Efficacy of intranasal naloxone compared to other administration routes in prehospital opioid overdose management and beyond: a narrative review

Luigi Venuso,[1] Francesco Ricciardi,[2] Antonio Del Prete,[1] Michele Virgolesi,[3] Gianluca Pucciarelli,[4] Luigi Langella,[1] Teresa Rea[3]

[1]Department of Emergency and Critical Care, A.S.L. Napoli 2 Nord, Frattamaggiore; [2]Department of Emergency and Critical Care, A.O.R.N Antonio Cardarelli, Naples; [3]Department of Public Health, University Federico II, Naples; [4]Department of Biomedicine and Prevention, University of Rome Tor Vergata, Italy

Abstract

Drug-related deaths in Italy, especially from opioid overdoses, increased by 6% among individuals aged 15-34 from 2014 to 2018. Opioid-related deaths rose by 6.6% in the 15-24 age group and by 5.4% in the 25-34 age group during this period. There is limited data on the effectiveness of different naloxone administration routes—intranasal (IN), intramuscular (IM), and intravenous (IV)—and no established guidelines for prehospital overdose management. Timely intervention is crucial to reduce overdose mortality. This review aims to assess the effectiveness of naloxone administration methods in opioid overdoses, focusing on prehospital settings and comparing IN, IM, and IV routes. A narrative review was conducted in accordance with PRISMA guidelines. The search included terms such as "naloxone," "opioid overdose," "intranasal administration," and "prehospital emergency care," with Boolean operators to refine the scope. The study selection was guided by the PICO framework (population, intervention, comparison, outcome). Studies were assessed for quality using the Dixon-Woods tool, and inclusion/exclusion criteria were applied. Studies will be selected based on populations treated with naloxone administered via intranasal, intramuscular, or intravenous routes, focusing on comparisons between these formulations in terms of onset time and intervention effectiveness. Out of 111 studies, five met the eligibility criteria. These studies showed that intranasal naloxone achieves higher plasma concentrations than intramuscular doses but with slower absorption and longer peak times. Additionally, intramuscular naloxone results in faster respiratory recovery and requires fewer doses. Intranasal naloxone has a bioavailability of 46.8% to 50.8% compared to intravenous naloxone, with efficacy outcomes varying by administration route. The review shows that intranasal naloxone, especially at a 2 mg dose, achieves plasma levels similar to intramuscular formulations and has linear pharmacokinetics across dosages. While its bioavailability is lower (46% to 50%) compared to intravenous administration, it is a safer and more practical option for non-clinical settings. Although intramuscular and intravenous routes work faster, the slower absorption of intranasal naloxone may help reduce withdrawal symptoms, supporting gradual dosing strategies. These findings emphasize the need for further research on optimizing naloxone dosing for synthetic opioid emergencies. This review highlights intravenous naloxone as the most effective route for opioid overdose treatment, with intramuscular and intranasal routes offering practical alternatives in prehospital settings. Intranasal naloxone, despite its lower bioavailability, provides a non-invasive option suitable for lay responders. Gradual dose escalation is recommended to minimize withdrawal symptoms. The increasing prevalence of synthetic opioids underscores the need for updated clinical guidelines on naloxone dosing and administration routes.

Correspondence: Michele Virgolesi, Department of Public Health, University Federico II, Naples, Italy.
E-mail: Michele.virgolesi@unina.it

Key words: opioid overdose; naloxone; prehospital emergency care; emergency medical services.

Contributions: LV, ADP, MV, contributed to the conception and design of the study; LV, FR, drafted the article; TR, GP, analyzed and interpreted the data; LL, critically revised the manuscript for important intellectual content. All authors provided final approval of the version to be published and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors report no conflict of interest.

Ethics approval and consent to participate: not applicable.

Consent for publication: not applicable.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

Funding: this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Received: 15 September 2024.
Accepted: 21 November 2024.
Early view: 22 January 2025.

Emergency Care Journal 2025; 21:13110
doi:10.4081/ecj.2025.13110

Introduction

The consumption of illicit drugs can be considered a global scourge. According to the World Drug Report,[1] approximately 61 million people worldwide used opioids for non-medical purposes in 2020, with 31 million being regular opioid users (mainly heroin). While opioid use remained stable between 2019 and 2020, there is concern about the upward trend observed between 2010 and 2020, during which the number of opioid users doubled. In 2019, opioid use disorders accounted for approximately 12.9 million healthy years of life lost due to disability and premature death. Intravenous drug use remains particularly widespread in Eastern Europe and, to a lesser extent, in Central Europe.[2] In Italy, according to the 2022 Report to Parliament,[3] wastewater analyses revealed that heroin use follows that of cannabis and cocaine, with an average of 3.2 daily doses per 1000 inhabitants. Heroin consumption is particularly high in the city of Perugia, with 12 doses per 1000 inhabitants per day, and ranges from 6 to 8 doses per day in cities such as Bologna, Fidenza, Ancona, Terni, Trieste, and Campobasso.[4,5] Despite the critical importance of timely intervention in opioid overdose cases, comprehensive and up-to-date guidelines on prehospital management remain scarce. A preliminary review of the literature identified three key documents addressing this topic. The 2014 WHO Recommendations provide general guidance but are now outdated, failing to incorporate recent advances in naloxone administration.[6] Similarly, a systematic review titled "Management of suspected opioid overdose with naloxone by emergency services," focusing on out-of-hospital overdoses, confirms naloxone's efficacy as a critical treatment but is limited by data variability and a lack of long-term follow-up.[7] Lastly, the American Heart Association (AHA) Scientific Statement emphasizes naloxone administration alongside conventional CPR for opioid-associated out-of-hospital cardiac arrest (OA-OHCA) yet lacks actionable guidelines on the practical use of intranasal (IN) naloxone in prehospital settings.[8] These documents offer valuable insights but underscore the absence of specific, evidence-based guidelines. Recent studies have highlighted the growing role of intranasal naloxone as a practical, effective tool for prehospital overdose interventions, particularly in non-medical settings.[9] This gap in the literature emphasizes the need for a comprehensive review of current evidence to inform best practices. Therefore, this review aims to examine the latest data, offering a methodologically rigorous assessment of the current state of knowledge and identifying optimal strategies for opioid overdose management, with a primary focus on prehospital environments. However, if the availability of studies solely addressing prehospital care is limited, relevant data from other settings may be considered to provide a more comprehensive view. The aim of this review is to examine the available evidence on the effectiveness of different routes of naloxone administration in opioid overdoses, with a primary focus on prehospital settings and a particular emphasis on comparing intranasal, Intramuscular (IM), and Intravenous (IV) routes. To address this, a search was conducted on PubMed, including articles published up to March 28, 2023.

Materials and Methods

A narrative review was conducted in compliance with the preferred reporting items for systematic reviews and meta-analyses statement (PRISMA)[10] and the guidelines for writing a narrative review to be published in peer-reviewed journals.[11]

Search strategy

Initially, several key words were selected based on the recommendations of experts in prehospital emergency care and verified using the MeSH thesaurus. PubMed was used as the primary source for the search. The search included terms such as "naloxone," "opioid overdose," "intranasal administration," and "prehospital emergency care," with Boolean operators to refine the scope. The search was completed on March 28, 2023, and all primary-level studies published up to that date were retrieved, with a filter set for no more than 6 years back (2017-2023). No contact with authors was necessary. Additional filters applied included study types such as "clinical trial," "controlled clinical trial," "multicenter study," "observational study," and "randomized controlled trial." Using this search strategy, 111 results were available as of March 28, 2023. All studies relevant to the research questions were selected.

Eligibility criteria

The research question was constructed using the PICO framework (Table 1). To ensure a comprehensive analysis, studies focusing on cases of opioid overdose in a prehospital setting were prioritized. Additionally, studies conducted in community or controlled research settings were included to encompass a broad range of evidence. This approach provides a balance between controlled experimental data, which offer robust pharmacological insights, and real-world studies, which capture the practical challenges of managing opioid overdose. The intervention studied was intranasal naloxone administration, and the comparison was made with intramuscular or intravenous naloxone administration. The primary outcomes observed were the restoration of spontaneous breathing, improvement in the Glasgow Coma Scale (GCS) score to at least 8, and the onset of action of naloxone, defined by the time to improvement in respiratory rate and peripheral oxygen saturation. Secondary outcomes included clinical stabilization and the need for additional naloxone administration. Descriptive clinical studies and randomized controlled trials (RCTs) involving adult patients were included. Exclusion criteria were the absence of data on naloxone route and dosage and studies focusing on the treatment of chronic opioid dependence. Full-text articles of selected records were retrieved, and relevant articles were summarized using a checklist designed based on PRISMA protocols. The data collected in the checklist included the name of the first author, publication year, patient characteristics, naloxone administration route, dosage, and outcomes.

Studies selection

Records were identified, screened, and assessed for eligibility.

Table 1. Question according to the PICO method.

PICO	Structure
Problem (P)	Opioid overdose in a prehospital setting
Intervention (I)	Intranasal naloxone administration
Comparison (C)	Intramuscular/intravenous naloxone administration/Other
Outcome (O)	Success rate and onset of action

The screening process involved reviewing abstracts and full-text articles to exclude studies not aligned with the research objectives. Studies were excluded if they focused on chronic opioid use disorder, economic analyses of the opioid epidemic, or overdose prevention programs unrelated to naloxone administration. To assess the methodological quality and homogeneity of the studies included in the review, the method proposed by Dixon-Woods was used by means of a specific checklist.[12] This checklist comprises five domains to assess the methodological quality of the studies, and each article was assigned an overall rating based on the assessment of these domains. Studies that received a score of less than 3 "yes" answers were excluded from the analysis. Those with 3 "yes" answers were considered discrete, while studies with 4 "yes" answers were classified as good, and those with 5 "yes" answers were considered to be of excellent quality (Table 2). Two authors independently conducted the critical quality assessment. In cases of disagreement on evaluations, a further comparison was made to reach a consensus.

Results

The initial search identified 111 results screened by reviewing the abstracts. This process led to the exclusion of 9 studies focused on HIV and/or overdose prevention. The full-text review of the remaining 102 articles was then conducted. Of these, 24 studies related to the "take-home" naloxone strategy, involving layperson administration in case of opioid overdose, were excluded. Additionally, 11 studies focusing on hospital-based overdoses, 38 discussing chronic opioid use disorder, 4 addressing the medical use of opioids for other conditions, 4 on the economic impact of the opioid epidemic, and 8 discussing opioid overdose monitoring techniques were excluded, along with other studies addressing topics unrelated to the research question. This process left 13 studies for more detailed analysis. The populations, research questions, and treatment techniques for opioid overdose were compared to identify any discrepancies. Further exclusions resulted in the removal of 7 studies that were not directly relevant to the research question. Specifically, 2 studies compared different formulations of intranasal naloxone, 1 investigated opioid receptor occupancy by naloxone, 2 examined the bioavailability of a 2 mg naloxone spray, and the other studies focused on the adverse effects of naloxone post-overdose treatment, regardless of formulation. Ultimately, five studies met the eligibility criteria and were included in the review (Figure 1).

The quality assessment, based on the Dixon-Woods checklist, revealed that the included studies achieved a minimum rating of

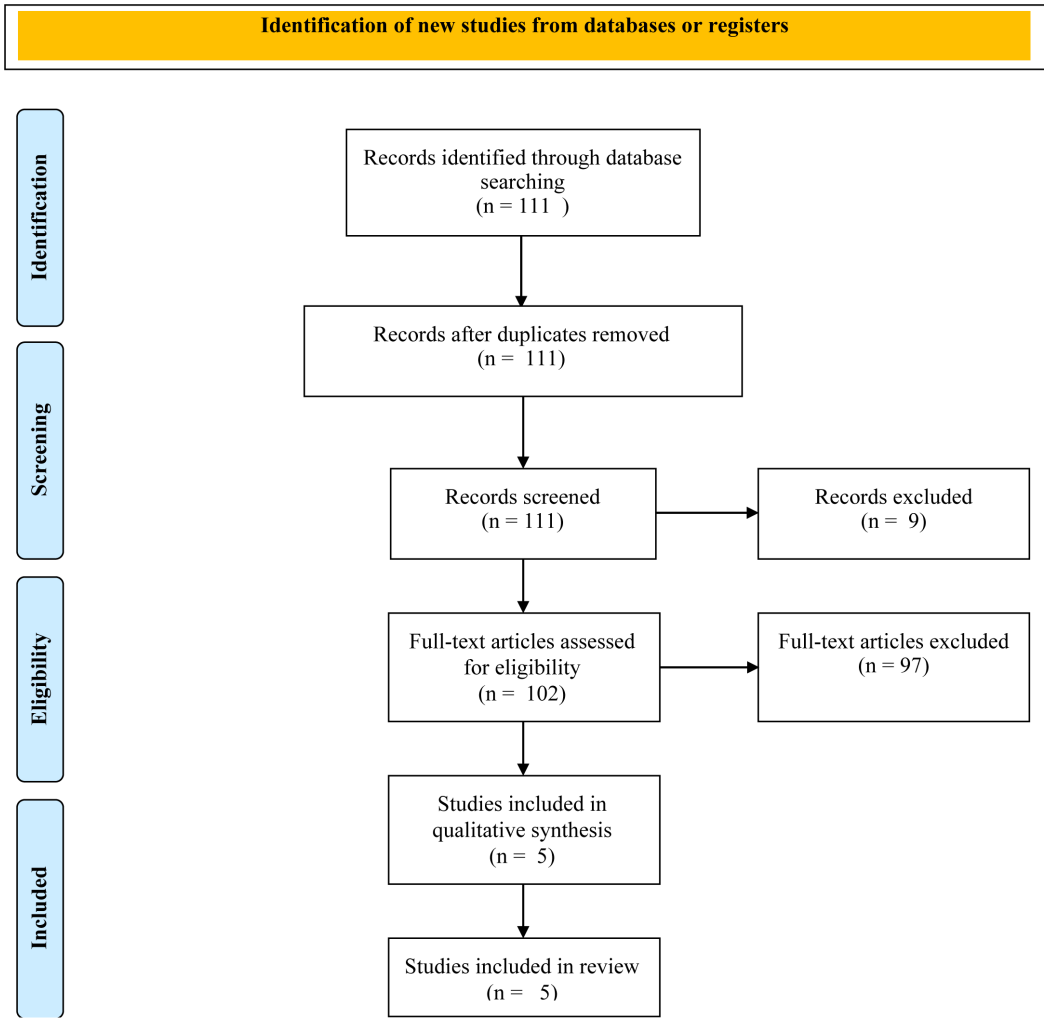

Figure 1. Summary of the study selection.

"discrete" and were considered sufficiently robust for inclusion (Table 2). The studies included in this review involved different populations, from healthy volunteers with no history of drug use to patients with active drug use. These differences in participant characteristics, including their previous exposure to opioids or other substances, influence the outcomes and should be considered when interpreting the results of the comparison between different naloxone formulations.

A summary of the study characteristics, including objectives and key findings, is provided in *Supplementary Materials Table 1*.

The studies can be divided into "pre-hospital" and "other settings." The studies by Skulberg *et al*. (2022)[13] and Dietze *et al*.[14] were conducted in prehospital settings, with Skulberg taking place in an ambulance during opioid overdose emergencies and Dietze *et al*. carried out in a community setting involving individuals with a history of opioid use. The studies by Skulberg *et al*. (2019),[15] Skulberg *et al*. (2018),[16] and McDonald *et al*.[17] were conducted in controlled clinical settings with healthy volunteers. While most studies focused on prehospital environments, additional data from other healthcare settings were also incorporated to address gaps in pre-hospital-specific evidence.

In the study by McDonald *et al*.,[17] three main objectives were pursued: i) to describe the pharmacokinetic profile of intranasal naloxone; ii) to compare early systemic exposure between intranasal and intramuscular naloxone; and iii) to estimate the bioavailability of intranasal naloxone. The pharmacokinetic parameters revealed that intravenous naloxone at 0.4 mg showed a rapid increase in plasma concentration, peaking at 5.94 ng/mL within 2 minutes, followed by a quick decline. In contrast, intramuscular naloxone at 0.4 mg had a slower absorption rate, with a peak concentration of 1.27 ng/mL at 10 minutes and a more gradual decline.

Intranasal naloxone at 1 mg, 2 mg, and 4 mg achieved peak plasma concentrations of approximately 0.95 ng/mL, 1.72 ng/mL, and 3.5 ng/mL, respectively, within 15-30 minutes, consistently surpassing those achieved with intramuscular naloxone in terms of total exposure. Among the intranasal doses, the 2 mg spray closely mirrored the intramuscular naloxone curve within the first 10 minutes post-dose and maintained higher plasma levels for two hours. The bioavailability of intranasal naloxone was estimated as 50.2% for 1 mg, 46.8% for 2 mg, and 48.1% for 4 mg, relative to intravenous administration. Relative bioavailability compared to intramuscular naloxone was 50.8% for 1 mg, 47.1% for 2 mg, and 48.3% for 4 mg.

In the study by Skulberg *et al*. (2018),[16] the primary endpoint was to evaluate the pharmacodynamic profile of intranasal *versus* intramuscular naloxone. Twelve healthy volunteers received remifentanil and were subsequently assessed for changes in pupillary diameter and heat pain threshold after naloxone administration. The baseline average pupillary diameter was similar between groups (6.6 mm in the intranasal group and 6.8 mm in the intramuscular group). After remifentanil administration, both groups showed a decrease in pupillary diameter (nadir at 2.9 mm). Post-naloxone, miosis reversal was more pronounced in the intramuscular group. Three remifentanil doses (1 ng/mL, 1.3 ng/mL, and 2.5 ng/mL) were tested with naloxone administered at 0.8 mg for both routes. The curves for intranasal and intramuscular naloxone diverged immediately after dosing but converged at 45 minutes. Miosis reversal peaked at 15 minutes for intramuscular naloxone and at 30 minutes for intranasal naloxone. Heat pain thresholds did not differ significantly between the two administration routes. The pharmacokinetic analysis revealed that the average dose for intranasal was 0.75 mg, and for intramuscular was 0.82 mg. The relative bioavailability of intranasal *versus* intramuscular naloxone was 0.75 (95% CI 0.63-0.87), with intranasal naloxone achieving a Tmax three times faster (7.75 minutes) compared to intramuscular naloxone (28 minutes). However, Cmax and AUClast were approximately double for intramuscular naloxone.

The study by Dietze *et al*.[14] aimed to compare the efficacy of 0.8 mg intramuscular *versus* intranasal naloxone. The results showed that intramuscular naloxone was associated with a lower likelihood of requiring additional doses compared to intranasal naloxone (8.6% *vs*. 23.1%; OR 0.35; 95% CI 0.15-0.66; P=0.002). For the endpoint of achieving a respiratory rate of at least 10 breaths per minute, the median time to achieve a respiratory rate of at least 10 breaths per minute was 8.0 minutes for intramuscular and 17.0 minutes for intranasal naloxone, reflecting an 81% increased hazard for intranasal administration (HR 1.81; 95% CI 1.28-2.56; P=0.001). Similarly, for the endpoint of achieving a Glasgow Coma Scale score of at least 13, the median time was shorter for intramuscular naloxone (8.0 minutes) compared to intranasal naloxone (15.0 minutes), indicating a 65% increased hazard for intranasal naloxone (HR 1.65; 95% CI 1.21-2.25; P=0.002).

In Skulberg *et al*. (2019),[15] 22 healthy volunteers received naloxone via three routes: intranasal (1.4 mg), intramuscular (0.8 mg), and intravenous (0.4 mg). The study aimed to compare the systemic distribution of 1.4 mg intranasal naloxone to 0.8 mg intramuscular and 0.4 mg intravenous doses. Absorption rates were higher for intramuscular naloxone, but intranasal naloxone achieved higher plasma concentrations by 15 minutes post-dose. The maximum concentrations (Cmax) of 1.4 mg intranasal naloxone and 0.8 mg intramuscular naloxone were comparable, with Tmax being similar (P=0.098). The time to 50% of Cmax was 10.1 minutes for intranasal naloxone and 6.5 minutes for intramuscular naloxone (P=0.061). In Skulberg *et al*. (2022),[13] 201 opioid overdose patients were randomized to receive either intramuscular (147 participants)

Table 2. Quality appraisal according to the Dixon-Woods scale.

Author(s) (year)	Are the aims and objectives of the research clearly stated?	Is the research design clearly specified and appropriate for the aims and objectives of the research?	Do the researchers provide a clear account of the process by the which their findings were reproduced?	Do the researchers display enough data to support their interpretations and conclusions?	Is the method of analysis appropriate and adequately explicated?	Score
McDonald *et al.* (2018)	Yes	Yes	Yes	Yes	Yes	Excellent
Skulberg *et al.* (2018)	Yes	Yes	Yes	Yes	Yes	Excellent
Dietze *et al.* (2019)	Yes	Yes	Yes	Yes	Yes	Excellent
Skulberg *et al.* (2019)	Yes	Yes	Yes	Yes	Yes	Excellent
Skulberg *et al.* (2022)	Yes	Yes	Yes	Yes	Yes	Excellent

or intranasal (139 participants) naloxone. The intramuscular group had a higher rate of achieving spontaneous respiration within 10 minutes (97.2%) compared to the intranasal group (79.6%). Intramuscular naloxone led to a faster return to spontaneous respiration, with an average of 2.3 minutes (95% CI 1.6-3.0) compared to 6.4 minutes for intranasal naloxone. Additional naloxone was administered to 9.3% of the patients in the intramuscular group and 29.0% of the intranasal group. Withdrawal symptoms occurred in 7.5% of the patients in the intramuscular group and 5.4% of the intranasal group.

Discussion

As indicated in the results section, the majority of the selected studies emphasize the benefits of using intranasal naloxone for overdose cases in out-of-hospital settings, an issue of growing urgency due to the rise in opioid overdoses, particularly those caused by synthetic opioids. The inclusion of studies from alternative settings highlights the limited availability of evidence specific to prehospital care. This approach provided a more comprehensive understanding of naloxone's effectiveness while stressing the need for further research in prehospital contexts.

These findings align with those from previous reviews, particularly Yousefifard *et al*.,[18] but several factors need to be considered, as they may obscure the efficacy of IN naloxone compared to the intramuscular formulation, particularly regarding the balance between the dosages of the two different formulations. In particular, it is noteworthy that McDonald *et al*.[17] demonstrated that a 2 mg IN dose of naloxone can achieve plasma levels comparable to those obtained with five 0.4 mg IM doses, totaling 2 mg. Despite the lower bioavailability of IN naloxone, this was in line with our results, where IN naloxone demonstrated comparable, if not higher, plasma levels over a longer duration. However, high doses of naloxone may induce severe withdrawal symptoms,[19-21] and therefore, it is advisable to gradually escalate the dose to 2 mg, as recommended by WHO guidelines.[9] Repeated simulations of 2 mg IN doses produced plasma levels comparable to a single 4 mg IN dose, suggesting that an initial 2 mg dose followed by a second dose, if necessary, could mitigate the risk of adverse effects and enhance safety for overdose victims and responders.[17] These findings highlight the concern about withdrawal symptoms, which may negatively influence naloxone's perception among opioid users, underscoring the need for a cautious approach in its administration.[22]

Furthermore, Skulberg *et al*. (2018)[13] emphasized that a target-controlled infusion of remifentanil serves as an effective model for studying naloxone pharmacodynamics. Their findings indicated that 0.8 mg of naloxone administered intramuscularly had a more rapid and pronounced effect compared to the same dose administered intranasally. Despite the lower intranasal bioavailability, IN naloxone can still be advantageous for reducing withdrawal symptoms, primarily due to its ease of administration in emergency situations. However, it is important to consider the slower absorption of IN naloxone and its implications for the timely management of opioid overdose.[23] Despite the lower bioavailability of IN naloxone, in cases of shock, the IM route may also encounter similar issues related to compromised circulation. In patients with severe opioid intoxication or shock, both routes can be less effective due to reduced absorption caused by hypotension and vasoconstriction, which affect circulation. This highlights the complexity of naloxone administration in such critical conditions, where both IM and IN routes may face challenges in ensuring optimal drug absorption. Additionally, intranasal naloxone offers an important pharmacokinetic advantage: it enters the central venous circulation immediately, bypassing the first hepatic pass and exploiting the highly vascularized mucosa in the nasal cavity. This allows for faster systemic absorption compared to intramuscular administration. Moreover, absorption at the level of the olfactory mucosa can facilitate the immediate passage of naloxone into the central nervous system, which is particularly beneficial in the rapid reversal of opioid toxicity.[24]

Skulberg *et al*. (2019)[15] highlighted that the absorption of 0.8 mg naloxone IM was slightly faster than that of 1.4 mg naloxone IN, with no significant differences in Cmax, Tmax, or AUC0-last between the two routes. The linear increase in systemic exposure with intranasal doses suggests that IN naloxone is suitable for repeated administrations.[25] New naloxone formulations, such as Nyxoid and Narcan Nasal, exhibit similar pharmacokinetic profiles and offer higher serum concentrations than those achieved with 0.4 mg IM. When administered 2.25 minutes prior to an IM dose, 1.4 mg IN naloxone can still provide higher blood concentrations, indicating a clinical benefit.[26]

Dietze *et al*.[14] confirmed that while intranasal naloxone is less effective than intramuscular naloxone at equivalent doses, it offers several advantages, including the elimination of accidental needle stick injuries and the need for less extensive training. These benefits support public health policies aimed at expanding immediate access and use of naloxone by both laypeople and first responders in community settings.[27-29] However, further research is required to determine whether higher doses of IN naloxone could achieve the same level of efficacy as IM administration.[29] Skulberg *et al*. (2022)[13] found that a single 1.4 mg IN dose of naloxone was less effective than 0.8 mg IM naloxone in achieving spontaneous respiration within 10 minutes of administration. Nevertheless, IN naloxone exhibited slower absorption, which may reduce the risk of withdrawal symptoms. While IM formulations have a faster onset, they are associated with a higher risk of adverse reactions.[31-33] Given the increasing prevalence of synthetic opioids, including illicitly manufactured fentanyl and fentanyl analogs (F/FA),[34] it is critical to evaluate the efficacy and optimal dosage of both IN and IM naloxone formulations in reversing overdoses caused by these substances. In emergency situations, it is often not possible to distinguish between overdoses caused by prescription opioids, synthetic opioids, and fentanyl.[35]

Limitations

The limitations of this review stem primarily from the small number of studies included and the use of a single database, PubMed. The search strategy yielded 111 results, but only 5 met the initial PICO criteria and demonstrated robust methodological quality. Additionally, the temporal filter, restricting the search to studies from the past 6 years, further limited the scope. Despite these constraints, efforts were made to identify other relevant reviews, including the recent work by Yousefifard *et al*.,[18] which covered studies excluded due to the time filter. Furthermore, the heterogeneity of the populations included in the studies—ranging from healthy volunteers to patients with active opioid use—limits the generalizability of the findings and highlights the need for further research with more homogeneous groups to better assess the efficacy of different naloxone formulations in specific patient populations.

Conclusions

This review underscores that intravenous naloxone remains the first-line treatment for opioid overdoses due to its superior efficacy. However, in prehospital settings, where establishing IV access is challenging, IM and IN routes serve as practical alternatives. Among these, IM naloxone demonstrates a faster onset of action, while IN naloxone offers the advantage of being non-invasive and easier to administer, particularly by lay responders. The findings suggest that IN naloxone may achieve comparable plasma concentrations to IM naloxone over time, despite its lower bioavailability, and highlight its potential for repeated administration to balance efficacy and safety. Gradual dose escalation, rather than a single high dose, appears to minimize the risk of severe withdrawal symptoms, aligning with WHO recommendations. Given the increasing prevalence of synthetic opioids such as fentanyl, this review emphasizes the urgent need for updated clinical guidelines to address optimal dosing and administration routes for naloxone in prehospital settings. Further research is crucial to evaluate the comparative effectiveness of IN and IM formulations in reversing overdoses caused by synthetic opioids, ensuring timely and safe interventions.

References

1. UNODC. World Drug Report 2021. United Nations Office on Drugs and Crime. Available from: https://www.unodc.org/unodc/en/data-and-analysis/wdr2021.html
2. GBD 2019 Diseases and Injuries Collaborators. Global Burden of Disease Study 2019 (GBD 2019). Lancet 2020. Available from: https://www.thelancet.com/gbd
3. Presidenza del Consiglio dei Ministri, Dipartimento per le Politiche Antidroga. Relazione al Parlamento 2022. Available from: http://www.politicheantidroga.gov.it
4. Istituto Nazionale di Statistica (ISTAT). Official data on mortality causes in Italy including drug-related deaths. 2021.
5. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Report on drug-related deaths in Europe. 2019.
6. World Health Organization. Community management of opioid overdose [Internet]. Geneva: World Health Organization; 2014. Available from: https://www.who.int/publications/i/item/9789241548816
7. Chou R, Korthuis PT, McCarty D, et al. Management of Suspected Opioid Overdose With Naloxone by Emergency Medical Services Personnel [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2017 (Comparative Effectiveness Reviews, No. 193). Available from: https://www.ncbi.nlm.nih.gov/books/NBK487477/
8. Dezfulian C, Orkin AM, Maron BA, et al. American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Council on Clinical Cardiology. Opioid-Associated Out-of-Hospital Cardiac Arrest: Distinctive Clinical Features and Implications for Health Care and Public Responses: A Scientific Statement From the American Heart Association. Circulation 2021;143:e836-70.
9. World Health Organization (WHO). Report on the global opioid overdose crisis. 2021.
10. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169:467-73.
11. Green BN, Johnson CD, Adams A. Writing narrative literature reviews for peer-reviewed journals: secrets of the trade. J Chiropr Med 2006;5:101-17.
12. Dixon-Woods M, Cavers D, Agarwal S, et al. Conducting a critical interpretive synthesis of the literature on access to healthcare by vulnerable groups. BMC Med Res Methodol 2006;6:35.
13. Skulberg AK, Tylleskär I, Valberg M, et al. Comparison of intranasal and intramuscular naloxone in opioid overdoses managed by ambulance staff: a double-dummy randomised controlled trial. Addiction 2022;117:1658-67.
14. Dietze P, Jauncey M, Salmon A, et al. Effect of Intranasal vs Intramuscular Naloxone on Opioid Overdose: A Randomized Clinical Trial. JAMA Netw Open 2019;2:e1914977. Erratum in: JAMA Netw Open 2020;3:e206593.
15. Skulberg A, Åsberg A, Khiabani HZ, et al. Pharmacokinetics of a novel, approved, 1.4 mg intranasal naloxone formulation for reversal of opioid overdose: a randomized controlled trial. Addiction 2019;114:859-67.
16. Skulberg A, Tylleskär I, Nilsen T, et al. Pharmacokinetics and -dynamics of intramuscular and intranasal naloxone: an explorative study in healthy volunteers. Eur J Clin Pharmacol 2018;74:873-83.
17. McDonald R, Lorch U, Woodward J, et al. Pharmacokinetics of concentrated naloxone nasal spray for opioid overdose reversal: Phase I healthy volunteer study. Addiction 2018;113:484-93.
18. Yousefifard M, Vazirizadeh-Mahabadi MH, Neishaboori AM, et al. Intranasal versus Intramuscular/Intravenous Naloxone for Pre-hospital Opioid Overdose: A Systematic Review and Meta-analysis. Adv J Emerg Med 2019;4:e27.
19. Banerjee S, Wright MD. Injectable Opioid Agonist Treatment for Patients with Opioid Dependence: A Review of Clinical and Cost-Effectiveness [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2020.
20. Wermeling DP. Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access. Ther Adv Drug Saf 2015;6:20-31.
21. Gowing L, Ali R, White JM. Opioid antagonists with minimal sedation for opioid withdrawal. Cochrane Database Syst Rev. 2017;5:CD002021.
22. Bennett AS, Freeman R, Des Jarlais DC, Aronson ID. Reasons people who use opioids do not accept or carry no-cost naloxone: qualitative interview study. JMIR Form Res 2020;4.
23. Lewis CR, Vo HT, Fishman M. Intranasal naloxone and related strategies for opioid overdose intervention by nonmedical personnel: a review. Subst Abuse Rehabil 2017;8:79-95.
24. Grassin-Delyle S, Buenestado A, Naline E, et al. Intranasal drug delivery: an efficient and non-invasive route for systemic administration: focus on opioids. Pharmacol Ther 2012;134:366-79.
25. Rock P, Slavova S, Westgate PM, et al. Examination of naloxone dosing patterns for opioid overdose by emergency medical services in Kentucky during increased fentanyl use from 2018 to 2021. Drug Alcohol Depend 2024;255:111062.
26. Saari TI, Strang J, Dale O. Clinical pharmacokinetics and pharmacodynamics of naloxone. Clin Pharmacokinet 2024;63:397-422.
27. Walsh SL, El-Bassel N, Jackson RD, et al. The HEALing communities study: protocol for a cluster randomized trial to

reduce opioid overdose deaths. Drug Alcohol Depend 2020;217:108335.
28. Oesterle S, Kuklinski MR, Hawkins JD, et al. Long-term effects of the communities that care trial on substance use, antisocial behavior, and violence through age 21 years. Am J Public Health 2018;108:659-65.
29. Irvine MA, Oller D, Boggis J, et al. Estimating naloxone need in the USA across fentanyl, heroin, and prescription opioid epidemics: a modelling study. Lancet Public Health 2022;7.
30. Rzasa Lynn R, Galinkin JL. Naloxone dosage for opioid reversal: current evidence and clinical implications. Ther Adv Drug Saf 2018;9:63-88.
31. Lemen PM, Garrett DP, Thompson E, et al. High-dose naloxone formulations are not as essential as we thought. Harm Reduct J 2024;21:93.
32. Moe J, Godwin J, Purssell R, et al. Naloxone dosing in the era of ultra-potent opioid overdoses: a systematic review. CJEM 2020;22:178-86.
33. Weaver L, Palombi L, Bastianelli KMS. Naloxone administration for opioid overdose reversal in the prehospital setting: implications for pharmacists. J Pharm Pract 2018;31:91-8.
34. D'Orsogna MR, Böttcher L, Chou T. Fentanyl-driven acceleration of racial, gender and geographical disparities in drug overdose deaths in the United States. PLOS Glob Public Health 2023;3:e0000769.
35. Prekupec MP, Mansky PA, Baumann MH. Misuse of novel synthetic opioids: a deadly new trend. J Addict Med 2017;11:256-65.

Online supplementary materials
Table 1. Summary of the study characteristics.