Guidance on take-home naloxone distribution and use by community overdose responders in Canada

Max Ferguson MPH MSN, Katherine Rittenbach PhD, Pamela Leece MD MSc, Alison Adams MPH, Farihah Ali PhD, Tara Elton-Marshall PhD, Charlene Burmeister, Thomas D. Brothers MD, Andrea Medley MPH, Paul Choisil, Carol Strike PhD, Justin Ng, Diane L. Lorenzetti PhD, Kat Gallant MPP, Jane A. Buxton MBBS MHSc; for the Naloxone Guidance Development Group

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Background: The increasing toxicity of opioids in the unregulated drug market has led to escalating numbers of overdoses in Canada and worldwide; take-home naloxone (THN) is an evidence-based intervention that distributes kits containing naloxone to people in the community who may witness an overdose. The purpose of this guidance is to provide policy recommendations for territorial, provincial and federal THN programs, using evidence from scientific and grey literature and community evidence that reflects 11 years of THN distribution in Canada.

Methods: The Naloxone Guidance Development Group — a multidisciplinary team including people with lived and living experience and expertise of drug use — used the Appraisal of Guidelines for Research & Evaluation (AGREE II) instrument to inform development of this guidance. We considered published evidence identified through systematic reviews of all literature types, along with community evidence and expertise, to generate recommendations between December 2021 and September 2022. We solicited feedback on preliminary recommendations through an External Review Committee and a public input process. The project was funded by the Canadian Institutes of Health Research through the Canadian Research Initiative in Substance Misuse. We used the Guideline International Network principles for managing competing interests.

Recommendations: Existing evidence from the literature on THN was of low quality. We incorporated evidence from scientific and grey literature, and community expertise to develop our recommendations. These were in 3 areas: routes of naloxone administration, THN kit contents and overdose response. Take-home naloxone programs should offer the choice of both intramuscular and intranasal formulations of naloxone in THN kits. Recommended kit contents include naloxone, a naloxone delivery device, personal protective equipment, instructions and a carrying case. Trained community overdose responders should prioritize rescue breathing in the case of respiratory depression, and conventional cardiopulmonary resuscitation in the case of cardiac arrest, among other interventions.

Interpretation: This guidance development project provides direction for THN programs in Canada in the context of limited published evidence, with recommendations developed in collaboration with diverse stakeholders.

Opioids relieve pain and cause euphoria by binding to μ-opioid receptors in the brain. If someone takes a higher dose of illegal or prescription opioids than their body can tolerate, they may experience opioid overdose. During opioid overdose, respiration is depressed, which may lead to cardiac arrest, failure of other organs and death from hypoxemia and hypercapnia.[1] The increasing toxicity of opioids in the unregulated (illegal or illicit) drug market has caused an escalating number of overdoses in Canada and worldwide.[2,3]

Naloxone is a μ-opioid antagonist that can temporarily reverse respiratory depression related to opioid overdose.[1] Naloxone cannot reverse overdose symptoms caused by classes of drugs other than opioids, such as stimulants or benzodiazepines, which complicates response in the event of a polysubstance overdose.[1]

Take-home naloxone (THN) programs in Canada are implemented on a territorial, provincial or federal level and provide kits containing the medication naloxone to THN sites that distribute these kits free of charge and without need for a prescription (see Box 1 for definitions).[5] These sites provide kits that contain naloxone as well as tools to safely administer the medication, to people who may witness an overdose. Naloxone is also available for purchase outside of THN programs.[5,8]

Box 1: Definitions

Community overdose responder: Although some literature on take-home naloxone (THN) refers to "lay people," we opted to use "community overdose responders," as many people using THN programs have substantial expertise responding to overdose.[1] For the purposes of this guidance, a community overdose responder is someone responding to overdose outside of health care or overdose prevention site settings. Although community responders are not exclusively people who use drugs, people who use drugs comprise a substantial proportion of those who respond to overdoses.[4] Some harm reduction workers and health care providers carry THN kits to respond to overdose outside of their professional roles and would be considered community overdose responders in that context.

Distribution site: An organization supported by a THN program that provides THN kits to community overdose responders. These sites can be based in different settings, such as community harm reduction organizations, social service organizations, health centres, community pharmacies and health care settings (e.g., hospital and emergency departments, correctional facilities, treatment and rehabilitation centres, fire and police branches, and St. John Ambulance branches).[5]

People with lived and living experience and expertise: In this article, when we discuss people with lived and living experience and expertise, we are referring to those with self-identified experience of drug use. We use the term "people with lived and living experience and expertise" in recognition of the diversity of ways that people identify and the expertise of lived experience.[6]

Take-home naloxone programs: In Canada, THN programs are administered by the provinces, territories and federal government, and provide naloxone kits and policy direction to distribution sites within their jurisdiction.[5,7] Federal programs that distribute THN include the Non-Insured Health Benefits Program (which provides coverage to some status First Nations or Inuit people), Correctional Service Canada (which provides coverage to people being released into the community after federal incarceration), Veterans Affairs Canada and the Canadian Armed Forces.[5,7]

Evidence on THN programs shows that the public health intervention is effective at reducing opioid-associated mortality.[9] Naloxone is frequently administered in the health care context, but this guidance for policy is specific to THN programs and the use of naloxone in the community setting by community overdose responders (see Box 1 for definition).

Between 2012 and 2017, all Canadian provinces and territories launched publicly funded THN programs to address the opioid toxicity crisis.[5] Advocacy from people who use drugs drove the development of THN programs; in the context of inadequate health policy or health systems structures in Canada before the development of these programs, advocates illegally imported naloxone from the United States.[10] People who use drugs are currently the main group to use THN kits to reverse overdoses.[4]

Although THN kits are available across the country, without prescription and at no cost to the recipient, Canadian provinces and territories developed THN programs independently. As there is no national guidance, each province and territory has different distribution systems, recommendations on overdose response, and naloxone formulations available, which can cause confusion and distress among end users.[5]

Our guidance development process identified questions important to THN programs, synthesized evidence and generated recommendations in collaboration with a Naloxone Guidance Development Group. The group consisted of people with lived and living experience and expertise of drug use and response to overdose (see Box 1 for definition), front-line overdose response and harm reduction workers, public health professionals, clinicians and academics with expertise in harm reduction from across Canada.

The aim of our project was to generate national Canadian policy guidance for territorial, provincial and federal programs distributing THN kits for use in the community by community overdose responders. The full report is available in Appendix 1 (available at www.cmaj.ca/lookup/doi/10.1503/cmaj.230128/tab-related-content) and will be posted online at https://crism.ca/naloxone-distribution/.

Scope

The purpose of this guidance is to provide policy recommendations for territorial, provincial and federal THN programs, which support THN sites in distributing naloxone kits to community overdose responders. Our aim was to address issues of national scope and support standardized practice across Canadian provinces and territories. This project synthesizes existing evidence and expert consensus relevant to THN programs that support community overdose responders outside of health care settings (see Box 1 for definitions).

The intended target audience of this guidance for policy is those involved in developing, funding or administering THN programs. The guidance may be of interest to distribution sites, harm reduction organizations, community overdose responders, harm reduction workers, public health professionals and clinicians. The guidance may also be useful for those developing programs internationally.

This guidance does not address how to train community responders to use naloxone or how programs should be monitored and evaluated.

Recommendations

Based on an engagement process in which we selected priority topics with stakeholders, we developed 3 recommendations on routes of naloxone administration, THN kit contents and overdose response. Box 2 provides more information on grading of recommendations and Table 1 summarizes the recommendations.

The recommendations are based on factors such as values and preferences, benefits and harms, taken from the published and grey literature and from community evidence. Community evidence was generated from the reported observations and experiences[13] of people with lived and living experience and expertise who participated in the Naloxone Guidance Development Group. More details are available in Appendix 2 (www.cmaj.ca/lookup/doi/10.1503/cmaj.230128/tab-related-content).

Box 2: Grading of recommendations

We graded recommendations according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework and determined them to be either strong or conditional.[11] The strength of recommendations was based on the balance of desirable and undesirable consequences, the quality of published evidence, the values and preferences of those affected, and resource use.[11] The quality of published evidence is graded as high, moderate, low or very low.[11]

As our guidance is most applicable to policy, strength of recommendations is defined as:

Strong recommendation: The recommendation can be adapted as policy in most situations or regions.[11]

Conditional recommendation: Policy-making will require substantial debate and involvement of many stakeholders. Policies are more likely to vary between regions.[11]

A strong recommendation is issued when the desirable effects of the recommendation outweigh the undesirable effects.[12] The GRADE framework states that the quality of the evidence and the strength of recommendations should be determined through separate judgments.[11] Although strong recommendations may be more judiciously issued in the context of low-quality evidence, doing so is consistent with the framework (section 1.2 in the GRADE handbook).[11]

Routes of administration

Take-home naloxone programs should offer both intramuscular and intranasal formulations of naloxone, so that people accessing naloxone kits can choose their preferred formulation (conditional recommendation, very low-quality evidence)

Take-home naloxone programs currently distribute intramuscular naloxone (injected into the muscle) and intranasal naloxone (sprayed into the nasal passages and absorbed into the nasal mucosa). With both routes of administration, naloxone is bioavailable even when a person experiencing overdose is not breathing.[14]

We did not identify primary evidence on routes of administration of naloxone specific to community overdose responders; however, we found reviews incorporating studies of naloxone administration in health care settings, which addressed our recommendation. Reviews identified included 2 systematic reviews,[15,16] an umbrella review,[17] 2 narrative reviews,[18,19] a rapid review,[20] and a guideline that used systematic review methodology.[21]

Several reviews concluded that intranasal and intramuscular naloxone were similarly effective in reversing overdose,[16,17,21] whereas Peprah and Frey found that intramuscular naloxone had "[at least] nominally higher efficacy."[20] See Appendix 1 for an in-depth discussion of the literature, and Appendix 3 (available at www.cmaj.ca/lookup/doi/10.1503/cmaj.230128/tab-related-content) for more details on findings and included studies.

We rated the quality of the published scientific evidence as very low for this document, as we could not identify any studies specific to community overdose responders (more details available in Appendix 3).

Benefits and harms

Advantages of intranasal formulations include perceived ease of use[22–24] and theoretically reduced risks of blood-borne illness transmission[22] and needlestick injury,[23] although we were unable to identify any reports in the literature of needlestick injury among those administering naloxone. These risks may be decreased by using retractable needles. Intramuscular naloxone has substantial advantages, including providing the ability to titrate doses[25] (whereas intranasal can be administered only in the dosage contained in the device[26]), perceived ease of use and familiarity among community overdose responders.[25]

Values and preferences of the affected community

According to the published evidence, most people who use opioids[24,27] prefer to administer intranasal over intramuscular naloxone during overdose response. In studies, participants who used opioids and responded to overdoses reported preferring intranasal route of administration because it was perceived to be more comfortable for those experiencing overdose, and quicker to administer, as responders did not need to draw up medication.[24] Some study participants also reported a preference for intranasal naloxone because of a general dislike of needles.[24] A smaller proportion preferred the intramuscular route of administration because of previous experience with intramuscular naloxone and perceived ease of intramuscular administration;[24] some reported believing that intramuscular naloxone is more effective.[27] We did not identify literature on preferences of people in Canada.

Community evidence and opinion

Although the published evidence suggested that people who use drugs prefer intranasal naloxone, Naloxone Guidance Development Group members with overdose response experience reported a strong preference for intramuscular naloxone, as they more frequently observed withdrawal precipitated by use of intranasal naloxone. However, they also raised concerns about challenges in administering intramuscular naloxone for people with manual dexterity or coordination issues.

There was strong support for this recommendation in public input, through both consultation groups and surveys. Most people who took part in the public input process and regularly responded to overdoses used and preferred intramuscular naloxone, because of the ability to titrate so as not to precipitate withdrawal symptoms. However, they still strongly supported increasing availability of intranasal naloxone.

Additional reasons why public-input participants supported increased intranasal naloxone availability included:

- Speed of administration: This is an important consideration when the person experiencing overdose has muscle rigidity and the responder is unable to administer rescue breathing.
- Accessibility: Consultation-session participants reported that many people who use drugs and are living in poverty face physical accessibility barriers when trying to administer intramuscular naloxone (e.g., missing digits or hands from infection arising from contamination of drug supply, or frostbite).
- Ease of use: Ease of use was identified as particularly important in difficult administration conditions, such as when a

Table 1: Summary of recommendations on take-home naloxone distribution and use by community overdose responders in Canada

Topic	Recommendation	Strength of recommendation	Quality of published academic and grey literature evidence
Route of administration	THN programs should offer both intramuscular and intranasal formulations of naloxone, so that people accessing naloxone kits can choose their preferred formulation.	Conditional	Very low

Kit contents	All THN kits should include:
	• A recognizable carrying case
	• Non-latex gloves
	• A rescue breathing mask
	• Instructions on naloxone administration:
	  • Instructions on how to administer naloxone should be designed in collaboration with people who use these kits
	  • THN programs can use previously developed instructions or develop their own in collaboration with the affected community
	Intramuscular THN kits should include:
	• Three or more 0.4 mg/mL naloxone ampoules or vials, according to program discretion and local experience (more ampoules or vials may be necessary in communities with high prevalence of illicitly manufactured fentanyl and other potent synthetic opioids)
	• A syringe and needle for each ampoule or vial of naloxone
	• Alcohol swabs
	• Ampoule breaker (in kits containing ampoules)
	Intranasal THN kits should include:
	• Two 4 mg/0.1 mL intranasal devices
		Strong	Very low

Overdose response	Response to suspected opioid overdose should depend on the skill and comfort level of the responder. People accessing services at THN distribution sites may be trained on overdose response through their peers, using online resources, a CPR training course or training developed by THN programs. Trained community responders should follow these steps: • Apply vigorous verbal and physical stimuli • Call EMS* • Administer naloxone† • If the individual experiencing overdose is in respiratory depression, provide rescue breathing • If the individual experiencing overdose is in cardiac arrest, provide conventional CPR, including rescue breathing and chest compressions THN distribution sites without capacity to offer overdose response education should direct people to services that offer training, if needed.	Strong	Very low

Note: CPR = cardiopulmonary resuscitation, EMS = emergency medical services, THN = take-home naloxone.
*We acknowledge that many people who use drugs do not feel safe calling EMS, especially in jurisdictions where police commonly attend EMS calls for overdose.
†There is differing guidance on the order of naloxone administration and resuscitation. Our recommendation does not address order of response interventions.

responder is experiencing extreme stress or administering naloxone in the dark. Most consultation-session participants reported preferring intramuscular naloxone, but it was frequently mentioned that people who do not use drugs may not feel comfortable using intramuscular naloxone. Participants noted that while they would prefer to receive titrated intramuscular naloxone, it was important to ensure that family and friends who do not use drugs still feel comfortable administering naloxone.

- Considerations for the physical environment: In areas with extremely low temperatures, such as Northern Canada, needles may not be able to penetrate through layers of clothing and it may be difficult or unsafe to remove layers. Consultation-session participants reported that their hands become numb in the cold, making intramuscular administration difficult.
- Safety considerations: Consultation-session participants reported being cut by broken vials or ampoules during overdose response.

Resource use

Intranasal naloxone is more expensive per dose than intramuscular naloxone for THN programs to purchase and distribute, although the price difference may vary across jurisdictions.[5,22,23] In an environmental scan of territorial, provincial and federal THN programs in Canada conducted as part of this project, key informants stated that the high cost of intranasal naloxone made it challenging to fund.[5] At the time of data collection, the cost to the THN program was about 10 times the cost of the equivalent intramuscular formulation. The consumer price outside of publicly funded THN programs for 2 doses of injectable naloxone and kit contents reportedly varies from $30 to $55, and between $120 and $200 for 2 doses of nasal naloxone spray.[5] In 2020, the Health Technology Assessment Unit at the University of Calgary noted that retail intranasal naloxone cost over 3 times more than intramuscular naloxone with equivalent effectiveness.[22]

Rationale

The strength of this recommendation is conditional, and the quality of published academic and grey literature evidence was very low. A key consideration was the substantially increased cost associated with THN programs offering both routes of administration. While we recommend that people who use THN kits be offered the choice between intramuscular and intranasal naloxone, we understand that it may not be financially feasible for all jurisdictions.

Kit contents

The recommendation on kit contents (naloxone, naloxone delivery device, personal protective equipment, instructions and carrying case) is presented in Table 1 (strong recommendation, very low-quality evidence).

Our recommendation on kit contents is based on grey literature that discussed current practice in different jurisdictions. Kits generally include naloxone, naloxone delivery devices (syringes or intranasal devices), personal protective equipment (disposable gloves and a rescue breathing mask), instructions on naloxone administration and a carrying case.[5]

Identified grey literature included a curriculum to support naloxone kit providers[28] and a decision support tool for intramuscular and nasal naloxone administration, released by Alberta Health Services;[29] guidance for community service providers from the Canadian Mental Health Association of Ontario;[30] a document with frequently asked questions on naloxone, released by the College of Pharmacists of Manitoba;[31] a guidance document from the Institut national d'excellence en santé et en services sociaux (INESSS);[32] and a Canadian environmental scan conducted by this research team.[5]

Research on the development of instructions for naloxone administration suggests that people who use the kits prefer simple, visual instructions. Instructions designed in collaboration with people who may use them improved performance of simulated overdose response and potentially increased the probability of successful naloxone administration.[33] Territorial, provincial and federal THN program instructions would likely be standardized for each program, but distribution sites should be able to tailor the instructions and training to a specific population and their requirements (e.g., aimed at youth or translated to a commonly spoken, nonofficial language). Organizations may also choose to include details relevant to their context, such as how to respond to overdose in extreme cold situations or in rural and remote jurisdictions.

We did not find any published evidence on how many vials or ampoules should be included in kits. Naloxone Guidance Development Group members with front-line harm reduction roles reported that many overdose reversals require more than 2 vials or ampoules of naloxone. Although there was concern that providing more ampoules or vials may increase rates of precipitated withdrawal, responders can receive education focused on preventing excess naloxone doses; ultimately, having enough naloxone to save a life was deemed a more important consideration. Naloxone Guidance Development Group members also reported that intranasal naloxone is less likely to require a repeat dose, so the recommendation on additional doses was limited to intramuscular kits.

An in-depth discussion of the literature is available in Appendix 1, and Appendix 3 includes more details on findings and included studies. The quality of the published scientific evidence was very low, as no empirical studies on the effects of different THN kit contents were identified (more details available in Appendix 3).

Benefits and harms

Although the risk of pathogen transmission, including SARS-CoV-2, during overdose response remains ill defined, rescue breathing masks and other forms of personal protective equipment may reduce the risk of infection transmission.[34] Personal protective equipment, including rescue breathing masks and gloves, may also increase willingness of community overdose responders to administer naloxone and provide rescue breaths.[1]

The benefits of including community members in design and usability testing when developing instructions are discussed above. Potential for precipitation of withdrawal symptoms was an important consideration when determining the number of doses of naloxone, as discussed in further detail below.

Values and preferences of the affected community

Inclusion of 3 ampoules rather than 2 may increase responder ability to reverse overdoses. Published evidence shows that responders frequently administer more than 2 vials or ampoules, although inferences cannot be drawn from the data on whether these additional doses were truly needed.[25] There is evidence suggesting that higher doses of naloxone are associated with increased risk of moderate or severe withdrawal symptoms;[25] however, this risk may be offset by providing additional training in dose titration. Studies show that community overdose responders preferred to use a barrier device when providing rescue breathing.[1]

Community evidence and opinion

Consultation-session participants supported this recommendation. Further suggestions included providing sturdier breathing masks and multiple pairs of gloves in case of glove damage, or in a situation where multiple responders are involved.

Resource use

A systematic review of economic evaluations of THN programs in a variety of settings showed that the evaluations consistently found the programs to be cost-effective, suggesting that the number of naloxone ampoules and other minor variations in kit contents (such as the type of carrying cases, syringes or personal protective equipment) are unlikely to affect overall cost-effectiveness.[35]

Rationale

We issued a strong recommendation on kit contents because of the consistency of practice in the Canadian context, despite low-quality published evidence. Factors contributing to this strong rating include the lack of identified negative consequences, acceptance by the affected community in multiple contexts (published literature, the Naloxone Guidance Development Group and public input, in both consultation groups and surveys), and lack of concerns about resource use.

Overdose response

The recommendation on overdose response, including the need for training and steps in the response, is presented in Table 1 (strong recommendation; very low-quality evidence).

Relevant literature on overdose response included 3 clinical guidelines,[1,21,32] 3 grey literature reports (a rapid review,[36] an evidence brief[37] and a report of a technical working group on resuscitation training[38]), and a pilot and feasibility study.[39] The conclusions in these resources differ on overdose response, notably on the role of rescue breathing and the order in which resuscitation steps occur. An in-depth discussion of the literature is available in Appendix 1, and Appendix 3 contains more detail on findings and included studies.

As the mandate of THN programs includes overdose response training, our recommendation focuses on trained overdose response. Evidence from the Naloxone Guidance Development Group indicates that community overdose responders are effectively trained through different methods. For the purposes of this document, we recognize that people using THN programs may be trained on overdose response through their peers, using online resources, THN programs or cardiopulmonary resuscitation (CPR) training courses.

In the literature, multiple sources identified naloxone administration and calling 911 or other emergency response numbers as critical steps in overdose response.[1,21,32,36,38,39] Three guidance documents included verbal and physical stimulation to assess whether someone is experiencing overdose and to stimulate breathing.[21,32,38]

For a responder trained in overdose response, guidance may differ according to whether the responder suspects respiratory depression or cardiac arrest. Overdose response must take the pathophysiology of opioid overdose into account. When someone experiences opioid overdose, regulation of breathing is impaired, respiration is depressed and insufficient oxygen reaches the brain and other organs.[1] Because the person experiencing overdose is not breathing effectively, oxygen also cannot reach the heart and the individual may experience cardiac arrest (i.e., their heart stops beating or beats too ineffectively to support their vital organs).[1]

Respiratory depression

Guidance from the Ontario HIV Treatment Network[36] and from the World Health Organization (WHO)[21] recommend that trained responders provide rescue ventilation (also called rescue breathing) in the absence of regular breathing. However, in this situation, the American Heart Association[1] recommends providing conventional CPR with both chest compressions and rescue breathing, by trained responders.

Rescue breathing is effective at reversing overdose. In a study of 767 people who experienced overdose at a Canadian supervised consumption site staffed by nurses and peer responders, all were managed with oxygen and ventilation and 93.2% received naloxone; none received chest compressions; and all who overdosed survived.[40]

We recommend rescue breathing–only resuscitation in the event of respiratory depression, given the perspectives of Naloxone Guidance Development Group members who stated that community overdose responders can be effectively trained to differentiate respiratory depression from cardiac arrest and because of the harms associated with chest compressions. We acknowledge the controversy on this topic; however, this guidance draws on community expertise in witnessing and responding to overdose events.

Cardiac arrest

Guidance for trained responders from the American Heart Association,[1] Ontario HIV Treatment Network[36] and the WHO[21] recommend providing conventional CPR, including both rescue breathing and chest compressions, in the context of cardiac arrest. Rescue breathing oxygenates the blood and chest compressions circulate the blood for someone experiencing cardiac arrest related to overdose.

We chose to focus on what actions should be taken during an overdose, rather than how people should be trained to respond or the order in which they should respond. More detail on included studies is available in Appendix 3, and Appendix 1 includes an in-depth discussion of the literature.

We determined the quality of the published scientific evidence to be very low, as we identified no empirical research comparing different strategies for community overdose response outside of health care settings (more detail in Appendix 3).

Benefits and harms

The most important considerations in overdose response are the preservation of life and mitigation of harms. Chest compressions are associated with broken ribs and sternum[41]

and should be reserved for when the responder suspects potential cardiac arrest or is physically unable or unwilling to perform other interventions, such as rescue breathing or naloxone administration.

Values and preferences of the affected community

Overdose response guidance in the literature varies, including with respect to the role of rescue breathing. We did not find published literature on values and preferences for this recommendation.

Community evidence and opinion

Members of the Naloxone Guidance Development Group suggested providing rescue breathing for someone experiencing respiratory depression related to opioid overdose. This recommendation was largely supported by individuals participating in public input — both consultation groups and surveys. However, there was some disagreement; 2 out of 148 public-input participants did not think that community overdose responders could be trained to check a pulse or provide rescue breathing. However, most public-input participants reported providing rescue breathing in the event of an overdose and being comfortable determining whether a person experiencing overdose is in cardiac arrest. Some stated they had not been trained to provide rescue breathing but would be interested in receiving such training. Consultation-session participants reported that people frequently experienced broken ribs from receiving chest compressions, which was identified as an undesirable outcome of the intervention.

Consultation-session participants reported the practice of providing rescue breathing before considering naloxone administration to ensure that those experiencing overdose received sufficient oxygen initially, while avoiding withdrawal symptoms associated with naloxone. Consultation-session participants reported that this approach maintains relationships with people who use drugs and ensures they are comfortable returning to services after an overdose. Many of these participants stated that they wanted additional training in overdose response and naloxone titration.

Another concern frequently raised in public-input sessions was excessive force used when applying stimuli to try to rouse a person experiencing overdose. Excessive force can result in unnecessary bruising and pain. Additionally, sternal rubs were perceived as invasive by many people with breasts.

Resource use

Overdose response training should include how to provide rescue breaths. However, this does not appear to have substantial resource implications.[21]

Rationale

We issued a strong recommendation for overdose response based on the need to preserve life, to avoid harm and to respect the expertise and preferences of the affected population. Although the quality of the published evidence was low, expert evidence on both overdose response and training others on overdose response was deemed to be of high quality.

Methods

Development of Canadian THN guidance for policy started in December 2018 and was finalized in October 2022. We used the Appraisal of Guidelines for Research & Evaluation (AGREE II) instrument to inform the development of our guidance[42] (Appendix 4, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.230128/tab-related-content). The THN guidance development project was funded by the Canadian Institutes of Health Research for the Canadian Research Initiative in Substance Misuse (CRISM) Implementation Science Program on Opioid Interventions and Services (OCC-154821). The funder had no role in the execution of the guidance development. (The authors acknowledge the stigmatizing nature of the term "Substance Misuse" in the CRISM name, respect the autonomy of people who use drugs and support person-centred language.)

Composition of participating groups

The guidance on THN in Canada was developed in collaboration with a Naloxone Guidance Development Group composed of people with lived and living experience and expertise of drug use and response to overdose, front-line overdose response and harm reduction workers, public health professionals, clinicians and academics with expertise in harm reduction. The recruitment strategy and the role of committees is detailed elsewhere.[43] Indigenous, Black and other racialized people, and 2SLGBTQIA+ individuals were explicitly invited in all Naloxone Guidance Development Group recruitment material and were represented in the final group (a list of all guidance development project members is available in Appendix 1).

The 52-member Naloxone Guidance Development Group consisted of 6 subcommittees (in order of chronological involvement). Members could take part in more than 1 committee and on all committees, people with lived and living experience and expertise were represented. The committees were:

- Leadership Group (3 members: J.A.B., K.R., P.L.): Provided formal academic supervision of the project. Members included clinicians and academics with expertise in harm reduction.
- Research Team (6 members, including M.F., A.A., J.N.): Provided leadership or support of research activities, including project coordination, systematic review work, meeting facilitation, competing interests review, and manuscript and report drafting. Members had experience in public health, harm reduction, health care, library sciences and legal studies.
- Guidance Steering Committee (9 members: K.R., C.B., T.D.B., A.M., P.C., C.S., P.L., T.E.M., D.L., with M.F. as facilitator): Steered guidance discussions, encouraged productive debate and provided oversight of the guidance development process. Members included people with lived and living experience and expertise of drug use and response to overdose, front-line overdose response and harm reduction workers, public health professionals, clinicians and academics with expertise in harm reduction.
- Methodology Advisory Committee (4 members: P.L., F.A., T.E.M., D.L., with M.F. as facilitator): Provided advice on guidance development methods from a health research perspective.

- Affected Community Committee (8 members, including P.C., with M.F. and J.A.B. as facilitators): Provided direction and advice on the values and preferences of people with lived and living experience and expertise related to THN distribution and use in opioid overdose. Members included front-line overdose response and harm reduction workers, and public health professionals.
- Clinical Expert Committee (11 members, including C.B., with M.F. as facilitator): Provided direction and advice on the use of naloxone in opioid overdose from a clinical viewpoint. Professional groups represented included harm reduction workers, pharmacists, nurse practitioners and physicians.
- Guidance Development Panel (14 members, including F.A., T.D.B., A.M., C.S., K.G., with M.F. as facilitator): Voted on key questions that the guidance addresses, as part of a Delphi process. The Affected Community Committee, Guidance Steering Committee and Clinical Expert Committee were all invited to join the Guidance Development Panel. Members included people with lived and living experience and expertise of drug use and response to overdose, front-line overdose response and harm reduction workers, public health professionals, clinicians, and academics with expertise in harm reduction.
- External Review Committee (8 members): Provided independent assessments of the process and conclusions attained throughout the guidance development process. Members included people with lived and living experience and expertise of drug use and response to overdose, public health professionals, clinicians and academics with expertise in harm reduction, from Canada and internationally.

Selection of priority topics

We identified questions for the guidance development project to address by using a 2-step Delphi method, which allowed the Guidance Development Panel to prioritize a list of potential questions.[43] Further details are available in our publication on the process.[43] In Appendix 5, Supplemental Table 1 and Supplemental Table 2 (available at www.cmaj.ca/lookup/doi/10.1503/cmaj.230128/tab-related-content) show a PICO (Patient/Problem, Intervention, Comparison and Outcome) breakdown of the 3 questions included.

Literature review and quality assessment

Before undertaking the systematic reviews, we performed an environmental scan of publicly funded territorial, provincial and federal THN programs, to gain a better understanding of programs and practices in Canada.[5]

The systematic review protocols were registered with PROSPERO (registration IDs: 2021 CRD42021265012, RD42021265032, CRD42021264838). In consultation with a research librarian (D.L.L.), databases (including MEDLINE, Embase [Ovid], CINAHL, APA PsycInfo [EBSCOhost], Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews, PROSPERO and Epistemonikos) and grey literature were initially searched using combinations of keywords and controlled vocabulary (e.g., Medical Subject Headings [MeSH]). The last search dates of the scientific literature for routes of administration, kit contents and overdose response were Oct. 18, 2021, June 23, 2021, and June 3, 2021, respectively, and the last search dates for grey literature for these 3 topics were July 30, 2021, Dec. 2, 2021, and Aug. 3, 2021, respectively (Appendix 5).

No date or publication type limits were applied. Language of publication was limited to English or French, based on the official languages of Canada and the linguistic capacity of the research team. Details of the search strategy and search dates are available in Appendix 5.

Titles and abstracts were screened against eligibility criteria to determine inclusion. Documents that seemed relevant were advanced to full-text screening. If full-text screening confirmed relevance, the document was included in the review. Each stage of screening was completed in duplicate by 2 members of the research team working independently, with disagreements resolved through discussion and consensus where possible. When necessary, a third member of the research team resolved disagreements. Screening was conducted in Covidence systematic review software.[44] Two members of the research team worked independently to extract study characteristics and study findings from documents included in the review in duplicate. In addition, each document was critically appraised using the Public Health Ontario Meta-tool for Quality Appraisal for Public Health Evidence (PHO MetaQAT) in duplicate, which incorporates assessment of relevancy, reliability, validity and applicability.[45] Disagreements were resolved through discussion and consensus. We used a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of evidence for each outcome of interest.[11,46]

Development of recommendations

We chose the GRADE tool because it is designed to grade the overall quality of the body of published academic and grey literature evidence and to help develop recommendations using systematic, transparent and reproducible methods, with the understanding that subjectivity exists in determining quality of published academic and grey literature evidence.[11,47] The identified published academic and grey literature evidence was graded according to GRADE criteria of risk of bias, imprecision, inconsistency, indirectness and publication bias, and we incorporated the quality of the evidence into our decision-making.[22]

The leadership group and research team generated preliminary recommendations and strength of recommendations based on the published evidence from the systematic reviews. The proposed recommendations and strength of recommendations were sent to the Guidance Steering Committee, Affected Community Committee and Clinical Expert Committee. We collected feedback on the content and wording of the recommendation, strength of recommendation and components contributing to strength of recommendation via Research Electronic Data Capture (REDCap) data collection software. Details on the feedback surveys are available in Appendix 6 (at www.cmaj.ca/lookup/doi/10.1503/cmaj.230128/tab-related-content).

Additionally, we used the feedback surveys to collect community expert evidence. Expert evidence can be an effective way to develop robust and trustworthy guidelines in addition to published evidence.[13] This data source was particularly important as the

published evidence was of very low quality, occasionally regionally specific to locations outside of Canada, and sometimes disagreed on key conclusions. Expert opinion and evidence (or community evidence) is a valuable resource in guideline development, especially in cases like this where scant published evidence exists.[13] Experts may include patient and patient representatives (in this context, people who use drugs) and health professionals.[13] Appendix 7 (available at www.cmaj.ca/lookup/doi/10.1503/cmaj.230128/tab-related-content) summarizes the expert evidence and opinion that the Naloxone Guidance Development Group used to inform recommendation development. We collected community evidence through feedback surveys and presented it at Naloxone Guidance Development Group meetings, where members could offer further context or clarification to the group if needed.

The leadership and research team, Methodology Advisory Committee, Guidance Steering Committee, Affected Community Committee and Clinical Expert Committee met virtually to discuss recommendations and arrive at a consensus. Community and published evidence were presented to the committees and informed debate on key topics and final decision-making on recommendations.

External review

Eight members sat on the External Review Committee and contributed content and methodological expertise to the guidance development process. This committee was asked to comment on the validity, reliability, reproducibility and feasibility of the guidance after the development of the draft report (available in Appendix 1). Several authors (M.F., J.A.B., K.R., P.L.) implemented edits and recirculated comments to the committee. The recommendation on overdose response was edited for clarity, but the committee identified no major changes in the recommendations as part of this external review.

After guidance development, we asked for public input on the draft report and our recommendations. Recruitment material for public input was circulated through members of the Naloxone Guidance Development Group and by contacting harm reduction organizations across the country. Indigenous, Black and other racialized people, and 2SLGBTQIA+ individuals were explicitly invited in all public consultation recruitment material and accessibility accommodations were offered and provided for those who needed them. A total of 73 people from across the country completed surveys online between Aug. 1 and Sept. 30, 2022 (survey available in Appendix 6). Those who completed the survey were eligible to enter a draw for 2 $100 Visa cards.

We also asked people who use or have used drugs or who respond to overdose in the community setting to participate in 90-minute consultation sessions, where we presented our recommendations. Consultation-session participants were compensated for their time with $50 honoraria. A total of 75 people participated in 15 consultation sessions, which took place between Aug. 1 and Sept. 30, 2022. Given that we received support for our recommendations from session participants, we used their input to help clarify wording and add context to our report. The session participants mentioned many of the same observations as the Naloxone Guidance Development Group (discussed in Appendix 7).

Management of competing interests

We adhered to the Guidelines International Network (GIN) principles on managing competing interests.[48] A conflict of interest form was developed by author J.N., based on recommendations generated by the Institute of Medicine.[49] We distributed the form to Naloxone Guidance Development Group members at the beginning of their involvement with the project. We asked committee members to disclose any financial, institutional or intellectual conflicts of interest. Completed forms were independently screened by 2 members of the team (M.F. and J.N. or J.A.B.) for any potential conflicts. Differences of opinion were resolved by discussion and informal consensus between the screeners.

Using a framework derived from the GIN principles,[48] we quantitatively assessed the competing interests of each member of the Naloxone Guidance Development Group on a "relevance index" on a scale from 0 to 5 or assessed them as "not applicable." Of the 52 members who participated in guidance development, 18 declared no interests and were "not applicable" on the scoring system. A total of 26 declared interests that were deemed not relevant to the project and were rated 0 on the relevance index scale. Research team members who were not involved with recommendation generation were not required to submit a conflict-of-interest form. No members were excluded from participation or had participation restricted because of direct financial conflict of interest. Further details on management of competing interests and a full list of Naloxone Guidance Development Group composition are available in Appendix 1.

Implementation

Our recommendations require further investment in THN programs on a provincial, territorial or federal level to include additional ampoules or vials of naloxone in kits, make intranasal naloxone more readily available, and potentially expand training opportunities for overdose response.

In addition to publishing recommendations in an open-access, peer-reviewed journal, we will also make a community-friendly report available on the CRISM website.

Although our current funding for this project does not allow for updates to this guidance for policy, we have published details on further questions that the Naloxone Guidance Development Group deemed important for inclusion in Canadian guidance,[43] as well as details on the systematic review methods used to identify relevant published academic and grey literature evidence (Appendix 5) so that new information can be identified using consistently rigorous methods.

Other guidelines

Six other guidance documents have been published with recommendations. Our review findings and recommendations on overdose response and route of administration are largely consistent with 2014 WHO guidance.[21] Our guidance mandate differed from a 2018 guideline published by INESSS, which focused on resuscitation approaches in community overdose response in Quebec.[32] Noting disagreement among experts and a lack of

empirical evidence, the INESSS guideline recommended promoting chest compression–only CPR if a community overdose responder had never received appropriate training. Although the INESSS guideline and our guidance noted similar concerns regarding responder knowledge, our guidance defined trained responders as people who have received training from peers, online resources, training developed by THN programs or CPR training courses, whereas the INESSS guideline defined trained responders as people fully trained specifically in CPR. A recent resource from the American Heart Association states that some "trained lay people," including those trained by overdose education and naloxone distribution programs, are able to perform high-quality CPR, rescue breathing and naloxone administration.[1] In addition, INESSS recommended specific strategies for improving overdose response training and for ongoing monitoring and evaluation of THN programs, which we did not address in our guidance.

The guideline on managing opioid-induced cardiac arrest from the American Heart Association includes separate recommendations for health care workers and lay responders.[1] The American Heart Association recommends that people who cannot reliably establish the presence of a pulse should initiate conventional CPR, including chest compressions and rescue breathing.[1]

Most existing guidelines do not speak to the same context or content. Wegner and colleagues published consensus guidance on best practices for community-based overdose education and THN programs in the US.[50] Their top recommendations involved ensuring low-barrier, needs-based access to naloxone and that there be ample naloxone available within communities. Tsuyuki and colleagues published a consensus guideline on THN prescribing by pharmacists in Canada, recommending that all patients receiving an opioid at a pharmacy be dispensed THN and counselled by a pharmacist.[51] The American Society of Addiction Medicine guideline on medication treatment for opioid use disorder includes recommendations that naloxone be given in case of overdose, and that people with opioid use disorder, their family and emergency first responders be trained in overdose response and equipped with naloxone.[52]

Gaps in knowledge

Little primary research has addressed our research questions specific to community overdose responders. The harm reduction field would benefit from research led by or created in close collaboration with people who use drugs, on topics including kit contents, routes of administration of naloxone and overdose response.

Harm reduction principles require more inclusion of the affected community relative to the average guideline development process.[53] Multiple Naloxone Guidance Development Group members with lived and living experience and expertise of drug use and overdose response described frustration at not being represented in bodies of literature that determine service provision for people who use drugs, and spoke about how people who use drugs generate and communicate strategies for responding to overdose.

During public input, consultation-session participants frequently discussed the importance of standardized and high-quality training. Although it was outside of our project's scope to issue recommendations on THN training, we recorded some of the important insights shared and have summarized them in Appendix 7.

A concern raised in public-input consultation sessions was the lack of availability of naloxone (Appendix 7). A valuable next step would be to identify barriers to accessing THN programs in Canada and different strategies for addressing these barriers and enabling access.

Limitations

We noted that the quality of published scientific and grey literature evidence was very low for our questions, which focused on community responders.

Given the very low quality of published evidence identified through systematic reviews and the high level of expertise brought by the Naloxone Guidance Development Group, expert evidence played a strong role in the guidance development process. In Appendix 2, we present the expert evidence and expert opinion to differentiate the facts[13] reported by the Naloxone Guidance Development Group from the conclusions that the Naloxone Guidance Development Group drew in light of these facts.

Conclusion

This guidance development project provides direction for THN programs in Canada in the context of scant published evidence. We provide recommendations on kit contents, routes of administration of naloxone and overdose response; these recommendations were developed in collaboration with diverse stakeholders.

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Affiliations: BC Centre for Disease Control (Ferguson, Adams, Burmeister, Choisil, Ng, Buxton), Vancouver, BC; Department of Psychiatry (Rittenbach), University of Calgary, Calgary, Alta.; Department of Psychiatry (Rittenbach), University of Alberta, Edmonton, Alta.; Public Health Ontario (PHO) (Leece); Dalla Lana School of Public Health (Leece, Elton-Marshall, Strike) and Department of Family and Community Medicine (Leece), University of Toronto; Institute for Mental Health Policy Research (Ali, Elton-Marshall), Centre for Addiction and Mental Health, Toronto, Ont.; School of Epidemiology and Public Health (Elton-Marshall), University of Ottawa, Ottawa, Ont.; Department of Medicine (Brothers), Dalhousie University, Halifax, NS; UCL Collaborative Centre for Inclusion Health (Brothers), University College London, London, UK; Center for Indigenous Health (Medley), Johns Hopkins Bloomberg School of Public Health, Baltimore, Md.; Overdose Emergency Response and Addictions Program (Medley), Vancouver Coastal Health, Vancouver, BC; Health Sciences Library (Lorenzetti), University of Calgary; Department of Community Health Sciences (Lorenzetti), Cumming School of Medicine, University of Calgary; O'Brien Institute for Public Health (Lorenzetti), University of Calgary, Calgary, Alta.; BC Centre on Substance Use (Gallant); School of Population and Public Health (Buxton), University of British Columbia, Vancouver, BC

Contributors: Farihah Ali, Jane Buxton, Tara Elton-Marshall, Max Ferguson, Kat Gallant, Pamela Leece, Diane Lorenzetti and Katherine Rittenbach contributed to the conception and design of the work. Max Ferguson, Alison Adams and Justin Ng contributed to the acquisition of data. Farihah Ali, Thomas Brothers, Paul Choisil, Charlene Burmeister, Jane Buxton, Max Ferguson, Kat Gallant, Pamela Leece, Andrea Medley, Katherine Rittenbach and Carol Strike contributed to the analysis and interpretation of data. Max Ferguson and Alison Adams drafted the manuscript. All of the authors revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work. All authors were part of the Naloxone Guidance Development Group. Jane Buxton, Katherine Rittenbach and Pamela Leece shared the role of senior author.

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Correspondence to: Jane Buxton, jane.buxton@bccdc.ca