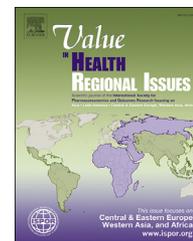




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Systematic Review

Evaluations of Morphine and Fentanyl for Mechanically Ventilated Patients With Respiratory Disorders in Intensive Care: A Systematic Review of Methodological Trends and Reporting Quality

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ABSTRACT

Background: Mechanically ventilated patients with respiratory disorders may require sedatives, such as opioids. **Objectives:** To define methodological trends, gaps, and the reporting quality of the comparative clinical and economic evaluations of fentanyl and morphine in ventilated patients in the intensive care unit. **Methods:** We conducted a literature review of the MEDLINE, Embase, OVID, ScienceDirect, Springer Link, and EconLit databases, comparing studies in the management of ventilated patients with respiratory disorders in the intensive care unit using either fentanyl or morphine, or both. We assessed the methodological aspects of the literature characteristics and trends of, for example, modeling, data sources, cost calculation, and data analysis, appraising the quality of reporting via the CONSolidated Standards Of Reporting Trials, STrengthening the Reporting of OBServational studies in Epidemiology, and the Consolidated Health Economic Evaluation Reporting Standards checklists. **Results:** Among 1327 articles, 33 (comprising 22 in adults, 8 in neonates, and 3 in pediatrics) met the inclusion criteria. No head-to-head morphine versus fentanyl evaluations

explicitly confined to subjects with respiratory conditions were undertaken. Studies relied on various scales to measure the sedation level as a primary study outcome, limiting the comparability of study conclusions. Seven articles of adults were identified to be economic studies from the hospital perspective. On the basis of different endpoints, the same sedation regimen performed differently in various studies. None of the randomized controlled trials, observational cohorts, or pharmacoeconomics studies met most of the assessed reporting quality criteria. **Conclusions:** Our review identified poor reporting quality and high heterogeneity of methods used, potentially limiting the degree to which studies could be interpreted, decisions could be influenced, and findings could be generalized.

Keywords: economic evaluation, fentanyl, intensive care unit, mechanical ventilation, morphine, sedation, systematic review

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Introduction

Subjects with respiratory disorders, including respiratory distress syndrome, require mechanical ventilation (MV) to maintain pulmonary function.^{1,2} MV, however, is an invasive procedure requiring the administration of sedatives to simplify the procedure.^{3,4}

Sedatives have been shown to improve ventilator synchrony.^{5,6} In the intensive care unit (ICU), the opioids fentanyl and morphine are widely used as sedatives. Morphine has less potential to cause tolerance, whereas fentanyl has a faster onset and shorter duration of action. Some may favor the former because of its therapeutic advantages, whereas others may favor the latter for its pharmacological advantages.⁶ In ICU settings, although

guided by best evidence, such as the guidelines by Barr et al,⁷ the use of morphine and fentanyl with MV in respiratory disorders is not necessarily based on local comparative studies. Local evaluations may also relate to the strategy of using either medication as a first-line agent, where this can vary between monotherapy and a midazolam combination. In addition, economic data justifying the use of any of these agents are lacking—an important factor, because approximately 20% of hospital budgets go to ICU expenses.⁸ Within the context of both research reporting and method standardization deficits and a typical lack of compliance with established standards, research providing a summary of current methodological trends and gaps in the relevant research is needed to guide and improve future research.

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In the present comprehensive systematic review, we aimed to summarize the characteristics and gaps in the methods and quality of reports of clinical and economic evaluations on the use of fentanyl and morphine in patients with respiratory disorders undergoing MV in ICU settings.

Methods

Literature Review

We used the electronic databases MEDLINE, Embase, OVID, ScienceDirect, Springer Link, and EconLit to identify all the relevant studies from the literature. We used the keywords “morphine,” “fentanyl,” “hypnotics,” “sedatives,” “sedation,” “respiration,” “respiratory,” “artificial, respiration,” “mechanical ventilator,” and “mechanical ventilation” to capture a broad sample of studies. We used the search strategy, including operators and Medical Subject Headings, given in Appendix 1 in Supplemental Materials found at <https://doi.org/10.1016/j.vhri.2018.11.001> for PubMed, and this was adapted for other databases. Figure 1 demonstrates the screening of articles. We included gray literature, such as books, dissertations, conferences, working papers, and governmental publications, in the database search, supplementing it with a screening of references in included articles and also a general Internet search using Google and Google Scholar, using the same search terms in the free-text searching as in the primary search.

Inclusion and Exclusion Criteria

The inclusion criteria included the PICO (population, intervention, comparison, and outcome) outline:

- Population: mechanically ventilated subjects with respiratory disorders in ICU;
- Intervention: study of either fentanyl or morphine, or both;
- Comparison: therapy-based comparative studies;
- Outcome: inclusion of comparative studies from inception until September 2017, with no considerations of whether articles are freely available and retrospective or prospective.

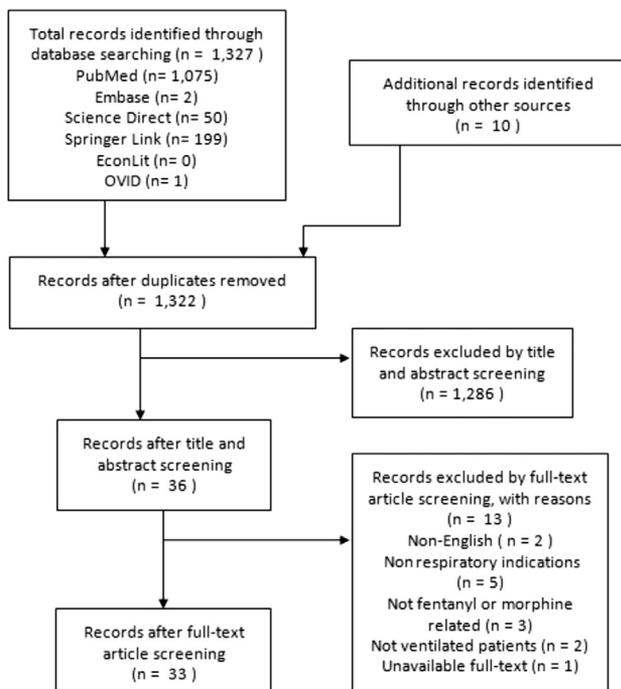


Fig. 1 – Flow diagram of literature search result.

The exclusion criteria included the following:

- non–English language;
- non–human studies;
- non–comparative research;
- nonrespiratory underlying indications.

Data Collection and Handling

We categorized the articles identified as eligible for inclusion on the basis of whether they were clinical or economic evaluations. We further discussed clinical studies on the basis of the ICU population because different age groups require different practices.

Two investigators independently performed article screening and data extraction. Appendix 2 in Supplemental Materials found at <https://doi.org/10.1016/j.vhri.2018.11.001> presents a list of the data extracted from the studies. All the investigators were trained pharmacoeconomics researchers. For validation purposes, the extraction of the relevant data from each included article was reviewed by a third investigator. Disagreements, including those regarding miscoding, were discussed further until consensus was achieved.

We used numerical and percentage measures to describe the distribution of variables, and cross-tabulation to compare the frequency data. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist for completing the systematic review (see Appendix 3 in Supplemental Materials found at <https://doi.org/10.1016/j.vhri.2018.11.001>).

Quality Assessment

Independent investigators conducted a quality assessment. We referred to the CONSolidated Standards Of Reporting Trials (CONSORT)⁹ to assess the reporting quality of randomized controlled trials (RCTs), STrengthening the Reporting of OBservational studies in Epidemiology (STROBE)¹⁰ for cohort studies, and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) to assess the reporting of pharmacoeconomics studies.¹¹

Although other appraisal tools also exist for various study designs, our review does not attempt to assess bias, generate evidence, or provide recommendations for best use of medications.

To note, the present systematic review is not registered at PROSPERO.

Results

Inclusion, Study Population, and Comparators

Our literature search generated 33 articles eligible for analysis (Fig. 1). Table 1 presents the included studies.^{12–44} We reviewed 22, 8, and 3 studies conducted between 1989 and 2014 in populations of adults, neonates, and pediatrics, respectively. The classification of age categories of the populations of studies was based on how studies identified their populations (Table 1). Although the pediatric population is defined in practices as one that has an age starting from birth, younger pediatrics are referred to as neonates in other settings, whereby a neonate is a pediatric patient, but not every pediatric patient is a neonate. To emphasize, the ages of pediatric and neonate populations in this review are defined only by the ages that were reported for each of them in the included studies. The underlying condition of interest was defined in 8 studies as a respiratory disorder. Appendix 4 in Supplemental Materials found at <https://doi.org/10.1016/j.vhri.2018.11.001> summarizes the underlying disorders in the studies.

Table 1 – Summary of the characteristics of the included studies.

No.	Subject (age)	Author; country	Study design	Interventions vs comparators	Duration of therapy	Primary outcome	Definition of primary outcome	Secondary outcome	Definition of secondary outcome	Main findings
1	Adult (16-80 y)	Aitkenhead et al ⁴¹ ; NA	RCT	Propofol + morphine vs midazolam + morphine	<24 h	Treatment success based on the desired level of sedation using RSS	Desired level was defined as cooperative, oriented, and tranquil, responding to command only, or showing a brisk response to light glabellar tap or a loud auditory stimulus	Weaning time, mortality, and hypotension episodes	NA	Higher desired RSS score and lower weaning time were in the propofol and morphine group Mortality and hypotension happened more frequently in the propofol and morphine group
2	Adult (>16 y)	Carrasco et al ¹² ; United States	RCT, economic evaluation	Propofol + morphine vs midazolam	NA	Treatment success based on the desired level of sedation using RSS and GCS	Adequate sedation (if sedation level was grade 2, 3, 4, or 5 on RSS or degree of reactivity was maintained between 8 and 13 points on GCS)	Sedatives cost and hypotension episodes	NA	Propofol and morphine provided significantly adequate sedation, more hypotension cases with higher short-term cost and lower medium and long-term cost
3	Adult (NA)	Watling et al ³⁵ ; Canada	Observational	Lorazepam with/without morphine	NA	Apnea and respiratory effort	NA	NA	NA	Lorazepam and morphine combination caused apnea and reduced the respiratory effort during 2-50 d of sedation
4	Adult (≥14 y)	Barrientos-Vega et al ³⁹ ; NA	RCT, economic evaluation	Midazolam + morphine vs propofol + morphine	>24 h	Weaning time and cost	NA	Tachyphylaxis, treatment failures associated with sedatives	Tachyphylaxis: NA Treatment failures (patients needing >12 mL/h of study medication)	Propofol and morphine reduced the weaning time, cost, and therapeutic failure
5	Adult (18-85 y)	Swart et al ²² ; United States	RCT, economic evaluation	Lorazepam + fentanyl vs midazolam + fentanyl	NA	Treatment success based on the desired level of sedation using Addenbrooke Scale	Adequate sedation level was considered as lightly asleep but easily roused by voice	Total cost of sedation	NA	Lorazepam provided easier management of the sedation level and offered significant cost savings
6	Adult (median = 57 y in the intervention group and 61 y in the control group)	Kress et al ¹³ ; United States	RCT	Midazolam + morphine vs propofol + morphine	NA	Duration of MV, ICU, and hospital stay	NA	The need for CT, MRI scan	NA	Duration of MV and ICU stay and need for diagnostic tests were significantly lower in the midazolam and morphine group The hospital stay did not differ between the groups
7	Adult (≥14 y)	Barrientos-Vega et al ³⁰ ; Spain	Observational, economic evaluation	Propofol 2% + morphine vs propofol 1% + morphine vs midazolam + morphine	14 d maximum	Treatment failure and the ability to reach the desired sedation using RSS	NA	ICU cost	ICU cost for duration of MV, sedative cost depending on dose used, and ICU cost during weaning	No difference was seen in the ability to reach the desired sedation score and the treatment failure between propofol 1% and 2% <i>continued on next page</i>

Table 1 – continued

No.	Subject (age)	Author; country	Study design	Interventions vs comparators	Duration of therapy	Primary outcome	Definition of primary outcome	Secondary outcome	Definition of secondary outcome	Main findings
8	Adult (>18 y)	Breen et al ¹⁴⁰ ; NA	RCT	Remifentanyl vs midazolam + morphine or fentanyl	10 d	Extubation time	NA	Weaning time, ICU stay, treatment success based on the desired level of sedation based on SAS, death, and hypotension	Adequate sedation was considered as level 3 or 4 ICU stay until discharge Other outcomes: NA	Lowest ICU cost in propofol 2% and highest in the midazolam group Extubation and weaning time and ICU stay were lower in remifentanyl with same sedation score More patients died in the remifentanyl group, whereas patients had hypotension in the other group
9	Adult (≥18 y)	Carson et al ¹⁴ ; United States	RCT	Lorazepam + morphine vs propofol + morphine	NA	Duration of MV	From the time of intubation to the first time of extubation for ≥3 d	MV-free days, ICU and hospital stay, and mortality	Mortality during hospital stay Other outcomes: NA	Lorazepam and morphine reduced significantly the MV duration No difference between the groups in the MV-free days, ICU and hospital stay, and mortality
10	Adult (mean = 59 y in the midazolam group and 54 y in the fentanyl group)	Richman et al ¹⁵ ; United States	RCT	Midazolam vs midazolam + fentanyl	NA	The number of hours per day that patients' RSS deviated from the target value	NA	Number of patient-ventilator asynchronous Events perday and hypotension	Number of times per day the chest wall respiratory rate exceeds the measured ventilator rate by 3/min Other outcomes: NA	Midazolam and fentanyl reduced significantly the off-target RSS score and number of patient-ventilator asynchronous No difference in the hypotension
11	Adult (55 y)	Cox et al ²⁶ ; Denmark	RCT, economic evaluation	Propofol vs lorazepam vs morphine	NA	MV-free days	Within 28 d from intubation	Cost	NA	Propofol dominated lorazepam because of its lower overall costs and greater MV-free days
12	Adult (≥18 y)	Mehta et al ³⁴ ; Canada	RCT	Midazolam + morphine (PS + DIS) vs midazolam + morphine (PS only)	NA	Treatment success based on the desired level of sedation using SAS	Adequate sedation level was scored as level 3 and 4	Duration of MV, ICU and hospital stay, and mortality rate	Duration of MV from the time of intubation to extubation for 2 d Mortality during stay Other outcomes: NA	PS achieved better desired SAS score No difference was observed in the duration of MV, ICU and hospital stay, and mortality
13	Adult (≥18 y)	Riker et al ³⁸ ; United States, Brazil, Australia, Argentina, New Zealand	RCT	Dexmedetomidine + fentanyl vs midazolam + fentanyl	30 d maximum	Time to reach the desired RASS score	Target sedation range (RASS score: -2 to 1)	The duration and free days of delirium ICU stay, and hypotension	Delirium-free days were calculated as days alive and free of delirium during study drug exposure Mortality after 30 d of ICU admission Other outcomes: NA	Time to reach the desired RASS score was not significantly lower in the midazolam and fentanyl group Delirium-free days were significantly lower in the midazolam group No difference between the comparators in the hypotension, ICU stay, and mortality

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14	Adult (≥18 y)	Rozendaal et al ²⁴ ; The Netherlands	RCT	Remifentanyl + propofol vs fentanyl or morphine + midazolam, propofol or lorazepam	10 d maximum	Duration of MV	NA	Weaning time, sedation level, ICU LOS, and hypotension	NA	Duration of MV, weaning time, sedation level, and ICU stay was statistically improved in the remifentanyl and propofol group No difference in the hypotension
15	Adult (≥18 y)	Al et al ²³ ; The Netherlands	RCT, economic evaluation	Remifentanyl + propofol vs fentanyl or morphine + midazolam, propofol or lorazepam	10 d maximum	Sedatives cost	NA	ICU and MV stay	NA	Remifentanyl and propofol was less costly No difference between the groups in relation to ICU and MV stay
16	Adult (≥18 y)	Strom et al ²⁵ ; Denmark	RCT	Morphine vs propofol	28 d	MV-free days, ICU and hospital stay, mortality	MV-free days in 28-d period Mortality during stay Other outcomes: NA	The need for CT or MRI brain scans, accidental removal of endotracheal tube, and VAP	VAP: new lung parenchymal opacity on a chest radiograph of a patient who had been intubated for >48 h, and simultaneous presentation of 2 or more of temperature of <36°C or >38°C; white blood cell count of <4 × 10 ⁹ /L or >10 × 10 ⁹ /L; or purulent secretions from the endotracheal tube Other outcomes: NA	MV-free days was statistically lower in the morphine and propofol group LOS in ICU and hospital, tracheostomy, VAP, and mortality were less but not significant in morphine monotherapy
17	Adult (≥18 y)	Karir et al ¹⁶ ; United States	Observational	Lorazepam vs midazolam vs diazepam vs propofol vs morphine vs fentanyl vs hydromorphone vs meperidine vs methadone vs oxycodone vs haloperidol vs quetiapine	14 d	Cumulative 14-d dose	NA	NA	NA	Most patients received lorazepam (88%), morphine and fentanyl were around equally given but the median dose of fentanyl was higher
18	Adult (≥16 y)	Jarman et al ¹⁷ ; United States	Observational	Morphine + propofol vs midazolam	NA	MV-free days	NA	ICU LOS, mortality rate	NA	MV-free days was significantly lower in the midazolam group ICU LOS was significantly lower in propofol and morphine group No difference between both in relation to mortality <i>continued on next page</i>

Table 1 – continued

No.	Subject (age)	Author; country	Study design	Interventions vs comparators	Duration of therapy	Primary outcome	Definition of primary outcome	Secondary outcome	Definition of secondary outcome	Main findings
19	Adult (≥ 18 y)	Shehabi et al ³³ ; Malaysia	RCT	Light vs deep sedation of (midazolam, propofol, morphine, fentanyl, dexmedetomidine, ketamine, haloperidol, and diazepam)	NA	Treatment success based on the level of sedation using RASS	Target sedation range (RASS score: –2 to 1)	Delirium and free days of delirium ICU, hospital and postdischarge mortality, and ICU stay	Delirium was defined when patients had positive results using the confusion assessment methods for intensive care Subjects were considered delirium-free if they had a RASS >3	Median target RASS scores and delirium-free days were higher in the lightly sedated group after 48 h The ICU, hospital and postdischarge mortality, and ICU stay were higher in the deeply sedated group
20	Adult (>18 y)	Tedders et al ¹⁸ ; United States	Observational	Fentanyl vs propofol	NA	Duration of MV	NA	ICU stay, the percentage of the desired level of pain, and sedation and frequency of hypotension	Hypotension defined as reduction in the systolic blood pressure to <90 mm Hg at 2 repeated periods or reduction in systolic blood pressure to >40 mm Hg Other outcomes: NA	Duration of MV was significantly lower in the fentanyl group No difference was associated between both groups in ICU stay, hypotension, and desired RASS score
21	Adult (≥ 18 y)	Junior et al ³⁷ ; Brazil	RCT	Intermittent sedation (fentanyl) vs daily interruption (fentanyl)	28 d	MV-free days	In a 28-d period	ICU and hospital mortality, ICU and hospital LOS, incidence of delirium, time to reach the desired SAS score	Target SAS (level 3 or 4) Delirium within 7 d Mortality during stay Other outcomes: NA	MV-free days and time to reach desired SAS score were higher in the intermittent group ICU and hospital mortality and delirium happened less in the intermittent group
22	Adult (>18 y)	Zhou et al ³² ; China	RCT, economic evaluation	Midazolam + fentanyl vs propofol vs sequential use of midazolam + propofol	>72 h	Recovery and extubation time	NA	ICU and hospital stay, ICU and hospital mortality, sedatives and ICU costs Hypotension episodes	Hypotension defined as reduction in systolic blood pressure $>20\%$ Mortality during stay Other outcomes: NA	Sequential use of propofol and midazolam was better in relation to earlier extubation, less sedation and total ICU costs, and less hypotension cases compared with the other groups Although propofol reduced the ICU stay significantly, no difference among the groups in the other outcomes
23	Neonate (≤ 34 -wk gestation)	Quinn et al ²⁹ ; Ireland	RCT	Morphine vs pancuronium vs morphine + pancuronium	Until O ₂ concentration fell below 45%	Duration of MV and mortality, IVH	NA	NA	NA	No difference among the groups in terms of MV reduction and mortality IVH happened least in the pancuronium group <i>continued on next page</i>

24	Neonate (26- to 36-wk gestation)	Orsini et al ¹⁹ ; United States	RCT	Fentanyl vs placebo	5 d	Behaviors of infants using behavioral state score	Low score reflects sedated neonate, whereas high score indicates not well sedated	Duration of ventilation use, incidence of IVH	NA	Fentanyl showed significantly lower behavioral state score compared with placebo No difference was seen in relation to other outcomes
25	Neonate (<35 wk of postconceptional age at birth)	Wood et al ²⁸ ; United Kingdom	RCT	Diamorphine vs morphine	25 h	Treatment success based on desired level of sedation using a study-specific scale	NA	Duration of MV and mortality, IVH	NA	No difference was seen after 24 h of optimum sedation score, duration of MV, and mortality Incidence of IVH was higher in the diamorphine group
26	Neonate (≤32-wk gestation)	Guinsburg et al ⁴⁴ ; Brazil	RCT	Fentanyl vs placebo	NA	Behaviors of infants using NFCS and PCS	NA	Blood pressure and heart rate	NA	Lower behavioral state score in the fentanyl group Fentanyl reduced heart rate and blood pressure
27	Neonate (24- to 32-wk gestation)	Anand et al ⁴² ; NA	RCT	Morphine vs midazolam vs placebo	14 d maximum	Severity of illness using PIPP scale and level of sedation using COMFORT scale	PIPP defined as no or mild pain if the score was between 0 and 6, moderate pain if the score was between 7 and 12, and severe pain if the score was >12 COMFORT score defined as target range of sedation between 17 and 26	Poor neurological outcomes Death, MV-free days, ICU stay, tolerance of enteral feeds	Poor neurological outcomes defined as neonatal death, IVH grade 3 or 4, or PVL Neonatal death occurring at age 0-28 d without discharge from NICU Other outcomes: NA	Only morphine had elevated COMFORT score, which decreased the level of sedation significantly Morphine and midazolam groups reduced the pain score significantly 3 deaths; 2 in the placebo group, 1 in the midazolam group, and none in the morphine group Poor neurological outcomes occurred more frequently in the placebo group and least in the morphine group No difference between both groups in MV-free days and ICU stay
28	Neonate (≥24-wk gestational age)	Saarenmaa et al ²⁷ ; Finland	RCT	Fentanyl vs morphine	2 d	Severity of illness using behavioral pain scale	NA	Decreased gastrointestinal motility, necrotizing enterocolitis, urinary retention	Decreased gastrointestinal motility through daily meconium passage assessment Urinary retention defined as the inability to urinate spontaneously with bladder	No difference was observed in the pain score response between both groups except in the β-endorphin in favor of the fentanyl group Decreased gastrointestinal motility occurred significantly less

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Table 1 – continued

No.	Subject (age)	Author; country	Study design	Interventions vs comparators	Duration of therapy	Primary outcome	Definition of primary outcome	Secondary outcome	Definition of secondary outcome	Main findings
29	Neonate (postnatal age younger than 3 d)	Simons et al ³¹ ; The Netherlands	RCT	Morphine vs placebo	7 d	Level of pain using VAS, NIPS, PIPP	VAS defined as scores ranging between 0 and 10, low scores indicate low pain, whereas high scores indicate severe pain NIPS defined as scores ranging between 0 and >4, 0 indicates no or mild pain and >4 means severe pain PIPP as defined by Anand et al ⁴² study	Poor neurological outcomes	enlargement or reversible hydronephrosis Other outcomes: NA Poor neurological outcome defined as severe IVH, PVL, or death within 28 d and the incidence of all grades of IVH	frequently in the fentanyl group Necrotizing enterocolitis and urinary retention were diagnosed more in the fentanyl group No significant differences between groups in pain scores Poor neurological outcome happened in the lower ages but not associated with sedative
30	Neonate (≤32-wk gestation)	Grunau et al ³⁶ ; Canada	Observational	Morphine vs placebo	NA	Neurodevelopmental outcomes	MDI measures cognitive and language function and includes eye-hand items such as stacking blocks, concrete problem-solving tasks, receptive and expressive vocabulary items; PDI measures the gross motor development	NA	NA	Morphine was associated with poor neurodevelopmental outcome at 8 mo only after sedation
31	Pediatric (3-7 y)	Tobias ⁴³ ; NA	Observational	Fentanyl + midazolam vs midazolam	3-7 d	Withdrawal symptoms prevention	NA	NA	NA	No subjects developed withdrawal symptoms in both groups
32	Pediatric (age in months, 36 ± 34 in the midazolam group, 54 ± 44 in the dexmedetomidine 0.25 µg, 39 ± 44 in the dexmedetomidine 0.5 µg)	Tobias and Berkenbosch ²⁰ ; United States	RCT	Midazolam + morphine vs dexmedetomidine + morphine	NA	Treatment success based on desired level of sedation using RSS, pediatric intensive care unit scale, and tracheal suctioning scale	NA	Blood pressure and heart rate	NA	No difference was seen between groups in relation to all the measured outcomes

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33	Pediatric (>37-wk postconceptional age and <18 y)	Anand et al. ²¹ ; United States	Observational	Morphine vs fentanyl	NA	Increased in opioid dose	NA	NA	Doubling the dose of opioids was more likely to happen after opioid infusion for 7 d or longer
<p>CT, computed tomography; DIS, daily interruption sedation; GCS, Glasgow Coma Scale; ICU, intensive care unit; IVH, intraventricular hemorrhage; LOS, length of stay; MDI, mental development index; MRI, magnetic resonance imaging; MV, mechanical ventilation; NA, not available; NFCS, neonatal facial coding system; NICU, neonatal intensive care unit; NIPS, Neonatal Infant Pain Scale; PCS, Postoperative Comfort Score; PDI, psychomotor development index; PICU, pediatric intensive care unit; PIPP, premature infant pain profile; PS, protocol sedation; PVL, periventricular leukomalacia; RASS, Richmond Agitation-Sedation Scale; RCT, randomized controlled trial; RSS, Ramsey Sedation Scale; SAS, Sedation-Agitation Scale; VAP, ventilator-associated pneumonia; VAS, visual analogue scale.</p>									

Only 7 studies featured head-to-head comparisons between morphine and fentanyl.^{16,21,23,24,27,33,40} Morphine was evaluated as monotherapy (n = 9) and/or in combination (n = 16) in 23 studies,^{12–14,16,17,20,21,23–31,33–36,39–42} whereas fentanyl was evaluated as monotherapy (n = 7) or in combination (n = 8) in 15 of the 33 studies.^{15,16,18,19,22–24,27,32,33,37,38,40,43,44} Table 1 and Appendices 5 and 6 in Supplemental Materials found at <https://doi.org/10.1016/j.vhri.2018.11.001> present the study interventions and comparators.

Outcome Measures

Table 1 presents the primary and secondary outcome measures used in the studies, including their varying definitions. Appendix 7 in Supplemental Materials found at <https://doi.org/10.1016/j.vhri.2018.11.001> summarizes the reported sample size calculations and statistical differences.

Adult patients

Adult studies included patients who were 14 years and older. The doses of morphine and fentanyl varied between 0.08 mg/kg/h and 5 mg/kg/h, and 0.5 µg/kg/h and 2 µg/kg/h, respectively. Of the 22 adult studies, 17 were RCTs and 5 were observational studies (Table 1).

Most of the studies (n = 8) measured optimum sedation—defined differently in different studies—as the primary endpoint. Four studies evaluated optimum sedation using the Ramsay Sedation Scale (RSS),^{12,15,30,41} whereas 1 study used the Addenbrooke Scale,²² 1 used the Sedation-Agitation Scale (SAS), and others^{33,38} used the Richmond Agitation-Sedation Scale.³⁴ All the scales were used differently without any specification about the outcome of the study or type of sedative.

Eight studies evaluated the duration of the MV—defined very differently in different studies—as another primary outcome.^{13,14,17,18,24–26,37}

In 3 studies, the optimum sedation level was assessed as a secondary outcome,^{24,37,40} using SAS in 2 studies.^{37,40} One study used the duration of MV as the secondary outcome, defining it as the time from intubation to extubation over 2 days.³⁴ The secondary outcome measures most frequently identified were the length of stay in ICU,^{14,17,18,23,24,32–34,38,40} adverse events,^{15,24,25,32,38,40,41} delirium events and days free of delirium,^{33,37,38} and mortality.^{14,17,30,32–34,37,38,40,41}

The ICU length of stay was defined by only 1 study as the patients' stay in the ICU until discharge. Others followed up stay only during sedation. Either ICU or hospital mortality comprised mortality events, but without clarification of whether this was sedation-related. In different studies, the duration over which mortality was measured also differed widely.

Adverse events were hypotension episodes^{12,15,18,24,32,38,40,41} and ventilator-associated pneumonia.²⁵ The management of such events, however, was not reported in any of the studies.

Delirium events were reported in 3 studies^{33,37,38} and were defined differently among them.

Neonatal patients

The neonatal population was younger than 3 years. Among 8 neonatal studies, only 1 directly comparing fentanyl and morphine using β-endorphin levels to measure pain reported a statistically significant outcome.²⁷ The doses of morphine and fentanyl varied between 0.01 mg/kg/h and 0.1 mg/kg/h, and 0.5 µg/kg/h and 1 µg/kg/h, respectively, from 7 RCTs and 1 observational study.

The most common primary endpoint in most of the studies (n = 6), as in studies of adults, was the desired level of sedation, measured in 1 study by the premature infant pain profile (PIPP)

and COMFORT scores to compare between the same medications.⁴² One study used 3 tools—the visual analogue scale, the Neonatal Infant Pain Scale, and PIPP³¹; another used 2 scales—the neonatal facial coding system and the postoperative comfort score, neither of which was clearly defined—to assess the behavior of neonates.⁴⁴ In the remaining 2 studies, the behavioral state of the neonates determined the outcome of sedation, with lower scores reflecting better sedated neonates.^{19,27}

One study measured the duration of MV and mortality as other primary, but undefined, outcomes.²⁹

Another primary outcome, neurodevelopmental function, measured cognitive and language function using the mental development index and gross motor development using the psychomotor development index.³⁶

The included studies reported, as secondary endpoints, mainly duration of MV,^{28,42} length of neonatal ICU stay,^{31,42} gastrointestinal motility,²⁷ urinary retention,²⁷ necrotizing enterocolitis,²⁷ poor neurological outcomes,⁴² and mortality.^{28,42}

MV duration, neonatal ICU stay, and mortality were defined and reported as in the adult studies. Gastrointestinal motility and urinary retention were reported by measuring the daily meconium passage and ability to urinate spontaneously with bladder enlargement or reversible hydronephrosis.²⁷

The neurological outcomes were defined as the occurrence of cases of death, intraventricular hemorrhage (grade 3 or 4), or periventricular leukomalacia.⁴²

Pediatric patients

The pediatric populations in the studies included patients aged 3 to 7 years. Of the 3 eligible studies, 2 did not specify patients' respiratory disorders. One study directly compared morphine and fentanyl.²¹ The doses of morphine and fentanyl varied between 0.08 mg/kg/h and 0.1 mg/kg/h, and 11 µg/kg/h and 19 µg/kg/h, respectively.

Of 2 observational studies^{21,43} and 1 RCT,²⁰ 1 study compared fentanyl and midazolam regarding their association with withdrawal symptoms after prolonged, but undefined, sedation.⁴³ Another study²⁰ measured the level of sedation using 3 different scales—the RSS, pediatric ICU, and tracheal suctioning scales. Optimum sedation was not identified. Only 1 study measured the increase in opioid use during management to maintain satisfactory levels of sedation.²¹

Secondary outcomes were measured only in 1 of the studies,²⁰ in which the heart rate was additionally reported in those receiving the therapy.

Economic Evaluations

All the 7 studies evaluating economic outcomes were in the adult population. Appendix 8 in Supplemental Materials found at [10.1016/j.vhri.2018.11.001](https://doi.org/10.1016/j.vhri.2018.11.001) presents the types of economic evaluations—cost analysis evaluations (n = 3), cost-benefit analyses (n = 2), cost-effectiveness analysis (n = 1), and cost-consequence analysis (n = 1)—and study perspectives. All the studies adopted a hospital perspective, including medications, ICU stay, and hospital stay costs. Only 1 study (a cost-benefit study) reported the extra costs of additional care, such as nursing, respiratory, or physiotherapy care.¹² Similar elements were considered for the total cost calculations in 2 of the cost analysis models,^{30,39} which included the costs associated with death, therapeutic failures, sedation time, medication, length of stay in ICU during sedation, and weaning. On the basis of simple linear regressions, both of these were predictive models. No decision analysis was conducted in the third cost analysis that included only the cost of medications.²² The only cost-effectiveness decision model compared 3 therapies and included the costs of medication, MV, hospital stay, physicians, and

laboratory tests.²⁶ The incremental cost-effectiveness ratio evaluation was the cost per additional MV-free day. In the 2 cost-benefit analyses, authors accounted for medication costs and additional therapy care costs such as physiotherapy and tracheal aspiration, and nursing care costs. In 1 of the latter 2, the total ICU stay cost was also included.³² Appendix 8 in Supplemental Materials summarizes the decision-analytic modeling approaches of the 4 studies using modeling approaches,^{23,26,30,39} with their definitions and time horizons. The Markov type of modeling was in the cost-consequence analysis,²³ which included 8 potential health states, over a time horizon of 28 days and a cycle length of 1 hour.

Deterministic, 1-way or multivariate sensitivity analyses were conducted in none of the studies. One study performed 1- and 2-way probabilistic analyses,²⁶ analyzing variables, including medication use during the MV procedure, medication failure leading to crossover, ICU stay, MV days, hospital mortality, and the costs of medications, ICU, hospital ward, and physicians. In a study by Al et al,²³ the uncertainty of ICU and sedation costs, ICU stay, and time spent on MV was approached through a probabilistic sensitivity analysis. Nevertheless, it was unclear whether a 1- or 2-way sensitivity analysis was performed. Appendix 8 in Supplemental Materials presents the sensitivity analyses.

Quality Assessment of the Studies

The reporting of the following items was especially consistently poor among all studies: important changes to methods after trial commencement (such as eligibility criteria), any changes to trial outcomes after the trial commenced, losses and exclusions after randomization for each group; for binary outcomes, presentation of both absolute and relative effect sizes, and where the full trial protocol can be accessed. To a lesser extent, the studies did poorly in relation to reporting several items: how sample size was determined (reported by only 44% of trials); explanations of any interim analyses and stopping guidelines (when applicable) (reported by only 28% of studies); methods for additional analyses, such as subgroup analyses and adjusted analyses (reported in only 22% of studies); results of other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory results (reported in only 17% of studies); generalizability (external validity and applicability) of the trial findings (discussed in only 25% of studies); and registration number and sources of funding and other support (reported in only 17% of studies).

No observational studies reported any methods used to assess subgroups and interactions, explained how missing data were addressed, or provided sensitivity analyses, the number of patients with missing data, follow-up time, category boundaries for continuous variables, translation of relative risk to absolute risk, other analyses such as subgroups, interactions, and sensitivity analyses, generalizability (external validity) of the study results, and funding for studies. To a lesser extent, studies poorly defined all outcomes, exposures, predictors, potential confounders, and effect modifiers (reported in only 25% of studies); the number of patients at each stage of study—for example, patients possibly eligible and confirmed eligible (reported in only 38% of studies); potential confounders, addressing bias and loss to follow-up (reported in only 13% of studies); and use of diagnostic criteria and a flow diagram (reported in only 25% of studies).

In most of the studies, the main shortcomings identified in economic evaluations were related to reporting the incremental costs and outcomes (absent in 86% of studies); time horizon, characterizing uncertainty and characterizing heterogeneity (absent in 71% of studies); assumptions (unreported in 57% of trials);

Table 2 – Quality assessment of the randomized controlled trials on the basis of CONSORT reporting criteria.

No.	Questions	Studies (part 1)									Quantitative overall scores
		Anand et al ⁴²	Saarenmaa et al ²⁷	Wood et al ²⁸	Quinn et al ²⁹	Simons et al ³¹	Orsini et al ¹⁹	Guinsburg et al ⁴⁴	Mehta et al ³⁴	Richman et al ¹⁵	
1a	Identification as a randomized trial in the title	NA	A	A	NA	A	NA	NA	A	PA	58%
1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts)	A	A	A	NA	A	A	A	A	A	89%
2a	Scientific background and explanation of rationale	A	A	A	A	A	A	A	A	A	100%
2b	Specific objectives or hypotheses	A	A	A	A	A	A	A	A	A	100%
3a	Description of trial design (such as parallel and factorial) including allocation ratio	A	A	A	PA	A	A	A	A	A	94%
3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA	NA	NA	NA	NA	NA	NA	NA	NA	0%
4a	Eligibility criteria for participants	A	A	A	A	A	A	A	A	A	100%
4b	Settings and locations where the data were collected	A	A	A	NA	A	NA	NA	A	A	83%
5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	A	A	A	A	A	A	A	A	A	100%
6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	A	PA	NA	NA	A	PA	NA	A	PA	50%
6b	Any changes to trial outcomes after the trial commenced, with reasons	NA	NA	NA	NA	NA	NA	NA	NA	NA	0%
7a	How sample size was determined	NA	A	NA	A	A	NA	NA	NA	NA	44%
7b	When applicable, explanation of any interim analyses and stopping guidelines	NA	NA	NA	NA	NA	NA	NA	NA	NA	28%
8a	Method used to generate the random allocation sequence	A	A	A	A	NA	A	A	A	NA	89%
8b	Type of randomization; details of any restriction (such as blocking and block size)	A	A	NA	NA	NA	A	A	A	NA	72%
9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	A	A	NA	NA	NA	A	A	A	NA	72%
10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	A	A	A	NA	NA	A	NA	A	NA	72%
11a	If done, who was blinded after assignment to interventions (eg, participants, care providers, or those assessing outcomes) and how	A	A	A	NA	A	A	A	A	NA	83%
11b	If relevant, description of the similarity of interventions	A	A	A	NA	A	A	A	A	A	94%
12a	Statistical methods used to compare groups for primary and secondary outcomes	A	A	A	A	A	A	A	A	A	94%
12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	A	A	NA	NA	NA	NA	NA	NA	NA	22%
13a	For each group, the number of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	A	A	A	A	A	A	A	A	A	100%
13b	For each group, losses and exclusions after randomization, together with reasons	NA	NA	NA	NA	NA	NA	NA	NA	NA	0%
14a	Dates defining the periods of recruitment and follow-up	NA	A	NA	A	A	NA	A	A	A	53%
14b	Why the trial ended or was stopped	NA	NA	NA	NA	NA	NA	NA	NA	NA	6%
15	A table showing baseline demographic and clinical characteristics for each group	A	A	A	PA	A	A	A	A	A	97%
16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	A	A	A	A	A	A	A	A	A	100%

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Table 2 – continued

No.	Questions	Studies (part 1)									
		Anand et al ⁴²	Saarenmaa et al ²⁷	Wood et al ²⁸	Quinn et al ²⁹	Simons et al ³¹	Orsini et al ¹⁹	Guinsburg et al ⁴⁴	Mehta et al ³⁴	Richman et al ¹⁵	Quantitative overall scores
17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	A	A	A	A	A	A	A	A	A	100%
17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA	NA	NA	NA	NA	NA	NA	NA	NA	0%
18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	A	NA	NA	NA	NA	NA	NA	NA	NA	17%
19	All-important harms or unintended effects in each group (for specific guidance, see CONSORT for harms)	A	A	A	A	A	A	NA	A	A	94%
20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	A	A	A	NA	A	PA	NA	A	A	75%
21	Generalizability (external validity and applicability) of the trial findings	PA	NA	NA	NA	NA	NA	NA	A	NA	25%
22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	A	A	A	A	A	A	A	A	A	100%
23	Registration number and name of trial registry	NA	NA	NA	NA	NA	NA	NA	NA	NA	17%
24	Where the full trial protocol can be accessed, if available	NA	NA	NA	NA	NA	NA	NA	NA	NA	0%
25	Sources of funding and other support (such as supply of drugs), role of funders	NA	NA	NA	NA	A	NA	NA	NA	NA	17%
No.	Questions	Studies (part 2)									
		Rozenda et al ²⁴	Breen et al ⁴⁰	Strom et al ²⁵	Riker et al ¹³⁸	Nassar Junior and Park ³⁷	Aitkenhead et al ⁴¹	Kress et al ¹³	Tobias et al ²⁰	Carson et al ¹⁴	
1a	Identification as a randomized trial in the title	A	A	A	A	A	NA	NA	NA	A	
1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts)	A	A	A	A	A	NA	A	A	A	
2a	Scientific background and explanation of rationale	A	A	A	A	A	A	A	A	A	
2b	Specific objectives or hypotheses	A	A	A	A	A	A	A	A	A	
3a	Description of trial design (such as parallel and factorial) including allocation ratio	A	A	A	A	A	A	A	PA	A	
3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA	NA	NA	NA	NA	NA	NA	NA	NA	
4a	Eligibility criteria for participants	A	A	A	A	A	A	A	A	A	
4b	Settings and locations where the data were collected	A	A	A	A	A	A	A	A	A	
5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	A	A	A	A	A	A	A	A	A	
6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	NA	PA	PA	A	A	PA	NA	PA	PA	
6b	Any changes to trial outcomes after the trial commenced, with reasons	NA	NA	NA	NA	NA	NA	NA	NA	NA	
7a	How sample size was determined	A	NA	A	A	A	NA	NA	NA	A	
7b	When applicable, explanation of any interim analyses and stopping guidelines	NA	NA	NA	A	A	NA	A	A	A	
8a	Method used to generate the random allocation sequence	A	A	A	A	A	A	A	A	A	
8b	Type of randomization; details of any restriction (such as blocking and block size)	A	A	A	A	A	A	A	NA	A	
9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	A	A	A	A	A	A	A	NA	A	

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Table 2 – continued

No.	Questions	Studies (part 2)								
		Rozenda et al ²⁴	Breen et al ⁴⁰	Strom et al ²⁵	Riker et al ³⁸	Nassar Junior and Park ³⁷	Aitkenhead et al ⁴¹	Kress et al ¹³	Tobias et al ²⁰	Carson et al ¹⁴
10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	A	A	A	A	A	A	A	NA	A
11a	If done, who was blinded after assignment to interventions (eg, participants, care providers, or those assessing outcomes) and how	A	A	A	A	A	A	A	NA	A
11b	If relevant, description of the similarity of interventions	A	A	A	A	A	A	A	A	A
12a	Statistical methods used to compare groups for primary and secondary outcomes	A	A	A	A	A	NA	A	A	A
12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA	NA	NA	NA	NA	A	A	NA	NA
13a	For each group, the number of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	A	A	A	A	A	A	A	A	A
13b	For each group, losses and exclusions after randomization, together with reasons	NA	NA	NA	NA	NA	NA	NA	NA	NA
14a	Dates defining the periods of recruitment and follow-up	NA	PA	NA	A	A	NA	NA	NA	A
14b	Why the trial ended or was stopped	NA	NA	NA	NA	A	NA	NA	NA	NA
15	A table showing baseline demographic and clinical characteristics for each group	A	A	A	A	A	A	A	A	A
16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	A	A	A	A	A	A	A	A	A
17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	A	A	A	A	A	A	A	A	A
17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA	NA	NA	NA	NA	NA	NA	NA	NA
18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	NA	NA	NA	NA	NA	A	A	NA	NA
19	All-important harms or unintended effects in each group (for specific guidance, see CONSORT for harms)	A	A	A	A	A	A	A	A	A
20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	A	NA	A	A	A	NA	A	A	A
21	Generalizability (external validity and applicability) of the trial findings	NA	NA	A	A	NA	NA	NA	NA	A
22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	A	A	A	A	A	A	A	A	A
23	Registration number and name of trial registry	NA	NA	A	A	A	NA	NA	NA	NA
24	Where the full trial protocol can be accessed, if available	NA	NA	NA	NA	NA	NA	NA	NA	NA
25	Sources of funding and other support (such as supply of drugs), role of funders	NA	NA	A	A	NA	NA	NA	NA	NA

A indicates adequate (information was explicitly presented in the text); CONSORT, CONSolidated Standards Of Reporting Trials; NA, not adequate (no information about the matter was available in the text); PA, partially adequate (information was not explicitly presented, but it was suggested).

analytical model and the choice of model (unreported in 43% of studies); estimation of resources and costs (absent in 36% of studies); and source of funding and conflicts of interest (unreported in 100% of studies).

Tables 2 to 4 present the results of the quality assessment of reports.

Discussion

The present systematic review sought to answer questions about the characteristics and quality of research reporting on fentanyl and morphine use in patients requiring MV in ICU, focusing on MV for respiratory disorders, for which no morphine versus fentanyl

Table 3 – Cohort evaluations according to STROBE reporting instrument.

No. Questions	Studies									Quantitative overall scores
	Tedders et al ¹⁸	Watling et al ³⁵	Karir et al ¹⁶	Jarman et al ¹⁷	Shehabi et al ³³	Tobias et al ⁴³	Anand et al ²¹	Grunau et al ³⁶		
1a	Indicate the study's design with a commonly used term in the title or the abstract	NA	NA	NA	NA	A	NA	NA	NA	13%
1b	Provide in the abstract an informative and balanced summary of what was done and what was found	A	A	A	A	A	A	A	A	100%
2	Explain the scientific background and rationale for the investigation being reported	A	A	A	A	A	A	A	A	100%
3	State specific objectives, including any prespecified hypotheses	A	A	A	A	A	A	A	A	100%
4	Present key elements of study design early in the article	A	NA	A	A	A	A	A	A	88%
5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	A	A	A	A	A	NA	PA	A	81%
6a	Give the eligibility criteria and the sources and methods of selection of participants; describe methods of follow-up	A	A	A	A	A	A	A	A	100%
6b	For matched studies, give matching criteria and number of exposed and unexposed	A	A	A	NA	A	A	A	NA	75%
7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers; give diagnostic criteria, if applicable	PA	NA	NA	NA	A	NA	NA	PA	25%
8	For each variable of interest, give sources of data and details of methods of assessment (measurement); describe comparability of assessment methods if there is more than 1 group	A	NA	A	A	NA	A	A	A	75%
9	Describe any efforts to address potential sources of bias	NA	NA	NA	A	NA	NA	NA	NA	13%
10	Explain how the study size was arrived at	NA	NA	NA	NA	A	NA	NA	NA	13%
11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	A	NA	A	NA	A	NA	A	A	63%
12a	Describe all statistical methods, including those used to control for confounding	A	NA	A	A	A	NA	A	A	75%
12b	Describe any methods used to examine subgroups and interactions	NA	NA	NA	NA	NA	NA	NA	NA	0%
12c	Explain how missing data were addressed	NA	NA	NA	NA	NA	NA	NA	NA	0%
12d	If applicable, explain how loss to follow-up was addressed	NA	NA	NA	NA	A	NA	NA	NA	13%
12e	Describe any sensitivity analyses	NA	NA	NA	NA	NA	NA	NA	NA	0%

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Table 3 – continued

No. Questions	Studies									Quantitative overall scores
	Tedders et al ¹⁸	Watling et al ³⁵	Karir et al ¹⁶	Jarman et al ¹⁷	Shehabi et al ³³	Tobias et al ⁴³	Anand et al ²¹	Grunau et al ³⁶		
13a	Report numbers of individuals at each stage of study, eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	NA	NA	NA	A	A	NA	A	NA	38%
13b	Give reasons for nonparticipation at each stage	NA	NA	NA	A	NA	NA	A	NA	25%
13c	Consider use of a flow diagram	NA	NA	NA	A	NA	NA	A	NA	25%
14a	Give characteristics of study participants (eg, demographic, clinical, and social) and information on exposures and potential confounders	A	A	A	A	A	A	A	NA	88%
14b	Indicate number of participants with missing data for each variable of interest	NA	NA	NA	NA	NA	NA	NA	NA	0%
14c	Summarize follow-up time (eg, average and total amount)	NA	NA	NA	NA	NA	NA	NA	NA	0%
15	Report numbers of outcome events or summary measures over time	A	A	A	A	A	NA	A	A	88%
16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval); make clear which confounders were adjusted for and why they were included	A	A	A	NA	A	NA	A	A	75%
16b	Report category boundaries when continuous variables were categorized	NA	NA	NA	NA	NA	NA	NA	NA	0%
16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	NA	NA	NA	NA	NA	NA	NA	0%
17	Report other analyses done, eg, analyses of subgroups and interactions, and sensitivity analyses	NA	NA	NA	NA	NA	NA	NA	NA	0%
18	Summarize key results with reference to study objectives	A	A	A	A	A	A	A	A	100%
19	Discuss limitations of the study, taking into account sources of potential bias or imprecision; discuss both direction and magnitude of any potential bias	A	NA	A	A	A	NA	A	A	75%
20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	A	A	A	A	A	A	A	A	100%
21	Discuss the generalizability (external validity) of the study results	NA	NA	NA	NA	NA	NA	NA	NA	0%

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Table 3 – continued

No. Questions	Studies									
	Tedders et al ¹⁸	Watling et al ³⁵	Karir et al ¹⁶	Jarman et al ¹⁷	Shehabi et al ³³	Tobias et al ⁴³	Anand et al ²¹	Grunau et al ³⁶	Quantitative overall scores	
22 Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA	NA	NA	NA	NA	NA	NA	NA	NA	0%

A indicates adequate (information was explicitly presented in the text); NA, not adequate (no information about the matter was available in the text); PA, partially adequate (information was not explicitly presented, but it was suggested); STROBE, STrengthening the Reporting of OBservational studies in Epidemiology.

studies exist. Our results on literature trends of methods and outcome measures will benefit future researchers by adding to their knowledge about the potential methods available for use and the justifications behind them, especially as they, together with decision makers, work to generate results that are comparable with existing results for better evidence generation. Results on the reporting quality and trends will be of practical value and motivation to journal editors and commentators in enhancing the quality of research and, hence, the quality assessment of the evidence generating research and to decision-making committees. In addition, although results on literature gaps will benefit researchers and decision makers as they look to enhance knowledge and practices in the area, identifying the methodological gaps and limitations in research will open the eyes of future researchers as they conduct research that better follows up and enhances previous research in the area. Clinical outcome measures in adult patient studies differed, together with the various types of scales used, including the RSS, the Richmond Agitation-Sedation Scale, the Addenbrooke Scale, and SAS. Here, the currently dated RSS, although not validated until 2000, was used in a study in 1993.^{45,46} Generally, however, the different scales have been validated for assessing agitation and sedation in critically ill patients and are highly correlated with each other.⁴⁷ Most of the studies in the review did not define the duration of sedation, which raises concerns about proper time management. Findings of studies performed with short-term follow-up, for example, cannot be applied to patients requiring more than 24 hours of sedation.⁴⁰ Most doses, but not all, were within therapeutic dose range. For example, Strom et al²⁵ reported doses given as a range, with an upper limit above 4 mg/kg/h propofol for more than 48 hours. This dose, however, was found to increase the risk of propofol infusion syndrome when not switched to alternatives.²⁵ The variability and lack of justification about such methods raise concerns about the validity and reliability of results and their interpretation.

Although the level of sedation was a more common outcome in neonates over adults, various studies also drew different conclusions about the same drugs. The PIPP and the Neonatal Infant Pain Scale that are used to assess sedation are specific for pain rather than agitation.^{31,42,44} The neonatal facial coding system and the postoperative comfort score were not defined in relation to targeted score levels, limiting the certainty of the standard measure use.⁴⁴

Among pediatric patients, each study used a different primary outcome, which included withdrawal symptoms and increased dosing.^{21,43}

To summarize briefly, the included study publications are characterized by some gaps and variations in endpoint measures and the methodological strategies used, and medications administered differently in different studies with similar

populations provide insufficient aggregate evidence to guide decision makers in other settings. To note, the identification of the heterogeneity in methodological trends, outcome measures, and interventions in populations does not imply that all studies should be unified in methods, which will enhance quality of evidence. This would actually be unrealistic and inconsistent with the legitimate versatility of local interests between different practices. The important point here, however, is that if future researchers and decision makers recognize specific inconsistencies about how methods are used and the extent of this, they will better reflect on their choices of study methods and the justification behind this, looking to enhance the comparability of generated results and, therefore, the quality of generated evidence.

Among all age groups, in most of the studies (n = 23), the intention-to-treat analysis in the RCTs was not reported, limiting the accurate interpretation of findings in clinical practices. In all populations, the stratification—essential in controlling for confounding factors to detect the relationships between the interventions and outcomes—was considered in only 5 studies: 3 in neonates, stratified on the basis of trial centers, birth weight, and gestational age,^{27,31,42} and 2 in adults, stratified on the basis of the severity of illness and the institution.^{14,41} Furthermore, most of the studies (n = 14) included patients with various identified underlying diseases that included respiratory disorders. In 11 studies, however, the underlying diseases were not explicitly identified. But given that these studies included all patients who received MV in the ICU, for which they were given sedation, it is safe to assume that they mostly included patients with respiratory disorders and, hence, were also included in the present review.

RCTs are optimal for achieving internal validity. Primarily because of the associated savings in time, effort, and expenses, when RCTs are infeasible because of ethical or resource availability, observational studies are a useful source of data. We were surprised by the limited number of economic evaluations in the studies. The pharmacoeconomics evaluation, now an integral type of research in practices, strengthens the multidimensional evidence in promoting the rational use of medications, but was included in less than a quarter of the reviewed studies.

Overall, the CONSORT and STROBE tools demonstrated that RCTs and observational studies did moderately to poorly in reporting several important items (Tables 2 and 3), mostly methods- and results-related, which, in addition to translating to limited identification of reliability, validity of interpretation, and generalizability to other settings, represent a weakness with regard to controlling for selection and confounding factors and channeling bias.

Table 4 – Quality assessment of the pharmacoeconomics evaluations on the basis of CHEERS reporting criteria.

Section/item	Study							Quantitative overall scores
	Carrasco et al ¹²	Al et al ²³	Barrientos-Vega et al ³⁰	Swart et al ²²	Barrientos-Vega et al ³⁹	Zhou et al ³²	Cox et al ²⁶	
Title/abstract/introduction								
Title	A	A	A	A	A	A	A	100%
Abstract	A	A	A	A	A	A	A	100%
Background/objectives	A	A	A	A	A	A	A	100%
Methods								
Population/subgroups	A	PA	A	A	A	A	A	93%
Setting/location	PA	A	PA	PA	PA	A	A	71%
Study perspective	A	A	A	A	A	A	A	100%
Comparators	A	A	A	A	A	A	A	100%
Time horizon	NA	A	NA	NA	NA	NA	A	29%
Choice of health outcomes	A	NA	A	A	A	A	A	86%
Measurement of effectiveness	A	A	A	A	A	A	A	100%
Estimating resources and costs	PA	PA	PA	PA	PA	A	A	64%
Currency, price date, and conversion	NA	A	PA	PA	PA	PA	A	57%
Choice of model	NA	A	A	NA	A	NA	A	57%
Assumptions	NA	A	NA	NA	A	NA	A	43%
Analytical model	NA	A	A	NA	A	NA	A	57%
Results								
Study parameters	A	A	A	A	A	A	A	100%
Incremental costs and outcomes	NA	NA	NA	NA	NA	NA	A	14%
Characterizing uncertainty	NA	A	NA	NA	NA	NA	A	29%
Characterizing heterogeneity	NA	A	NA	NA	NA	NA	A	29%
Discussion/others								
Study findings, limitations, generalizability, current knowledge	PA	PA	PA	PA	PA	PA	PA	50%
Source of funding	NA	NA	NA	NA	NA	NA	NA	0%
Conflicts of interest	NA	NA	NA	NA	NA	NA	NA	0%

A indicates adequate (information was explicitly presented in the text); CHEERS, Consolidated Health Economic Evaluation Reporting Standards; NA, not adequate (no information about the matter was available in the text); PA, partially adequate (information was not explicitly presented, but it was suggested).

The lack of proven treatments, where the utility of pharmacoeconomics becomes questionable unless there is an advantage because of reduced adverse events, accounts for the relatively limited pharmacoeconomics research. Four economic evaluations did not identify the respiratory disorder in the population receiving MV, none among neonates or pediatrics. The CHEERS checklist indicated that all the included pharmacoeconomics evaluations were poor in reporting quality (Table 4).

In economic evaluations, an understanding of the effect and cost of the intervention is simplified by modeling analysis. Only 1 study contained Markov modeling,²³ which is ideal for recurrent diseases, but not for the agitation because of MV. Outcomes, although variable in different studies, as discussed earlier, were mostly clinically relevant and short-term in nature—unsurprising because of the acute nature of the ICU setting. Except for a single study,³⁹ the included studies were evaluated from the perspective of the hospital, including the direct medical costs, which is anticipated and appropriate given that the nonhealth resource use and work productivity are minimally affected by sedatives used in the ICU setting. An issue needing discussion is the lack of clarity of costing methodology and components. Unclear descriptions of costs, methods, and components frustrate efforts to allow different settings to benefit from (and apply) results. For example, none of the studies differentiated hospital charges from costs; hospital charges are not ideal estimations of cost in the

hospital setting because the hospital uses them to compensate for the cost of other services in the setting. Only 2 studies reported the financial year of cost values,^{23,26} confounding efforts to judge the need for and appropriateness of time adjustment of cost. Cost terminologies were misused, and marginal or indirect cost was referred to as a secondary medical cost to be included under the hospital perspective.¹²

The sensitivity analysis, a cornerstone in any economic evaluation, was conducted in only 2 studies,^{23,26} which is unacceptable. Conducted sensitivity analyses, although limited in type, indicated study robustness; nevertheless, no justification for changes in variables was provided. Most of the studies conducted only 1-way sensitivity analyses, which, without multivariate analyses, and even if interpreted correctly, can underestimate uncertainty.⁴⁷

In addition, although studies included the analysis of adverse event costs, none modeled the discontinuations associated with adverse events, the impact of which is unclear in studies, and was also absent in the sensitivity analyses conducted.

On the basis of observations in the present study, we propose several general priority research and literature reporting recommendations.

- In studies of, especially, neonates and pediatrics, economic evaluations should more often be incorporated. The availability of relevant research experiences and better cost data, including

secondary costs of interventions, must be ensured in future work. Cost-effectiveness research, rather than cost and cost-consequence analyses, will best support economic evaluations.⁴⁸

- Identification and presentation of study details need improvement and should include sample size and power analysis, follow-up, generalizability, missing data, effect size, sensitivity analyses, cost and costing methods, and funding. Several quality assessment checklists, including CONSORT and Jadad for RCTs, STROBE and Good Research for Comparative Effectiveness for observational studies, Quality of Health Economic Studies and CHEERS for economic evaluations, and the National Institute of Health quality assessment tools for various study designs, are available to guide methods and their reporting.^{49–51}
- Future work should include head-to-head comparisons of morphine with fentanyl in subjects with respiratory disorders. Their current unavailability, and the differences in design, reporting, assumptions, definitions, and estimations, hinders the ability to make informed choices between the 2 medications.
- Adherence to methodological standards—following good practice guidelines for RCTs, observational studies, and economic evaluations—should be enhanced by increasing the use of power and sample size calculations in studies and using reliable outcome measures to evaluate sedation and justified tools for their assessment. Future research needs to account for the uncertainty associated with economic evaluations, by incorporating comprehensive sensitivity analyses in studies and including correlation effects of variables,⁴⁸ and to evaluate adverse events that result in discontinuation in isolation from those that do not.
- Long-term outcomes, especially in the neonatal and pediatric populations, should be incorporated more often. For example, only 1 study evaluated neurodevelopmental function as an outcome, which requires the availability of long-term data, including cost, and the use of analytical models adopting longer term horizons. Future research should map beyond-ICU effects and associations between intermediate and final outcomes.
- Finally, the narrow scope of most study questions limits the ability of decision makers to prioritize sedatives; studies have focused on drug performance-based 1 or 2 outcomes. Methods to better synthesize multidimensional evidence should be used in decision making, via, for example, multicriteria decision analysis.^{52,53}

Limitations in the review include the English-restricted search, possibly excluding relevant studies. Nevertheless, the authors did not have the resources to translate potentially relevant non-English literature. Moreover, despite the comprehensive search conducted via several search engines in the study, relevant studies were possibly missed because of unused additional search terms and/or combinations among them. In addition, all journals were weighted equally in this study, which could be associated with bias.

Conclusions

The heterogeneity of studies on the (very high) use of sedative regimens to manage mechanically ventilated patients with respiratory disorders disables the comparison of findings and, consequently, the construction of cumulative evidence regarding the most effective and cost-effective sedatives. On the basis of various endpoints, particularly in adults, morphine and fentanyl regimens achieved different outcomes in different studies. None of the similar comparisons relied on the same

type of scale. Rigorous data comparing morphine and fentanyl in subjects with respiratory disorders in adult, pediatric, and neonatal ICUs are lacking. The quality of reporting was moderate to poor in literature, mostly poor in the economic evaluations in particular. Poor reporting may jeopardize the assessment of risk of bias by decision makers when generating evidence.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.vhri.2018.11.001>.

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