Supplementary materials

Table 1. Summary of the study characteristics.

Author(s) (year)	Type of study	Participants	Study context and setting	Age	Objectives	Results and Conclusions
Skulberg *et al.* (2022)	Randomized Clinical Trial	201 subjects, 36 females	Ambulance, emergency	>18 years old (average 38.9 years)	To measure and evaluate clinical response to nasal naloxone in opioid overdoses in the prehospital environment	Spontaneous respiration within 10 minutes was restored in 97.2% of the intramuscular group and 79.6% of the intranasal group. The risk difference favored the intramuscular group by 17.5%, while the need for additional naloxone was 19.4% higher in the intranasal group. Adverse reactions were similar across both groups, except for withdrawal symptoms, which were 6.8% less frequent in the intranasal group.
Skulberg *et al.* (2019)	Randomized Clinical Trial	22 subjects, 10 females	Healthy volunteers, Hospital	18-45 years old	To determine the systemic exposure of 1.4 mg I.N. naloxone compared to that of 0.8 mg I.M.	Intranasal 1.4 mg naloxone and intramuscular 0.8 mg naloxone showed no significant difference in area under the curve (AUC), Cmax, or Tmax (P = 0.33). Intranasal naloxone exhibited 52% relative bioavailability compared to intramuscular administration. The conclusions suggest that intranasal 1.4 mg naloxone provides sufficient systemic exposure, making it appropriate for both peer and professional administration in opioid overdose treatment.
Dietze *et al.* (2019)	Randomized Clinical Trial	197 subjects, 24 females	Community-based setting	18-55 years old	To test whether a dose of naloxone administered intranasally is as effective as the same dose of intramuscularly administered naloxone in reversing opioid	In a trial of 197 participants, intramuscular naloxone was associated with a lower need for rescue doses (8.6% *vs.* 23.1%) compared to intranasal naloxone. The intranasal group showed slower

					overdose.	recovery in respiratory rate and Glasgow Coma Scale scores. No major adverse events occurred. These findings confirm that while intranasal naloxone reverses opioid overdose, it is less efficient than intramuscular naloxone, suggesting a need to optimize intranasal dosing.
Skulberg *et al.* (2018)	Clinical Trial	12 healthy volunteers, Sex N.A.	Healthy volunteers, Clinical setting	18-40 years old	This study aimed to develop a model for pharmacodynamic and pharmacokinetic studies of naloxone under steady-state opioid agonism and to compare a high-concentration intranasal naloxone formulation (8 mg/ml) with intramuscular naloxone (0.8 mg).	The relative bioavailability of intranasal naloxone compared to intramuscular was 0.75. Pupillometry revealed significant opioid antagonism differences, while no differences were found in the heat pain threshold. The study concluded that pupillometry is more effective than heat pain threshold for assessing naloxone's pharmacodynamics. Additionally, 0.8 mg intranasal naloxone was less effective than the equivalent intramuscular dose.
McDonald *et al.* (2018)	Clinical Trial	35 healthy volunteers, 11 females	Healthy volunteers, Clinical trials facility	18-55 years old	The study aimed to: (1) estimate the pharmacokinetic profiles of intranasal naloxone, (2) compare early systemic exposure between intranasal and intramuscular naloxone, and (3) estimate the bioavailability of intranasal naloxone	Intranasal naloxone (1 mg, 2 mg, and 4 mg) achieves higher peak concentrations than 0.4 mg intramuscular naloxone, reaching over 50% of peak levels within 10 minutes and peaking at 15-30 minutes. The bioavailability of intranasal naloxone is 47-51% relative to intramuscular. Simulations show that repeated doses of 2 mg intranasal naloxone achieve plasma concentrations similar to 0.4 mg intramuscular. In conclusion, 2 mg intranasal naloxone is rapidly absorbed and maintains higher blood levels for up to 2 hours.