Effectiveness of take-home naloxone programs and availability of naloxone nasal spray in different jurisdictions

Questions

- What is the evidence of the effectiveness of take-home naloxone programs and administration of naloxone by laypeople?
- Which jurisdictions provide take-home naloxone programs?
- What is the current availability of naloxone nasal spray in different jurisdictions?

Key Take-Home Messages

- There is wide support of take-home naloxone programs as they are associated with decreased mortality (1–8), but there is some evidence that take-home naloxone alone may not be sufficient to significantly reverse the risk of negative health outcomes as a result of a drug overdose (6, 9–11).
- Higher-concentration intranasal naloxone (at least 2 mg/mL) has the efficacy similar to that of intramuscular naloxone (2 mg) for reversal of opioid overdose, with no difference in adverse events (12, 13).
- Take-home naloxone programs are in place in many jurisdictions across North America, Europe and Australia, but few of them have switched to using intranasal naloxone sprays. These include Ontario (14), the Northwest Territories (15), New York State (16), California (17), three Australian states (18) and Norway (19).
- Little research has been completed on using naloxone nasal spray in real-world settings, but initial results are encouraging as they indicate that the nasal spray formulation is successful at reversing the effects of opioid overdose in most cases (20).

Rapid Response: Evidence into Action

The OHTN Rapid Response Service offers quick access to research evidence to help inform decision making, service delivery, and advocacy. In response to a question, the Rapid Response Team reviews the scientific and grey literature, consults with experts if required, and prepares a review summarizing the current evidence and its implications for policy and practice.

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The Issue and Why it's Important

Naloxone, an opioid antagonist, is an effective method, if used in a timely manner, to reverse the action of opioids (1). Naloxone take-home kits are becoming increasingly available to the public and laypersons, and there are more programs being established to provide these kits as well as corresponding education on proper use and signs of opioid overdose (1, 3).

There are several formulations of naloxone available in Canada. The injectable formulations (for intramuscular, intravenous, or subcutaneous use) are available in 0.4mg/ml and 1mg/ml strengths (21). Although not approved by Health Canada or the U.S. Food and Drug Administration (FDA), the practice of using an atomization device to deliver the injectable formulation through the nasal route has also been reported and studied (21). In 2016, Health Canada approved a nasal spray formulation of naloxone, Narcan® Nasal Spray – a needleless device that delivers a fixed intranasal dose of naloxone (21). Additionally, an auto-injector formulation of naloxone, Evzio is also available in the U.S., but it is not yet approved in Canada (21).

Naloxone take-home kits were reportedly being distributed in the early 1990s as a harm reduction strategy in syringe exchange clinics mostly for heroin users in Italy (1, 22). Since then, naloxone take-home kits have been widely implemented in programs that place naloxone in the hands of users, caregivers, laypersons, and emergency personnel for opioid overdose administration (1, 22). Naloxone take-home kits have been deployed in many community-based programs with an aim to decrease mortality in the growing number of opioid overdoses (1, 22). Framed as a public health tool for harm reduction, take-home naloxone programs have overcome social, clinical, and legal barriers in many jurisdictions (22). Nonetheless, the rising death toll due to opioid overdoses illustrates that current take-home naloxone coverage is insufficient, and greater public investment in overdose prevention will be required if take-home naloxone is to achieve its full potential impact (22).

A study of 1,137 people who use drugs in Vancouver (including 392 opioid users) found that 727 (64%) reported at least one previous overdose, and 220 (19%) had witnessed an overdose in the previous six months (23). Although 769 (68%) participants reported awareness of take-home naloxone, only 88 of 392 (22%) opioid users had a take-home naloxone kit, 18 (20%) of whom had previously administered naloxone (23). The results were similar among Vancouver's street involved youth aged 14–28 years: while 126 of 177 participants (71.2%) reported knowledge of take-home naloxone, only 40 (22.6%) possessed a take-home naloxone kit (24).

The purpose of this review is to describe take-home naloxone programs, with a focus on those using naloxone nasal sprays; to summarize evidence of the effectiveness of take-home naloxone

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programs and/or administration of naloxone by laypeople; and to provide a jurisdictional review of take-home naloxone programs.

What We Found

Naloxone use in opioid overdose

Guidelines produced by the World Health Organization (WHO) (25) and the American Society of Addiction Medicine (ASAM) (26) 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 (2). It is recommended that opioid users and those likely to witness an opioid overdose (such as family members) should be trained for naloxone administration (2). In the WHO guideline, regardless of the administration routes, naloxone is recommended due to its effectiveness for opioid overdose (2, 25). Individuals should choose a route of naloxone administration depending on the formulation available, administration skills, and settings (2, 25).

Naloxone dosage and comparison of different formulations

Naloxone hydrochloride nasal spray is a needleless device that delivers a fixed intranasal dose of naloxone (27). Larger doses are needed for intranasal administration (e.g., 2mg per 0.1 mL) to match the plasma levels of 400 μg when given intramuscularly (28). These larger, more concentrated intranasal doses are now available in products that have been approved by Health Canada (4mg per 0.1 mL), the U.S. FDA (4mg per 0.1 mL), the Australian Therapeutic Goods Administration (2mg per 0.1 mL) (28) and are licensed in the UK and other countries in Europe (1.8mg per 0.1mL) (29).

According to a systematic review, higher-concentration intranasal naloxone (2 mg/mL) seems to have efficacy similar to that of intramuscular naloxone (2 mg) for reversal of opioid overdose, with no difference in adverse events (12, 13). Based on the findings of this systematic review, the U.S. Guidelines for EMS Administration of Naloxone recommend intranasal over intramuscular routes of administration (30). The recommendation was driven among other factors by considerations related to ease of administration and practitioner safety, especially in relation to agitation and adverse opioid withdrawal reactions (30). Needlestick injuries might be of particular concern for those who may have less experience with intramuscular injections (30). Comparing intranasal and intravenous naloxone, the guideline panel equally recommends the intranasal and intravenous routes of administration, but there are many variables which determine the preferred route of administration for an individual case (30). Emergency medical service practitioners with less training may not be able to obtain intravenous access, making intranasal naloxone the preferred route of administration in

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those cases (30).

A 2019 study compared pharmacokinetic properties of naloxone Intranasal (Narcan® nasal spray, 2-mg and 4-mg strengths, 0.1 mL/dose) and intramuscular (autoinjector Ezvio, 2mg) devices with a common improvised nasal naloxone device (prefilled syringe containing 2 mg of naloxone, 1 mg/mL, attached to a mucosal atomization device) (31). This study found that the highest maximum plasma concentration was achieved using the 4-mg Narcan® nasal spray, and the highest exposures (plasma concentration over time) at five minutes post-dose were after administration with the autoinjector and the 4mg Narcan® nasal spray, and at 10, 15, and 20 minutes post-dose, the 4-mg Narcan® nasal spray yielded the greatest exposure (31). Even after two administrations, the improvised nasal naloxone device (atomizer) failed to achieve naloxone plasma levels comparable to the Narcan® nasal spray at any timepoint (31). The authors concluded that the ease of use and higher plasma concentrations achieved using the 4-mg Narcan® nasal spray should be considered when deciding which naloxone device to use (31).

The effectiveness of take-home naloxone

Most take-home naloxone kits usually consist of vials of naloxone and sterile syringes and needles for intramuscular delivery that are dispensed at no cost (32). There is limited evidence of using intranasal sprays as part of take-home naloxone kits as these became available only recently.

A review of 20 years of experience with take-home naloxone for the prevention of overdose deaths notes that there was a lack of familiarity with take-home naloxone that challenged the early distribution schemes (2001–2006), leading to further testing, evaluation, and assessment of challenges and perceived medical and legal barriers (22). From 2006–2011, response to social and legal concerns led to the expansion of take-home naloxone programs, followed by high-impact research and efforts to widen take-home naloxone availability from 2011 to 2016 (22).

There is wide support of take-home naloxone programs as they are associated with decreased mortality (1–8). The effectiveness of naloxone take-home kits is demonstrated by decreased mortality rates, increased successful opioid reversals due to use of naloxone, or increased survival rates (1, 8, 33). The authors recommend that take-home kits be made more widely available for implementation throughout communities as a method for decreasing mortality rates associated with opioid overdose (1). Although there is a concern that distribution of naloxone to persons at risk of experiencing an opioid overdose may reduce the perceived negative consequences of drug use or lead to riskier patterns of use (34), a study from New York City found no evidence of such compensatory drug use risk behavior among heroin users after receiving take-home naloxone (35).

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A systematic review of 22 observational studies published in 2016 assessed the effectiveness of take-home naloxone in terms of its impact of opioid overdose mortality (3). Because of a lack of randomized controlled trials and a wide range in the methodological quality of the research studies, a meta-analysis was dismissed in favour of an analysis using the Bradford Hill criteria of causation (3, 7). Based on their analysis, the authors concluded that take-home naloxone programs lead to improved survival rates among program participants and to reduced overdose mortality rates in the community (3, 7). A later publication, which also based its analysis on the Bradford Hill criteria, reached an almost identical conclusion (7, 36).

A cost-effectiveness evaluation of distribution of intramuscular naloxone in the UK concluded that distribution of take-home naloxone decreased overdose deaths by around 6.6% (37). In a population of 200,000 heroin users this equates to the prevention of 2,500 premature deaths at an incremental cost per quality-adjusted life year (QALY) gained of GBP 899 (37). The authors considered this cost-effective with an incremental cost per QALY gained well below the willingness-to-pay threshold (GBP 20,000) set by UK decision-makers (37). But this evaluation was done for intramuscular naloxone that was the only available formulation in the UK during the study publication in 2018 (37). Although the intranasal spray formulations are more expensive, the authors suggest that introduction of naloxone nasal spray would have an added value over an intramuscular route of administration (37). Similar efficacy, in terms of time to reversal of overdose, has been demonstrated, however, there is no risk of needle-stick injury and subsequent risk of infection from blood-borne pathogens with the intranasal route of administration, a particular concern for nonmedical responders given the high rate of HIV and hepatitis B or C among people who use drugs (37). It is also easier to use, requires less training, and the nose is often readily available (37). Such benefits may increase distribution and the likelihood of use during an overdose (37). Furthermore, studies suggest that the proportion of people who inject drugs with prescribed intramuscular naloxone who carry it with them could be as low as 5% (37, 38). Because of higher acceptability and ease of use, the availability of intranasal formulation may lead to higher carriage rates (37).

At the same time, there is some evidence that take-home naloxone alone may not be sufficient to significantly reverse the risk of negative health outcomes as a result of drug overdose.

A study from Scotland that found that the supply of take-home naloxone kits through a National Naloxone Programme was not clearly associated with a decrease in ambulance attendance at opioid-related overdose incidents in the 4-year period after it was implemented in April 2011 (39). Scotland's National Naloxone Programme also did not show an anticipated 20% reduction over six years in opioid-related deaths after hospital discharge; opioid-

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related deaths were 10% at baseline and 9% during 2011–2016 (6). Possible explanations include opioid users being unaware of their increased opioid-related death risk in the four weeks following hospital discharge and naloxone kits not being accessed by older (aged ≥35 years) users of methadone (6).

Another study from Cuyahoga County in Ohio (which includes Cleveland) also did not demonstrate a significant benefit in the patient level composite outcome of repeat emergency department visit, hospitalization, and death (at 0–3 months and 3–6 months) between patients who received a naloxone rescue kit in the emergency department following a non-fatal heroin overdose and those who did not (9). In fact, all fatalities and most patients who reached the composite outcome (i.e. died or were readmitted in the emergency department or hospitalized) were in the group that received a naloxone rescue kit at emergency department discharge (9). The authors suggested that this finding may be due to the greater proportion of overdose survivors (71%) that received a naloxone rescue kit (distribution of kits became standard care for overdose aftercare in the emergency department during the study period and increased over time), and the overall increase in overdose mortality in Cuyahoga County during the study period driven by the introduction of more lethal fentanyl into the illicit drug market (9).

A study from two emergency departments in Seattle randomized heroin or pharmaceutical opioids users to overdose education combined with a brief behavioral intervention and take-home naloxone or usual-care (10). During the follow-up period, 24% of the 241 participants had at least one overdose event, 85% had one or more emergency department visits, and 55% had at least one hospitalization, with no significant differences between intervention and comparison groups (10). These null findings may have been due to the severity of the population in terms of housing insecurity (70% in temporary housing), drug use, unemployment, and acute health care issues (10).

The investigation of a cohort of heroin-overdose deaths in the state of Victoria, Australia, found that there were 235 fatal heroin overdose cases identified over the study period, and the majority of these cases occurred at a private residence (n=186, 79%) and where the decedent was alone at the time of the fatal overdose event (n=192, 83%) (11). There were only 38 cases (17%) where the decedent was with someone else or there was a witness to the overdose event, and in half of these cases the witness was significantly impaired, incapacitated, or asleep at the time of the fatal heroin overdose (11). There were 19 fatal heroin overdose cases (8%) identified where there was the potential for appropriate and timely intervention by a bystander or witness (11). The authors suggested that take-home naloxone alone could have led to a very modest reduction in the number of fatal heroin overdose cases over the study period and a lack of supervision or a witness to provide meaningful and timely

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intervention was evident in most of the fatal heroin overdose cases (11).

Take-home naloxone programs in different jurisdictions

In 2011, Scotland became the first jurisdiction to implement a National Naloxone Programme with naloxone kits made available to those at risk of opioid-related overdose and after brief training in the community or in prisons (6).

Since then, several countries and jurisdictions have implemented their own versions of take-home naloxone programs:

Since 2013, the Ontario Naloxone Program (ONP) was distributing injectable naloxone kits and training supplies to needle exchange programs housed at both public health units and community-based organizations, and ministry-funded Hepatitis C teams (40). In 2016, naloxone injection kits were made available in pharmacies at no charge to eligible persons such as a current user, a past user at risk of opioid overdose, friends and families of persons at risk, or a person in a position to assist a person at risk of an overdose from opioids (40). Beginning in January 2017, the ONP began transitioning from naloxone injection kits to naloxone nasal spray kits (40). In the fall of 2017, as part of the expansion of naloxone distribution, public health units began sub-distributing naloxone kits to eligible community-based organizations (40). Additionally, naloxone nasal spray has recently started to be distributed to at-risk inmates being released from provincial correctional facilities (40).

The British Columbia Take Home Naloxone (BCTHN) program was implemented in 2012 by the BC Centre for Disease Control (BCCDC) funded through the provincial ministry of health (41). With about 1,000 opioid-related deaths related to fentanyl-contaminated heroin in 2016, British Columbia rapidly increased its distribution of naloxone kits from 3,390 kits in 2015 to 13,757 kits in the first 10 months of 2016 (5, 6). This change was coincident with a reversal in opioid-related deaths (5). Since September 2016, in British Columbia, the status of naloxone was changed to an unscheduled drug which allowed it to be available anywhere and accessible by anyone (41). To streamline the ordering process, a program-wide policy of standing orders was introduced in January 2017 (41). A standing order is an automatic weekly delivery for sites that regularly order a high volume of kits (41).

Alberta's provincial take-home naloxone program was implemented on December 23, 2015 (42). This collaborative program resulted in a coordinated response across jurisdictional levels with wide geographical reach (42). Between December 2015 and December 2016, 953 locations (including 759 community pharmacies, seven harm reduction agencies, provincial correctional facilities, post-secondary institutions, opioid dependency treatment facilities,

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community health centres, inner city agencies, First Nations communities, and urgent care centres) registered to dispense take-home naloxone kits, where 9,572 kits were distributed, and 472 reversals were reported (42). The provincial supply of take-home naloxone kits has more than tripled from 3,000 to 10,000 during this period (42).

The Government of Manitoba launched a provincial take-home naloxone program in January 2017. By the end of September 2017, there were over 60 sites operating in Manitoba (43). These sites distributed 765 kits to people at risk of opioid overdose, and 93 of these kits were replacement kits used in overdose events (43).

Other Canadian provinces and territories also have take-home naloxone programs in place (40, 44, 45):

Saskatchewan residents who are at risk of an opioid overdose and/or might witness an opioid overdose, such as friends and family of people who use opioids, are eligible for free training and a free take-home naloxone kit (46). The training covers overdose prevention, recognition and response, including how to administer naloxone (46).

In Quebec, anyone 14 years of age or older can obtain naloxone in injectable or nasal spray for free with their Health Insurance Card from a pharmacy (45).

The New Brunswick Take Home Naloxone (NBTHN) program offers injectable naloxone kits free of charge to people who are at risk of an overdose and to family, friends, and those who are most likely to witness and respond to an opioid overdose (45). Kits are available for pick up by the general public from community agencies (45). Training is required through British Columbia's Toward the Heart's Take Home Naloxone website (47). Once an individual completes the training, they receive a certificate which whey must show to collect their kit (45). All other individuals can purchase kits on their own from a participating pharmacy (45).

The Take Home Naloxone Program in Nova Scotia offers training and injectable naloxone kits free of charge to people who are at risk of an overdose and to family, friends, and those who are most likely to witness and respond to an opioid overdose (45). Kits can also be obtained free of charge and without a health card from over 300 locations across the province (45). Teachers, faculty, and students can obtain kits free of charge upon request through the provincial naloxone program (45).

The Prince Edward Island's Take Home Naloxone program distributes kits free of charge to people who are at risk of an overdose or to the friends and family of someone at risk (45). All other individuals can purchase kits on their own from a participating pharmacy (45).

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The Take Home Naloxone program in Newfoundland and Labrador distributes kits free of charge to people who are at risk of an overdose or to the friends and family of someone at risk (45). All other individuals can purchase kits on their own from a participating pharmacy (45).

There are no restrictions on naloxone access in Yukon (45). Anyone – people who use drugs, friends and family, businesses – can access a free take-home naloxone at community health centres and in all pharmacies across the territory (45, 48). Individuals who wish to purchase more kits for use in other settings (campuses, workplaces) can purchase them at a pharmacy (45).

There are no restrictions on naloxone access in the Northwest Territories. Anyone – people who use drugs, friends and family, businesses – can access a free naloxone kit at community health centres and in all pharmacies across the territory (no health card or ID necessary) (45, 49).

The Nunavut Take Home Naloxone Program offers training and injectable naloxone kits free of charge to people who are at risk of an overdose and to family, friends, and those who are most likely to witness and respond to an opioid overdose (no ID or health card required) (45). The Department of Health coordinates distribution of naloxone kits to take-home naloxone distribution sites, and naloxone is not available for purchase in retail pharmacies (45).

In 2019, take-home naloxone initiatives were reported to exist in 12 European countries delivered by a variety of different providers including clinics, prisons and outreach services: Austria, Denmark, Estonia, France, Germany, Ireland, Italy, Lithuania, Norway, Spain (Catalonia), Sweden and the UK (50). In 2018, the legal framework for establishing such programs was created in Cyprus and preparatory steps for introducing naloxone were taken in Finland (50).

In England, where opioid-related deaths per year averaged 1,027 in 2006–2010, 117 of 151 local authorities reported an estimated distribution of 23,100 naloxone kits in 2016–2017, which is above the National Naloxone Programme target for England (20 times the country's annual number of opioid-related deaths) (6). Wales' National Naloxone Programme began in 2011, shortly after Scotland's, and has exceeded its distribution target of 1,600 naloxone kits per year (20 times Wales' annual number of opioid-related deaths) since 2013–2014 (6).

The first take-home naloxone programs in Australia were developed in the early 2010s across a number of peer-led and health service settings (51). The programs now operate in five Australian jurisdictions and peer drug user groups currently play a central role in the development, delivery and scale-up of take-home naloxone programs in Australia (52). Between 2012 and 2017, over 2,500 Australians at risk of overdose have been trained and provided

38. McAuley A, Munro A, Bird SM, Hutchinson SJ, Goldberg DJ, Taylor A. Engagement in a National Naloxone Programme among people who inject drugs. Drug and alcohol dependence. 2016;162:236–40.

39. McAuley A, Bouttell J, Barnsdale L, Mackay D, Lewsey J, Hunter C, et al. Evaluating the impact of a national naloxone programme on ambulance attendance at overdose incidents: A controlled time-series analysis. Addiction. 2017;112(2):301–8.

40. Pant S, Severn M, Canadian Agency for Drugs and Technologies in Health. Funding and management of naloxone programs in Canada. CADTH rapid response report: Summary with critical appraisal. 2018. Available from: https://www.cadth.ca/sites/default/files/pdf/ES0319_funding_and_management_of_naloxone_programs_in_canada.pdf. Accessed September 11, 2020.

41. Young S, Williams S, Otterstatter M, Lee J, Buxton J. Lessons learned from ramping up a Canadian take home naloxone programme during a public health emergency: A mixed-methods study. BMJ Open. 2019;9(10):e030046.

42. Freeman LK, Bourque S, Etches N, Goodison K, O'Gorman C, Rittenbach K, et al. Alberta's provincial take-home naloxone program: A multi-sectoral and multi-jurisdictional response to overdose. Canadian Journal of Public Health Revue Canadienne de Sante Publique. 2017;108(4):e398–e402.

naloxone (52). Evaluation data from four programs recorded 146 overdose reversals involving naloxone that was given by take-home naloxone program participants (52). This number was derived from a total of 358 participants formally followed-up 3–6 months post training – suggesting 41% of trained participants used their naloxone to help revive someone during that time period (52). There are a further 484 anecdotal reports of overdose reversals involving take-home naloxone programs (52).

The New South Wales' Overdose Response with Take-Home Naloxone project developed, implemented, and evaluated a brief (15 minutes) take-home naloxone intervention targeting people at high risk of opioid overdose – specifically those with a history of opioid use disorder and/or injecting drug use, attending services such as alcohol and other drug treatment, needle and syringe programs, and related health services targeting this population (51). The evaluation concluded that approximately 10% of clients who received the intervention successfully reversed an overdose within three months and this widespread distribution through low-threshold services and funded medication was well suited to roll-out more broadly (51).

Take-home naloxone at emergency departments

The strongest predictor of a fatal overdose is a non-fatal overdose (53), as nearly 6% of patients discharged from the emergency after an opioid overdose die within the following year and over 1% die within one month (54, 55). With many of non-fatal overdoses managed by emergency departments, and escalating opioid-mortality rates, there is a potential to deliver evidence-based overdose prevention in these settings (53, 55).

The American College of Emergency Physicians (ACEP), the Centers for Disease Control and Prevention (CDC), and the surgeon general recommend dispensing naloxone to discharged emergency department patients at risk for opioid overdose (55).

Several studies report on take-home naloxone programs at hospital emergency departments (32, 53).

A recent systematic review identified seven emergency-department delivered programs that focused on the provision of take-home naloxone and overdose education (53). Six of these programs were implemented in the U.S., and one in British Columbia (56). Three of these programs used nasal naloxone kits (56–58), but these included atomizer devices and not nasal sprays.

Several research articles provided insights into aspects of take-home naloxone at emergency departments. For example, an emergency department of a Chicago hospital had 669 unique visits for opioid overdose over 16 months, and dispensed 168 take-home naloxone kits (10.5 per month), with at least three cases in which the kits were used to reverse opioid overdose (32). Different emergency

43. Bozat-Emre S, Marshall SG, Zhong C, Reimer J. At-a-glance – Lessons learned from launching the Manitoba Take-Home Naloxone Program. Health Promotion and Chronic Disease Prevention in Canada. 2018;38(6):252–5.

44. Government of Canada. Where to get naloxone in your province or territory. 2019. Available from: https://www.canada.ca/en/health-canada/services/substance-use/problematic-prescription-drug-use/opioids/naloxone.html#5. Accessed September 11, 2020.

45. Canadian Mental Health Association (CMHA). What is naloxone? 2019. Available from: https://cmha.ca/wp-content/uploads/2019/08/CMHA-Naloxone-Toolkit-Naloxone101-ENG-Final.pdf. Accessed September 11, 2020.

46. Saskatchewan. Take home Naloxone program sites. 2020. Available from: https://www.saskatchewan.ca/residents/health/accessing-health-care-services/mental-health-and-addictions-support-services/alcohol-and-drug-support/opioids/take-home-naloxone-program-sites. Accessed September 11, 2020.

47. BCCDC Harm Reduction Services, St. Paul's Foundation, Toward the Heart. Take home naloxone. 2020. http://www.naloxonetraining.com/. Accessed September 11, 2020.

48. Yukon Government Department of Health and Social Services. Fentanyl and naloxone information. 2020. Available from: http://www.hss.gov.yk.ca/fentanyl.php. Accessed September 11, 2020.

departments across the Chicago area used different naloxone take-home formulations (intramuscular injection, intranasal atomizers, and intranasal sprays), with the costs of Narcan nasal spray being much higher compared with the other two types (55, 59). A study conducted among 555 patients at two Rhode Island hospitals showed that emergency department naloxone distribution and consultation with a community-based peer recovery coach was feasible, acceptable, and could be maintained over time (60).

Although the emergency department is an opportune setting for overdose prevention as people who use opioids frequently present for emergency care, a retrospective review of 342 admissions with primary diagnosis of opioid overdose at a large, urban tertiary hospital located in Edmonton, Alberta found that in this real-world situation, only half of patients with opioid overdose were offered take-home naloxone (61). This is in line with a systematic review of five studies that showed that when patient follow-up was attempted, success was low, limiting the evidence for the programs' effectiveness (62). Overall, in the included studies there was evidence that distributing take-home naloxone from the emergency department has the potential for harm reduction; however, the uptake of the practice remained low (62). Barriers to implementation included time allocated for training hospital staff and the burden on workflow (62).

According to a study in Pennsylvania, electronic health record prompts are associated with increased take-home naloxone distribution for emergency department patients discharged after opioid overdoses (63).

Take-home naloxone at other settings

Different studies investigated the role of take-home naloxone in other settings, such as settings in which kits are supplied to patients in opioid treatment programs (64).

A 2017 systematic review take-home naloxone for people released from correctional settings identified 9 studies reporting on take-home naloxone programs (65). Prison-based take-home naloxone distribution has been introduced to varying degrees in several jurisdictions including Canada, the UK, and the U.S., and the feasibility of take-home naloxone in the context of release from a correctional setting has been established, but there is a need for rigorous research into health outcomes and program implementation (65).

Naloxone nasal spray

Currently there are several different products of naloxone nasal spray in use globally (7, 59). These include: Narcan Nasal Spray®, Nalscue®, Nyxoid®, Ventizolve®, Respinal®.

The U.S. FDA approved a first naloxone nasal spray product in November 2015 (22). Health Canada approved non-prescription

49. Government of Northwest Territories. NWT naloxone kit distribution. 2019. Available from: https://www.hss.gov.nt.ca/en/naloxone-kit-distribution. Accessed September 11, 2020.

50. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Take-home naloxone. 2020. Available from: https://www.emcdda.europa.eu/publications/topic-overviews/take-home-naloxone_en. Accessed September 11, 2020.

51. Lintzeris N, Monds LA, Bravo M, Read P, Harrod ME, Gilliver R, et al. Designing, implementing and evaluating the overdose response with take-home naloxone model of care: An evaluation of client outcomes and perspectives. Drug & Alcohol Review. 2020;39(1):55–65.

52. Dwyer R, Olsen A, Fowlie C, Gough C, van Beek I, Jauncey M, et al. An overview of take-home naloxone programs in Australia. Drug & Alcohol Review. 2018;37(4):440–9.

53. Chen Y, Wang Y, Nielsen S, Kuhn L, Lam T. A systematic review of opioid overdose interventions delivered within emergency departments. Drug & Alcohol Dependence. 2020;213:108009.

54. Weiner SG, Baker O, Bernson D, Schuur JD. One-year mortality of patients after emergency department treatment for nonfatal opioid overdose. Annals of emergency medicine. 2020;75(1):13–7.

use of naloxone for emergency reversal of opioid overdose in pre-hospital settings in March 2016 (27), and authorized the sale for naloxone hydrochloride nasal spray in Canada on July 5, 2017 (27). Naloxone hydrochloride nasal spray is a needleless device that delivers a fixed intranasal dose of naloxone (27). Other formulations of naloxone, including injectable for intramuscular, intravenous, or subcutaneous use, are also available in Canada (27). Atomizer devices have been used in practice to deliver injectable naloxone solution intranasally (27). Both intranasal and intramuscular naloxone formulations are available for pre-hospital use, including by laypersons in the community (27).

Inexperienced users, such as nonmedical first responders and bystanders, are at the highest risk of incorrectly administering naloxone, particularly in high-stress emergency opioid overdose situations (66). Usability research found that 0% untrained and about 60% of trained users were able to successfully administer a full dose of naloxone using an atomizer kit (67), whereas more than 90% of untrained users were able to successfully administer a full dose using Narcan® nasal spray (68). A comparative human factors evaluation also found that Narcan® nasal spray requires fewer steps and is easier to administer than a naloxone nasal atomizer, and using Narcan® nasal spray should increase the likelihood that nonmedical personnel correctly deliver naloxone in time-critical, high-stress opioid overdose rescue situations (66).

In a study assessing the ability of untrained individuals to administer naloxone successfully in a simulated opioid overdose setting, participants were randomly assigned to administer naloxone using a nasal spray device, an intramuscular kit, or an improvised nasal atomizer kit (69). The primary outcome was successful administration, defined as administration within seven minutes and without critical errors (69). The nasal spray (66.7%, $p<0.001$) and intramuscular (51.5%, $p<0.001$) devices had much higher rates of successful administration than the improvised nasal atomizer device (2.9%) (69). The nasal spray device was administered more rapidly (median 16 seconds) than the intramuscular device (median 58 seconds, $p<0.001$) or improvised nasal atomizer device (median 113 seconds, $p=0.012$) (69). Overall, participants administered the nasal spray more successfully and rapidly than the intramuscular and atomizer devices, and nasal sprays were easiest to use (69).

Similar results were obtained from another usability study where after watching a two-minute video, community members were able to administer nasal spray naloxone with a higher rate of success (100%) than intramuscular naloxone (67%) in a simulated overdose setting. Participants were also able to administer nasal spray naloxone more rapidly (median time 34 seconds) than both intramuscular (median time 100 seconds) and multi-step atomized nasal (median time 110 seconds) naloxone (70).

A survey of first responders and community-based organizations

55. Eswaran V, Allen KC, Bottari DC, Splawski JA, Bains S, Aks SE, et al. Take-home naloxone program implementation: Lessons learned from seven Chicago-area hospitals. Annals of Emergency Medicine. 2020;30:30.

56. Kestler A, Buxton J, Meckling G, Giesler A, Lee M, Fuller K, et al. Factors associated with participation in an emergency department-based take-home naloxone program for at-risk opioid users. Annals of Emergency Medicine. 2017;69(3):340–6.

57. Dwyer K, Walley AY, Langlois BK, Mitchell PM, Nelson KP, Cromwell J, et al. Opioid education and nasal naloxone rescue kits in the emergency department. The Western Journal of Emergency Medicine. 2015;16(3):381–4.

58. Kaucher KA, Acquisto NM, Broderick KB. Emergency department naloxone rescue kit dispensing and patient follow-up. The American Journal of Emergency Medicine. 2018;36(8):1503–4.

59. Bell J, Strang J. Medication treatment of opioid use disorder. Biological Psychiatry. 2020;87(1):82–8.

60. Samuels EA, Baird J, Yang ES, Mello MJ. Adoption and utilization of an emergency department naloxone distribution and peer recovery coach consultation program. Academic Emergency Medicine. 2019;26(2):160–73.

from seven different U.S. states provides a real-world experience with Narcan® nasal spray (20). To our knowledge this is the first published study on using Narcan® nasal spray in real-world settings. Eight first-responder or community-based organizations provided case report data on 261 attempted overdose reversals using Narcan® nasal spray, with survival reported for 245 cases (20). Successful overdose reversals were reported in 98.8% (242 of 245) of cases; most cases (73.5%; 125 of 170) reported a time to response of ≤5 minutes after Narcan® nasal spray administration (20). Heroin was the substance reportedly involved in a majority (95.4%; 165 of 173) of these cases; fentanyl was reported to be involved in 5.2% (9/173) of the cases (20). Many reversals (97.6%; 248 of 254) involved administration of ≤2 units of Narcan® nasal spray (20). Three deaths were reported (Narcan® nasal spray was reported to have been administered too late for two cases - the individuals were deceased prior to Narcan® nasal spray administration; details were not provided for the third case) (20). This survey of first-responder and community- based organizations indicated that the new Narcan® nasal spray formulation was successful at reversing the effects of opioid overdose in most reported cases (20).

With the introduction of naloxone nasal spray, more research is under way to facilitate the understanding of its effects. For example, in a five-year randomized controlled trial in New York City the types of take-home naloxone kits evolved over the years (71). At the beginning of the study, from September 2014 to August 2017, participants who chose intranasal naloxone were provided with multi-step naloxone, assembled by combining a pre-filled syringe with a nasal atomizer that administers a dose concentration of 2 mg/2 ml, where 1 ml is administered to each nostril (71). In November 2015, the FDA approved a nasal spray formulation delivered in an atomizer that no longer required assembly (Narcan® nasal spray), providing a potential time-saving advantage over the multi-step device (71). Following the recommendation from the National Institute on Drug Abuse (NIDA), the trial switched from providing multistep atomizer intranasal naloxone to single-step intranasal devices in August 2017 (71).

Jurisdictional review of naloxone nasal spray

Canada

In December 2016, the National Association of Pharmacy Regulatory Authorities (NAPRA) recommended that naloxone nasal spray, when indicated for emergency use for opioid overdose, be made available as a Schedule II drug in Canada (72). This means that any patient or patient's agent can obtain Narcan® Nasal Spray directly from a community pharmacist without a prescription (72). In British Columbia, Alberta, and Saskatchewan, Narcan® Nasal Spray has been made an unscheduled drug, meaning that it can be purchased outside of pharmacies (72).

61. O'Brien DC, Dabbs D, Dong K, Veugelers PJ, Hyshka E. Patient characteristics associated with being offered take home naloxone in a busy, urban emergency department: A retrospective chart review. BMC Health Services Research. 2019;19(1):632.

62. Gunn AH, Smothers ZPW, Schramm-Sapyta N, Freiermuth CE, MacEachern M, Muzyk AJ. The emergency department as an opportunity for naloxone distribution. The Western Journal of Emergency Medicine. 2018;19(6):1036–42.

63. Marino R, Landau A, Lynch M, Callaway C, Suffoletto B. Do electronic health record prompts increase take-home naloxone administration for emergency department patients after an opioid overdose? Addiction. 2019;114(9):1575–81.

64. Katzman JG, Takeda MY, Greenberg N, Moya Balasch M, Alchbli A, Katzman WG, et al. Association of take-home naloxone and opioid overdose reversals performed by patients in an opioid treatment program. JAMA Network Open. 2020;3(2):e200117.

65. Horton M, McDonald R, Green TC, Nielsen S, Strang J, Degenhardt L, et al. A mapping review of take-home naloxone for people released from correctional settings. International Journal of Drug Policy. 2017;46:7–16.

Narcan® Nasal Spray is available for free from pharmacies everywhere in Ontario and Québec, and for Non-Insured Health Benefits (NIHB) Program for First Nations and Inuit clients across Canada (72).

In Ontario, Narcan® Nasal Spray was publicly funded on March 27, 2018 (72, 73). Publicly-funded naloxone (both injectable and nasal spray kits) for Ontarians is distributed through the:

- Ontario Naloxone Program (ONP) sites: needle/syringe exchange, hepatitis C programs and participating community-based organizations; for clients of participating organizations at risk of opioid overdose, and friends and family of clients (14)

- Ontario Naloxone Program for Pharmacies (ONPP): participating pharmacies; for someone currently using opioids, a past opioid user at risk of returning to opioid use, or a family member or friend of someone who is at risk of an opioid overdose (14)

- Ministry of Community Safety and Correction Services: Take Home Naloxone Program at the provincial correctional facilities; for at-risk individuals in provincial correctional facilities where they are given kits when released from custody (14).

In Québec, Narcan® Nasal Spray became covered under the free naloxone program for pharmacies on May 9, 2018 (72, 74).

In British Columbia, since 2018 First Nations may request both injectable and/or nasal naloxone directly from their pharmacy, free of charge by providing their Status Number and Personal Health Number (75).

In Northwest Territories, injectable naloxone has been available territory-wide since 2016, and intranasal naloxone has become the preferred alternative in June 2019 (15). Kits are available at no cost in all 33 Northwest Territories communities at retail pharmacies, health centres, clinics, hospitals and health cabins (15).

Effective March 27, 2018, Narcan® Nasal Spray became an open benefit under the NIHB Program for First Nations and Inuit clients (72).

Veterans Affairs Canada (VAC) provides eligible veterans with Narcan® Nasal Spray free of charge from pharmacies under the Program of Choice (POC) 10 coverage since March 2019 in all provinces (45, 76).

66. Tippey KG, Yovanoff M, McGrath LS, Sneeringer P. Comparative human factors evaluation of two nasal naloxone administration devices: NARCAN® Nasal Spray and naloxone prefilled syringe with nasal atomizer. Pain and Therapy. 2019;8(1):89-98.

67. Edwards ET, Edwards ES, Davis E, Mulcare M, Wiklund M, Kelley G. Comparative usability study of a novel auto-injector and an intranasal system for naloxone delivery. Pain and Therapy. 2015;4(1):89–105.

68. Krieter P, Chiang N, Gyaw S, Skolnick P, Crystal R, Keegan F, et al. Pharmacokinetic properties and human use characteristics of an FDA-approved intranasal naloxone product for the treatment of opioid overdose. Journal of Clinical Pharmacology. 2016;56(10):1243–53.

69. Eggleston W, Calleo V, Kim M, Wojcik S. Naloxone administration by untrained community members. Pharmacotherapy: The Journal of Human Pharmacology & Drug Therapy. 2020;40(1):84–8.

70. Eggleston W, Podolak C, Sullivan RW, Pacelli L, Keenan M, Wojcik S. A randomized usability assessment of simulated naloxone administration by community members. Addiction. 2018;113(12):2300–4.

U.S.

In the U.S., Narcan® (naloxone HCl) Nasal Spray is available at pharmacies without a prescription (77). Narcan® is also covered by most major insurance plans (77). According to the naloxone state-wide standing order and/or state naloxone access laws, pharmacists can fill Narcan® Nasal Spray without an individualized prescription (77).

Overall, Narcan® Nasal Spray has extensive public and private insurance coverage in the U.S.: 97% of insured persons have access to Narcan® Nasal Spray, 49% of prescriptions for Narcan® Nasal Spray have no co-pay, 72% have a co-pay of USD 10 or less, and 76% have a co-pay of USD 20 or less (77). Although Narcan® Nasal Spray is a prescription medication, all states have passed laws to increase access to naloxone in the community and in homes where opioids are present (77). In every state, residents can purchase Narcan® Nasal Spray directly from a pharmacist under a Statewide Naloxone Standing Order or Collaborative Practice Agreement (77).

In addition to the pharmacies, several other locations are eligible to receive Narcan® Nasal Spray at no cost in the U.S.:

- Public libraries are eligible to receive one carton of Narcan® Nasal Spray (two doses) along with educational materials (78).
- Every YMCA is eligible to receive one carton of Narcan® Nasal Spray (two doses) and educational materials (78).
- Every high school throughout the U.S. has access to two cartons of Nasal Spray (four doses) and up to four cartons (eight doses) for Title IV, degree-granting, two- and four-year educational institutions (78).

In 2017 the New York State Department of Health has switched from the atomizer naloxone kit requiring multi-step assembly to the nasal spray (16). This was the result of a partnership between Adapt Pharma, Inc. and the New York State Department of Health, New York City Health Department, and NYC Health+Hospitals (the New York City Health and Hospitals Corporation that operates the public hospitals and clinics) to equip law enforcement, first responders, government and community organizations in New York State with Narcan® Nasal Spray (79).

The Naloxone Distribution Project (NDP) in California is funded by the Substance Abuse and Mental Health Services Administration (SAMHSA) and administered by the California Department of Health Care Services (DHCS) (17). Through the NDP, qualified entities (community organizations, homeless programs, first responders, etc.) are able to request free naloxone in its nasal spray formulation from DHCS and have it directly shipped to their address (17). Since October 2018, the NDP had distributed over 400,000 units of

71. Parkin S, Neale J, Brown C, Campbell ANC, Castillo F, Jones JD, et al. Opioid overdose reversals using naloxone in New York City by people who use opioids: Implications for public health and overdose harm reduction approaches from a qualitative study. International Journal of Drug Policy. 2020;79:102751.

72. ADAPT Pharma Canada Ltd. Narcan (Naloxone HCl) Nasal Spray 4mg. 2019. Available from: https://www.narcannasalspray.ca/en#:~:text=NARCAN%C2%AE%20Nasal%20Spray%20is%20available%20for%20free %20from%20pharmacies,Program%20for%20Pharmacies%20(ONPP. Accessed September 11, 2020.

73. Ministry of Health and Long-Term Care, Ontario Public Drug Programs. Updated notice from the executive officer: Funding of naloxone nasal spray through the ONPP and updates to the existing program. 2018. Available from: http://www.health.gov.on.ca/en/pro/programs/drugs/opdp_eo/notices/exec_office_20180321.pdf. Accessed September 11, 2020.

74. Régie de l'assurance maladie Québec. Ajout du vaporisateur nasal NarcanMC et de certaines fournitures au Programme de gratuité du médicament naloxone et de certaines fournitures. 2018. Available from: https://www.ramq.gouv.qc.ca/SiteCollectionDocuments/professionnels/infolettres/2018/info046-8.pdf. Accessed September 11, 2020.

naloxone, and recorded over 14,000 overdose reversals (17).

Europe

France was the first country in Europe in 2016 to license a nasal naloxone spray (Nalscue®, by Invidor Inc.) with a strength of 0.9 mg/0.1 ml – of which two to four doses are administered in an emergency (50). Authorized initially in the context of a trial, the product received national marketing authorization in 2017. In the same year, naloxone was listed among medicinal products that may be dispensed in hospitals, drug treatment centres, and public harm reduction facilities in France without prescription (50).

The European Commission authorized a naloxone nasal spray of 1.8 mg/0.1 mL (Nyxoid®, by Mundipharma Corporation Ireland Limited) in November 2017 for marketing throughout the European Union (50, 80). Other naloxone nasal sprays available in Europe include of Ventizolve® and Respinal® (by Sanivo Pharma AS) containing 1.26 mg of naloxone hydrochloride and approved in June 2018 (81).

The Norwegian naloxone program began with 2mg/2mL pre-filled syringes with a nasal atomizer (82), but in 2018 it switched to Nyxoid® 1.8mg single dose nasal sprays (19). The program began as a pilot project in Norway's two largest cities, Oslo and Bergen (19, 83), and has since expanded to be available in most municipalities that experience opioid overdoses. The program continues to be part of the National Overdose Strategy (19). Staff working in municipal facilities that serve people who use drugs are trained to distribute naloxone. Naloxone is primarily distributed via low-threshold facilities, but is also available at treatment centers, shelters, and prisons (19). Other groups who are in contact with people at risk of overdosing have also been trained in the use of naloxone (family support organizations, police, security staff, etc) (19). The program is open to anyone who is interested in learning how to respond to opioid overdose (19). Take home naloxone is currently distributed in over 100 facilities and is available without an individual prescription and at no cost to the client (19). To date, over 10,000 naloxone nasal sprays have been distributed (19).

In the UK, under regulations that came into force in October 2015, people working in or for drug treatment services can, as part of their role, supply naloxone that their drug service has obtained to others, if it is being made available to save a life in an emergency (84). No prescription is needed to supply naloxone in this way (84). The regulations were amended in February 2019 to include nasal naloxone (84). Regulations do not limit supply to specific individuals, except to state that the "supply shall be for the purpose of saving life in an emergency" (84). Therefore, drug services can supply naloxone to an outreach worker, a drug user at risk, a carer, a friend, or a family member of a drug user at risk, or any individual working in an environment where there is a risk of overdose for which the naloxone may be useful (84).

75. College of Pharmacists of British Columbia. Emergency use naloxone in BC. 2018. Available from: https://www.bcpharmacists.org/naloxone. Accessed September 11, 2020.

76. Veteran Affairs Canada. Program of Choice (POC) 10 – Prescription drugs. Important information regarding Narcan® Nasal Spray, all provinces. 2019. Available from: http://pub.medavie.bluecross.ca/pub/0001/PublicDocuments/VAC%20POC%2010%20Narcan%20Nasal%20Spray%20Bulletin%20EN%20Final.pdf. Accessed September 11, 2020.

77. ADAPT Pharma Inc. Getting NARCAN® is simple. 2020. Available from: https://www.narcan.com/patients/how-to-get-narcan. Accessed September 11, 2020.

78. ADAPT Pharma Inc. NARCAN® Nasal Spray. Community programs. 2020. Available from: https://www.narcan.com/community/education-awareness-and-training-resources. Accessed September 11, 2020.

79. Emergent Biosolutions. Adapt Pharma® announces partnership with New York to provide NARCAN® (naloxone HCI) Nasal Spray 4mg. 2019. Available from: https://www.emergentbiosolutions.com/news/adapt-pharmar-announces-partnership-new-york-provide-narcanr-naloxone-hci-nasal-spray-4mg. Accessed September 11, 2020.

80. DTB Team. Naloxone Nasal Spray. Drug & Therapeutics Bulletin. 2019;57(9):137–40.

Australia

On November 1, 2019, naloxone nasal spray 1.8 mg/0.1 mL (Nyxoid®) was listed on the Pharmaceutical Benefits Scheme (PBS) as an unrestricted General Schedule listing (85). When purchasing naloxone nasal spray over the counter, patients can expect to pay AUD 48 (86). With a prescription as a PBS-listed medicine, patients without a concession card can expect to pay a maximum of AUD 41.00 for naloxone nasal spray, while concessional patients pay AUD 6.60 (86).

Access points for free take-home naloxone distributed to people at high risk of harm from opioids are increasing across Australia and include drug and alcohol services and needle syringe programs. From December 2019 to February 2021, New South Wales, South Australia, and Western Australia are participating in a PBS-subsidized (at a cost of CAD 10 million) take-home naloxone pilot (18, 86). Under the pilot, naloxone is provided free for people at risk of opioid overdose, and for those who are likely to witness an opioid overdose (18, 86). Naloxone nasal spray and pre-filled injectable naloxone are available without a prescription as part of the pilot (18, 86).

Factors That May Impact Local Applicability

Only studies and data from high-income countries examining various aspects of take-home naloxone programs were included in this review. The specifics of naloxone programs vary widely in terms of their scope, setting, and particular naloxone formulation available and/or approved by the respective national or regional health authorities. Using an atomization device to deliver the injectable formulation through the nasal route is not approved by Health Canada. Most research is based on injectable formulations or atomizer devices of naloxone and few articles provide direct evidence based on naloxone intranasal spray as part of take-home naloxone programs. The body of the available evidence may not be directly applicable to Ontario's and Canada's health care system and the findings may not be generalizable.

What We Did

We searched Medline (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations) using text terms (take home naloxone) or ([Narcan* or Naloxone] and [nasal or intranasal]). Searches were conducted on August 4, 2020 and results limited to English articles published from 2010 to present. Reference lists of identified review articles and web-sites of intranasal naloxone spray manufacturers were also searched. The searches yielded 407 references from which 86 were included.

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