride Spray versus intramuscular naloxone for opioid overdose was identified; therefore, no summary can be provided.

Clinical effectiveness of Naloxone Hydrochloride Nasal Spray versus naloxone administered intranasally using a mucosal atomizer

No relevant evidence regarding the clinical effectiveness of naloxone hydrochloride nasal spray versus naloxone administered intranasally using a mucosal atomizer for opioid overdose was identified; therefore, no summary can be provided.

Clinical effectiveness of naloxone administered intranasally using a mucosal atomizer versus intramuscular naloxone

No relevant evidence regarding the clinical effectiveness of naloxone administered intranasally using a mucosal atomizer versus intramuscular naloxone hydrochloride was identified; therefore, no summary can be provided.

Cost-effectiveness of Naloxone Hydrochloride Nasal Spray, naloxone administered intranasally using a mucosal atomizer or intramuscular naloxone

Appendix 4 presents a table of the main study findings and authors' conclusions.

One included economic evaluation[13] reported that in the base case, a school naloxone program is likely to be cost-effective at a cost less than the willingness-to-pay threshold of CAD$50,000 per QALY-gained if the frequency of opioid overdose was at least once each year and the reduction in related mortality was at least 40%; or if the frequency of opioid overdose was at least two per year with a reduction in related mortality of at least 20%. The results were sensitive to the intensity and cost of staff training, the lifetime costs and life-expectancy of overdose survivors, and the probability of an overdose being fatal in the absence of a school naloxone program.

In a scenario where the program leads to no overdose-related mortality, an ICER of less than $50,000 per QALY-gained was projected if the overdose frequency was 0.4 per year (approximately once every 2.5 years). However, in the least optimistic case, which assumed a 15% reduction in the mortality rate, it was estimated that the program would achieve an ICER of $50,000 per QALY-gained if there were approximately 2.7 overdoses per year and an ICER of $100,000 per QALY-gained if there were about 1.3 overdoses per year.

The cost-effectiveness analyses were based on Toronto high schools with no known reports of opioid overdoses, and the investigators assumed overdoses rates with unspecified rationale. Thus, it is unknown if the findings and conclusions of the economic evaluation[13] would be generalizable in populations with different incidences of opioid overdoses.

Evidence-based guidelines associated with the use of naloxone in the treatment of opioid overdose in the pre-hospital setting

Appendix 4 presents a table of the main study findings and authors' conclusions.

One evidence-based guideline[15] for EMS practitioners makes a weak recommendation that naloxone administered by the intranasal route be preferred over intramuscular naloxone while in the field. The recommendation was based on evidence of very low quality about similarity in efficacy of intranasal and intramuscular naloxone. Other considerations for the recommendation were ease of administration and reduced potential for patient withdrawal symptoms such as agitation, thus promoting patient and practitioner safety. The guideline also suggests that the initial dose should be enough to achieve adequate respiratory function without triggering withdrawal symptoms and should be selected with consideration for factors such the opioids in use in the local area.[15] The strength of this recommendation and the evidence supporting it were not reported.

The guideline did not provide clear information about facilitators and barriers to its application and did not discuss monitoring criteria and the potential resource implications of

applying the recommendations. That may be a source of limitation to its applicability, especially for community use.

Limitations

A key limitation is that no new relevant evidence was identified to answer the question about the clinical effectiveness of naloxone hydrochloride nasal spray versus intramuscular naloxone or versus naloxone administered intranasally using a mucosal atomizer from what had been reported in a previous CADTH Rapid Response report[1]

The included economic evaluation[13] targeted naloxone for opioid overdose in high school settings in Toronto. Although different devices are available for intranasal naloxone administration, the analysis did not specify the type considered for the cost estimates, and there was no active comparison to different devices such as autoinjector for intramuscular administration developed for layperson use.

Assumptions were made about the incidence rate of opioid poisoning in high schools without well-explained basis, and the cost items included costs of training teachers and school staff needed for the implementation of the school naloxone program that may not reflect what pertains in the communities and the general public. Therefore, the generalizability of the cost-effectiveness study is unknown.

The guideline[15] was meant for use by emergency service professionals. Thus, it is unclear how helpful it would be to laypersons in the community who may be relied upon to aid suspected overdose patients before the EMS practitioner arrive on scene. Also, the recommendation was based on evidence of very low quality, implying very little confidence and a likelihood that the actual effect is substantially different from the effect estimate. Furthermore, the primary studies which provided the evidence in the systematic review[16] supporting the guideline[15] were conducted before the newer naloxone formulations and delivery systems, including the currently available commercial nasal spray with a 50% bioavailability relative to intramuscular and the autoinjector for intramuscular administration, were developed for layperson use. Moreover, several potent synthetic opioids, such as fentanyl and analogs, which have been implicated in recent overdose-related deaths, became available after the studies were performed.[13] Thus, it is unknown if the evidence base of the guideline[15] was sufficient for the necessary recommendations to deal with opioid intoxication due to the newer synthetic products.

Conclusions and Implications for Decision or Policy Making

One economic evaluation[13] and one evidence-based guideline[15] were included in this Rapid Response report. Using estimated model inputs from the medical literature and Toronto-specific sources, whenever available, the economic evaluation demonstrated that a naloxone program to reduce opioid overdose mortality in TDSB secondary schools is likely to be cost-effective if there were at least two overdoses every year. A major limitation of the cost-effectiveness analysis was that the authors assumed opioid overdose rates of between one and 50 every 10 years across the entire school system without providing rationale.

The recommendations in the included guideline[15] that were relevant to this Rapid Response report favored intranasal naloxone over the intramuscular route based on evidence very low quality that suggested comparable efficacy for the two routes. However, the recommendation also considered ease of use and safety of EMS practitioners and patients due to reduced adverse events associated with the intranasal formulation. The guideline

suggests that the initial dose should be selected based on factors such as the opioids in use in the local area and should be enough to achieve adequate respiratory function without triggering withdrawal symptoms. The 2015 American Heart Association Guidelines Update,[28] which was included in the previous CADTH report[1] does not make a statement of preference for any formulation over another or discuss initial doses. Instead, it recommends either intramuscular or intranasal naloxone administration by lay rescuers and health care providers as first aid treatment of patients with known or suspected opioid overdose. Moreover, it 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.[28]

The literature search did not identify any studies which evaluated the comparative effectiveness of Naloxone Hydrochloride Nasal Spray versus intramuscular naloxone or naloxone administered intranasally using a mucosal atomizer. Also, no new evidence was identified about the clinical effectiveness of naloxone administered intranasally using a mucosal atomizer versus intramuscular naloxone other than a more recently published systematic review which included primary studies that were identified in a previously published CADTH Rapid Response report.[1]

One systematic review[16] (published in 2017) assessing the effects of route of administration and dosing of naloxone for suspected opioid overdose in out-of-hospital settings on mortality, reversal of overdose, and harms, was identified. However, that systematic review was not included because the portion of interest to this Rapid Response report was based on the two studies[11,29] captured in a previous CADTH report[1] and did not provide additional relevant evidence.

The previous CADTH Rapid Response report[1] found that at a concentration of 2mg/mL, the efficacy of intranasal naloxone was not significantly different from intramuscular naloxone in terms of the proportion of patients with adequate response (defined as >10 breaths within 8 to 10 minutes), time to adequate response, and hospitalization rate. However, the need for rescue naloxone due to inadequate response to initial dose was significantly higher among patients treated with the intranasal than the intramuscular route of administering naloxone. Overall, the efficacy outcomes with a lower concentration of intranasal naloxone (2mg/5mL) preparation were significantly less than the intramuscular naloxone. The differences in the incidence of adverse events were not statistically significant for the comparison of either the 2mg/mL or 2mg/5L with the intramuscular naloxone.

Given the limitations discussed here and elsewhere in this report, an economic evaluation with incidence rates of opioid overdoses more representative of the general population, and research considering the various routes of naloxone administration and different delivery devices are needed. Such studies should also examine the impact of a wider variety of opioids including the relatively new and more potent synthetic opioids to comprehensively respond to the research questions under review.

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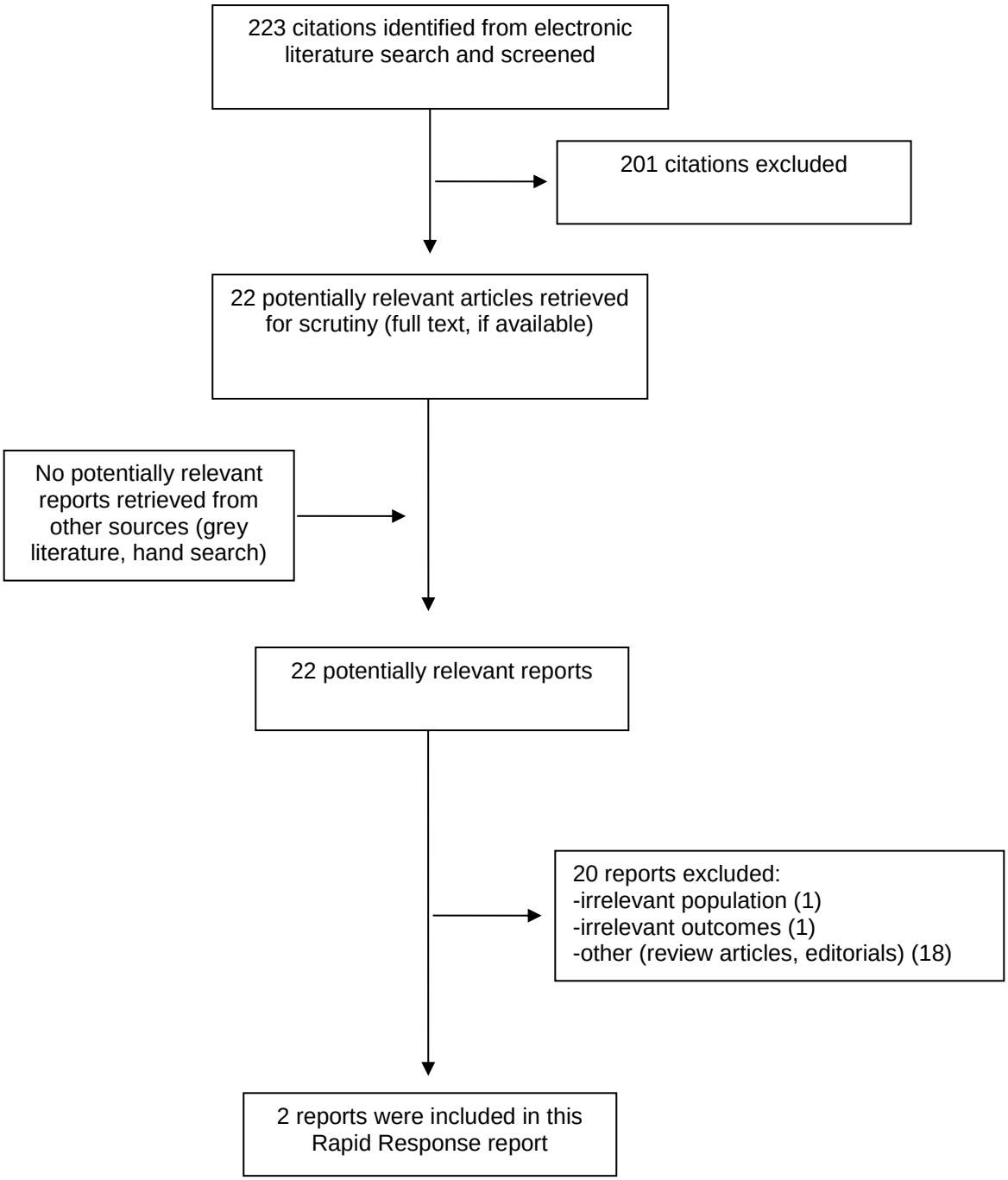
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Economic Evaluations

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
Cipriano and Zaric, 2018 Canada[13]	Cost-effectiveness evaluation with a decision-analytic model that considered a societal perspective and a lifetime horizon	To identify conditions under which it would be cost-effective to equip high schools in the TDSB with naloxone kits for opioid overdose	74,000 students, (assumed age 16 years; range: 13–18 years), in a total of 112 secondary schools under the TDSB	Naloxone kit for opioid overdose compared with status quo	A decision-analytic model	Costs, expressed in 2017 Canadian dollars and were adjusted for inflation, were calculated for various aspects including • Initial supply of naloxone, • training, teachers or staff • program maintenance, • medical care costs. • The inputs were estimated from the literature, or Toronto-specific sources.	The base case assumed: • 0.1 to 5 opioid overdoses per year • Ambulance transport to ED following all overdoses • Startup costs amortized over 10 years • Naloxone kits replaced every two years • Retraining of all staff every 3 years, plus 10% training for new hire staff each year • All fatalities occur after admission • Chronic SUD in all overdose survivors, • SUD associated higher mortality and costs, and lower quality-of-life than average.

ED = Emergency department; SUD = substance use disorder; TDSB = Toronto District School Board

Table 3: Characteristics of Included Guideline

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Guidelines for EMS Administration of Naloxone – Williams, 2019[15]						
Intended User – EMS practitioners; Targeted population – Persons with suspected opioid overdose	Naloxone–administered by the IM, IN, IV, or SQ route to reduce opioid toxicity-related mortality rate in prehospital settings	• Resumption of SSRE assessed by ○ GCS > 11 at 8 minutes or ○ Mean response time • Proportion of patients requiring rescue naloxone	• Based on a SR involving a total of 13 studies from 1996 to 2014. • The SR was sponsored by AHRQ and published in 2017. • Of the 13 primary studies, two RCTs were of interest to this RR report.	• The strength of evidence in AHRQ-sponsored SR was evaluated using criteria adapted from the Methods Guide for Effectiveness and Comparative Effectiveness Reviews[17] and the Procedure Manual of the USPSTF.[18] • Confidence in the estimate of effect was evaluated based on GRADE standards	• A Technical Expert Panel developed recommendations using GRADE methodology based on evidence presented in the AHRQ-sponsored SR • Other considerations were ease of administration, practitioner safety, potential for agitation leading to transport refusal and adverse opioid withdrawal reactions.	The Guideline was developed through collaboration of relevant stakeholders, including the NASEMSO, NAEMSP, the EMS Committee of the ACEP, and a patient advocate, with the approval of the National EMS Advisory Council

ACEP = American College of Emergency Physicians, AHRQ = Agency for Healthcare Research and Quality, EMS = Emergency Medical Services; GCS = Glasgow Coma Scale, GRADE = Grading of Recommendations Assessment, Development and Evaluation, IM = intramuscular, IN = intranasal, IV = intravenous, NAEMSP = National Association of EMS Physicians, NASEMSO = National Association of State EMS Officials; RCT = randomized controlled trial, SQ = subcutaneous, SSRE = sufficient spontaneous respiratory effort, USPSTF = United States Preventive Services Task Force

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Economic Studies using the Drummond Checklist (Higgins 2011 Drummond Checklist)[12]

Strengths	Limitations
Cipriano and Zaric, 2018[13]	
• A well-defined question was posed, and the effectiveness of a naloxone program for patients with confirmed or suspected opioid overdose in out-of-hospital setting was supported by information from the medical literature; • The perspective adopted, time horizon, and assumptions were described; • Important and relevant costs values were identified from official sources and the literature and there were no concerns about their credibility; • The cost-effectiveness was measured in incremental costs per QALY gained relative to commonly applied benchmark of $50,000 per QALY-gained; • Costs analyses adjusted for different times using prescribed discount and inflation rates, where necessary, and sensitivity analysis was performed; • The discussion of the results considered the limitations of the study and the conclusions reflected the evidence used to derive them.	• The evaluation did not consider competing alternatives for treating patients with confirmed or suspected opioid overdose in out-of-hospital setting, • Assumptions were made about the incidence rate of confirmed or suspected opioid overdose in high schools without providing rationale, • The cost items included costs of training teachers and school staff needed for the implementation of the school naloxone program. While this is suitable for the TDSB, it may not reflect what pertains in the communities and the general public. • Since the focus of the economic evaluation was high schools in the TDSB, it is unclear if the results will be generalizable in the general population.

QALY = quality-adjusted life-year.

Table 5: Strengths and Limitations of Guidelines using AGREE II(AGREE 2017 AGREE II)[14]

Item	Guideline
	Guidelines for EMS Administration of Naloxone – Williams, 2019[15]
Domain 1: Scope and Purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes
Domain 2: Stakeholder Involvement	
4. The guideline development group includes individuals from all relevant professional groups.	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes
6. The target users of the guideline are clearly defined.	Yes
Domain 3: Rigour of Development	
7. Systematic methods were used to search for evidence.	Yes
8. The criteria for selecting the evidence are clearly described.	Yes

Item	Guideline
	Guidelines for EMS Administration of Naloxone – Williams, 2019[15]
9. The strengths and limitations of the body of evidence are clearly described.	Yes
10. The methods for formulating the recommendations are clearly described.	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Unclear
14. A procedure for updating the guideline is provided.	No
Domain 4: Clarity of Presentation	
15. The recommendations are specific and unambiguous.	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes
17. Key recommendations are easily identifiable.	Yes
Domain 5: Applicability	
18. The guideline describes facilitators and barriers to its application.	Unclear
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes
20. The potential resource implications of applying the recommendations have been considered.	No
21. The guideline presents monitoring and/or auditing criteria.	No
Domain 6: Editorial Independence	
22. The views of the funding body have not influenced the content of the guideline.	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes

EMS = Emergency Medical Services.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings of Included Economic Evaluation

Main Study Findings	Authors' Conclusion
Cipriano and Zaric, 2018[13]	
• At a cost less than the willingness-to-pay threshold of CAD$50,000 per QALY-gained, a school naloxone program is likely to be cost-effective assuming ○ Confirmed or suspected opioid overdose frequency ≥ once each year and a reduction in related mortality ≥40%; ○ Confirmed or suspected opioid overdose opioid frequency ≥ two per year and a reduction in related mortality of ≥20%. • The results were sensitive to the intensity and cost of staff training, the lifetime costs and life-expectancy of overdose survivors, and the probability of an overdose being fatal in the absence of a school naloxone program	"If the risk of an overdose in a Toronto high school is low, then other programs aimed at improving the health and wellbeing of students may be better use of limited resources. However, our analysis demonstrates that making naloxone available in TDSB secondary schools is likely to be cost-effective if there are at least two overdoses every year."[13] P.359

CAD$ = Canadian dollar; QALY = quality-adjusted life-year; TDSB = Toronto District School Board

Table 7: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Guidelines for EMS Administration of Naloxone – Williams, 2019[15]	
The IN naloxone is preferred over the IM naloxone due to ease of use, reduced chance of needlestick injury and adverse opioid withdrawal reactions, practitioner and patient safety, and availability to more EMS practitioners	Very low; Weak/Conditional

EMS = emergency medical service; IM = intramuscular, IN = intranasal; NR = not reported