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SUMMARY WITH CRITICAL APPRAISAL

Administration of Naloxone in a Home or Community Setting: A Review of the Clinical Effectiveness, Cost-effectiveness, and Guidelines

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Authors: Yi-Sheng Chao, Hannah Loshak

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Abbreviations

RCT	randomized controlled trial
SR	systematic review
WHO	World Health Organization

Context and Policy Issues

Opioid overdose can induce acute respiratory and central nervous system depression that may lead to death.[1] Recently the numbers of opioid-related deaths or hospitalizations have increased in Canada and there is an ongoing opioid crisis.[2,3] There were 3,023 and 4,588 apparent opioid-related deaths that occurred in 2016 and 2018 respectively.[3] The rate of apparent opioid-related deaths was 7.9 per 100,000 population in 2016 nationally.[2] This rate can be as high as 20.7 deaths and 14.4 deaths per 100,000 population in British Columbia and Alberta respectively in 2016.[2] Synthetic opioids that are extremely potent, such as fentanyl, are used more prevalently than non-synthetic opioids.[2]

Naloxone, a medication that temporarily blocks the effects of opioids, has been advocated for a wider use in the communities.[2] Naloxone works by competing for opioid receptors with opioids[4] and remains active in the body for 20 to 90 minutes, shorter than most opioids.[5] Without opioids, naloxone has little pharmacologic activity.[6] Data from non-comparative studies suggest that naloxone use in a home or community setting for opioid overdose is associated with a low mortality rate.[7]

In Canada, take-home naloxone kits are available at most pharmacies without a prescription and are free in some provinces.[6,8] A 2018 CADTH Environment Scan report identified that there are two to three doses of 0.4 mg or 1 mg naloxone in the naloxone kits in Canadian provinces.[5] The formulations of naloxone available in the kits include naloxone nasal spray in Ontario or naloxone intramuscular injection in other provinces.[5] Both take less than five minutes to take effect.[5] In a 2017 CADTH report that evaluated different formulations of naloxone available in take-home naloxone kits, two randomized controlled trials (RCTs) were identified and compared intramuscular naloxone with naloxone administered intranasally using an atomization device.[7] Higher proportions of patients receiving intramuscular naloxone achieved adequate response than those receiving intranasal naloxone.[7] However, comparative evidence to support the use of take-home naloxone kits in pre-hospital settings may be limited. A 2014 CADTH Rapid Response report did not identify any primary studies or reviews on the effectiveness of naloxone administration in a home or community setting compared with naloxone use by health professionals.[7] Since the release of the 2014 CADTH report, the use of naloxone in home and community settings has been evaluated in several studies or reviewed because of the ongoing opioid crisis and the potential benefits of naloxone use in such settings.[9-11] This report aims to update the previous CADTH review[7] on the clinical effectiveness and cost-effectiveness of the administration of naloxone in a home or community setting, as well as to identify evidence-based guidelines for its use.

Research Questions

1. What is the clinical effectiveness of naloxone administered in a community or home setting?
2. What is the cost-effectiveness of naloxone administered in a home or community setting?

3. What are the evidence-based guidelines for the administration of naloxone?

Key Findings

There was one systematic reviews (SR), two non-randomized studies, one cost-effectiveness study, and two guidelines identified. In the SR, there was evidence that take-home naloxone was associated with a reduction in overdose mortality. One review in the SR showed take-home naloxone was also associated with more successful reversals and minimal adverse events than usual care. One non-randomized study indicated that patients using opioids for long-term pain who received naloxone co-prescriptions had significantly fewer subsequent emergency department visits than those who did not receive naloxone. However, in a population study that did not describe the intervention and populations clearly, the implementation of a national take-home naloxone program was not significantly associated with ambulance call-outs to opioid-related overdoses in Scotland.

In a cost-effectiveness analysis in which 30% of the heroin users were prescribed naloxone, the base case scenario demonstrated that there might be a decrease in overdose deaths by 6.6% and 2,500 fewer premature deaths with community naloxone distribution at an incremental cost per quality-adjusted life year gained of £899 in a population of 200,000 heroin users.

Guidelines produced by the World Health Organization (WHO) and the American Society of Addiction Medicine (ASAM) recommend that naloxone should be given in case of opioid overdose and should be accessible to people with opioid use disorder and people likely to witness an opioid overdose. It was recommended that the patients and those likely to witness an opioid overdose should be trained for naloxone administration. In the WHO guideline, regardless of the administration routes, naloxone is recommended due to its effectiveness for opioid overdose. Individuals should choose a route of naloxone administration depending on the formulation available, administration skills, and settings. In the ASAM guideline, in which the supporting evidence was not linked to the recommendations, naloxone is not recommended for use in pregnant women with opioid use disorder, except for life-threatening situations.

The limitations to this report included a lack of RCTs, a lack of studies in Canadian contexts, a lack of studies specifically focusing on the safety of naloxone, and a lack of direct comparison between non-health professionals and professional first responders.

Further research on the clinical effectiveness and cost-effectiveness of the currently available naloxone kits for use in home and community settings in Canada may help to reduce uncertainties.

Methods

Literature Search Methods

This report makes use of a literature search strategy developed for a previous CADTH report. For the current report, a limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts

were naloxone, community or self-administration. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and November 12, 2019.

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 receiving opioids
Intervention	Naloxone administered in a community or home setting (by patient, friends, family, police, or other non-health care professionals)
Comparator	Naloxone administered by a health professional (e.g. in hospital, clinic, or by EMTs); no treatment
Outcomes	Q1: Clinical effectiveness (e.g., mortality, morbidity, quality of life, ease of use, administration errors, safety Q2: Cost-effectiveness (e.g., cost per quality adjusted life year, cost per clinical outcome) Q3: Recommendations related to naloxone administration
Study Designs	Health technology assessments, systematic reviews randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines

EMT = emergency medical technician.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using the A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2) checklist,[12] non-randomized studies were critically appraised using the Downs and Black checklist,[13] economic studies were assessed using the Drummond checklist,[14] and guidelines were assessed with the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument.[15] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 450 citations were identified in the literature search. Following screening of titles and abstracts, 429 citations were excluded and 21 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 17 publications were excluded for various reasons, and six publications

met the inclusion criteria and were included in this report. These comprised one systematic review (SR), two non-randomized studies, one economic evaluation, and two evidence-based guidelines. Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[16] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Study Design

Systematic reviews

One SR was identified.[17] Chimbar and Moleta searched multiple databases for articles published from 2014.[17] The end of the search time frame and the search date were not defined.[17] Four SRs, one randomized controlled trial (RCT), and three non-randomized studies were included.[17]

Non-randomized studies

Two non-randomized studies were identified.[18,19] McAuley et al. conducted a controlled time-series analysis using population data from Scotland.[18] Coffin et al. implemented an interventional study without randomization in several clinics.[19]

Economic evaluations

One cost-effectiveness analysis by Langham et al. was identified.[20] Langham et al. extended a model previously published and adopted a health care perspective and lifetime horizon.[20] The clinical and cost data were mostly from the UK health care system and literature searches.[20] Langham et al. used a Markov model with an integrated decision tree that tracked heroin users in four states: heroin use, discontinuation, resuming heroin use, and death.[20] Various assumptions were made, including intramuscular naloxone distribution reaching 30% of heroin users and 85% of overdoses witnessed.[20]

Guidelines

Two guidelines were identified.[21,22] One guideline was produced by the American Society of Addiction Medicine.[21] PsycINFO and PubMed were searched for guidelines, randomized and non-randomized studies.[21] The number of researchers screening the literature or extracting the data was not reported.[21] The ratings of the quality of evidence were based on the RAND Corporation/University of California Los Angeles (RAND/UCLA) Appropriateness Method rules, but the strength of recommendations were not reported.[21] The recommendations were reviewed by external experts and approved by the committee.[21] The other guideline was published by the World Health Organization (WHO).[22] Multiple databases were searched for RCTs or controlled prospective studies.[22] One and two researchers screened in the two steps of literature selection respectively.[22] The ratings of the quality of evidence were based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.[22] The recommendations were made by the WHO Guideline Development Group and externally reviewed.[22]

Country of Origin

Systematic reviews

Chimbar and Moleta were based in the USA.[17]

Non-randomized studies

The first authors of two non-randomized studies were based in the UK and the USA respectively.[18,19]

Economic evaluations

Langham et al. were based in the UK.[20]

Guidelines

The ASAM guidelines were intended to be applied in the USA.[21] The WHO guideline was published in Switzerland and the recommendations would be disseminated to various countries .[22]

Patient Population

Systematic reviews

Chimbar and Moleta included studies that recruited patients who abused opioids.[17]

Non-randomized studies

McAuley et al. analyzed data from the population in Scotland and reported the numbers of ambulance call-outs for people who injected drugs.[18] However, the overall population sizes and characteristics in Scotland in the target study duration were not reported.[18] Coffin et al. recruited 1,985 adults receiving long-term opioid therapy for pain.[19]

Economic evaluations

Langham et al. modeled based on adults at risk of heroin overdose in a European healthcare setting (UK) in the cost-effectiveness evaluation model.[20]

Guidelines

The intended users in the ASAM guideline were clinicians involved in evaluating patients and providing authorization for pharmacological treatments at any level.[21] The target populations in the ASAM guideline were patients with opioid use disorder.[21] The intended users in the guideline by the WHO were people likely to witness an opioid overdose and provide care for patients in the community.[22] The target populations were patients at risk of opioid overdose or requiring care in the community.[22]

Interventions and Comparators

Systematic reviews

Chimbar and Moleta compared take-home naloxone with no take-home naloxone.[17] Naloxone dosages and routes were not reported in the SR.[17]

Non-randomized studies

McAuley et al. compared the incidence of overdose before and after implementation of a national naloxone program in Scotland.[18] There were three early adopter regions and the other regions later adopted the same intervention.[18] The locations and distributions of the early adopter and later adopting regions were not described.[18] The dosage and route of naloxone were not reported.[18] Coffin et al. compared naloxone co-prescription with no naloxone co-prescription along with long-term opioid therapy for pain.[19] Naloxone dosages were not reported in the non-randomized studies.[18,19] The proportions of patients receiving

naloxone in a home or community setting or by health professionals in different groups were not reported; the compliance with the interventions were not reported.[18,19]

Economic evaluations

Langham et al. studied the cost-effectiveness of naloxone use (intramuscular injection: 1mg/ml, 2 ml prefilled syringe) by non-medical responders, compared with no naloxone distribution in a European healthcare setting (UK).[20]

Guidelines

In the ASAM guideline, interventions for the evaluation and treatment of opioid use disorder and for the management of opioid overdose were considered.[21] In the WHO guideline, naloxone use in the pre-hospital settings was considered.[22]

Outcomes

Systematic reviews

Chimbar and Moleta studied mortality as an outcome of interest in the SR.[17]

Non-randomized studies

McAuley et al. analyzed weekly incidence of ambulance call-outs to opioid-related overdoses at national and regional Health Board levels.[18] Coffin et al. studied proportions of patients prescribed naloxone, opioid-related emergency department visits, and subsequent prescribed opioid doses (doses adjusted if overdoses occurred).[19]

Economic evaluations

Langham et al. studied the cost-effectiveness of naloxone use by non-medical responders.[20] The outcomes included lifetime overdose deaths averted (%), incremental cost of naloxone distribution (£), incremental quality adjusted life year (QALY) of naloxone distribution, and incremental cost-effectiveness ratio (ICER) of naloxone distribution (£).[20]

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

Summary of Critical Appraisal

Systematic reviews

The clarity of reporting is fundamental for the assessment of risk of bias. Chimbar and Moleta reported the population, intervention, comparator, and outcome (PICO) components in the research questions and inclusion criteria.[17] The included studies were reported.[17] The review authors' competing interests were reported.[17] However, the review protocol was not published *a priori*.[17] There were risks of deviating from original study plans. The selection of study designs was not reported.[17] The excluded studies were not reported.[17] The funding sources of the primary studies were not reported.[17] There were uncertainties about the quality of review implementation.

The risk of bias can be minimized if the SRs are well implemented. A comprehensive literature search was conducted in the SR by Chimbar and Moleta.[17] Chimbar and Moleta did not perform study selection and data extraction in duplicate.[17] The risk of bias in the primary studies was not assessed[17] and not considered while discussing or interpreting the results.[17] The heterogeneity between the primary studies was not discussed.[17]

Non-randomized studies

The clarity of reporting is fundamental to assess the risk of bias in the primary studies. McAuley et al. and Coffin et al. reported research hypotheses, study objectives, main outcomes to be measured, main findings, and actual probability values.[18,19] The staff, places, and facilities where the patients were treated, did not seem to be different from the treatment the majority of patients receive.[18,19] However, only Coffin et al. reported the characteristics of the included patients and interventions of interest.[19] McAuley et al. used national data for analysis that provided a large sample size, but the authors did not describe the characteristics of the population in two time periods.[18]

Bias to the study internal validity can be minimized if the study was well designed, outcomes precisely measured, and results well analyzed. The statistical methods to assess the main outcomes were appropriate.[18,19] The main outcome measures were accurate.[18,19] However, McAuley et al. compared populations of two time periods that might not be comparable.[18] McAuley et al. and Coffin et al. did not blind the patients or outcome assessors.[18,19] The compliance with the interventions was not reported in these two studies.[18,19]

Confounding that can lead to erroneous conclusions can also be minimized. McAuley et al. and Coffin et al. recruited patients from the same populations.[18,19] The uncertainties in the comparison between populations of two time periods by McAuley et al. was not assessed.[18] Confounding was adjusted in the analysis.[18,19] However, the patients were not randomized into different groups and the interventions were not concealed.[18,19]

Coffin et al. did not conduct power analysis for sample sizes,[19] while McAuley et al. analyzed population data in Scotland.[18]

Economic evaluations

The clarity of reporting is important for assessing the risk of bias in cost-effectiveness analyses. Langham et al. reported the research questions, the economic importance of the research questions, the viewpoints of the analysis, the form of economic evaluations, the rationale for the economic evaluations, sources of effectiveness estimates, the design and results of the study, the alternatives, the primary outcome measures, the subjects from whom valuations were obtained, the methods for the estimation of quantities and unit costs, currency data, price adjustments, model specifications, key parameters in the model, time horizon, the discount rate and its rationale, statistical tests, sensitivity analysis, the variables for sensitivity analysis, the ranges over which the variables were varied in the sensitivity analysis, relevant alternatives, incremental analysis, the answers to study questions, conclusion, and limitations.[20] The assumptions might be applicable to the contexts, because the coverage was based on the target set by the Scotland naloxone take-home program and the heroin use and cost data were based on the epidemiologic studies in the UK.[20] Langham et al. replicated the methods from a previously published study.[20] However, productivity changes, the relevance of productivity change, and quantities of resource use were not reported.[20]

Guidelines

The scope and purpose of guidelines should be described. In the ASAM guidelines and the WHO, the overall objectives, health questions, intended users, and target populations were described.[21,22]

Stakeholders can be involved to ensure different perspectives are included in clinical recommendations. In the two guidelines, relevant professional groups were included and the target users were defined.[21,22] However, the views and preferences of the target populations were not sought.[21,22]

The rigor of guideline development involves well-developed methods and systematic approaches. Systematic literature searches were used to identify evidence.[21,22] The criteria for selecting the evidence were reported.[21,22] The methods for formulating the recommendations were described.[21,22] The health benefits, side effects, and risks were considered in formulating the recommendations.[21,22] However, only in the WHO guideline, the strengths and limitations of the body of evidence, and the links between the recommendations and the supporting evidence, were reported.[22] Procedures to update the guidelines were not reported in the WHO guideline.[22]

The clarity of presentation helps readers to find and use recommendations. In both guidelines, the recommendations were specific and unambiguous and different options for management of the condition were listed if available.[21,22] Key recommendations were easily identifiable.[21,22]

The applicability of the recommendations should be addressed in the guidelines. In both guidelines, the facilitators and barriers, the advices and tools to implement the recommendations, and the potential resource implications were reported.[21,22] However, there were no monitoring criteria described in the guidelines.[21,22]

The role of the funding agencies for the guidelines were not reported.[21,22] The competing interests of the guideline development group were reported in both guidelines.[21,22]

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

Summary of Findings

Clinical Effectiveness of Naloxone in a Home or Community Setting

Systematic reviews

Mortality

Chimbar and Moleta narratively synthesized the evidence from five SRs and four primary studies and concluded that there was overwhelming support of take-home naloxone for the prevention of fatal opioid overdoses.[17] Specifically, take-home naloxone was associated with decreased mortality or higher survival rates in three included SRs and one primary study.[17] The statistics were not reported.[17] Mortality rates in other primary studies were not reported.[17]

Opioid overdose

In one SR identified by Chimbar and Moleta, take-home naloxone was associated with significantly lower rates of opioid overdose in communities with such programs, compared with the communities without such programs.[17]

Successful reversals

Chimbar and Moleta found strong evidence in support of take-home naloxone programs in one included SR.[17] The definition of successful reversals and specific statistics were not reported.[17]

Adverse events

Chimbar and Moleta concluded that adverse events were minimally noted in one included SR.[17] The statistics were not reported.[17]

Non-randomized studies

Ambulance call-outs to opioid-related overdose incidents

McAuley et al. did not find significant associations between ambulance call-outs and take-home naloxone kits in Scotland.[18]

Magnitude of association between take-home naloxone kits and ambulance call-outs

McAuley et al. did not find significant differences between early adopter and later adopting regions.[18]

Opioid-related emergency department visits

Coffin et al. found that patients with a naloxone co-prescription with opioids for chronic pain had significantly fewer emergency department visits six months and one year after the prescription than those did not receive co-prescription.[19]

Opioid dose

Coffin et al. found no net change over time among patients who received naloxone co-prescription and those who did not.[19]

Cost-Effectiveness Naloxone in a Home or Community Setting

Overdose deaths

In the base case scenario assuming take-home naloxone distribution reaching 30% of heroin users and assuming other situations including £15.30 each intra-muscular naloxone injection (1mg/ml, 2ml) and 0.80 QALY for heroin users, Langham et al. reported a decrease in overdose deaths by around 6.6% and prevented 2,500 premature deaths at an ICER of £899 per QALY gained in a population of 200,000 heroin users, compared with no such programs.[20] In the sensitivity analyses that tested key assumptions, naloxone distribution remained cost-effective under a variety of circumstances and Langham et al. considered that the robustness of the results was confirmed.[20]

Guidelines

Naloxone distribution

The ASAM guidelines recommend that naloxone should be given in case of opioid overdose (no strength of recommendation reported).[21] The ASAM guideline and the WHO guideline recommend that naloxone should be accessible to people likely to witness an opioid overdose, including patients and their families and they should be trained for naloxone administration (consensus opinion by ASAM; strong strength of recommendation, very low quality of evidence in the WHO guideline).[21,22]

The SR by the WHO did not identify any studies that met the low risk of bias inclusion criterion for the research question regarding naloxone distribution to non-health care professionals; however, some data were discussed that suggested that the mortality rate with take-home naloxone was lower than estimated rates without community naloxone, with limited adverse events.[22] Also, values and preferences, costs and resource use, and feasibility related to community naloxone distribution were considered when formulating the

WHO recommendation.[22] The ASAM guideline did not provide a summary of the systematic literature review on naloxone but did refer to a comprehensive review on the use of naloxone by non-medical personnel that concluded that bystanders can and will use naloxone when property trained, but noted a lack of RCT evidence.[21]

Formulation and dose of naloxone

In the WHO guideline, two RCTs were meta-analyzed and naloxone administration routes were compared.[22] Naloxone is recommended for intravenous, intramuscular, subcutaneous, and intranasal administration because of similar effectiveness (strong strength of recommendation; very low-quality evidence).[22] The preferred route of administration depends on the formulation available, administration skills, and settings (conditional recommendation [less certainty about the evidence; this recommendation may not apply to all conditions]; very low-quality evidence).[22] Naloxone is not recommended for use in pregnant women with opioid use disorder, except for life-threatening situations in the ASAM guideline (no strength of recommendation reported).[21]

Limitations

There were several limitations to this report. The dosages and routes of naloxone in the eligible studies were not reported in the SR[17] and the primary studies.[18,19] The compliance of naloxone use in some studies were not reported.[18] Chimbar and Moleta found that there were a limited number of RCTs on the effectiveness of naloxone use in home or community settings.[17] The cost-effectiveness analysis was built based on several assumptions[20] that might not fit Canadian contexts, such as the rate of naloxone use and the cost of naloxone kits. The most recent evidence-based guideline was published in 2015 and might need to be updated.[21] There was a lack of studies focusing on safety outcomes, such as the safety of naloxone use by non-health professionals and adverse events, which was reported in one primary study in the SR by Chimbar and Moleta.[17] Moreover, there was a lack of evidence that directly compared the effectiveness of naloxone administered by non-health professionals and professional first responders.

Conclusions and Implications for Decision or Policy Making

In contrast with the previous report that did not identify any comparative studies,[7] there was one SR,[17] two non-randomized studies,[18,19] one cost-effectiveness study,[20] and two guidelines identified for this Rapid Response report.[21,22] Take-home naloxone programs were associated with low mortality in two non-comparative studies in the previous report.[7] In this report, there was evidence to support the use of naloxone in a home or community setting. Chimbar and Moleta narratively synthesized the primary studies and found evidence showing significant reduction in mortality due to take-home naloxone programs in three included SRs and one primary study.[17] Chimbar and Moleta also identified one SR that showed take-home naloxone was associated with more successful reversals and minimal adverse events than no take-home naloxone.[17] In a non-randomized interventional study, naloxone co-prescription with opioids for patients with chronic pain was associated with significantly fewer opioid-related emergency department visits six months and one year after the intervention than those not receiving co-prescription.[19]

However, in a time series analysis of Scotland population data, McAuley et al. did not find significant associations between take-home naloxone kits with ambulance call-outs to opioid-related overdose incidents and failed to identify a significant difference in ambulance

call-outs between early adopter and later adopting regions.[18] The exact reason for the lack of association was not reported and there might be unmeasured confounding.[18]

Langham et al. conducted a cost-effectiveness analysis and proposed a base case scenario in which 30% of the heroin users were prescribed naloxone among other assumptions.[20] In the base case scenario, with distribution of take-home naloxone there might be a decrease in overdose deaths by 6.6% and 2,500 fewer premature deaths than without naloxone distribution, at an incremental cost per QALY gained of £899 in a population of 200,000 heroin users.[20] Langham et al. concluded naloxone take-home program in the UK seemed highly cost-effective.[20]

The guidelines by the ASAM and the WHO recommend that naloxone should be accessible to patients or people likely to witness an opioid overdose and they should be trained for naloxone administration.[21,22] The WHO guideline recommends naloxone administration regardless of the administration routes and the preferred route of administration depends on the formulation available, administration skills, and settings.[22] The ASAM does not recommend naloxone for pregnant women with opioid use disorder, except for life-threatening situations.[21]

The limitations to this report included a limited number of RCTs,[17] a lack of studies in Canadian contexts, a lack of safety studies in the literature,[21] and a lack of direct comparisons between non-health professionals and professional first responders.

Further research on the clinical effectiveness and cost-effectiveness of currently available naloxone kits in a home or community setting in Canadian provinces may help to reduce uncertainties.

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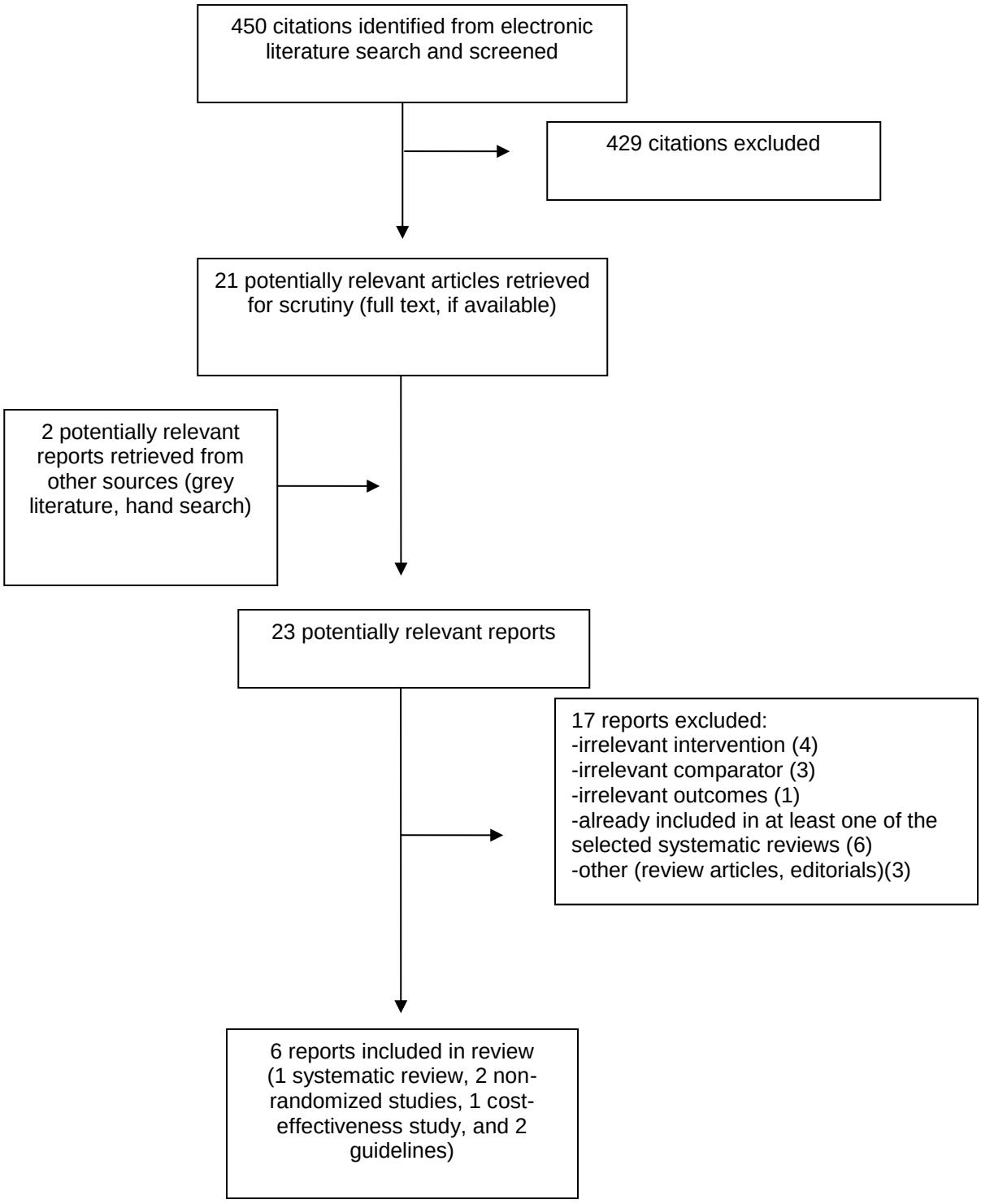
22. Community management of opioid overdose. Geneva (CH): World Health Organization; 2014: http://apps.who.int/iris/bitstream/10665/137462/1/9789241548816_eng.pdf?ua=1&ua=1. Accessed 2019 Dec 18.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Chimbar and Moleta 2018,[17] USA	9 studies (4 systematic reviews, 1 RCT and 4 time-series analyses) Multiple databases searched Inclusion criteria: English language, with exceptions of hallmark studies, and studies that included results of decreased opioid-related mortalities due to take-home naloxone programs Search time frame: articles from 2014 to present Search dates not reported	Those who abuse opioids Age and sex distribution not reported	Take-home naloxone (including naloxone kits and corresponding education of overdose recognition; naloxone dosages not specified) versus usual care (i.e., no take-home naloxone)	Mortality, clinical effectiveness, and cost-effectiveness Follow-up durations: not reported

RCT = randomized controlled trial.

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
McAuley et al. 2017,[18] UK	Non-randomized study, controlled time–series analysis, Scotland, UK, 2008 to 2015.	People who inject drugs, sizes of the population at risk not reported (3721 ambulance attendances for the pre-national naloxone program implementation period and 5258 attendances in the post-implementation period)	National naloxone program (naloxone dosages not reported) Pre-National naloxone program between 1 April 2008 to 31 March 2011 [3 early adopter regions and later adopting regions (not defined)] versus	"*Weekly incidence (counts) of [ambulance] call-outs to opioid-related overdoses at national and regional Health Board level*" (p. 301) Follow-up durations: not applicable

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
			Post-implementation between 1 April 2011 and 31 March 2015	
Coffin et al. 2016,[19] USA	Non-randomized intervention study, multi-centre	1,985 adults receiving long-term opioid therapy for pain	Naloxone co-prescription (dosages not reported) versus No naloxone prescription	Proportion of patients prescribed naloxone, opioid-related emergency department visits, and prescribed opioid dose based on chart review Follow-up durations: 2 years

RCT = randomized controlled trial.

Table 4: 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
Langham et al. 2018,[20] UK	Cost-effectiveness analysis, lifetime horizon and discounted at 3.5% Health care perspective 1-year cycle	The cost-effectiveness of distributing naloxone to adults at risk of heroin overdose for use by non-medical responders	Adults at risk of heroin overdose in a European healthcare setting (United Kingdom)	Naloxone use by non-medical responders (intramuscular injection: 1mg/ml, 2 ml prefilled syringe) versus No naloxone distribution in a European healthcare setting (United Kingdom) Outcomes: lifetime overdose deaths averted (%), incremental cost of naloxone distribution (£), incremental QALY of naloxone distribution, and ICER of naloxone distribution (£)	Markov model with an integrated decision tree using UK data Deterministic and probabilistic sensitivity analyses	UK health care system (costs, clinical and epidemiologic data) and literature searches (clinical data)	Intramuscular naloxone distribution reaching 30% of heroin users (target coverage set by the Scotland naloxone take-home program) Joint probability that distributed naloxone used each year (calculated): 0.17 Proportion of witnessed overdoses: 0.85 (95% CI, 0.32 to 0.94) Proportion of witnessed overdoses when naloxone available: 0.75 (95% CI, 0.40 to 0.85) Intra-muscular naloxone (1mg/ml, 2ml): £15.30 each

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
							Utility for heroin user: 0.80 (0.73–0.90) See article for other assumptions

ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year

Table 5: Characteristics of Included Guidelines

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
American Society of Addiction Medicine 2015,[21] USA						
Clinicians involved in evaluating patients and providing authorization for pharmacological treatments at any level Patients with opioid use disorder	Interventions for the evaluation and treatment of opioid use disorder and for the management of opioid overdose	Morbidity and mortality	RAND/UCLA Appropriateness Method, "*a deliberate approach encompassing review of existing guidelines, literature reviews, appropriateness ratings, necessity reviews, and document development*" (p. 4) PsycINFO and PubMed searched for guidelines, randomized and non-randomized studies The number of researchers screening articles or extracting data not reported Search time frame: 2008 to present Synthesis and approval by a committee and externally reviewed	RAND/UCLA Appropriateness Method to determine the appropriateness scores	Recommendations made based on the appropriateness scores and secondary reviews for 254 statements Recommendations approved by the committee and externally reviewed	Not reported

Table 5: Characteristics of Included Guidelines

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
World Health Organization 2014,[22] Switzerland						
People likely to witness an opioid overdose and provide care for patients in the community Patients at risk of opioid overdose or requiring care in the community	Naloxone use in the pre-hospital settings	Morbidity and mortality of opioid overdose	Based on the GRADE methods and WHO Handbook for Guideline Development Multiple databases searched One and two reviewers screened the literature in the first and second steps of literature selection Systematic reviews and meta-analyses conducted for selected research questions if feasible Inclusion criteria: RCTs or controlled prospective studies published in peer-reviewed journals, or abstracts at scientific conferences, between 1 January 1966 and 1 January 2014	Based on the GRADE criteria	Recommendations made by a Guideline Development Group and externally reviewed	Not reported

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RAND/UCLA = RAND Corporation/University of California Los Angeles; RCT = randomized controlled trial; WHO = World Health Organization.

Appendix 3: Critical Appraisal of Included Publications

Table 6: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR 2 checklist[12]

Strengths	Limitations
Chimbar and Moleta, 2018[17]	
- PICO components described in the research questions and the inclusion criteria - Comprehensive literature searches - Included studies described - Review authors' conflicts of interest declared	- Review protocol not published *a priori* - Selection of study designs not explained - Study selection not in duplicate - Data extraction not in duplicate - Excluded studies not provided - The risk of bias in the included studies not critically appraised - The sources of funding for the included studies not reported - The risk of bias in the included studies not considered in the discussion - Heterogeneity between the included studies not explained

AMSTAR = A Measurement Tool to Assess Systematic Reviews; PICO = population, intervention, comparator, and outcome.

Table 7: Strengths and Limitations of Clinical Studies using the Downs and Black checklist[13]

Strengths	Limitations
McAuley et al., 2017[18]	
- Hypotheses and objectives described - Main outcomes described - Main findings described - Estimates of random variability in the main outcome data provided - Actual probability values (***P*** values) reported - The staff, places, and facilities where the patients were treated probably representative of the treatment the majority of patients received - Appropriate statistical tests used to assess the main outcomes - The main outcome measures accurate - Different groups of patients recruited from the same population - All residents eligible to the study - Confounding adjusted in the analysis	- Important adverse events not reported - Patients not blinded - Outcome assessors not blinded - The compliance with the intervention not assessed - Assigned interventions not concealed from the patients or the outcome assessors - Characteristics of the participants not described - Interventions not described - Distributions of the principal confounders not described - The time period between the intervention and outcome not estimated for individuals - Different groups of patients not recruited in the same period of time - Patients not randomized to different groups
Coffin et al., 2016[19]	
- Hypotheses and objectives described - Main outcomes described - Characteristics of the participants described - Interventions described - Distributions of the principal confounders described - Main findings described	- Important adverse events not reported - Patients not blinded - Outcome assessors not blinded - The compliance with the intervention not assessed - Assigned interventions not concealed from the patients or the outcome assessors

Table 7: Strengths and Limitations of Clinical Studies using the Downs and Black checklist[13]

Strengths	Limitations
- Estimates of random variability in the main outcome data provided - The actual probability values (***P*** values) for the main outcomes reported - The staff, places, and facilities where the patients were treated probably representative of the treatment the majority of patients received - The time period between the intervention and outcome the same - Appropriate statistical tests used to assess the main outcomes - The main outcome measures accurate - Different groups of patients recruited from the same population - Different groups of patients recruited in the same period of time - Confounding adjusted in the analysis of the main outcomes	- Patients lost to follow-up not included in the data analysis - Patients not randomized to different groups - Power analysis for sample sizes not conducted

Table 8: Strengths and Limitations of Guidelines using AGREE II[15]

Item	Guideline	
	American Society of Addiction Medicine 2015[21]	World Health Organization 2014,[22]
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	No	No
6. The target users of the guideline are clearly defined.	Yes	Yes
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	Yes	Yes
8. The criteria for selecting the evidence are clearly described.	Yes	Yes

Table 8: Strengths and Limitations of Guidelines using AGREE II[15]

Item	Guideline	
	American Society of Addiction Medicine 2015[21]	World Health Organization 2014,[22]
9. The strengths and limitations of the body of evidence are clearly described.	No	Yes
10. The methods for formulating the recommendations are clearly described.	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	No	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Yes	Yes
14. A procedure for updating the guideline is provided.	Yes	No
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	Yes	Yes
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	Yes
20. The potential resource implications of applying the recommendations have been considered.	Yes	Yes
21. The guideline presents monitoring and/or auditing criteria.	No	No
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	Uncertain	Uncertain
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes

AGREE = Appraisal of Guidelines for Research and Evaluation.

Table 9: Strengths and Limitations of Economic Studies using the Drummond Checklist[14]

Strengths	Limitations
Langham et al., 2018[20]	
- Research questions stated - The economic importance of the research questions stated - The viewpoint of the analysis stated - The form of economic evaluation stated - The choice of form of economic evaluation justified - The sources of effectiveness estimates stated - The results of the effectiveness studies given - The primary outcome measures of the economic evaluation stated - The subjects from whom the valuations were obtained described - Methods for the estimation of quantities and unit costs described - Currency and price data reported - Price adjustment given - Models used described - Time horizon of costs and benefits described - Discount rates stated and justified - Statistical tests and confidence intervals given - Sensitivity analyses described - The choice of variables for sensitivity analysis justified - The ranges over which the variables were varied justified - Relevant alternative compared - Incremental analysis reported - The answers to the study questions reported - The conclusions following the data reported - The conclusions accompanied by the appropriate caveats	- The rationale for choosing alternative programs not stated - The alternative compared not clearly described - Productivity changes not reported - The relevance of productivity changes not discussed - Quantities of resource use not separately reported from their unit costs - Main outcomes not presented in both aggregated and disaggregated forms

Appendix 4: Main Study Findings and Authors' Conclusions

Table 10: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Chimbar and Moleta, 2018[17]	
Take-home naloxone versus no take-home naloxone Mortality - Confidence intervals of successful opioid survivals: 95.5 and 97.1 in one SR; significant reduction in another SR; high survival rates after administration of naloxone in the primary studies in the other SR and one primary study; decreased mortality in one primary study Opioid overdose - Lower rates in communities that have take-home naloxone programs in effect when compared with communities without programs in place in one SR - Statistics not reported Successful reversals - "*strong evidence in support of THN programs*" in one SR (p. 170) - Statistics not reported Adverse events - "*Minimally noted*" in one SR (p. 170) - Statistics not reported	Effectiveness of take-home naloxone - "*there is overwhelming support of take-home naloxone programs being effective in preventing fatal opioid overdoses*" (p. 167) - "*A significant limitation of this systematic review is the lack of randomized controlled trials as it is viewed as unethical withholding a known lifesaving medication from an at-risk population*" (p. 167) - "*On the basis of the most current evidence, there is overwhelming support of take-home naloxone programs associated with decreased mortality among those who abuse opioids*" (p. 167)

SR = systematic review; THN = take-home naloxone.

Table 11: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
McAuley et al., 2017[18]	
National naloxone program in Scotland Ambulance call-outs to opioid-related overdose incidents - No significant association with take-home naloxone kits in issue for Scotland as a whole: coefficient = 0.009 (95% CI, -0.01 to 0.03, ***P*** = 0.39) Magnitude of association between take-home naloxone kits and ambulance call-outs - Not significantly different between pilot and non-pilot regions (interaction test, ***P*** = 0.62)	"*The supply of take-home naloxone kits through a National Naloxone Programme in Scotland was not associated clearly with a decrease in ambulance attendance at opioid-related overdose incidents in the 4-year period after it was implemented in April 2011*" (p. 301)
Coffin et al., 2016[19]	
Naloxone co-prescription with opioids versus no co-prescription Co-prescription rate - 38.2% of 1,985 patients receiving long-term opioids prescribed naloxone	- "*Naloxone can be coprescribed to primary care patients prescribed opioids for pain*" (p. 245) - "*naloxone can be successfully prescribed to a substantial proportion of patients receiving opioids for chronic pain in primary care practices*" (p. 251)

Table 11: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Factors significantly associated with naloxone co-prescription - Higher doses of opioids prescribed an opioid-related emergency department visit in the past 12 months Opioid-related emergency department visits per month - Patients with a naloxone prescription compared with patients who did not receive naloxone - 47% significantly fewer visits 6 months after the prescription [IRR= 0.53 (95% CI, 0.34 to 0.83, ***P*** = 0.005) - 63% fewer visits after 1 year [IRR = 0.37 (95% CI, 0.22 to 0.64), ***P*** < 0.001] Opioid dose - No net change overtime among those who received naloxone and those who did not [IRR = 1.03 (95% CI = 0.91 to 1.27), ***P*** = 0.61]	- "*Naloxone coprescribing was associated with reduced opioid-related ED visits*" (p. 251)

CI = confidence interval; HR = hazard ratio; IRR = incidence rate ratio.

Table 12: Summary of Findings of Included Economic Evaluations

Main Study Findings	Authors' Conclusion
Langham et al., 2018[20]	
Naloxone use by non-medical responders versus No naloxone distribution Overdose deaths (base case scenario, see article for details) - Distribution of take-home naloxone: decrease overdose deaths by around 6.6% - Prevention of 2,500 premature deaths at an incremental cost per QALY gained of £899 in a population of 200,000 heroin users Base case scenario - Incremental cost of naloxone distribution (£): 146 - Incremental QALY of naloxone distribution: 0.163 - ICER of naloxone distribution (£): 899 Sensitivity analyses - Naloxone distribution remained cost-effective when assumptions were varied, confirming the robustness of the results	- "*Our evaluation suggests that the distribution of take-home naloxone decreased overdose deaths by around 6.6% and was cost-effective with an incremental cost per QALY gained well below a £20,000 willingness-to-pay threshold set by UK decision-makers*" (p. 407) - "*A naloxone take-home program in a European market, in this case the United Kingdom, targeted at 30% of heroin users, was shown to be highly cost-effective*" (p. 413)

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

Table 13: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
American Society of Addiction Medicine 2015[21]	
Part 8: Special Populations: Pregnant Women - "*Naloxone is not recommended for use in pregnant women with opioid use disorder except in situations of life-threatening overdose*" (p. 9)	- Reference, strength of recommendation, and quality of evidence not reported
Part 13: Naloxone for the Treatment of Opioid Overdose - "*Naloxone should be given in case of opioid overdose*" (p. 10) - "*Naloxone can and should be administered to pregnant women in cases of overdose to save the mother's life*" (p. 9) - "*patients who are being treated for opioid use disorder and their family members/significant others be given prescriptions for naloxone. Patients and family members/ significant others should be trained in the use of naloxone in overdose*" (p. 10)	- Reference, strength of recommendation, and quality of evidence not reported - Reference, strength of recommendation, and quality of evidence not reported - Recommendation based on consensus opinion
World Health Organization, 2014[22]	
Key question 1 – naloxone distribution - "*People likely to witness an opioid overdose should have access to naloxone and be instructed in its administration to enable them to use it for the emergency management of suspected opioid overdose*" (p. 9)	- Strength of recommendation: Strong; Quality of evidence: Very low
Key questions 2 and 3 – formulation and dose of naloxone - "*Naloxone is effective when delivered by intravenous, intramuscular, subcutaneous and intranasal routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting and local context*" (p. 12)	- Strength of recommendation: Conditional (less certainty about the evidence of effect and values, preferences, benefits and feasibility of this recommendation; this recommendation may not be applicable to all conditions); Quality of evidence: Very low

Appendix 5: Additional References of Potential Interest

Reviews without comprehensive literature searches or independent literature selection

Bell J, Strang J. Medication Treatment of Opioid Use Disorder. *Biol Psychiatry.* 2020; 87(1):82-88.

Farrugia A, Fraser S, Dwyer R, et al. Take-home naloxone and the politics of care. *Sociol Health Illn.* 2019;41(2):427-443.

Kim HK, Connors NJ, Mazer-Amirshahi ME. The role of take-home naloxone in the epidemic of opioid overdose involving illicitly manufactured fentanyl and its analogs. *Expert Opin Drug Saf.* 2019;18(6):465-475.

Strang J, McDonald R, Campbell G, et al. Take-home naloxone for the emergency interim management of opioid overdose: the public health application of an emergency medicine. *Drugs.* 2019;79(13):1395-1418.

Visconti AJ, Sell J, Greenblatt AD. Primary care for persons who inject drugs. *Am Fam Physician.* 2019;99(2):109-116.

Mueller SR, Walley AY, Calcaterra SL, Glanz JM, Binswanger IA. A review of opioid overdose prevention and naloxone prescribing: implications for translating community programming into clinical practice. *Subst Abus.* 2015;36(2):240-253.