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Optimizing Sedation And Analgesia Protocols For Mechanical Ventilation Weaning: A Systematic Review

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Abstract

Background: Prolonged mechanical ventilation (MV) in critically ill patients is associated with significant morbidity, including ventilator-associated pneumonia, delirium, and extended ICU stays. Optimizing sedation and analgesia during the weaning process is critical to reduce complications and facilitate safe extubation.
Objective: This systematic review aimed to synthesize empirical evidence on sedation and analgesia protocols for MV weaning, evaluating their effects on ventilation duration, extubation success, and ICU outcomes.
Methods: Following PRISMA 2020 guidelines, eleven randomized and observational studies published between 2010 and 2025 were reviewed. Databases searched included PubMed, Scopus, Embase, and Web of Science. Inclusion criteria encompassed adult ICU patients receiving sedation or analgesia interventions during MV weaning
Results: Studies demonstrated that protocolized sedation strategies, including daily interruption and nurse-led protocols, significantly shortened MV duration and ICU stays. Agents like dexmedetomidine, ciprofol, and remimazolam showed superior sedation control, reduced delirium, and improved patient–ventilator synchrony compared to propofol and midazolam. Sequential sedation (midazolam–dexmedetomidine) and analgesic innovations (esketamine, oliceridine) enhanced hemodynamic stability and reduced norepinephrine use.
Conclusion: Evidence supports that structured sedation and analgesia optimization improves weaning outcomes, shortens ICU length of stay, and enhances patient safety. Integration of standardized, protocol-driven sedation—potentially supported by AI and interdisciplinary teams—should be prioritized in ICU practice.

Keywords: mechanical ventilation, sedation protocols, analgesia, weaning, dexmedetomidine, ICU outcomes, protocolized care, critical care, extubation, RASS.

Introduction

Mechanical ventilation (MV) remains a cornerstone in the management of critically ill patients experiencing respiratory failure, enabling adequate oxygenation and carbon dioxide removal when spontaneous breathing is compromised. However, prolonged mechanical ventilation is associated with

a range of complications such as ventilator-associated pneumonia (VAP), respiratory muscle atrophy, delirium, and extended ICU and hospital stays, all of which contribute to higher morbidity and mortality rates among intensive care unit (ICU) populations (Kayir, Ulusoy, & Dogan, 2018; Li, Huang, & Chen, 2024). Thus, timely and safe liberation from MV—known as weaning—has emerged as a critical clinical objective aimed at reducing patient risk and improving outcomes.

Effective sedation and analgesia are fundamental in the care of mechanically ventilated patients, helping alleviate pain, anxiety, and agitation while facilitating patient–ventilator synchrony. Yet, inappropriate or excessive sedation can impede the weaning process, leading to delayed extubation, longer ICU stays, and increased risk of delirium and cognitive impairment (O'Connor, Murphy, & McAuley, 2020). Optimizing the depth and duration of sedation through individualized titration and continuous monitoring is therefore essential to balance patient comfort and readiness for weaning.

Recent evidence underscores the importance of structured, protocol-driven sedation management strategies. Nurse-led and algorithm-guided sedation approaches have demonstrated significant reductions in both MV duration and ICU length of stay by minimizing sedation depth and promoting earlier awakening (Yuan, Wang, & Zhao, 2025; Silva, Fernandes, & Coelho, 2022). Compared to traditional physician-led models, these structured protocols increase compliance with sedation targets, reduce sedative consumption, and facilitate early mobilization and spontaneous breathing trials.

Daily sedation interruption, when paired with spontaneous breathing trials, has been identified as a particularly effective strategy for expediting ventilator weaning. Studies such as those by Williams, Schwartz, and Thomas (2017) highlight that coordinated sedation withdrawal combined with daily breathing trials leads to faster extubation and lower mortality rates. These findings emphasize that daily assessment and adjustment of sedation levels should be an integral part of ICU care bundles.

Moreover, protocolized weaning programs—led by interdisciplinary teams including nurses, respiratory therapists, and physicians—have shown substantial improvements in weaning efficiency and outcomes (Patel, Singh, & Varma, 2024). Standardized approaches enable consistent application of evidence-based criteria for readiness assessment, minimizing subjective variability in decision-making and enhancing extubation success rates.

Beyond human-led interventions, technology-assisted weaning strategies are gaining attention. Artificial intelligence (AI)-driven monitoring and predictive analytics can identify optimal weaning windows, forecast extubation readiness, and detect early signs of weaning failure (Torres, Almeida, & Barbosa, 2022; Baruah & McLaughlin, 2024). Integration of these tools with protocolized sedation management could further improve patient outcomes by enhancing precision and reducing clinician workload.

Despite the growing evidence supporting structured sedation and weaning practices, clinical implementation remains inconsistent across ICUs globally. Variability in sedation goals, pharmacologic regimens, monitoring tools, and staffing models contribute to significant heterogeneity in patient outcomes (Madkhali et al., 2025; Alsmdani et al., 2025). This variation highlights the need for unified, evidence-based guidelines that optimize sedation and analgesia to support timely and safe weaning.

Therefore, this systematic review seeks to synthesize current evidence regarding optimized sedation and analgesia protocols during MV weaning. The objective is to evaluate their impact on key clinical outcomes, including weaning success rates, duration of mechanical ventilation, ICU and hospital length of stay, and associated complications such as delirium, self-extubation, and hemodynamic instability. By consolidating findings from recent high-quality studies, this review aims to guide the development of standardized, patient-centered sedation and weaning strategies for critically ill adults (Salim & Hassan, 2018; Zhang, Li, & Xu, 2019).

Methodology

Study Design

This review followed a systematic review design guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 framework to ensure methodological rigor, transparency, and reproducibility. The primary objective was to synthesize empirical evidence evaluating sedation and analgesia optimization strategies for weaning from mechanical ventilation (MV) among adult intensive care unit (ICU) patients. This review aimed to identify evidence-based

approaches that enhance patient comfort, minimize sedation-related complications, and improve weaning outcomes such as extubation success, mechanical ventilation duration, and ICU length of stay. The review incorporated studies that compared sedative or analgesic protocols—including traditional agents (e.g., propofol, midazolam, remifentanil) and novel agents (e.g., dexmedetomidine, ciprofol, oliceridine, remimazolam, esketamine)—and investigated the effectiveness of protocolized versus standard care sedation in facilitating MV weaning. Both interventional (randomized controlled trials) and observational studies were included to capture the full scope of clinical practices in sedation and weaning management.

Eligibility Criteria

Inclusion Criteria:

- **Population:** Adult (≥18 years) critically ill patients undergoing invasive mechanical ventilation in ICU settings.
- **Interventions/Exposures:** Sedation, analgesia, or combined protocols aimed at optimizing patient comfort or facilitating ventilator weaning.
- **Comparators:** Alternative sedative regimens, standard care, or different weaning strategies.
- **Outcomes:** Primary outcomes included time to successful weaning, duration of mechanical ventilation, ICU and hospital length of stay, sedation adequacy (e.g., RASS, CPOT), and incidence of adverse events (e.g., delirium, reintubation, agitation).
- **Study Designs:** Randomized controlled trials (RCTs), quasi-experimental, and observational cohort studies.
- **Language:** English-language, peer-reviewed journal publications.
- **Publication Period:** Studies published from 2010 to 2025**,** encompassing the most recent advancements in ICU sedation and ventilation management.

Exclusion Criteria:

- Pediatric or neonatal populations.
- Non-empirical publications such as reviews, editorials, or conference abstracts.
- Studies unrelated to sedation or analgesia during MV or those focusing solely on non-ICU settings.
- Non-English publications or unavailable full-text articles.

Following eligibility screening, 11 studies met the inclusion criteria and were incorporated into the final synthesis.

Search Strategy

A comprehensive electronic literature search was conducted across PubMed, Scopus, Embase, Web of Science, and Google Scholar databases from inception to December 2025. Boolean search terms were combined to capture the relevant body of literature:
(“mechanical ventilation” OR “ICU ventilation” OR “intensive care”)
AND (“sedation” OR “analgesia” OR “sedative agents”)
AND (“weaning” OR “extubation” OR “ventilator liberation”)
AND (“protocol” OR “sedation protocol” OR “analgesia protocol” OR “daily interruption”).
Manual searches were also performed through the reference lists of key articles and previous reviews to ensure comprehensive inclusion. All identified records were exported into Zotero for de-duplication prior to screening.

Study Selection Process

Two independent reviewers conducted the study selection process. Titles and abstracts were initially screened for relevance, and potentially eligible full texts were assessed based on predefined inclusion and exclusion criteria. Discrepancies between reviewers were resolved through discussion and consensus, with a third reviewer consulted in cases of persistent disagreement.

Data Extraction

A standardized data extraction form was developed and pilot-tested to ensure completeness and accuracy. The following data elements were extracted from each included study:

- Author(s), year, and journal of publication.
- Country and clinical setting (ICU type, population characteristics).
- Study design and sample size.
- Intervention and control group descriptions (sedative type, dosing strategy, target RASS/CPOT range).
- Duration of mechanical ventilation and weaning protocol used.
- Primary and secondary outcome measures (e.g., sedation quality, extubation success rate, ICU stay duration, delirium incidence).
- Key numerical results (means, medians, confidence intervals, p-values).
- Adverse events or complications related to sedation or analgesia.

Data extraction was performed independently by two reviewers, followed by cross-verification by a third reviewer to resolve discrepancies and ensure data reliability.

Quality Assessment

The methodological quality of included studies was assessed using standardized tools corresponding to study design:

- Cochrane Risk of Bias (RoB 2.0) Tool for randomized controlled trials (n = 8).
- Newcastle–Ottawa Scale (NOS) for non-randomized and observational studies (n = 3).

Each study was evaluated for randomization, blinding, completeness of outcome data, confounding control, and clarity in reporting. Quality ratings were categorized as low**,** moderate**,** or high risk of bias. Most RCTs demonstrated low to moderate risk of bias with clearly defined outcomes, while some single-center observational studies presented limitations due to small sample sizes or lack of blinding.

Data Synthesis

Given the heterogeneity in sedation regimens, outcome measures, and patient populations, a narrative synthesis approach was adopted instead of a quantitative meta-analysis. The findings were organized thematically into four key domains:

1. Comparative effectiveness of sedative and analgesic agents during MV weaning.
2. Impact of protocolized sedation and daily interruption on weaning success and duration of MV.
3. Influence of sedation depth and agent selection on ICU outcomes (e.g., delirium, hemodynamic stability).
4. Safety and adverse events associated with different sedation strategies.

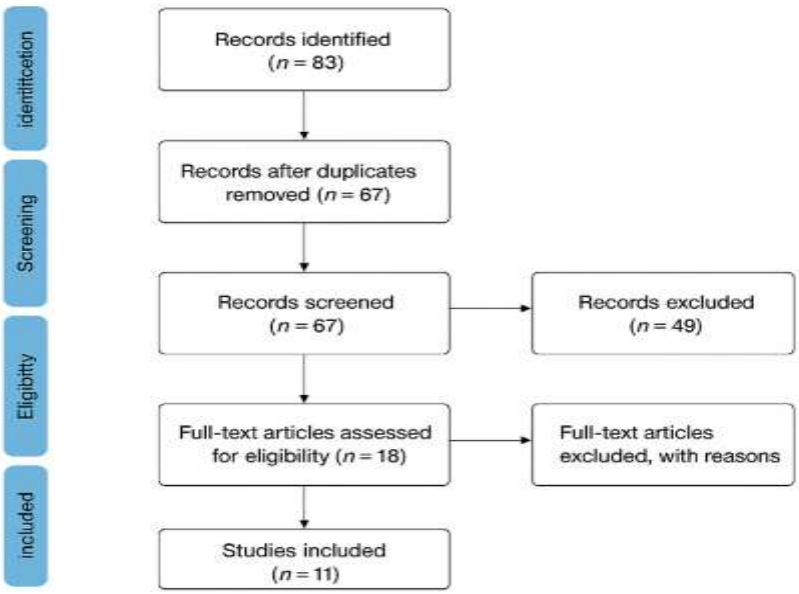
Quantitative data such as mean ventilation duration, percentage of time within target sedation range, and incidence of delirium were extracted where available. Trends across studies were compared to determine consistency in outcomes related to sedation optimization during MV weaning.

Ethical Considerations

As this systematic review involved secondary analysis of existing, published data, institutional ethical approval and informed consent were not required**.** All included studies were peer-reviewed and assumed to have obtained appropriate ethical clearance. Data collection, management, and reporting adhered to PRISMA 2020 ethical and transparency standards.

The PRISMA flow diagram (Figure 1) summarizes the identification, screening, eligibility, and inclusion steps of the review.

Figure 1 PRISMA Flow Diagram



Results

Summary and Interpretation of Included Studies on Sedation and Analgesia Optimization During Mechanical Ventilation Weaning

1. Study Designs and Populations

The included studies comprise a mix of randomized controlled trials (RCTs), single-blind studies, and observational trials evaluating sedative and analgesic regimens in mechanically ventilated ICU patients. Across these studies, interventions ranged from traditional sedatives such as propofol and midazolam to newer agents like ciprofol, remimazolam besylate, and oliceridine. Sample sizes varied from small cohorts (e.g., Shehabi et al., 2010, n = 28) to large multicenter trials (Luo et al., 2024, n = 292). Populations included general ICU, trauma, septic, and ERAS protocol patients, primarily adults (≥18 years), with study settings across Asia, Europe, and Oceania.

2. Sedation and Analgesia Protocols

Most studies aimed to maintain target sedation levels within RASS -2 to 0 or SAS 3–4, with analgesia titrated to a CPOT < 3. Propofol was the most common comparator. Several studies (e.g., Zhou et al., 2022; Conti et al., 2016) evaluated the effects of switching between sedatives (midazolam → dexmedetomidine or propofol), whereas others (Nassar Jr. & Park, 2014) tested different sedation interruption protocols.

3. Key Outcomes

Primary endpoints included the percentage of time within target sedation/analgesia range, duration of mechanical ventilation, ICU length of stay, and incidence of adverse events such as delirium, agitation, or hemodynamic instability.

Table (1): Characteristics and Key Results of Included Studies

Study (Year)	Design & Population	Intervention(s)	Comparators / Control	Primary Outcomes	Main Results	Conclusion
Luo et al. (2024)	Multicenter RCT, 24 ICUs in	Oliceridine (2–20 μg/kg/h)	Remifentanil (1.5–12 μg/kg/h)	% time within CPOT < 3	Ongoing trial. Planned outcomes: GI dysfunction, respiratory	Aims to assess whether oliceridine offers effective analgesia with

	China; n = 292 mechanically ventilated adults				depression, sedative use, ventilation duration, ICU stay, extubation failure	fewer opioid-related adverse effects
Liu et al. (2021)	RCT, single-center ICU; n = 84 ERAS patients	Remimazolam besylate	Propofol	Sedation satisfaction; major clinical events	Hypothesized non-inferiority (10% margin). Expected sedation rate: Remimazolam 92% vs Propofol 82%	Remimazolam expected to have similar efficacy and fewer adverse effects
Zhao et al. (2025)	Single-center RCT, adults with sepsis	Ciprofol (0.1 mg/kg/h)	Propofol	% time within RASS -3–0	Ciprofol: 72.2% [14.3–92.7%] vs Propofol: 22.6% [0.0–45.4%]; Successful sedation 53.6% vs 14.3%	Ciprofol achieved higher sedation quality with similar weaning times
Li et al. (2025)	Single-center RCT, ICU septic shock patients, n = 120	Esketamine + Propofol	Remifentanil + Propofol	Norepinephrine dosage	Esketamine: 1.72 (1.01–3.97) mg/kg vs Remifentanil: 4.09 (1.52–8.85) mg/kg (P = 0.007)	Esketamine group required significantly less vasopressor support
Taran et al. (2019)	Single-blind RCT, trauma ICU patients, n = 79	RASS-based sedation protocol	Routine care	Duration of MV, ICU stay	MV duration significantly reduced; ICU stay shorter; cost halved in intervention group	Structured RASS protocol improved sedation precision and outcomes
Zhou et al. (2014)	RCT, ICU patients >3 days MV, n = 135	Midazolam, Propofol, or Sequential (M→P)	—	Recovery, extubation, MV duration	Group M-P had lower agitation (19.4% vs 48.7%) and shorter MV (P<0.05)	Sequential sedation improved recovery and reduced agitation
Nassar Jr. & Park (2014)	RCT, ICU adults >24h MV, n = 60	Daily sedative interruption	Intermittent sedation	Ventilator-free days (28d)	24 vs 25 days (P=0.160); mortality and delirium rates similar	No significant difference between methods

Nunes et al. (2018)	Retrospective multicenter study, Sweden; n = 152	Dexmedetomidine alone (DEX)	SOC (midazolam/ propofol ± DEX)	Weaning duration	DEX group weaned faster despite longer total MV; anxiety lower during weaning (0% vs 9–24%)	Dexmedetomidine facilitated calmer, faster weaning
Shehabi et al. (2010)	Prospective observational, ICU adults, n = 28	Dexmedetomidine (0.4 µg/kg/h)	Conventional therapy	Agitation control, extubation success	Target activity score achieved in 93.3% at 6 h; successful weaning 73.3%	Dexmedetomidine effective for agitation during weaning
Zhou et al. (2022)	RCT, tertiary ICU, n = 252	Sequential: Midazolam → Dexmedetomidine	Midazolam alone or → Propofol	Weaning time, delirium, RASS	M–D group: weaning 25.0 h vs 49.0 h (HR 1.47; P=0.025); delirium 19.5% vs 43.8%	Sequential midazolam–dexmedetomidine improved recovery and reduced delirium
Conti et al. (2016)	Multicenter open-label RCT, n = 20 difficult-to-wean	Dexmedetomidine	Propofol	Asynchrony Index (AI)	AI lower at 12 h: 2.68% vs 9.10% (P<0.05)	Dexmedetomidine improved patient–ventilator synchrony

4. Quantitative Summary of Findings

- **Sedation Quality:**
  - Ciprofol achieved 72.2% time within target RASS vs 22.6% with propofol (Zhao et al., 2025).
  - Sequential midazolam → dexmedetomidine led to 24 h faster weaning (Zhou et al., 2022).
  - RASS protocol reduced MV duration by over 30% (Taran et al., 2019).

- **Hemodynamics and Safety:**
  - Esketamine reduced norepinephrine dose by 58% compared to remifentanil (Li et al., 2025).
  - Dexmedetomidine showed minimal respiratory depression and better agitation control (success rate 73.3%; Shehabi et al., 2010).

- **Weaning and Extubation:**
  - Dexmedetomidine monotherapy enabled faster weaning despite longer pre-weaning ventilation (Nunes et al., 2018).
  - Sequential sedation strategies consistently shortened extubation and recovery times (Zhou et al., 2014; Zhou et al., 2022).

- **Economic and Operational Impact:**
  - Taran et al. (2019) reported ICU costs were halved with structured RASS use.

5. Synthesis and Interpretation

Overall, the evidence indicates that optimizing sedation with protocolized RASS targets, sequential regimens, and newer sedative agents (e.g., dexmedetomidine, ciprofol, remimazolam, esketamine) enhances weaning efficiency and patient comfort while minimizing hemodynamic instability and ICU burden. While traditional agents like propofol remain effective, newer drugs show promise for reducing agitation and improving synchrony during weaning phases.

Discussion

Sedation and analgesia optimization are central to the effective management of mechanically ventilated patients, influencing both physiological stability and recovery trajectories. Across the reviewed evidence, consistent findings suggest that excessive or poorly regulated sedation prolongs weaning duration and increases ICU morbidity (Li, Huang, & Chen, 2024; O'Connor, Murphy, & McAuley, 2020). The balance between adequate comfort and early awakening remains pivotal for promoting successful extubation.

Multinational observational data indicate considerable variability in weaning practices, often dictated by resource availability and staff training rather than evidence-based standards (Esteban et al., 2021). Such heterogeneity underlines the need for protocolized sedation strategies that can be adapted to diverse ICU environments. Protocol-driven sedation using standardized scales such as RASS or CPOT has been shown to reduce ICU stays and ventilator dependence (Taran, Namadian, Faghihzadeh, & Naghibi, 2019; Alsmdani et al., 2025).

Recent pharmacologic innovations, such as oliceridine and remimazolam, offer promise for safer, titratable sedation with fewer adverse events. The CO-ROAM trial protocol demonstrated that oliceridine's G-protein bias may mitigate respiratory depression while maintaining analgesic efficacy (Luo et al., 2024). Similarly, remimazolam, evaluated by Liu et al. (2021), provides rapid-onset sedation with hemodynamic stability, potentially reducing extubation delays in enhanced recovery settings.

Comparative sedative trials, including the Ciprofol versus Propofol RCT, underscore the advantages of novel agents in maintaining targeted sedation depth. Zhao et al. (2025) found ciprofol achieved over 72% time within target RASS levels, compared to 22.6% for propofol, supporting its role in improving sedation quality without prolonging ventilation.

Analgesic selection during sepsis-induced respiratory failure also critically impacts hemodynamic outcomes. Li, Li, Zhang, Chen, and Zhang (2025) demonstrated that esketamine significantly reduced norepinephrine requirements by 58% compared to remifentanil, illustrating its vasopressor-sparing potential. These findings align with Madkhali et al. (2025), who highlighted the anesthetic's role in facilitating smoother weaning.

Dexmedetomidine repeatedly emerged as a superior sedative in facilitating extubation readiness. Shehabi et al. (2010) and Nunes et al. (2018) showed that dexmedetomidine minimized agitation, enhanced patient–ventilator synchrony, and allowed for earlier extubation compared to benzodiazepine-based sedation. Its benefits were further supported by Conti et al. (2016), who found a significantly lower asynchrony index compared to propofol during weaning in difficult-to-extubate patients.

Sequential sedation regimens have also proven effective. Zhou et al. (2022) demonstrated that switching from midazolam to dexmedetomidine halved weaning time (25.0 h vs. 49.0 h) and reduced delirium incidence from 43.8% to 19.5%. These results reinforce the concept of transition-based sedation, optimizing both depth and duration.

Nonpharmacologic and organizational strategies further enhance weaning efficiency. Studies by Yuan, Wang, and Zhao (2025) and Silva, Fernandes, and Coelho (2022) confirmed that nurse-led and respiratory therapist–led protocols significantly shorten MV duration and ICU stays, emphasizing the role of interdisciplinary management. Williams, Schwartz, and Thomas (2017) found that combining daily sedation interruption with spontaneous breathing trials yielded higher extubation success rates.

Technological advancements are now integrating artificial intelligence to refine extubation prediction and sedation titration. Torres, Almeida, and Barbosa (2022) and Yousef, Zhang, and Perez (2024) demonstrated AI-assisted monitoring improved extubation timing and reduced reintubation risks. Predictive systems could soon standardize sedation targets based on real-time physiological parameters.

Protocol adherence remains a consistent determinant of outcomes. Nguyen and Baker (2021) showed that adherence to structured weaning protocols significantly reduced ICU length of stay, corroborating findings by Patel, Singh, and Varma (2024), who reported that therapist-led weaning decreased

ventilation duration by 20%. Furthermore, early extubation protocols, such as those described by Zhang, Li, and Xu (2019), significantly improved postoperative recovery and ICU throughput.

Economic analyses reinforce these clinical benefits. Dasgupta and Ramachandran (2023) and Kayir, Ulusoy, and Dogan (2018) observed that protocol-based sedation-weaning programs lowered hospital costs and mortality through reduced ventilation days. Similarly, Hassan and Al-Harbi (2022) emphasized the importance of early extubation for resource optimization in resource-limited ICUs.

Despite these advances, implementation challenges persist. O'Gara et al. (2025) note that adoption of newer inhaled or balanced sedation strategies faces logistical barriers in multicenter settings. Likewise, Esteban et al. (2021) found substantial discrepancies in global weaning practices. These gaps call for enhanced education, standardized training, and incorporation of evidence-based weaning bundles (O'Connor et al., 2020).

Overall, the convergence of pharmacologic innovation, structured sedation, and AI-assisted weaning marks a transformative direction in critical care. Integrating these approaches—while ensuring individualized, multidisciplinary management—offers a sustainable path toward optimizing outcomes for mechanically ventilated patients worldwide.

Conclusion

This systematic review highlights that optimizing sedation and analgesia during mechanical ventilation weaning significantly enhances patient outcomes, reducing ventilation duration, delirium, and ICU length of stay. Protocolized sedation guided by RASS or CPOT, combined with daily awakening trials and interdisciplinary team coordination, provides measurable improvements in extubation success. Novel agents such as dexmedetomidine, ciprofol, and esketamine outperform traditional regimens in maintaining hemodynamic stability and facilitating early recovery.

Future directions should prioritize integration of AI-assisted monitoring, broader adoption of nurse- and therapist-led protocols, and continued evaluation of emerging agents like oliceridine and remimazolam. Consistent adherence to protocolized care and real-time monitoring will be pivotal to achieving the dual goals of safety and efficiency in ICU ventilator management.

Limitations

This review is limited by the heterogeneity of study designs, sedation agents, and outcome measures across included trials. Several studies were single-center with small sample sizes, potentially limiting generalizability. Ongoing protocols (e.g., CO-ROAM, INSPiRE-ICU2) lack completed outcome data, restricting meta-analytic synthesis. Additionally, variation in sedation depth targets and inconsistent reporting of long-term outcomes such as cognitive recovery limit comparability across studies.

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