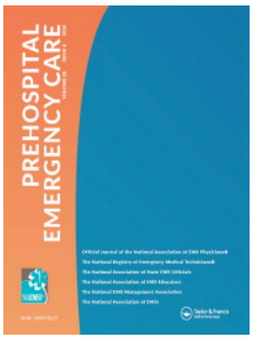

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What is the Evidence for Using Intranasal Medicine in the Prehospital Setting? A Systematic Review

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ABSTRACT

Objectives: Intranasal (IN) medications offer a safe non-invasive way to rapidly deliver drugs in situations where intravenous (IV) access and intramuscular (IM) administration is challenging or not feasible. In the prehospital setting, this can be an essential alternative in time critical situations including trauma management, seizures, and agitated patients. However, there is a paucity of evidence summarizing its efficacy in this environment. This systematic review aims to assess the current evidence supporting the use of IN medicine (midazolam, ketamine, fentanyl, morphine, glucagon, and naloxone) in the prehospital setting alone.

Methods: A systematic literature search (PROSPERO CRD42023440713) of PubMed, Web of Science, OVID Medline, "Cochrane Central Register of Controlled Trials," Cochrane reviews and Embase was performed from inception to June 2023 to identify studies where IN medications were administered to patients in the prehospital setting. All randomized controlled trials, observational cohort studies, case series, and case reports were included. Papers not written in English, review articles, abstracts, and non-published data (including letters to the editor) were excluded. The methodological quality of the included studies was interpreted using the Cochrane risk of bias tool and rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. No funding was received.

Results: From 4818 studies, 39 were included (seven for midazolam, five for ketamine, twelve for fentanyl, one for diamorphine, two for glucagon, and twelve for naloxone). A total of 24,097 patients were treated with IN medications across all the studies. There were five moderate quality, four low quality, and thirty very low quality studies. The potential efficacy of IN fentanyl and ketamine was demonstrated consistently throughout the studies with less clear evidence for midazolam, morphine, glucagon, and naloxone. This review was severely limited by the study quality, with most studies demonstrating "high concerns" for bias.

Conclusions: Prehospital IN medication administration has wide-ranging potential, particularly for administering analgesia. There are likely to be certain populations, for example, pediatrics, that will benefit the most, although conclusions are limited by the quality of evidence currently available. We encourage additional research in this area, particularly with robust prospective double-blind RCTs.

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Introduction

Intranasal (IN) medications offer a safe non-invasive way to rapidly deliver vital drugs in situations where intravenous (IV) access and intramuscular (IM) administration is challenging or not desired (1), for example in the pediatric setting. In the prehospital setting, this can be an essential alternative in time critical situations including trauma management, seizures, and agitated patients (1). The nasal vestibule allows for efficient drug absorption *via* its large surface area of capillaries, bypassing first-pass hepatic metabolism (2). Drug absorption *via* the olfactory neuroepithelium to the CSF also occurs (3). Together, this allows for direct absorption, predictable bioavailability, and rapid onset of action (2).

Additionally, IN drugs can be delivered successfully regardless of body habitus, patient cooperation, or age (1). Medication administration *via* the IN route has been shown to have favorable pharmacokinetics when delivery is optimized with a mucosal atomization device (MAD) (4), a device that disperses medication to the nasal passage without patient assistance. This method delivers a predictable dose IN, whereas IM dosing relies on delivery into muscle which may be difficult to localize in overweight patients (5). Compared to delivering medications IV, IN offers a faster time to drug administration, especially where multiple attempts at IV access are required or in patient populations with historically difficult access, such as pediatrics or

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Table 1. The advantages and disadvantages of intranasal administration (3, 4).

Advantages	Disadvantages
Faster drug administration times	Maximum volume of ~0.5 ml into each nare (due to surface area of the vestibule) limits dosing capabilities
Good bioavailability	Recent use of nasal vasoconstrictors limits absorption
Less technical skill, no IV access required	Contraindicated by maxillofacial trauma and epistaxis
Relatively painless (compared to IV/IM administration)	Drug absorption can be affected by decreased mucociliary clearance (such as rhinitis, nasal secretions, cystic fibrosis, and nasal polyps)
No risk of sharps injuries	May cause mucosal irritation

Table 2. Medical subject headings (MeSH) for electronic database search.

Terms for medicines	"Midazolam" OR "ketamine" OR "s-ketamine" OR "esketamine" OR "morphine" OR "naloxone" OR "narcan" OR "glucagon" OR "fentanyl"
AND	
Terms for intranasal	"Intranasal" OR "intranasally" OR "intra-nasal" OR "IN"
AND	
Terms for prehospital	"Prehospital" OR "pre-hospital" OR "non-hospital" OR "out of hospital" OR "out-of-hospital" OR "EMS" OR "emergency medical service" OR "ambulance service" OR "air ambulance" OR "HEMS" OR "helicopter emergency medical service"

chronic intravenous drug abusers. The perceived advantages and disadvantages of IN administration are broadly summarized in Table 1 (3, 4).

The scope of IN drug use in hospital has markedly increased for a wide range of indications (4). For example, the utilization of IN fentanyl for pediatric analgesia has been demonstrated widely throughout emergency care to be effective, safe, and well-tolerated (6–9). It has been shown that IN fentanyl results in a significantly decreased time to receive analgesia compared to IV morphine in children with long bone fractures (10). However, it is unclear what the standards for IN medications are throughout the prehospital setting; there are likely multiple emergency medications, often carried by prehospital teams, that may benefit from this route of administration. These include Midazolam, Ketamine, Fentanyl, Morphine, Gucagon and Naloxone.

The aim of this systematic review was to assess the current evidence of using IN medicine in the prehospital setting only, evaluating the efficacy (analgesic/sedative effect, reversal of toxicity/hypoglycemia), adverse effects, and optimal dosing of the drugs administered by the IN route.

Methods

Data Collection and Analysis

A systematic review of the literature reporting prehospital use of the following intranasal medications (midazolam, ketamine, morphine, diamorphine, fentanyl, naloxone, glucagon) was performed.

This systematic review was carried out in accordance with the Preferred Reporting Items for Meta-Analyses (PRISMA) guidelines (11). Electronic database searching of PubMed, Web of Science, OVID Medline, "Cochrane Central Register of Controlled Trials," Cochrane Reviews, and Embase were searched independently by two reviewers (AB and SM). Table 2 shows the terms searched using Medical Subject Headings combined with Boolean operators. Defined search dates start from the inception of each database to the date each search was performed (15/06/2023). This review was registered on the Prospero database (CRD42023440713) (12); no amendments to the protocol occurred.

All papers were uploaded to EndNote 20 (Clarivate Analytics, Boston, MA, USA). Two independent review (AB and SM) authors accessed each title and abstract for review, with relevant full-text papers retrieved for further assessment against the inclusion criteria. Duplicates were removed and reference lists of selected titles were screened for completeness. In case of disagreement, a third reviewer (CD) was utilized to decide eligibility.

Selection Criteria

All randomized controlled trials (RCTs), observational cohort studies, case series, and case reports assessing the listed IN drugs in any prehospital patient population were included. "Prehospital" was defined as any patient receiving an initial medication dose by emergency personnel outside of the hospital. The term "emergency personnel" included any emergency medical service clinician with medical training, such as paramedics, doctors, nurses, mountain rescue, and combat technicians but excluded law enforcement and other first responders without formal medical training.

Papers not written in English, review articles, abstracts, and non-published data (including letters to the editor) were excluded. Any studies using animals or cadavers were excluded.

Data Extraction

Study design, sample size, inclusion criteria, interventions and dose given, comparator method of administration, demographics of the patients, and their outcomes were extracted from full texts. The primary outcome and secondary outcomes for each drug are summarized in Table 3. Outcome assessments were performed at multiple time points post-medication administration if reported.

A variety of pain scales were used as outcome measures for the analgesic medications including a verbal numerical

Table 3. Types of outcome measures evaluated to investigate the evidence of IN drugs used in the prehospital setting.

IN medication	Indication	Primary outcome	Secondary outcome(s)
Midazolam	Agitation and anxiolysis Seizures	Sedative effect—subjective clinical change Median seizure time, termination of seizure, rescue therapy required	Second dose required Further seizures, admission to hospital, ventilatory support, adverse events
Ketamine	Agitation, sedation and analgesia	Reduction in pain score—Wong-Baker, FLACC scale, numeric rating scale, visual analogic scale, quality assessment *via* categories	Further doses required, adverse events, vital signs, patient reported satisfaction, time spent on scene, failed IV access attempts, time to administration
Fentanyl	Analgesia	Reduction in pain score—Wong-Baker, FLACC scale, numeric rating scale, visual analogic scale, quality assessment *via* categories	Further doses required, adverse events, vital signs, patient reported satisfaction, time spent on scene, failed IV access attempts, time to administration
Morphine	Analgesia	Reduction in pain score—Wong-Baker, FLACC scale, numeric rating scale, visual analogic scale, quality assessment *via* categories	Further doses required, adverse events, vital signs, patient reported satisfaction, time spent on scene, failed IV access attempts, time to administration.
Glucagon	Hypoglycemia	Reversal of hypoglycemia-blood glucose levels pre and post-administration	Mental status/GCS
Naloxone	Opioid toxicity	Reversal of toxicity—return of spontaneous respiratory effort and GCS	Time to restoration of spontaneous respiration, number of doses, rescue doses, recurrence of overdose within 12 h and adverse events

FLACC: "faces, legs, activity, cry, consolability" scale; GCS: Glasgow Coma Scale.

rating scale (VNRS) or Wong Baker Faces Rating (WBFR) (13). Most commonly the VNRS, a numerical scale where patients are asked to rate their pain out of 10, has been used to report pain in adults as it is simple, quick, and easy to comply with (13) and is therefore likely to be feasible in the prehospital setting. The WBFR scale presents six faces of increasing pain from left to right and is often used when participants are not able to verbalize their pain scores, such as in children (14). Other validated tools that have been utilized include the FLACC Scale (Face, Legs, Activity, Cry, Consolability), for children 2 months–7 years (15) and the visual analog scale (VAS), a 10 mm line anchored at each end from no pain to the worst pain imaginable.

Where possible data was extracted directly from the full text, and, in case of missing data, such as specific sample size in some studies, this was calculated retrospectively using available data. Meta-analysis could not be performed due to the heterogeneous nature of the data extracted, variety of outcomes reported, and concerns of bias in the selected studies. Structured reporting of available effects are displayed in Table 4 and Online Appendix Table S1.

Quality Assessment of Included Studies

The Cochrane "Grading of Recommendations, Assessment, Development, and Evaluation" (GRADE) approach (16) was used to rate the reliability of evidence from each included study by two independent authors (AB and SM). A baseline quality rating was set for each study ('high' for RCTs and "low" for observational studies) and then subsequently up- or down-graded against six quality assessment criteria (risk of bias, inconsistency, indirectness, imprecision, publication bias, and others). As part of this, the limitations of each study were assessed using the Cochrane risk of bias tool (17) independently by two authors (AB and SM). The risk of bias tool evaluates the risk of confounding, selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each study was subsequently graded independently as low risk, unclear risk, or high risk of bias. A study was considered to have a low risk of bias when all the domains assessed were adequate and to have a high risk of bias when one or more of the domains were inadequate or unclear. In case of disagreement, a third author (CD) made the final decision.

Results

Study Selection and Characteristics

A total of 4818 studies were identified. After duplicates were removed, 2749 studies were screened with a total of 39 studies included (Figure 1). In total, 24,097 patients were treated with IN medications across all the studies: 3319 patients with IN midazolam; 156 patients with IN ketamine; 16,650 patients with IN fentanyl; 18 patients IN diamorphine; zero patients with morphine; 45 patients with IN glucagon and 3909 patients with IN naloxone.

The summary of study characteristics are displayed in Table 4. Full details of the findings of each individual study are available in Online Appendix Table S1; the full quality of evidence (GRADE) findings are available in Online Appendix Table S2. Of the 39 studies included, five were moderate quality, four were low quality and thirty were very low quality.

Midazolam

Seven observational studies for IN midazolam were found (18–24); six indicated for seizure management and one for behavioral emergencies. No RCTs were found but three of the studies focused on a purely pediatric population (<14 to <18 years).

For the three retrospective studies (18–20) with purely pediatric populations, two (18, 19) investigated rates of redosing with midazolam while one (20) investigated seizing on arrival at the emergency department (ED). Shavit et al. (18) and Whitfield et al. (19) compared IN midazolam against different routes of midazolam administration, including IV and IM, whereas Holsti et al. (20) compared against

Table 4. Summary of study characteristics (18–56).

Reference (publication year)	Study design	Sample size relevant to IN medication	Population	Exposure	Primary outcome	Final grade of evidence (16)
Midazolam						
Shavit et al. (2023) (18)	Retrospective cohort	454	Pediatric (0–18 yrs) seizure patients.	IN midazolam *vs.* IV/IM midazolam	The administration of rescue therapy (additional doses given after initial administration).	Very low
Whitfield et al. (2022) (19)	Retrospective observational analysis	461	Non-traumatic seizures in pediatric patients (≤14 yrs).	IN midazolam *vs.* IV/IM/IO midazolam	Proportion of patients requiring redosing of midazolam after initial treatment IN.	Very low
Holsti et al. (2007) (20)	Retrospective time series analysis	39	Seizing children (<18 yrs).	IN midazolam *vs.* PR diazepam	Seizing on arrival at the ED.	Very low
Guterman et al. (2020) (21)	Cross-sectional analysis	702	Any adult patient treated for status epilepticus.	IN midazolam *vs.* IV/IM/IO midazolam	Treatment with a second benzodiazepine dose.	Very low
Guterman et al. (2022) (22)	Retrospective cohort	1500	Adult patients (≥18 yrs) with out-of-hospital status epilepticus receiving midazolam.	IN midazolam *vs.* IM/IV midazolam	Administration of rescue therapy as an indicator of ongoing seizure activity.	Low
Theusinger et al. (2019) (23)	Retrospective time series analysis	56	Adults (>18 yrs) and children (<18 yrs) treated for seizures.	IN midazolam *vs.* PR/IV diazepam *vs.* IV midazolam	Seizure cessation without recurrence over the period until arrival at hospital.	Very low
Huebinger et al. (2020) (24)	Retrospective cohort	107	Adult patients (18–60 yrs) treated for behavioral emergency.	IN midazolam *vs.* IV/IM midazolam	Recorded route and dosage of midazolam in addition to the patient's response to therapy.	Low
Ketamine						
Andolfatto et al. (2019) (25)	Double-blind RCT	60	Adult patients (>18 yrs) with acute pain (VNRS >5).	IN ketamine *vs.* placebo	Proportion of patients with VNRS score reduction ≥2 at 30 min.	Moderate
Dubecq et al. (2023) (26)	Case series	76	Combat trauma patients requiring analgesia—penetrating or blast trauma (WBFR >7).	IN ketamine *vs.* IV ketamine *vs.* IV/SC morphine	Effective analgesia defined by the WBFR rating scale before administration and 10–15 mins after pain was considered controlled if WBFR <3.	Very low
Bebarta et al. (2023) (27)	Retrospective cohort	10	Non-intubated injured casualties attended to by a US combat team.	IN ketamine *vs.* IV/IM/IO ketamine	Dose and route of ketamine in comparison to TCCC guidelines.	Very low
Johansson et al. (2013) (28)	Case series	9	Adult patients treated with traumatic injuries requiring vascular access which was foreseen or proven problematic.	IN S-ketamine	VAS pain score before and 5–10 min after treatment.	Very low
Reid et al. (2011) (29)	Case report	1	9 year old boy with burn injuries.	IN ketamine	Resolution of pain by monitoring of observations.	Very low
Fentanyl						
Middleton et al. (2010) (30)	Retrospective observational	3778	Adult patients (16–100 yrs) with moderate to severe pain (VNRS >5).	IN fentanyl *vs.* IV morphine *vs.* inhaled methoxyflurane *vs.* any combination	Effective analgesia, defined as a reduction in pain severity of ≥30% of initial pain score using VNRS-11.	Very low
Bendall et al. (2011) (31)	Retrospective observational	305	Pediatric patients (5–15 yrs) who had moderate to severe pain (VNRS ≥5).	IN fentanyl *vs.* IV morphine *vs.* inhaled methoxyflurane *vs.* any combination	Effective analgesia, defined as a reduction in pain severity of ≥30% of initial pain score using VNRS-11.	Very low

Johnston et al. (2011) (32)	Retrospective observational	397	All patients with presumed visceral pain.	IN fentanyl *vs.* inhaled methoxyflurane *vs.* any combination	Pain was assessed with Visual/Verbal Analogue Scale pain scores, a change of ≥2 was considered clinically significant.	Very low
Lynch et al. (2022) (33)	Retrospective observational	247	Any patient seen for acute, painful orthopedic injuries (NRS-11 > 7).	IN fentanyl	Reduction in pain score using the NRS-11 from 0 to 5, 10, and 15 min.	Very low
Murphy et al. (2017) (34)	Prospective cross-sectional study.	94	Any child (1–16 yrs) with a pain score of ≥7 out of 10.	IN fentanyl *vs.* IV/PO morphine	Effective reduction in pain score >2 points, documented at 10 min intervals—VNRS (>8 yrs), FLACC (<5 yrs), or WBFR (5–7 yrs).	Very low
Tanguay et al. (2020) (35)	Retrospective observational	719	All patients (≥14 yrs) with VNRS ≥7.	IN fentanyl *vs.* SC fentanyl	Recorded clinically significant pain relief score (minimal ≥1.5 points on NRS, and clinically relevant ≥3 on NRS) and vital signs.	Low
Karlsen et al. (2014) (36)	Prospective observational	903	Adults and children (>8 yrs) with severe pain (orthopedic, abdominal, or ACS refractory to nitroglycerin spray).	IN fentanyl	NRS (0–10) pain scores before and after treatment (minimal relevant clinical difference ≥2).	LOW
Rickard et al. (2007) (37)	RCT (open-label).	127	Adult patients requiring analgesia (VRS >2/10 non-cardiac or >5/10 cardiac).	IN fentanyl *vs.* IV morphine	Difference in baseline/destination VRS.	Moderate
Eidenbenz et al. (2016) (38)	Retrospective observational	92	Prehospital trauma patients with isolated limb injury.	IN fentanyl *vs.* IV ketamine *vs.* IV fentanyl	Determinants of prehospital analgesia administration and choice of agent—recorded route, dose and type of analgesia, pain (NRS-11), injury severity score, physician experience.	Very low
Lord et al. (2019) (39)	Retrospective time-series analysis	9883	Patients (<15 yrs) with an initial pain severity score >3.	IN fentanyl (±IM morphine ± inhaled methoxyflurane)	Proportion of patients having a >2/10 reduction in pain severity score (VRNS-11) before and after protocol change. If difficulty with VRNS-11, WBFR was used.	Very low
O'Donnell et al. (2013) (40)	Retrospective cohort	13	Pediatric trauma patients (<16 yrs) with GCS 15 and VNRS >3 or WBFR score >4.	IN fentanyl *vs.* IV fentanyl	Frequency of fentanyl use and factors influencing fentanyl use.	Very low
Pasquier et al. (2017) (41)	Retrospective observational	92	All patients with isolated limb injuries.	IN fentanyl *vs.* IV ketamine *vs.* IV fentanyl	To describe the different analgesic strategies used with corresponding monitoring and medical co-treatments—pain intensity was assessed at scene and at the hospital (VRNS-11), vital signs were collected and attempts at IV access were recorded.	Very low
Morphine						
Ellerton et al. (2013) (42)	Prospective descriptive	18	Mountain rescue patients with a pain score >4/10 on movement.	IN diamorphine *vs.* Entonox/IM opioid/IV opioid/oral analgesia/fentanyl lozenge	Effectiveness of pain relief (VRNS-11) defined as a >50% reduction in initial score at 15 min and at handover.	Very low

(*continued*)

Table 4. Continued.

Reference (publication year)	Study design	Sample size relevant to IN medication	Population	Exposure	Primary outcome	Final grade of evidence (16)
Glucagon						
Haamid et al. (2023) (43)	Retrospective analysis of consecutive cases	44	All patients with suspected hypoglycemia administered IN glucagon.	IN glucagon	Clinical response to IN glucagon documented as "no improvement," "slight improvement," or "substantial improvement" regarding mental status.	Very low
Sibley et al. (2013) (44)	Case report	1	39 year old patient with insulin induced hypoglycemia.	IN glucagon	Response (consciousness, pre- and post-blood sugar measurements).	Very low
Naloxone						
Skulberg et al. (2022) (45)	Double-dummy blinded RCT	93	Adult patients (>18 yrs) with suspected opioid overdose (miosis, RR < 8, GCS <12).	IN naloxone *vs.* IM naloxone *vs.* IN/IM placebo	Restoration of spontaneous respiration of >10 breaths a min within 10 min.	Moderate
Barton et al. (2005) (46)	Prospective non-randomized trial	95	All adult (>14 yrs) patients with suspected opiate overdose, found down, or with altered mental status.	IN naloxone ± IV naloxone	Number of patients responding, and time of response, to IN naloxone. Response was defined as a significant improvement in level of consciousness.	Very low
Barton et al. (2002) (47)	Prospective non-randomized trial	30	Patients found unconscious, with altered mental status, or with suspected opioid overdose.	IN naloxone ± IV naloxone	Rate and time of patient response to IN naloxone, defined as a significant improvement in level of consciousness.	Very low
Merlin et al. (2010) (48)	Retrospective cohort	66	Adult patients who have overdosed on opioids.	IN naloxone *vs.* IV naloxone	Initial and final unassisted respiratory rate and GCS were used as indicators of naloxone effectiveness.	Very low
Robertson et al. (2009) (49)	Retrospective review following implementation of an IN protocol.	50	Patients with suspected opioid overdose.	IN naloxone *vs.* IV naloxone	Time from administration to clinical response and time from patient contact to clinical response. Clinical response was defined as an increase in respiratory rate (breaths/min) or GCS of ≥6.	Very low
Zuckerman et al. (2014) (50)	Case report	1	26-year-old male with exposure to fentanyl.	IN naloxone + IV naloxone	Observations—heart rate, respiratory rate, and oxygen saturations.	Very low
Liu et al. (2023) (51)	Retrospective cohort	2090	All patients (>18 yrs) administered naloxone.	IN naloxone *vs.* IM/IV naloxone	Naloxone dosages, routes, frequency of administrations, change in respiratory rate and GCS were recorded. Analysis of the change in ratio of IN to IV naloxone administrations were performed. Respiratory recovery was defined as respiratory rate of >12 per minute.	Very low

Maloney et al. (2020) (52)	Retrospective observational	306	Adults (>18 yrs) who received naloxone for suspected opioid overdose.	IN naloxone *vs.* IV/IM naloxone	Assessed whether the individual dose, route, total dose, number of prehospital naloxone administrations, or occurrence of a prehospital adverse event were associated with the occurrence of adverse events in the ED.	Very low
Kerr et al. (2009) (53)	RCT (unblinded).	83	Patients treated for suspected opiate overdose.	IN naloxone *vs.* IM naloxone	Proportion of patients who responded within 10 min of naloxone treatment. Response was defined as an effective and spontaneous respiration rate ≥10 and/or GCS ≥13.	Moderate
Thompson et al. (2022) (54)	Retrospective cross-sectional	218	Adult patients (>18 yrs) receiving IN naloxone.	IN naloxone at 2 different doses	Response to initial dose (yes, no, or unclear—defined as changes in mental status, respiratory rate, or oxygenation), requirement of additional dosing, and incidence of adverse effects.	Very low
Kelly et al. (2005) (55)	RCT	84	Adult patients with suspected opioid overdose.	IN naloxone *vs.* IM naloxone	Response time to regain a respiratory rate of ≥10 breaths/min.	Moderate
Weiner et al. (2017) (56)	Retrospective review following widening of IN use amongst care providers.	793	Adults (>18 yrs) treated for known/suspected opioid abuse.	IN naloxone	Number of patients requiring additional naloxone post-BLS administration. Effective naloxone dosing was defined as respiratory rate >8 and/or improvement in mental status using AVPU.	Very low

SC: subcutaneous; IM: intramuscular; IV: intravenous; IN: intranasal; IO: intraossesous; yrs: years; min: minute(s); VRNS: verbal numeric rating scale; WBFR: Wong-Baker Faces Rating; TCCC: tactical combat casualty care; VAS: visual analogue scale; NRS: numerical rating scale; FLACC: faces, legs, activity, cry, consolability scale; ACS: Acute Coronary Syndrome; GCS: Glasgow Coma Scale; post-BLS: post-basic life support; AVPU: alert verbal pain unresponsive; Rescue therapy: additional doses given after initial administration.

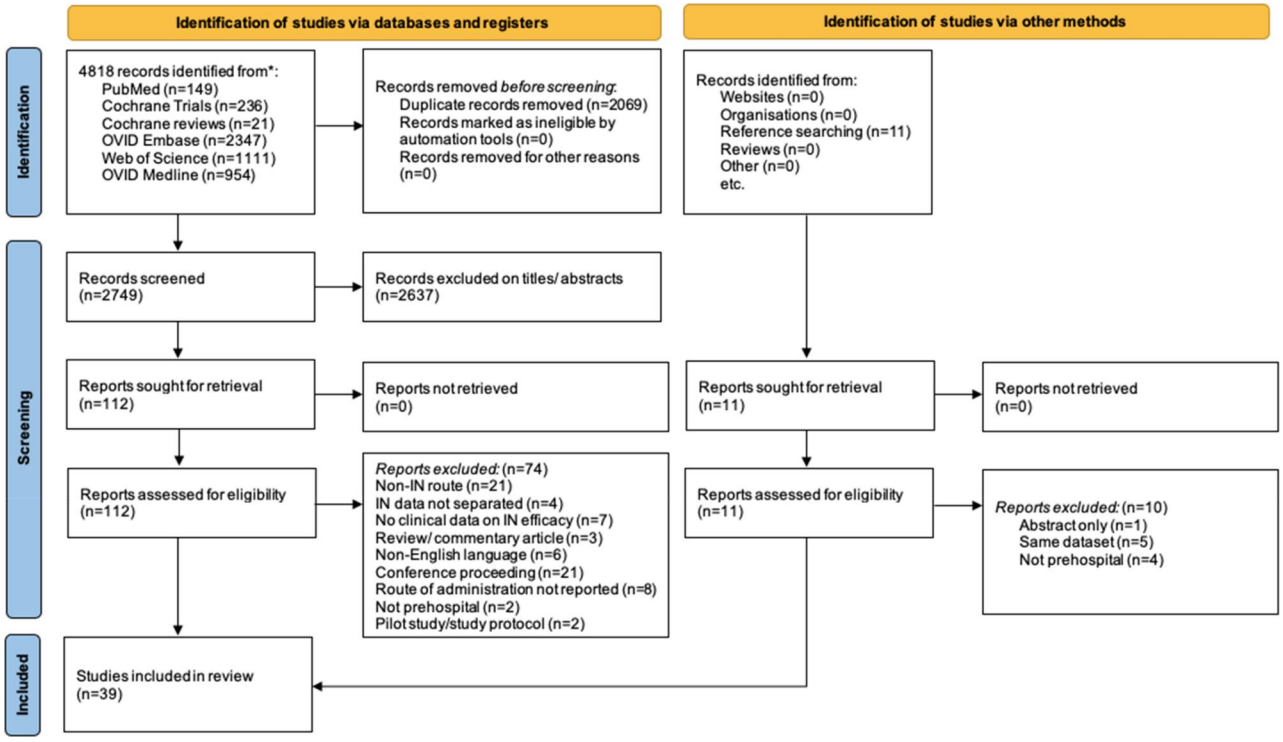

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the study question (11).

PR diazepam. Despite all papers using different weight based initial IN dosing regimens, Shavit et al. (18) and Whitfield et al. (19) reported similar age adjusted odds ratios (OR) for IN patients requiring redosing compared to alternate routes of administration [1.65 (95%CI 1.13–2.42) and 2.0 (95%CI 1.5–2.5), respectively]. Of those patients requiring re-dosing, higher rates of needing respiratory support were reported. In Shavit et al. (18), 1.6% of all patients requiring a second dose of either IV, IM, or IN medication also required BVM ventilation, rising to 42.5% if four or more doses were required. For Whitfield et al. (19), the age adjusted OR for BVM ventilation (IN *vs.* IM/IV/IO) was 1.1 (95% CI 0.7–1.7, $p = 0.6$).

While both studies found IN midazolam to be inferior to IV midazolam, neither recorded the timing of seizures or medication administration, rates of unsuccessful cannulation, or defined seizure activity. Holsti et al. (20) found median seizure time was 19 minutes longer for PR diazepam than IN midazolam ($p = 0.003$), suggesting that IN midazolam was superior to PR diazepam.

The remaining three studies (21–23) investigating the efficacy of IN midazolam in adult populations had similar findings to the pediatric studies suggesting IN midazolam was inferior to other routes for seizure management. Guterman et al. (22) found that the risk of rescue therapy (requiring additional doses of midazolam following initial administration) was increased for IN midazolam compared to IM (Risk Difference 6.5%, 95%CI: 2.4–10.5), though like Shavit et al. (18) and Whitfield et al. (19), the timing of seizures and medication administration was not recorded. While Theusinger et al. (23), reporting on seizure cessation without recurrence as the primary outcome, showed that a single dose of IV diazepam successfully terminated seizures in 98% compared to 57% for IV midazolam and 64% for IN midazolam ($p = 0.001$). However, both Guterman et al. (21, 22) papers agreed that higher doses of IN midazolam were less likely to require rescue therapy [unadjusted OR 0.8 (95%CI: 0.7–0.9), Risk Difference −11.1% (95%CI: −3.3 to −1.9), respectively]. Theusinger et al. (23) also compared adult findings against a small pediatric population, showing that the first IN dose of midazolam was more successful in children compared to adults (100 *vs.* 64%, $p = 0.012$).

Huebinger et al. (24) assessed the effect of IN midazolam on behavioral emergency against IV and IM midazolam, finding no significant difference between the effectiveness of IM and IN midazolam (71 *vs.* 75.4%, $p = 0.24$). Although a standardized aggression scoring system was not used, instead favoring paramedic impression to grade improvement.

Ketamine

Only five studies were identified to investigate the efficacy of IN ketamine as an analgesic; one RCT (25), two military-based observational studies (26, 27), one case series (28), and one pediatric case report (29). All papers had substantial variations in study design and outcome reporting.

Andolfatto et al. (25) assessed the effect of IN ketamine for acute pain relief against an IN placebo, using a verbal numerical rating score (VNRS) to report pain out of 10, in adults. They found that 76% of IN ketamine patients *vs.* 41% of IN placebo patients reported a ≥2 point VNRS reduction at 30 min (35% difference, $p = 0.002$), demonstrating the superiority of IN ketamine to placebo. All adverse events reported were minor, requiring no intervention. Although double-blinded, the sample size was relatively small and there was no comparison to usual treatment e.g., IV ketamine.

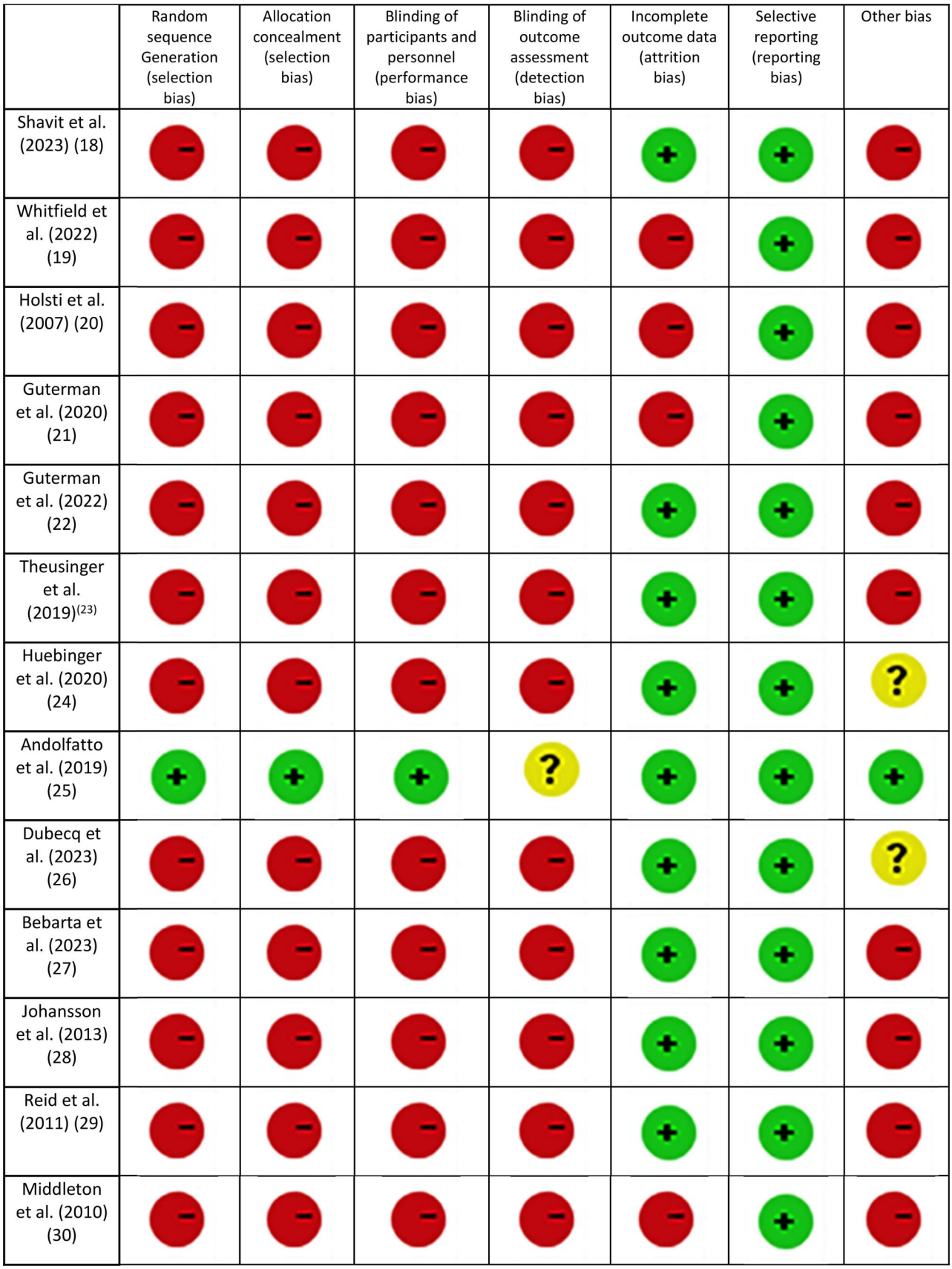

Figure 2. Risk of bias assessment of included studies using the Cochrane risk of bias tool (17).

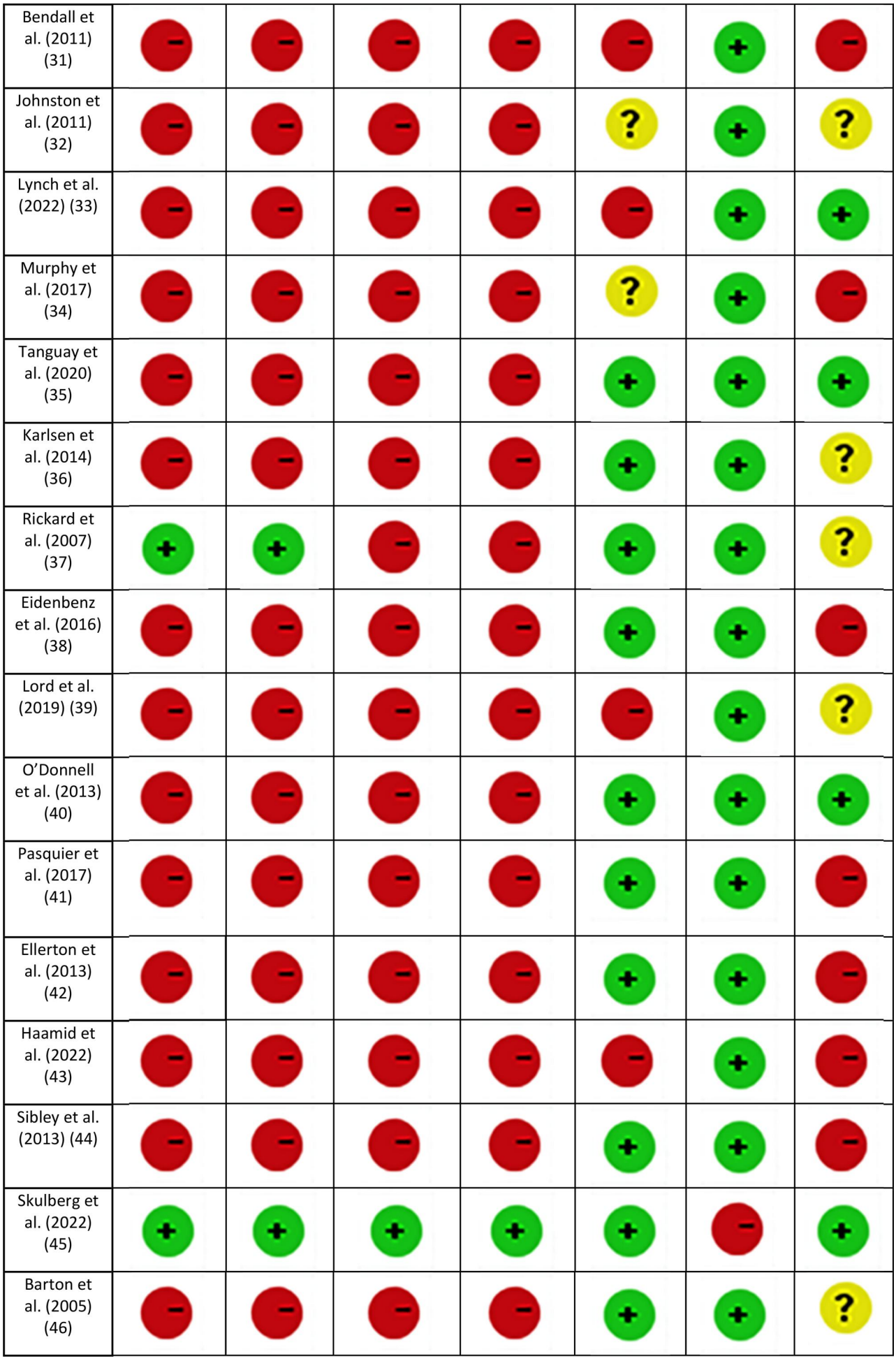

Figure 2. Continued.

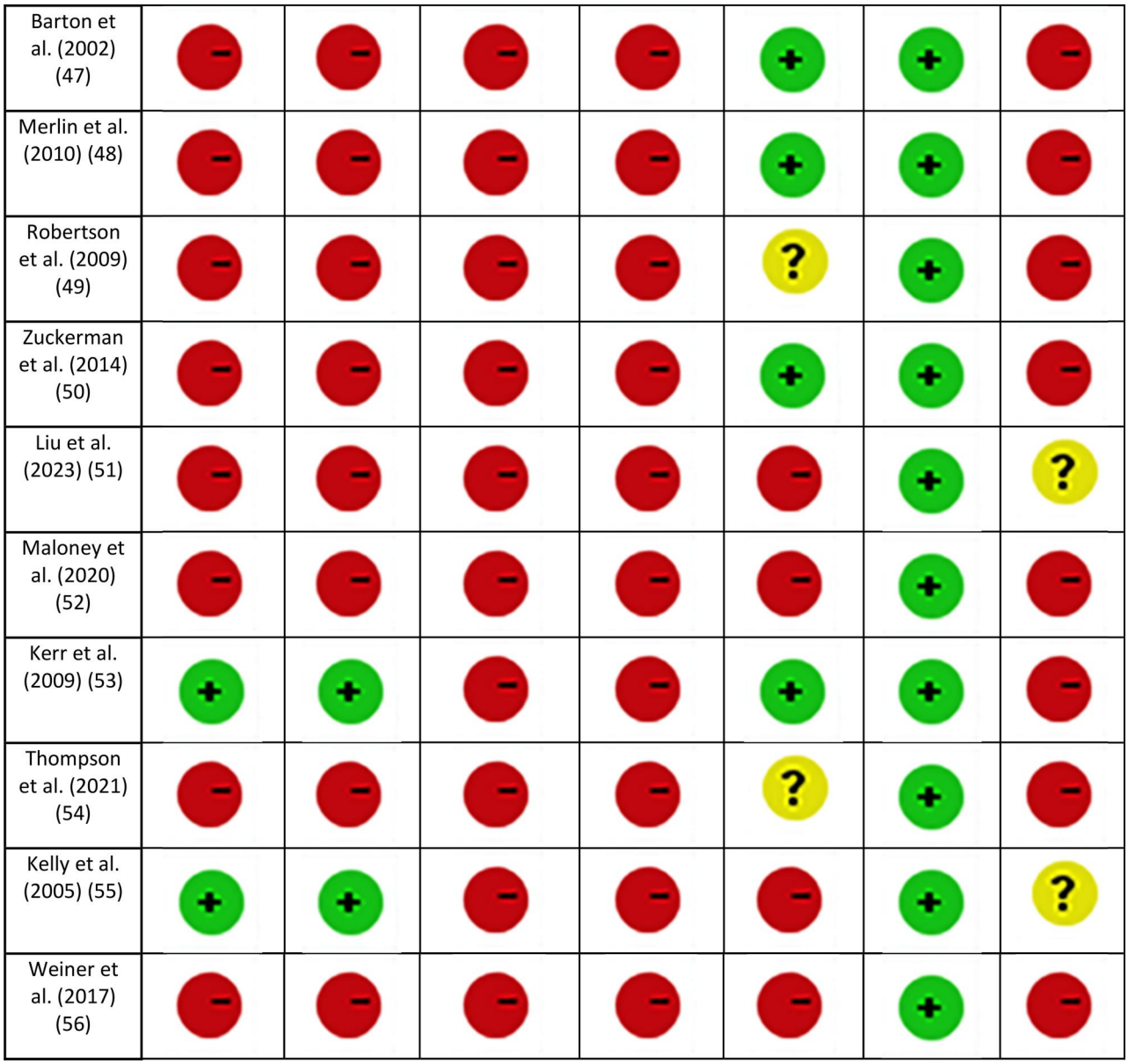

Figure 2. Continued.

While both military studies, Dubecq et al. (26) and Bebarta et al. (27), did compare IN ketamine to other routes they were retrospective and only observational. Dubecq et al. (26) assessed effective analgesia using the Wong-Baker Faces Rating (WBFR) scale at 0–10 mins before and 10–15 mins after administration, finding that 78% of causalities in the IN group had a WBFR score of <3 at 10 min and did not require IV access. Additionally, the injury severity score for the IN group was significantly worse than the subcutaneous/IV group (28.2 *vs.* 16.4, $p < 0.05$). Bebarta et al. (27) compared the different routes and doses of ketamine given to injured casualties, finding that an initial 50 mg dose of IN ketamine would likely be effective as repeat dosing was not required. However, no data on individual pain scores pre- and post-administration were reported.

Johansson et al. (28) reported nine cases where IN S-ketamine was used as a last resort due to difficulties gaining IV access. Overall, the median pain score decreased from 10 (IQR 8–10) pre-treatment to 3 (IQR 2–4) post-treatment ($p = 0.018$), demonstrating efficacy in cases with limited analgesic options. Reid et al. (29), while only reporting on one 9-year-old patient, demonstrated the use of IN ketamine as an effective analgesic in this scenario.

Fentanyl

Twelve studies (30–41) assessing IN fentanyl as an analgesic were included with the majority using a VNRS to report pain. Despite substantial variation in primary outcomes, populations (pediatric and adult), and prehospital settings (HEMS, EMS, and Ski patrol), the consensus between the studies was largely in favor of the use of prehospital IN fentanyl as an alternate analgesic (31–39, 41) with a safe side effect profile (32–37, 41), but of note, there was no clear

recommendation that it should replace other routes as a first line agent.

Bendall et al. (31) and Lord et al. (39), both investigated pediatric patients <15 years old. Bendall et al. (31) assessed effective analgesia (≥30% reduction of initial VNRS) of IN fentanyl compared to IV morphine, finding that 89.5% of IN fentanyl patients achieved this efficacy with no clinical or significant difference to IV morphine (OR 1.21, 95%CI: 0.74–2.01). These results held even after controlling for age and sex. Lord et al. (39) compared the use of IN fentanyl pre- and post-guideline change (allowing the administration IN fentanyl for all levels of paramedic in children of any age at an initial dose of 2 μg/kg, up to 4 μg/kg post-guideline change) and defined effective analgesia as >2/10 reduction in VRNS. Finding that fentanyl use rose from 2.1 to 30.6%, and recorded rates of effective analgesia increased from 88.1 to 94.2% ($p < 0.0001$) post-intervention (OR 2.33, $p < 0.0001$).

As the only RCT, Rickard et al. (37), measured the difference between baseline and destination VNRS of IN fentanyl to IV morphine in adults. There was no significant difference between either group—mean VNRS reduction for IN fentanyl was 4.22 (95%CI: 3.74–4.71), compared to IV morphine at 3.57 (95%CI: 3.10–4.03, $p = 0.08$). Safety profile and acceptability were found to be comparable to IV morphine; however, this trial's results are limited by the fact that it was unblinded.

Of note, Middleton et al. (30) found IN fentanyl to be inferior to IV morphine, when defining effective analgesia as a ≥30% reduction of initial VNRS in patients >16 years old. While IN fentanyl resulted in a mean VNRS decrease of 4.5, the same as IV morphine alone, IN fentanyl only had an 80% efficacy *vs.* morphine at 81.8% (univariate OR 0.90, 95%CI: 0.82–0.98). Even after controlling for age, sex, and condition, the adjusted OR of the efficacy of fentanyl *vs.* morphine remained in favor of morphine at 0.86 (95%CI: 0.78–0.94), $p = 0.002$.

O'Donnell et al. (40), assessed the rates of fentanyl use pre- and post-protocol change that allowed IN fentanyl to be delivered with a MAD to children. They found that there was no significant uptake of use (pre-MAD 30.4%, post-MAD 37.8%, $p = 0.238$), despite IV previously being identified as a barrier to administering fentanyl to children, contradicting Lord et al. (39).

Morphine/Diamorphine

No study was found that evaluated morphine. Ellerton et al. (42) investigated the effects of IN diamorphine against other forms and routes of analgesic agents (including Entonox, IM/IV opioids, oral analgesia, and fentanyl lozenges) in different mountain rescue teams across the UK. Ranking as "intermediate" in efficacy, 40% of patients receiving IN diamorphine achieved $a > 50\%$ reduction in VRNS at 15 mins, rising to 50% at handover, while IV opioids ranked the best (55% achieved a >50% reduction in VRNS at 15 mins, rising to 85% at handover). No serious adverse events were recorded.

Glucagon

Only two studies (43, 44) assessed the efficacy of IN glucagon. Haamid et al. (43) retrospectively analyzed the data from 44 cases where IN glucagon was exclusively used to treat hypoglycemia. Overall, 62% of patients had "substantial improvement" or "slight improvement" in mental status on treatment. Although blood glucose was measured before and after treatment, primary outcome relied on paramedic impression of clinical improvement. Sibley et al. (44) reported the first success of IN glucagon use prehospital in a 39-year-old patient with insulin-induced hypoglycemia and difficult IV access. From only responding to pain, the patient experienced improved alertness, communication, and blood glucose levels post-treatment. Neither study directly compared IN glucagon to the usual treatment.

Naloxone

Twelve studies investigating IN naloxone were found (45–56). While all studies assessed the effect of IN naloxone on opiate reversal, there was variation in comparators, primary outcomes, and conclusions. There was a clear deviation in results with seven studies reporting non-inferiority (46–49, 51, 53, 56) and three inferiority (45, 50, 55).

Three RCTs were performed (45, 53, 55). Kerr et al. (53) and Kelly et al. (55) compared 2 mg IN naloxone to 2 mg IM (unblinded) in adults with similar primary and secondary outcomes, in parallel settings, but found conflicting results. Kerr et al. (53) found no difference in observed mean response time [IN 8.0 *vs.* IM 7.9 mins; difference 0.1 (95%CI: −1.3 to 1.5)], which held when controlled for other variables (multivariate OR 0.8 (95%CI: 0.6–1.2); $p = 0.29$); while Kelly et al. (55) found that the IN group required a significantly longer mean time to achieve a return of spontaneous respiration (>10 breathes a minute, IN 8 mins (95%CI: 7–8) *vs.* IM 6 mins (95%CI: 5–7), $p = 0.006$).

Although both studies reported overall similar rates of successful toxicity reversal (Kerr 82% *vs.* Kelly 74%) there is an obvious discrepancy between response times. Neither study reported any major adverse events. Unlike Kerr (53) and Kelly et al. (55), Skulberg et al. (45) completed a blinded double dummy RCT to assess the effect of 1.4 mg IN naloxone against 0.8 mg IM. They found IN naloxone to be inferior to IM naloxone for return of spontaneous respiration [80% IN *vs.* 97% IM, Risk Difference 17.5% (95%CI: 8.9–26.1)].

Both Skullberg et al. (45) and Kerr et al. (53) reported a higher risk of requiring additional doses (rescue therapy) when naloxone was administered IN compared to IM, 19.4% (95%CI: 9–29.7) and 13.6% (95%CI: 4.2–22.9), respectively, Maloney et al. (52) also reported similar results [44% IN group *vs.* 12% IV/IM/IO group ($p < 0.001$)]. However, when Kerr et al. (53) adjusted for confounders, the difference was non-significant [multivariate OR 4.8 (95%CI: 1.4–16.3), $p = 0.29$]. Kelly et al. (55) and Robertson et al. (49) agreed with this, finding that rescue doses did not differ significantly between groups, 26% IN *vs.* 13% IM, $p = 0.0558$, OR 2.4 (95%CI: 1–5.7) (55) and 34% IN *vs.* 18% IV, $p = 0.05$ (49).

Although average response times from initial IN naloxone administration were longer compared to IV/IM (46, 49, 55), Barton (46) and Robertson et al. (49) reported similar times from initial contact to response (9.9 ± 4.4 min IN *vs.* 12.8 ± 7.6 IV, and, IN 20.3 *vs.* IV 20.7 min, $p = 0.9$, respectively).

Maloney et al. (52) and Kelly et al. (55) reported a reduced risk of adverse events compared to other routes. Although Thompson et al. (54) reported a higher risk of adverse events with the higher 2 mg dose of IN compared to lower 0.4 mg dose (29 *vs.* 2.1%, respectively, $p < 0.001$), the reasons surrounding this difference were unconfirmed.

No study evaluated the effect of factors surrounding the overdose (type of opioid, presence of other substances, etc.), performed subgroup analysis on population demographics, or concluded why certain routes of administration were chosen over others (where applicable).

Meta-Analysis

There was significant clinical heterogeneity across the included trials precluding meta-analysis. Specifically, there was substantial variation in dosing, primary outcome measurement, and data timepoints, as well as concerns of bias in the studies.

Risk of Bias of Included Studies

Figure 2 summarizes the risk of bias assessment of all the studies, according to the Cochrane risk of bias tool (17). Overall, the quality of the included studies was found to be low, with most studies demonstrating "high concerns" for bias in numerous domains (18–24, 26–36, 38–44, 46–52, 54, 56).

Discussion

This systematic review examines the use of intranasal medication in the prehospital setting only, demonstrating that this administration method may be feasible, but more work is needed to rigorously demonstrate non-inferiority. It does however indicate to prehospital clinicians that this route is possible for multiple medications (fentanyl, midazolam, glucagon, diamorphine, naloxone, and ketamine) and it may therefore be of great value in certain clinical situations.

Interpretation of Results in the Context of Other Evidence

Previous reviews have concluded that midazolam, ketamine, fentanyl, and glucagon may be an effective, safe, and well-tolerated alternative to other routes of administration in both ED and prehospital settings (1, 2, 4). This systematic review shows comparable results when controlling for a purely prehospital setting. Whilst IN Midazolam was shown to be mostly inferior (18, 19, 21–23) to IV and IM, the dose-dependent correlation for rescue therapy as reported by Guterman et al. (21, 22) needs to be further elucidated to see whether efficacy may in fact be improved. IN midazolam was found to be superior to PR diazepam (21) but not IV diazepam (23) prehospitally. Interestingly, in the ED setting, no significant difference in seizure cessation or adverse event occurrence was reported when comparing IN midazolam to PR or IV diazepam under meta-analysis (57). When there is a needle phobia or IV access is impossible, IN may be a safer, and perhaps more dignified alternative to a PR route, particularly in a public setting.

Throughout the studies assessing IN ketamine, all demonstrated utility for its use as a safe analgesic (25–29). However, further studies with larger sample sizes and comparisons with other agents are needed to confirm these findings. The review by Rech et al. (4) agrees with this, maintaining that the literature for IN ketamine is unclear due to the high degree of patient variability and dosing effects shown.

IN fentanyl appears to be an effective prehospital analgesic, particularly in pediatric patients. Good side effect profiles were consistently reported throughout the included studies (32–37, 41), with literature analysis suggesting that the only adverse effect directly related to IN administration seems to be mucosal irritation (58). Furthermore, there is some consensus that the benefits of IN administration may outweigh IV analgesia by offsetting the need for IV access (30) and reducing on scene times (41).

Further evidence is needed to confirm the efficacy of IN diamorphine due to the limited number of patients treated in the prehospital setting. Whilst efficacy cannot be confirmed, no serious adverse events were reported.

Conclusions about the efficacy of IN Glucagon prehospitally are also limited by the small sample sizes available. A new formulation of IN glucagon powder (59) has since been developed with an additional absorption enhancer that is ready to use (rather than reconstitution as previously needed). Although no studies have yet been published confirming its efficacy in the prehospital setting, recent studies have shown successful treatment in a small number of patients (60, 61).

Overall, the majority IN naloxone studies reported non-inferiority with a good safety profile. However, there was substantial variation in response times between similar studies (53, 55), with some studies reporting higher rates of rescue therapy (45, 52, 53). The reason for this is unknown. Like IN fentanyl, total time from initial patient contact to response for IN naloxone was similar to IV (46, 49) suggesting some benefit incurred for the administration of IN. Interestingly, one study reported a lower rate of drug withdrawal reaction compared to IM naloxone (45). Further studies are required to confirm this finding but, if true, this could be an advantage for prehospital IN naloxone use when patients refuse transfer to hospital.

Clinical Implications

Data from 2014 suggests that 75% of UK HEMS providers were currently using or planning to use IN analgesia (62). London Ambulance Service's Advanced Paramedic Practitioners now also carry ketamine suitable for IN administration (63). While IN medication is becoming increasingly common in the prehospital setting, there seems to be varying levels of uptake on a local and even international level.

To the best of our knowledge, there is no current guidance for air ambulance use of IN medication and an up-to-date survey of current IN medication use is likely warranted.

Even when there has been a guideline change to encourage IN use, reported uptake rates of IN use have differed e.g., O'Donnell et al. (40) *vs.* Lord et al. (39). The reasons for this disparity may be due to education on the topic or reluctance to try new techniques, but further studies are needed to investigate this to be able to better predict clinical uptake. Whilst there certainly is not enough evidence to substitute IN medication as a first-line agent, due to the poor-quality evidence and consistent non-standard reporting, having IN medication as an alternate option expands the scope of care available to patients.

Implications for Future Research

It should be noted that most of the included studies are low or very low quality (18–24, 26–36, 38–44, 46–52, 54–56), which limits the utility of their evidence due to their susceptibility to bias and confounding. Performing RCTs in the prehospital setting presents many difficulties for practical and ethical reasons, meaning many of the studies available were observational in nature. Reported explanations for this difficulty include issues surrounding consent, limited sample sizes, and time constraints (64).

Although observational studies have their benefits, such as large sample sizes (21, 22, 30, 35, 36, 39, 51, 56) and prolonged periods of observation (20, 23, 33, 34, 39), there is no doubt that RCTs are superior evidence allowing causality to be examined. Further RCTs, than the five reported (25, 37, 45, 53, 55), are required to generate better evidence that could guide clinical practice. Studies directly comparing IN administration to other routes (IM and IV) are warranted along with meaningful outcome data including time from on-scene arrival to, for example, pain reduction. The added complexity of investigating an innovative administration method perhaps historically deterred active research into this emerging field, but promisingly there is evidence of planned RCTs to come (65, 66).

Limitations

Of all the primary outcomes reported for midazolam, ketamine, fentanyl, diamorphine, glucagon, and naloxone, most were subjective in nature making it difficult to establish true effect sizes. For example, seizure activity was not defined in any of the studies reporting IN midazolam (18–24), with administration of rescue therapy as an outcome measure for efficacy only serving as a proxy for seizure termination. Whilst some studies utilized standardized scoring systems, such as VNRS for analgesia, and adjusted for confounding to help limit subjective reporting, many study designs failed to account for this or used scales validated for the wrong population (26). The methodological heterogeneity between study outcomes meant it was difficult to assess the true intervention effect. Even among studies assessing the same medications, outcomes, and doses differed greatly, again limiting the ability to perform meta-analysis.

This review incorporates several diverse prehospital groups, including EMS, HEMS, mountain rescue, and the military, whilst this could be perceived as a strength, the training within in these groups is distinct on an international scale and the scope of operating practices differs greatly. This may limit the external validity of the evidence to certain prehospital populations. Law enforcement and other first responders without formal medical training were excluded due to the substantial variation in first aid training and ability to administer naloxone. This study was designed to assess the evidence and feasibility of IN medications in the pre-hospital setting and these professionals are not as well-equipped to evaluate efficacy and safety than trained medical clinicians. While excluding law enforcement may limit the data available, if future research were to focus on IN medication use in the community, this cohort would be an invaluable resource.

As already highlighted, the majority of studies included in this review were not RCTs, and as such the evidence available is prone to significant bias (Online Appendix Table S2). The conclusions that can be made from using IN medications in the prehospital setting are thus restricted until further robust data is reported.

Conclusions

Intranasal administration of medications within the prehospital setting appears feasible, however, these findings are severely limited by the quality of evidence available. Overall, the reported efficacy of IN fentanyl and ketamine seemed to be demonstrated consistently throughout the studies with less clear evidence for midazolam, diamorphine, glucagon, and naloxone. For the latter, whether this is a true variation in effect or due to differences in study morphology is unclear and yet to be elucidated. Robust prospective, double-blind RCTs in the prehospital setting are urgently needed to confirm the results. Having IN medication available for use by clinicians in the prehospital setting may be a useful resource in times of absence, difficult, or unwanted IV access.

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Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its Supplementary Materials.

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