Comparing the effectiveness and adverse events of intranasal and intramuscular naloxone formulations for opioid overdose reversal

Question

What is the evidence of the effectiveness and adverse events of intranasal naloxone (NARCAN® Nasal Spray, 4 mg/0.1 mL) compared to intramuscular naloxone (0.4 mg/1 mL) for reversal of opioid overdose?

Key Take-Home Messages

- Various intranasal and intramuscular naloxone formulations have been successful in reversing opioid overdoses (1–4). With the rise of highly potent synthetic drugs such as fentanyl and the increase of opioid-related deaths in all Canadian provinces, including Ontario, ensuring safe and effective naloxone administration to reverse opioid overdose is critical (5–9).
- In Canada, two types of take-home kits to reverse the effects of opioid overdoses are available: NARCAN® Nasal Spray (4 mg/0.1 mL) and intramuscular naloxone injection (0.4 mg/1 mL) (1).
- Comparative clinical effectiveness of NARCAN® Nasal Spray versus intramuscular naloxone has not been studied (10), but research shows that they both have comparable pharmacokinetic properties (11, 12). Generally, intranasal route of administration may be favoured over the intramuscular route when used by emergency medical services (EMS) due to ease of use, reduced chance of needlestick injury, and availability to more EMS practitioners (13). However, this recommendation is limited by the scarcity of relevant research, the advent of more potent synthetic opioids, and by the fact that the guideline was developed based on evidence from studies using naloxone atomizer devices and not NARCAN® Nasal Spray (13).

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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Prepared by
Emily Robinson

Program Leads/Editors
David Gogolishvili

Contact
rapidresponse@ohtn.on.ca

For more information visit
www.ohtn.on.ca/rapid-response-service

The Ontario HIV Treatment Network
1300 Yonge Street, Suite 600
Toronto ON M4T 1X3
www.ohtn.on.ca

- Few studies evaluated efficacy of NARCAN® Nasal Spray specifically; however, NARCAN® Nasal Spray has shown to be successful in reversing opioid overdose in real-world settings (14). Adverse reactions of NARCAN® Nasal Spray may include precipitation of severe opioid withdrawal as well as symptoms such as increased blood pressure, constipation, toothache, muscle spasms, musculoskeletal pain, headache, nasal dryness, nasal edema, nasal congestion, nasal inflammation, or dry skin (12).

- Similarly, 0.4 mg/1 mL intramuscular naloxone was found to be safe and effective in treating opioid overdoses in a pre-hospital setting (15). Adverse reactions following the reversal of an opioid overdose using intramuscular naloxone may include acute opioid withdrawal syndrome and symptoms such as nausea, vomiting, sweating, tachycardia, increased blood pressure, and tremulousness (16).

- Although acute withdrawal symptoms have been reported after administration of both intranasal and intramuscular naloxone, there are some data suggesting a lower risk of withdrawal in those given intranasal spray compared to those administered intramuscular injections (14, 17).

- Pharmacokinetic studies suggest that higher intranasal and intramuscular doses may be more effective for rapid reversal of opioid overdoses caused by more potent synthetic opioids (18, 19).

- More research evaluating and directly comparing the approved concentrations of intranasal (4 mg/0.1 mL) and intramuscular naloxone (0.4 mg/1 mL) is needed to gain a better understanding of comparative effectiveness and adverse events of these naloxone formulations (9, 10).

The Issue and Why it's Important

Since 2016, opioid-related deaths have been rapidly rising in Canada (7). In 2021, the Public Health Agency of Canada reported 20.9 opioid-related deaths per 100,000 individuals (n=8,006), rising from 7.8 opioid-related deaths per 100,000 individuals (n=2,830) in 2016 (7). At the time of this review, the Public Health Agency of Canada had only published data for January to September of 2022, reporting a rate of 19.0 opioid-related deaths per 100,000 individuals (n=5,360) (7). Between January 2016 to September 2022, there were 34,455 apparent opioid-related deaths and 34,886 opioid-related overdose hospitalizations in Canada, with the majority of deaths occurring in British Columbia, Alberta, and Ontario (7, 20). A steady increase of opioid-related harms has been observed in Ontario for more than a decade, and the number of opioid-related deaths per 100,000 individuals increased from 6.2 (n=868) in 2016 to 19.1 (n=2,866) in

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3. Weaver L, Palombi L, Bastianelli KMS. Naloxone administration for opioid overdose reversal in the prehospital setting: Implications for pharmacists. Journal of Pharmacy Practice. 2018;31(1):91–8.

4. Yousefifard M, Vazirizadeh-Mahabadi MH, Neishaboori AM, Alavi SNR, Amiri M, Baratloo A, et al. Intranasal versus intramuscular/intravenous naloxone for pre-hospital opioid overdose: A systematic review and meta-analysis. Advanced Journal of Emergency Medicine. 2020;4(2):e27.

5. Moss RB, Carlo DJ. Higher doses of naloxone are needed in the synthetic opiod era. Substance Abuse Treatment, Prevention, & Policy. 2019;14(1):6.

6. Irvine MA, Kuo M, Buxton JA, Balshaw R, Otterstatter M, Macdougall L, et al. Modelling the combined impact of interventions in averting deaths during a synthetic opioid overdose epidemic. Addiction. 2019;114(9):1602–13.

2021 (8).

Naloxone, a fast-acting opioid antagonist, is a medication that has been successfully used to reverse opioid overdoses by blocking the effects of opioids such as fentanyl, heroin, oxycodone, and hydrocodone (1, 21). In March 2016, Health Canada amended the prescription status of naloxone to increase public access by allowing for the non-prescription use of naloxone in suspected opioid overdose emergencies (22, 23). According to a 2021 Naloxone Scan produced by the Canadian Pharmacists Association, naloxone in Alberta, British Columbia, Manitoba, and Saskatchewan has been given unscheduled status and can be distributed without professional supervision through any retail outlet (24). In Ontario and Quebec, NARCAN® Nasal Spray is available through publicly-funded provincial take-home naloxone (THN) programs (24). NARCAN® Nasal Spray is available anonymously and free of charge in clinics, pharmacies, health centres, and hospitals in the Northwest Territories (24). Additionally, injectable intramuscular naloxone is available in THN kits in most Canadian provinces and territories (Ontario, British Columbia, Alberta, Saskatchewan, Quebec, Nova Scotia, Northwest Territories, Yukon) (24).

Currently, two types of take-home naloxone kits are available in Canada: intranasal spray known by its trade name NARCAN® Nasal Spray, and intramuscular/injectable naloxone (1). NARCAN® Nasal Spray contains 4 mg/0.1 mL naloxone per dose which is administered into the nostril of an individual experiencing a potential opioid overdose (25). Intramuscular naloxone is known by its generic name in Canada, naloxone hydrochloride, and one dose contains 0.4 mg/1 mL that is administered into the muscle (25). There are several generic formulations of intramuscular naloxone currently available in Canada (22). Intranasal and intramuscular naloxone are the same medication administered into different locations of the body, and individuals experiencing opioid overdoses may need to be given additional doses of both intranasal or intramuscular naloxone after three to five minutes if the person is unresponsive (25, 26). Intravenous naloxone is another formulation available in Canada, but it is not available as a take-home kit (23).

New naloxone products are becoming available in other jurisdictions to battle the opioid crisis. In April 2021, the U.S. Food and Drug Administration (FDA) approved Kloxxado® Nasal Spray, containing 8 mg/0.1 mL of naloxone hydrochloride (27, 28), which is double the dosage of NARCAN® Nasal Spray (23). Additional doses can be given every 2 to 3 minutes in alternating nostrils using a new device for each dose (28). The manufacturer of Kloxxado® Nasal Spray states that higher concentrations of naloxone may be required with the increasing prevalence of potent synthetic opioids (27, 29). A prescription is required to get Kloxxado® in the U.S. (30). Additionally, a new single-dose, pre-filled syringe 5 mg/0.5 mL form of naloxone (ZIMHI™) was released in October 2021 in the U.S. for intramuscular or subcutaneous use (31, 32). Prior to this, the U.S.

7. Public Health Agency of Canada. Apparent opioid and stimulant toxicity deaths. 2023. Available from: https://health-infobase.canada.ca/src/doc/SRHD/Update_Deaths_2023-03.pdf Accessed June 6, 2023

8. Public Health Ontario. Opioid-related morbidity and mortality in Ontario. 2023. Available from: https://www.publichealthontario.ca/en/data-and-analysis/substance-use/interactive-opioid-tool#/drug Accessed June 6, 2023.

9. Moe J, Godwin J, Purssell R, O'Sullivan F, Hau JP, Purssell E, et al. Naloxone dosing in the era of ultra-potent opioid overdoses: A systematic review. Canadian Journal of Emergency Medical Care. 2020;22(2):178–86.

10. The Canadian Agency for Drugs and Technologies in Health (CADTH). Intranasal and intramuscular naloxone for opioid overdose in the pre-hospital setting: A review of comparative clinical and cost-effectiveness, and guidelines. 2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554777/pdf/Bookshelf_NBK554777.pdf Accessed January 20, 2023.

11. McDonald R, Lorch U, Woodward J, Bosse B, Dooner H, Mundin G, et al. Pharmacokinetics of concentrated naloxone nasal spray for opioid overdose reversal: Phase I healthy volunteer study. Addiction. 2018;113(3):484–93.

FDA had previously approved the 0.4 mg/0.4 mL and 2 mg/0.4 mL intramuscular or subcutaneous pre-filled autoinjectors (EVZIO®) (33, 34) and other various injectable naloxone formulations under the trade name NARCAN® (32, 35–40); however, EVZIO® has been discontinued, and injectable naloxone is no longer marketed under the NARCAN® trade name (35–41).

A 2019 article examined pharmacology of fentanyl and reviewed data on the number of repeat (sequential) doses of naloxone to treat fentanyl overdoses (5). The authors concluded that higher doses of naloxone are needed to reverse overdoses with more potent synthetic drugs (5). Abdelal *et al.* (2022) in their literature review identified that multiple naloxone administrations during opioid overdose reversals have occurred in up to 89% of all opioid overdoses, and have significantly increased over time (42). The authors also suggested that higher naloxone formulations may be needed to combat the rising number of opioid overdoses due to highly potent synthetic opioids (42).

Both intranasal and intramuscular naloxone have shown to be successful in reversing opioid overdoses. This review compares the effectiveness of intranasal and intramuscular naloxone, primarily focusing on the two formulations available in Canada (NARCAN® Nasal Spray 4 mg/0.1 mL and naloxone intramuscular injection 0.4 mg/1 mL), explores their potential adverse events, and summarizes evidence on naloxone formulations available in other jurisdictions (Europe, U.S. and Australia).

What We Found

There are various intranasal and intramuscular naloxone formulations to reverse opioid overdoses (1–4, 14). Overall, both intranasal and intramuscular routes of administration of naloxone are effective in reversing opioid overdoses (2–4). Two literature reviews published by the Canadian Agency for Drugs and Technologies in Health (CADTH) in 2017 and 2019 were not able to identify any studies addressing the question on comparative clinical effectiveness of naloxone nasal spray versus intramuscular naloxone (10, 41). However, one guideline published in 2019 makes a recommendation favouring intranasal naloxone over intramuscular naloxone for patients with confirmed or suspected opioid overdose in out-of-hospital settings for use by emergency medical services (EMS) (13). Considerations for the recommendation were comparable effectiveness across the two routes of administration, as well as ease of use and reduced adverse events associated with the intranasal formulation, which promotes increased safety of EMS practitioners and patients (13). The guideline suggests that the initial dose should be enough to achieve adequate respiratory function without triggering withdrawal symptoms, considering factors such as the opioids in use in the local area (13). However, this recommendation is limited by the fact that the guideline was developed based on evidence from studies using

12. U.S. Food and Drug Administration. NARCAN® (naloxone hydrochloride) Nasal Spray. 2020. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/8411Orig1s004lbl.pdf Accessed March 24, 2023.
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16. Baxter Corporation. Naloxone hydrochloride injection, USP. 2021. Available from: https://www.baxter.ca/sites/g/files/ebysai1431/files/2021-07/Naloxone_EN.pdf Accessed April 10, 2023.
17. Skulberg AK, Tylleskar I, Valberg M, Braarud AC, Dale J, Heyerdahl F, et al. Comparison of intranasal and intramuscular naloxone in opioid overdoses managed by ambulance staff: A double-dummy, randomised, controlled trial. Addiction. 2022;117(6):1658-67.

naloxone atomizer devices and intranasal spray formulations other than NARCAN® Nasal Spray (13).

Despite the lack of research directly comparing effectiveness of NARCAN® Nasal Spray and naloxone intramuscular injection, there are numerous publications that evaluate the pharmacokinetics, effectiveness, and other aspects of various doses of both naloxone formulations (2, 14, 15).

NARCAN® Nasal Spray

Few studies evaluate 4 mg/0.1 mL NARCAN® Nasal Spray specifically. Since NARCAN® Nasal Spray is the only intranasal naloxone formulation currently available in Canada, literature examining its effectiveness, pharmacokinetic properties, and adverse events will be assessed separately in the following paragraphs.

NARCAN® *Nasal Spray: Effectiveness*

In a 2018 study, 152 U.S. organizations known to have received 4 mg/0.1 mL naloxone intranasal spray kits (NARCAN®) were surveyed on their experiences using the product (14). Out of 40 organizations participating in the initial interview, only eight first-responder or community-based organizations provided data (14). In 261 opioid overdose events, information on the number of NARCAN® doses administered was available for 254 events, and successful opioid overdose reversal occurred in 98.8% (n=245) of these cases (14). Only 173 cases reported the presumed substances involved in the overdose: 95.4% (n=165) heroin, 5.2% (n=9) fentanyl, 1.2% (n=2) morphine, 1.2% (n=2) oxycodone, 0.6% (n=1) buprenorphine, and 0.6% (n=1) codeine (14). Overall, 97.6% (n=248) of opioid overdose reversals required two or less doses of NARCAN®; of these reversals, 66.5% (n=165) required only one dose of the intranasal naloxone spray (14). The collected survey data from the first-responder and community-based organizations demonstrated that 4 mg/0.1 mL of NARCAN® was successful at reversing opioid overdose in most reported cases (14).

NARCAN® *Nasal Spray: Pharmacokinetic properties*

In a pharmacokinetic study of 30 healthy adult subjects, the median time to achieve maximum naloxone plasma concentration (T_{max}) after intranasal administration of NARCAN® Nasal Spray (one nasal spray in one nostril [2 mg or 4 mg] or two nasal sprays, one spray in each nostril [4 mg or 8 mg]) was not significantly different compared to the 0.4 mg dose of intramuscular naloxone (12). The relative bioavailability (the percentage of an administered dose that reaches the systemic circulation as intact drug) of one dose (2 mg or 4 mg) or two doses (4 mg or 8 mg) of NARCAN® Nasal Spray was 52%, 44%, 54%, and 43%, respectively, compared to 0.4 mg intramuscular naloxone (12).

18. Moss RB, Pryor MM, Baillie R, Kudrycki K, Friedrich C, Reed M, et al. Higher naloxone dosing in a quantitative systems pharmacology model that predicts naloxone-fentanyl competition at the opioid mu receptor level. PLoS ONE. 2020;15(6):e0234683.

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20. Health Canada. Opioid and stimulant poisoning hospitalizations. 2023. Available from: https://health-infobase.canada.ca/src/doc/SRHD/Update_Hospitalizations_2023-03.pdf Accessed June 6, 2023.

21. Centre for Addiction and Mental Health. Naloxone. 2018. Available from: https://www.camh.ca/en/health-info/mental-illness-and-addiction-index/naloxone Accessed January 23, 2023.

22. The Canadian Agency for Drugs and Technologies in Health (CADTH). Funding and management of naloxone programs in Canada. 2018. Available from: https://www.cadth.ca/sites/default/files/pdf/ES0319_funding_and_management_of_naloxone_programs_in_canada.pdf Accessed January 24, 2023.

A systematic review by Ryan *et al.* (2018) evaluated pharmacokinetic properties of community-use naloxone formulations for the emergency treatment of opioid overdose (43). Seven studies were included: two examining FDA-approved intramuscular naloxone products, one FDA-approved intranasal naloxone product, two examining unapproved intranasal kits with atomizers, and two assessing intranasal naloxone products that were in development (43). Pharmacokinetic information on NARCAN® Nasal Spray 2 mg, 4 mg (one spray total and one spray of 2 mg in each nostril), and 8 mg (one spray of 4 mg in each nostril) (44), along with the unapproved intranasal products and now-discontinued EVZIO® autoinjector (34), were reviewed (43). No study populations observed in any of the included studies experienced an opioid overdose as they all were healthy volunteers (43). Based on the pharmacokinetic data, the intranasal spray (2 mg and 4 mg) was deemed to be adequate for reversing opioid overdose as it demonstrated rapid uptake and adequate naloxone exposure when compared with the standard 0.4 mg intramuscular injection (43).

NARCAN® *Nasal Spray: Adverse events*

The use of NARCAN® Nasal Spray in patients who are opioid-dependent may precipitate opioid withdrawal characterized by the following signs and symptoms: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, goosebumps, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure (12). There are limited data to inform if the 2 mg dose of NARCAN® Nasal Spray will avoid precipitation of severe opioid withdrawal in the setting of opioid dependence (12). However, the 2 mg dose may not provide an adequate and timely reversal in persons who may be exposed to an overdose of a potent or very high dose of opioids (12).

In a pharmacokinetic study of 30 healthy adult volunteers exposed to one spray of NARCAN® Nasal Spray in one nostril or two sprays of NARCAN® Nasal Spray, one in each nostril, the most common adverse reactions were: increased blood pressure, constipation, toothache, muscle spasms, musculoskeletal pain, headache, nasal dryness, nasal edema, nasal congestion, nasal inflammation, nose pain, and dry skin (12).

Clinical studies are conducted under widely varying conditions, therefore adverse reaction rates observed in different clinical studies of NARCAN® Nasal Spray cannot be directly compared to each other and may not reflect real-world setting rates (12). A 2018 U.S. study identified commonly observed adverse events based on case report data on attempted opioid overdose reversals using NARCAN® Nasal Spray which was provided by surveyed first-responders and community-based organizations (14). The most commonly observed adverse events included withdrawal symptoms (14.3%; n=28), nausea, vomiting, gagging and/or retching (10.2%;

23. Government of Canada. Frequently asked questions: Access to naloxone in Canada (including NARCAN™ Nasal Spray). 2017. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/narcan-nasal-spray-frequently-asked-questions.html Accessed January 23, 2023.

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27. Hikma Specialty USA Inc. US FDA approves Kloxxado® (naloxone HCl) Nasal Spray 8 mg to treat opioid overdose. Available from: https://kloxxado.com/blog/us-fda-approves-kloxxado-naloxone-hcl-nasal-spray-8-mg-to-treat-opioid-overdose/ Accessed January 23, 2023.

n=20), and irritability or anger (8.7%; n=17) (14).

Intramuscular naloxone (0.4 mg/1 mL)

As previously mentioned, intramuscular naloxone available in Canada as part of take-home kits has a concentration of 0.4 mg/1 mL (1, 25). Literature evaluating the effectiveness, pharmacokinetic properties, and adverse events of 0.4 mg/1 mL intramuscular naloxone is presented below.

Intramuscular naloxone (0.4 mg/1 mL): Effectiveness

A five-year observational study on patients treated with naloxone by the Oslo City Center Emergency Medical Services in Norway between 2014 and 2018 examined the effects of 0.4 mg or 0.8 mg intramuscular naloxone administration (15). A total of 2,215 patients were treated with naloxone, and 91.9% of them (n=2,035) were given intramuscular naloxone (15). Individuals who were unconscious or in respiratory arrest were more likely to be given 0.8 mg and receive multiple doses (15). Of those who received intramuscular naloxone, 56.5% (n=1,150) were treated with 0.8 mg, and 39.9% (n=811) with 0.4 mg (15). An additional 3.6% (n=74) received different doses of intramuscular naloxone (15). Fifteen percent (n=172) of patients given 0.8 mg intramuscular naloxone required additional naloxone administration, and 16.5% (n=134) administered 0.4 mg intramuscular naloxone needed additional doses (15). Overall, initial doses of 0.4 mg and 0.8 mg in pre-hospital settings appeared to be safe and effective in treating opioid overdoses (15).

Intramuscular naloxone (0.4 mg/1 mL): Pharmacokinetic properties

One study evaluated the pharmacokinetic properties of various naloxone formulations and concentrations, including 0.4 mg/1 mL intramuscular naloxone (11). McDonald *et al.* (2018) compared three doses of intranasal naloxone (1 mg/0.1 mL, 2 mg/0.1 mL, and 4 mg/0.2 mL administered as atomized spray with the unit dose system), one dose of 0.4 mg intramuscular naloxone, and one dose of 0.4 mg intravenous naloxone in 38 healthy volunteers in the UK (11). The mean values of peak concentration (i.e. maximum observed plasma concentration, C_{max}) for 1 mg, 2 mg, and 4 mg intranasal naloxone were all higher (1.51 ng/mL, 2.87 ng/mL, 6.02 ng/mL) than peak concentration of 0.4 mg intramuscular naloxone (1.27 ng/mL) (11). On the other hand, the mean values of bioavailability (i.e. the fraction of an administered dose that reaches the systemic circulation as intact drug) of all intranasal doses (1 mg, 2 mg, and 4 mg) ranged from 47% to 51% relative to 0.4 mg intramuscular naloxone (11).

Intramuscular naloxone (0.4 mg/1 mL): Adverse events

According to the product monograph of 0.4 mg/1 mL intramuscular naloxone, it should be administered with caution to persons who

28. The Medical Letter Inc. Higher-dose naloxone nasal spray (Kloxxado) for opioid overdose. The Medical Letter on Drugs & Therapeutics. 2021;63(1633):151–2.

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30. Hikma Pharmaceuticals USA Inc. Kloxxado® (naloxone HCl) nasal spray 8mg. Prescriber resources. Available from: https://kloxxado.com/for-prescribers/ Accessed February 1, 2023.

31. U.S. Food and Drug Administration. ZIMHI (naloxone hydrochloride injection) for intramuscular or subcutaneous use. 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212854s000lbl.pdf Accessed January 31, 2023.

32. U.S. Food and Drug Administration. FDA announces preliminary assessment that certain naloxone products have the potential to be safe and effective for over-the-counter use. 2021. Available from: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-naloxone-injection-counteract-opioid-overdoses Accessed January 19, 2023.

are known or suspected to be physically dependent on opioids (16). In such cases, an abrupt and complete reversal of opioid effects may precipitate an acute opioid withdrawal syndrome (16). The severity of such a syndrome will depend on the degree of physical dependence, the dose, affinity, and potency of the opioid that induced the overdose, and the dose of naloxone administered (16). The signs and symptoms of an acute opioid withdrawal syndrome include body aches, pain, fever, sweating, runny nose, sneezing, goosebumps, yawning, weakness, asthenia, shivering, chills, trembling, convulsions/seizures, nervousness, restlessness, irritability, aggressive behavior, diarrhea, nausea, vomiting, abdominal cramps, increased blood pressure, and tachycardia (16).

A 2021 observational study explored adverse events related to intramuscular 0.4 mg/1 mL naloxone administration by bystanders using take-home naloxone kits in cases of suspected opioid overdose in British Columbia (45). Most individuals given naloxone survived the suspected opioid overdose (98.1%, n=3,046 of 3,104), and the presence or absence of an adverse event(s) was reported in 2,372 individuals (45). Overall, 69.2% were reported to have experienced mild or no withdrawal effects (n=1,642) and 24.2% (n=573) experienced moderate or severe withdrawal effects (45). "Other" was reported in 14.6% (n=345) individuals, which included responses such as "don't know" or comments describing how the individual was feeling (e.g. tired, happy, frustrated, disoriented) (45). Specific withdrawal symptoms were not reported in this study (45).

Other naloxone formulations and doses

A number of studies evaluating various intranasal and intramuscular formulations other than NARCAN® Nasal Spray 4 mg/0.1 mL or intramuscular naloxone 0.4 mg/1 mL will be discussed for the remainder of the review.

A 2019 Australian study assessed the use of 0.8 mg/1 mL naloxone in both intranasal (syringe attached to a mucosal atomization device) and intramuscular forms among clients with a history of injection drug use at a medically supervised injection facility (2). There were 197 overdoses recorded in 127 unique clients; 52.8% (n=104) were randomized to receive intranasal naloxone, 47.2% (n=93) to receive intramuscular naloxone (2). Clients who were experiencing an overdose and did not respond adequately to the initial naloxone dose after ten minutes were given a second rescue dose of intramuscular naloxone (2). Individuals who were administered intramuscular naloxone as their first dose were less likely to need a secondary/rescue dose compared to those who received intranasal naloxone; 8.6% (n=8) of those who received intramuscular naloxone required a rescue dose compared to 23.1% (n=24) who received intranasal naloxone (odds ratio [OR] = 0.35; 95% CI 0.15–0.66) (2).

Opioid overdose management with naloxone administration in a

33. U.S. Food and Drug Administration. EVZIO (naloxone hydrochloride injection) auto-injector for intramuscular or subcutaneous use. 2014. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/ label/2014/205787Orig1s000lbl.pdf Accessed January 31, 2023.

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36. U.S. Food and Drug Administration. FDA-approved drugs: EVZIO (autoinjector) (NDA #209862). Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=209862 Accessed March 28, 2023.

37. U.S. Food and Drug Administration. FDA-approved drugs: NARCAN (NDA #016636). Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=016636 Accessed March 28, 2023.

pre-hospital environment was studied in Norway from 2018 to 2020 (17). The interventions included intranasal (nasal spray produced by Sanivo Pharma, Norway; administered as 1.4 mg/0.1 mL nasal spray using a unidose device by Aptar Pharma) and intramuscular (0.8 mg/2 mL) naloxone, and the primary outcome was the return of spontaneous respiration within ten minutes of drug administration (17). Overall, 201 participants were observed during the study period; 46.3% (n=93) were given intranasal naloxone, and 53.7% (n=108) were administered intramuscular naloxone (17). The intramuscular form restored spontaneous respiration within ten minutes of administration with one dose in 97.2% (n=105) of participants compared to 79.6% (n=74) in overdose patients given intranasal naloxone (17). Authors concluded that intramuscular naloxone was found to be more effective than the intervening intranasal dose in achieving the spontaneous respiration within ten minutes of drug administration (17).

A systematic review and meta-analysis published in 2020 assessed the effectiveness of various intranasal and intramuscular/intravenous naloxone in pre-hospital settings (4). Six studies were included (4). The success rate to reverse opioid overdose was 82.54% (95% CI 57.97–97.89) for intranasal naloxone administration, and 80.39% (95% CI 57.38–96.04) for intramuscular/intravenous; there was no statistically significant difference between intranasal and intramuscular/intravenous administrations (odds ratio [OR] = 1.01; 95% CI 0.42–2.43, p=0.98) (4). On the other hand, the odds of requiring a rescue dose was 2.17 times higher and statistically significant for intranasal compared to intramuscular/intravenous naloxone (OR = 2.17; 95% CI 1.53–3.09, p≤0.0001) (4). It is important to note that only two of the six studies included in this review compared intranasal (2 mg) and intramuscular (2 mg) naloxone use, each conducted in Australia prior to 2010 (4). Both of these studies have examined mucosal atomization devices and not the currently approved nasal spray that makes direct NARCAN® Nasal Spray comparison difficult (46, 47). These two studies have been included in several other reviews (3, 11, 14, 17, 41, 45, 48) and will be explained briefly below.

- Kelly *et al.* (2005) randomized 155 patients requiring treatment for suspected opiate overdose to receive either intranasal (n=84, 2 mg, using an atomization device) or intramuscular (n=71, 2 mg) naloxone (4, 46). Those who received intramuscular naloxone had a faster response to treatment compared to the intranasal group, with a mean time of six minutes (95% CI 5–7) and eight minutes (95% CI 7–8), respectively (4, 46). Additionally, 82% of those receiving intramuscular naloxone had greater than ten spontaneous respirations in less than eight minutes, compared to 63% in the intranasal group (OR = 2.6; 95% CI 1.5–5.5) (4, 46). There was no statistically significant difference between the groups for needing a rescue dose (4, 46).

38. U.S. Food and Drug Administration. FDA-approved drugs: NARCAN (NDA #071083). Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=071083 Accessed March 28, 2023.

39. U.S. Food and Drug Administration. FDA-approved drugs: NARCAN (NDA #071084). Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=071084 Accessed March 28, 2023.

40. U.S. Food and Drug Administration. FDA-approved drugs: NARCAN (NDA #071311). Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=071311 Accessed March 28, 2023.

41. The Canadian Agency for Drugs and Technologies in Health (CADTH). Intranasal and intramuscular naloxone for opioid overdose in the pre-hospital setting: A review of comparative clinical and cost-effectiveness, and guidelines. 2017. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470680/pdf/Bookshelf_NBK470680.pdf Accessed January 20, 2023.

42. Abdelal R, Banerjee AR, Carlberg-Racich S, Darwaza N, Ito D, Epstein J. The need for multiple naloxone administrations for opioid overdose reversals: A review of the literature. Substance Abuse. 2022;43(1):774–84.

- Kerr *et al.* (2009) enrolled and randomized 172 patients into the study; 83 were administered intranasal naloxone (2 mg, using an atomization device) and 89 intramuscular naloxone (2 mg) (4, 47). In both groups, the rates of response within ten minutes were similar: 72.3% (n=60) in the intranasal group, 77.5% (n=69) in the intramuscular (4, 47). No statistically significant difference was observed in the mean response time to each form of naloxone (intranasal = 8.0 minutes, intramuscular = 7.9 minutes) (4, 47).

Conversely, a retrospective study published in 2020 evaluated the impact of a large dose of intramuscular naloxone given to patients presenting with potential heroin overdose at a clinical toxicology unit in an Australian hospital from 2015 to 2017 (49). The dose given to patients was 1.6 mg injectable naloxone (49). In this study, 108 unique patients presented to the hospital a total of 117 times (49). Pre-hospital intramuscular naloxone was administered to 49% (n=57) of suspected heroin overdose cases, 81% (n=46) receiving 1.6 mg of intramuscular naloxone (49). Nine percent (n=4) of these 46 individuals received additional intravenous naloxone (49). Sixty of the 117 presentations received naloxone in-hospital, 97% (n=58) of which received intravenous naloxone (49). The median intravenous dose administered was 0.4 mg (range: 0.05 mg–1 mg) given over a median of three doses (range: 1–10) (49). A single large dose of 1.6 mg of intramuscular naloxone proved to be effective in reversing opioid overdoses, and patients in the study treated with this formulation was significantly less likely to require additional doses of naloxone than those given intravenous naloxone (49).

Chou *et al.* (2017) conducted a systematic review assessing the management of suspected opioid overdoses with naloxone in out-of-hospital settings (48). Thirteen eligible studies reported on results of various intranasal, intramuscular, and intravenous naloxone administrations (48). Nearly all studies (n=12) were conducted in high-income countries, though none evaluated the FDA-approved intranasal naloxone (NARCAN® Nasal Spray) formulations of 2 mg and 4 mg/0.1 mL (48). Two randomized controlled trials analyzed intranasal (atomization device) and intramuscular concentrations: Kelly *et al.* (2005) and Kerr *et al.* (2009), both of which have already been discussed above. An ongoing non-randomized trial in New York reported in this review was examining the administration of 2 mg/2 mL versus 4 mg/0.1 mL intranasal naloxone concentrations to those experiencing suspected overdoses (50). Though data collection was ongoing at the time, from preliminary observation, the results appeared to be statistically similar between populations: secondary rescue doses were provided to 55% of individuals who received 2 mg/2 mL intranasal spray and 48% of those given 4 mg/0.1 mL intranasal spray (50). The authors of this systematic review were able to conclude that overall, higher concentrations of intranasal naloxone (2 mg/mL) appear to have similar efficacy to that of intramuscular naloxone for the reversal of opioid overdoses (48).

43. Ryan SA, Dunne RB. Pharmacokinetic properties of intranasal and injectable formulations of naloxone for community use: A systematic review. Pain Management. 2018;8(3):231-45.

44. 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. The Journal of Clinical Pharmacology. 2016;56(10):1243–53.

45. Moustaqim-Barrette A, Papamihali K, Williams S, Ferguson M, Moe J, Purssell R, et al. Adverse events related to bystander naloxone administration in cases of suspected opioid overdose in British Columbia: An observational study. PLoS ONE. 2021;16(10):e0259126.

46. Kelly AM, Kerr D, Koutsogiannis Z, Dietze P, Patrick I, Walker T. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. Medical Journal of Australia. 2005;182(1):24–7.

47. Kerr D, Kelly AM, Dietze P, Jolley D, Barger B. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction. 2009;104(12):2067–74.

48. Chou R, Korthuis PT, McCarty D, Coffin PO, Griffin JC, Davis-O'Reilly C, et al. Management of suspected opioid overdose with naloxone in out-of-hospital settings: A systematic review. Annals of Internal Medicine. 2017;167(12):867–75.

Two articles assessing pharmacokinetic properties (e.g. bioavailability, plasma concentration levels) of various naloxone formulations in healthy volunteers were identified (19, 51).

- An article by Moss *et al.* (2020) evaluating pharmacokinetic characteristics of 5 mg/0.5 mL of intramuscular naloxone injection and 2 mg/0.4 mL intramuscular autoinjector in 14 healthy individuals demonstrated that higher doses resulted in higher maximum plasma concentrations and may be more desirable in reversing opioid overdoses caused by more potent synthetic opioids (19).

- A study conducted in Ohio comparing 8 mg/0.4 mL and 16 mg/0.4 mL intranasal (atomized solution using metered dose nasal spray device) and 1 mg/mL intravenous naloxone in 12 healthy volunteers identified that the mean naloxone absorption (i.e. mean value of maximum plasma concentration) from dosing to 30 minutes was greater with both intranasal doses compared to 1 mg/mL of intravenous naloxone (51).

Although literature varies considerably when analyzing pharmacokinetics of intranasal, intramuscular, and intravenous naloxone, overall, the doses explored in these articles show promise in reversing opioid toxicity using different naloxone formulations (19, 51).

While naloxone is considered to be a relatively safe drug (21), some adverse events have been observed. The following studies and official documents report on adverse events of various intranasal and intramuscular naloxone formulations and dosages:

The systematic review published by Chou *et al.* (2017) found no difference in the adverse events reported for 2 mg/mL intranasal naloxone and 2 mg of intramuscular naloxone (48). Two key studies included by Chou *et al.* (2017) discussing adverse events are Kelly *et al.* (2005) and Kerr *et al.* (2009) (46–48).

- Kelly *et al.* (2005) found that agitation and/or irritation occurred in 2.4% (n=2/84) of patients given 2 mg/5 mL intranasal naloxone (using atomization device) compared to 14% (n=10/71) of patients given 2 mg intramuscular naloxone (46, 48). Intranasal naloxone was associated with a decreased risk for agitation and irritation compared to intramuscular naloxone (2.4% versus 14%; relative risk [RR]=0.19, 95% CI 0.004–0.83) (46, 48). Authors suggested that intramuscular naloxone is associated with significantly higher levels of agitation and/or irritation due to a faster response and differences in absorption compared to the intranasal dose (46). Additional adverse events included nausea and/or vomiting, headaches, tremors, and sweating; however, these recorded events were statistically non-

49. Harris K, Page CB, Samantray S, Parker L, Brier AJ, Isoardi KZ. One single large intramuscular dose of naloxone is effective and safe in suspected heroin poisoning. Emergency Medicine Australasia. 2020;32(1):88–92.

50. Dailey M. Report of a field trial for comparison of two intranasal naloxone delivery devices: An equipoise trial. Society for Academic Emergency Medicine. 2017.

51. Mundin G, McDonald R, Smith K, Harris S, Strang J. Pharmacokinetics of concentrated naloxone nasal spray over first 30 minutes post-dosing: Analysis of suitability for opioid overdose reversal. Addiction. 2017;112(9):1647–52.

52. Thompson J, Salter J, Bui P, Herbert L, Mills D, Wagner D, et al. Safety, efficacy, and cost of 0.4-mg versus 2-mg intranasal naloxone for treatment of prehospital opioid overdose. Annals of Pharmacotherapy. 2022;56(3):285–9.

53. Adamis Pharmaceuticals Corporation. ZIMHI prescribing information. 2021. Available from: https://zimhi.com/wp-content/uploads/2022/03/ZIMHI-Prescribing-Information.pdf Accessed January 18, 2023.

significant (46, 48).

- Kerr *et al.* (2009) found no difference in the risk for agitation or violence in patients given 2 mg/mL intranasal naloxone using atomization device (6.0%, n=5/83) and 2 mg/5 mL intramuscular naloxone (7.9%, n=7/89) (relative risk [RR] =0.77, 95% CI 0.25–2.3) (47, 48). Other adverse events included nausea and/or vomiting, and headaches (47, 48). In addition, one patient experienced a grand mal epileptic seizure after intramuscular naloxone administration; this was classified as a major adverse event (47, 48). However, these adverse events were statistically non-significant (47, 48).

A 2020 systematic review evaluated the relationship between naloxone (initial and additional doses), the reversal of opioid toxicity, and adverse events in undifferentiated and presumed fentanyl/ultra-potent opioid overdoses (9). In total, 174 studies were included with 86 studies reporting adverse events (9). Among 4,414 participants across 86 studies, 11% (n=490) reported withdrawal and 1% (n=52) experienced pulmonary edema (9). However, the systematic review states that reporting of adverse events throughout the literature has been inconsistent, and that authors were unable to associate event occurrence with a naloxone dose (9). Challenges arose as in some situations it was unclear whether the events were due to the naloxone administration or the overdose (9). Additionally, this systematic review did not differentiate between intramuscular and intranasal naloxone administration (9).

Three studies observing the presence or absence of adverse events potentially connected to naloxone administration in medical care settings have been identified and are discussed in detail below.

- A retrospective study conducted in two Michigan counties both bordering Detroit metropolitan area, Oakland and Washtenaw, assessed pre-hospital overdose reversal with intranasal naloxone between 2015 and 2017 (52). Oakland County used an initial dose of 0.4 mg intranasal naloxone spray, Washtenaw County used 2 mg intranasal naloxone spray, and both counties recorded adverse events associated with naloxone administration (52). In Oakland County, 58.5% of 94 patients (n=55) required a secondary dose of naloxone after initial administration, whereas in Washtenaw County, 54.8% of 124 patients (n=68) required a secondary dose of naloxone (52). Adverse events were reported in both counties: agitation was the only adverse event recorded by 2% of those receiving 0.4 mg of intranasal naloxone in Oakland County, whereas agitation (11%), nausea (5%), vomiting (3%), and headaches (2%) were among the effects found in patients who were administered 2 mg of intranasal naloxone in Washtenaw County (52). An additional 5% of patients in Washtenaw County had unique adverse events (e.g. hypotension, chest pain, seizure, hallucination) (52). It is important to note that in both dosage groups, naloxone was administered via addition of an atomizer to the syringe for intranasal administration (52).

- Skulberg *et al.* (2022) observed the administration of 1.4 mg/0.1 mL intranasal and 0.8 mg/2 mL intramuscular naloxone in opioid overdose reversals in a Norwegian pre-hospital environment and found that adverse reactions were evenly distributed across the naloxone formulations (17). However, an analysis demonstrated a lower risk of withdrawal in those given intranasal naloxone compared to patients administered intramuscular naloxone (risk difference [RD] =6.8%; 95% CI 0.2%–13%) (17).

- Another study mentioned earlier in this review assessed 0.8 mg/1 mL of both intranasal (attached to a mucosal atomization device) and intramuscular naloxone in patients experiencing an opioid overdose at a medically supervised injection facility in Australia (2). No major adverse events were reported (2). An adverse event in this article was defined as "…any untoward medical occurrence in a participant that may or may not have a causal relationship with the study

treatment." (2).

The U.S. FDA press release approving the new 5 mg/0.5 mL form of intramuscular naloxone (ZIMHI™) in October 2021 highlighted adverse reactions of naloxone (e.g. body aches, nausea, vomiting, diarrhea, increased heart rate, fever, sneezing, goosebumps, irritability, weakness, abdominal cramps, increased blood pressure) (32). The Prescribing Information for ZIMHI™ intramuscular naloxone listed a summary of adverse reactions commonly observed in their clinical trials, which included dizziness, light-headedness, and increased levels of bilirubin (53). Similarly, Moss *et al.* (2020), who compared 5 mg/0.5 mL intramuscular naloxone in a prefilled syringe with 2 mg/0.4 mL intramuscular naloxone autoinjector in healthy subjects, found that the administration of naloxone was tolerated well with no adverse events reported during the study period (19).

Factors That May Impact Local Applicability

Intranasal and intramuscular naloxone doses are considerably inconsistent across studies. Furthermore, in some publications, using a syringe and an atomizer or nebulizer which fits onto the syringe to generate a nasal spray is reported as intranasal administration, which is considerably different from devices such as NARCAN® Nasal Spray manufactured by a pharmaceutical company. This poses challenges when directly comparing the effectiveness and adverse events of intranasal and intramuscular naloxone formulations. Additionally, adverse events of naloxone were not consistently reported in a number of studies. Furthermore, the reported data on adverse events did not always differentiate between intranasal and intramuscular formulations; instead, the adverse events potentially related to both intranasal and intramuscular naloxone were grouped together and listed as the adverse reactions of naloxone. Evidence from Canada on the effectiveness and adverse events of intranasal and intramuscular naloxone is very limited. Due to varying naloxone guidelines and other inconsistencies across studies, it may be difficult to directly apply the findings in this review to the local context.

What We Did

We searched Medline (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) using terms Naloxone in titles OR NARCAN* in titles or abstracts. Searches were conducted on December 2, 2022 and results limited to English articles published from 2017 to present. Studies from low- and middle-income countries were excluded. Reference lists of identified articles were also searched. Google (grey literature) searches using different combinations of these terms were also conducted. The searches yielded 1,373 references from which 53 were included.