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Research Article

Evaluation of Sedation Strategies in Mechanically Ventilated Patients

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ABSTRACT
Background: Sedation is given to most patients who receive invasive mechanical ventilation, to relieve distress, facilitate ventilator synchrony and ensure safety. However, the depth, duration and choice of sedative influence the duration of ventilation, the risk of delirium and the long-term outcome of survivors, and practice has moved considerably over the last two decades from deep, continuous sedation towards lighter and more targeted strategies.
Objective: To evaluate and compare the principal sedation strategies used in mechanically ventilated adults, namely deep versus light sedation, continuous versus interrupted or protocolised sedation, minimal or no sedation, and benzodiazepine-based versus non-benzodiazepine-based regimens.
Methods: A structured narrative review of randomized trials, systematic reviews, cohort studies and clinical practice guidelines was conducted, and the findings were organised within a five-domain framework covering ventilation outcomes, delirium and cognition, haemodynamic and adverse effects, long-term outcomes, and feasibility. No new patient data were collected.
Results and Discussion: Lighter sedation, daily awakening paired with spontaneous breathing trials, and nurse-led protocols are associated with shorter ventilation and better outcomes than deep continuous sedation. Minimal-sedation strategies are feasible in well-staffed units but are accompanied by more agitation and have not been shown to improve mortality. Propofol and dexmedetomidine are preferred to benzodiazepines in most patients, although large trials show little difference in mortality between dexmedetomidine and usual care. A stepwise, analgesia-first framework is proposed. **Conclusion:** Sedation should be treated as a titrated and regularly reassessed therapy with an explicit target, rather than as a default accompaniment to ventilation. Light sedation, non-benzodiazepine agents and a daily structured review represent the best-supported approach, while research is needed on resource-limited settings and on patients requiring deep sedation.

Keywords: Sedation, Mechanical Ventilation, Critical Care, Dexmedetomidine, Propofol, Delirium, Light Sedation.

INTRODUCTION

Invasive mechanical ventilation is among the most common life-supporting interventions in intensive care units (ICUs), and the great majority of ventilated patients receive sedative and analgesic drugs. The traditional rationale for sedation is compelling: an endotracheal tube, positive pressure ventilation, suctioning, immobility and the underlying illness are uncomfortable and frightening, and sedation relieves anxiety, reduces oxygen consumption, improves synchrony between patient and ventilator and protects against accidental removal of lines and tubes. For many years the prevailing philosophy was to keep patients deeply sedated and, in some cases, pharmacologically paralysed, on the assumption that a calm, unresponsive patient was a safe patient.

This philosophy has been progressively challenged. Sedatives are not benign drugs. Continuous infusions accumulate, particularly in patients with hepatic or renal dysfunction, and prolong the time to awakening and to

extubation. Deep sedation makes neurological assessment and delirium detection difficult, suppresses respiratory drive and delays mobilisation. Observational studies have linked early deep sedation to longer ventilation and higher long-term mortality [1], and benzodiazepines in particular have been associated with delirium and prolonged cognitive impairment [2]. At the same time, inadequate sedation and analgesia are harmful in their own right, leading to agitation, self-extubation, ventilator dyssynchrony and the distressing memories that contribute to post-intensive care syndrome. The clinical problem is therefore not whether to sedate, but how deeply, with which agent, for how long, and with what systematic process for review.

A series of trials and consensus guidelines has reshaped practice. Daily interruption of sedative infusions [3], protocols that pair sedation interruption with spontaneous breathing trials [4], nurse-implemented targeted sedation [5], light or no sedation [6], [7], and the preferential use of propofol or dexmedetomidine over benzodiazepines [8] have all been proposed as improvements over deep continuous sedation. These strategies overlap, they were tested in different populations and settings, and their results are not always concordant. A clinician choosing a sedation strategy for a ventilated patient is therefore faced with a body of evidence that is rich but fragmented.

The aim of this article is to provide a comparative evaluation of sedation strategies in mechanically ventilated adults. The specific objectives are: (i) to describe the sedative agents and strategies in current use; (ii) to compare light with deep sedation, interrupted with continuous sedation, minimal-sedation protocols with conventional care, and benzodiazepine-based with non-benzodiazepine regimens across clinically relevant outcomes; (iii) to discuss delirium, long-term outcomes and special populations; and (iv) to propose a practical framework for decision-making. Section 2 reviews related work, Section 3 describes the methodology, Section 4 presents and discusses the results, and Section 5 concludes.

RELATED WORK

Clinical Practice Guidelines

Guidelines have been the main vehicle through which the evidence on sedation has been translated into practice. The 2013 guidelines for the management of pain, agitation and delirium in adult ICU patients recommended that sedation be titrated to defined targets and that light sedation be preferred [9]. They were superseded in 2018 by the guidelines for the prevention and management of pain, agitation or sedation, delirium, immobility and sleep disruption, which suggest the use of light rather than deep sedation in critically ill ventilated adults, and suggest the use of propofol or dexmedetomidine rather than benzodiazepines, while acknowledging that the certainty of the supporting evidence is low [8]. Complementary clinical reviews have summarised the pharmacology of the commonly used agents and the practical application of sedation protocols [10]. These documents agree on the principle of an analgesia-first approach, in which pain is assessed and treated before sedatives are added, and on the need to monitor depth of sedation and delirium with validated tools.

Assessment Tools

Systematic sedation requires reliable measurement. The Richmond Agitation–Sedation Scale (RASS) is a ten-point scale ranging from unrousable to combative that has been validated in adult ICU patients and is now widely used to set and document sedation targets [11]. The Confusion Assessment Method for the ICU (CAM-ICU) provides a validated approach to identifying delirium in ventilated patients who cannot speak [12]. These tools are the common language of the trials discussed in this article and the basis of most sedation protocols.

Interruption, Protocols and Bundles

Kress and colleagues showed in a randomized trial of 128 patients that daily interruption of continuous sedative infusions shortened the duration of mechanical ventilation and ICU stay [3]. The Awakening and Breathing Controlled trial subsequently demonstrated that pairing daily sedation interruption with a spontaneous breathing trial improved ventilator-free days and one-year survival compared with a spontaneous breathing trial alone [4]. A nursing-implemented sedation protocol with intermittent dosing was earlier shown to shorten ventilation [5]. The picture was complicated by a later multicentre trial in units that already used protocolised sedation, in which adding daily interruption did not shorten ventilation [13]. More recently, implementation of the ABCDEF bundle, which combines pain assessment, awakening and breathing trials,

appropriate choice of sedation, delirium monitoring, early mobility and family engagement, has been associated with better survival and more days free of delirium and coma in a large multicentre cohort [14].

Minimal-Sedation Strategies

At the lighter end of the spectrum, a single-centre randomized trial from Denmark found that a protocol of no sedation, with bolus morphine for analgesia, increased the number of ventilator-free days compared with sedation with daily interruption [6]. A light-versus-deep sedation trial reported that lighter sedation did not worsen psychological outcomes after critical illness [15]. The multicentre NONSEDA trial subsequently compared nonsedation with light sedation and found no significant difference in mortality, while agitation was more common in the nonsedation group [7].

Choice of Agent

Comparisons between sedative drugs have produced a large literature. Dexmedetomidine, an alpha-2 agonist, was compared with lorazepam [2] and with midazolam [16], and in two trials against midazolam or propofol during prolonged ventilation [17]. Large trials have since tested dexmedetomidine as the primary early sedative [18] and against propofol in sepsis [19]. Meta-analytic and cohort evidence has compared benzodiazepine-based and non-benzodiazepine-based regimens [20], [21].

Research Gap

Although each of these strands is well represented in the literature, the strategies are usually analysed in isolation. Clinicians, however, make a combination of decisions at the bedside: the target depth, the agent, whether to interrupt, and how to monitor. In addition, much of the evidence originates from well-resourced units in high-income countries, and its applicability to settings with lower nurse-to-patient ratios, limited drug availability and limited monitoring is uncertain. This article addresses these gaps by evaluating the major strategies within a single framework and by proposing a stepwise approach.

METHODOLOGY

Study Design

This work is a structured narrative review with a comparative synthesis. A narrative design was selected, rather than a quantitative meta-analysis, because the available studies differ markedly in patient population, in the definition and measurement of sedation depth, in the agents and doses used, in the background level of nursing and protocolisation and in the outcomes reported. Several relevant sources are guidelines and observational cohorts that cannot be pooled numerically. No patient data were collected and no interventions were performed. Effect estimates quoted in this article are those reported by the original authors.

Information Sources and Search Approach

The literature was explored through PubMed/MEDLINE, Embase and the Cochrane Library, supplemented by Google Scholar and by hand-searching the reference lists of key trials, reviews and guidelines. The search combined terms for the population (mechanical ventilation, mechanically ventilated adults, intensive care, critical illness) with terms for the intervention (sedation, deep sedation, light sedation, no sedation, daily interruption, sedation protocol, propofol, dexmedetomidine, midazolam, lorazepam, benzodiazepine, analgesia-first) and for the outcomes (duration of ventilation, ventilator-free days, delirium, mortality, post-intensive care syndrome). Searches were limited to publications in English.

Eligibility Criteria

Randomized controlled trials, systematic reviews and meta-analyses, large prospective or retrospective cohort studies and professional society guidelines were eligible if they involved adults receiving invasive mechanical ventilation in an ICU and compared two or more sedation strategies, or described a sedation strategy together with clinical outcomes. Studies restricted to paediatric or neonatal patients, to procedural sedation outside the ICU, to non-invasive ventilation only, or to palliative sedation at the end of life were excluded, as were case reports and abstracts without full text. Where several reports described the same trial, the primary report was used.

Comparison Framework and Data Extraction

A five-domain framework was defined to allow strategies of different design to be compared on a common footing. The first domain, ventilation outcomes, covers the duration of mechanical ventilation, ventilator-free days, time to extubation and length of ICU stay. The second, delirium and cognition, covers the occurrence and duration of delirium and coma and the cognitive consequences of critical illness. The third, haemodynamic and adverse

effects, covers bradycardia, hypotension, agitation, self-extubation and other drug-related events. The fourth, long-term outcomes, covers mortality and psychological and functional outcomes after discharge. The fifth, feasibility, covers the staffing, monitoring, drug availability and training needed for safe implementation. For each eligible source, the population, intervention, comparator, principal outcomes and reported effect estimates were extracted into a structured table by one author and verified by a second.

Appraisal and Synthesis

Trials were appraised narratively for the adequacy of randomization and allocation concealment, the possibility of blinding, which is generally limited for strategy trials, the completeness of follow-up and the precision of estimates. Findings were synthesised descriptively within each domain and the strength of conclusions was graded as strong, moderate or limited according to the consistency of the results, the number of participants and the directness of the evidence to the question. Disagreements were resolved by discussion.

Ethical Considerations

As the review analysed only published literature and involved no human participants, institutional ethical committee approval and individual informed consent were not required.

RESULTS AND DISCUSSION

Principal Sedative and Analgesic Agents

Five groups of drugs are used for sedation and analgesia in ventilated patients: opioids, propofol, dexmedetomidine, benzodiazepines (principally midazolam and lorazepam) and, in selected circumstances, other agents such as ketamine and volatile anaesthetics. Their characteristics are summarised in Table 1.

Table 1. Principal Agents Used for Analgesia and Sedation in Mechanically Ventilated Adults.

Agent	Principal Role	Advantages	Limitations
Opioids (E.G. Fentanyl, Morphine)	Analgesia; Basis Of Analgesia-First Care; Mild Sedation	Treat Pain, A Frequent Cause Of Agitation; Titratable; Allow Lighter Use Of Sedatives	Respiratory Depression, Ileus, Tolerance; Accumulation Of Some Agents In Organ Dysfunction
Propofol	Sedation Of Intubated Patients	Rapid Onset And Offset; Easy To Lighten; Preferred Over Benzodiazepines In Guidelines	Dose-Related Hypotension; Hypertriglyceridaemia; Rare Propofol Infusion Syndrome; Lipid Load
Dexmedetomidine	Light Sedation; May Be Used In Patients Who Need To Cooperate	Patients Are Easily Roused; Little Respiratory Depression; Lower Delirium Than Benzodiazepines In Trials	Bradycardia And Hypotension; Cost And Availability; Supplementary Sedatives Often Needed
Benzodiazepines (Midazolam, Lorazepam)	Sedation Where Other Agents Are Unsuitable; Alcohol Withdrawal; Seizures	Inexpensive; Widely Available; Anxiolytic And Anticonvulsant	Accumulation And Delayed Awakening; Associated With Delirium; Avoided As First-Line Agents
Other Agents (Ketamine, Volatile Anaesthetics)	Adjuncts Or Alternatives In Selected Patients	May Reduce Opioid Or Sedative Requirement; Useful When Deep Sedation Is Difficult	Limited Evidence In Ventilated Adults; Specific Equipment Or Adverse Effects

Three Features Of Table 1 Shape The Choice Of Strategy. First, Analgesia And Sedation Are Not Interchangeable: An Opioid Addresses Pain And Also Provides Some Sedation, And Its Use As The First-Line Agent Underpins Analgesia-First Approaches [9], [8]. Second, The Pharmacokinetic Profile Determines How Easily Sedation Can Be Lightened. Propofol And Dexmedetomidine Have Short Context-Sensitive Half-Times, Whereas Midazolam And Lorazepam Accumulate, Particularly In Organ Dysfunction, So That Continuous Benzodiazepine Infusions Are More Likely To Prolong Awakening [10]. Third, Each Agent Has A Characteristic Adverse-Effect Profile. Propofol Causes Dose-Dependent Hypotension And, Rarely, Propofol Infusion Syndrome And Hypertriglyceridaemia; Dexmedetomidine Causes Bradycardia And

Hypotension; And Benzodiazepines Are Associated With Delirium [2].

The Analgesia-First Principle Deserves Emphasis Because Pain Is A Frequent And Under-Recognised Cause Of Agitation In Ventilated Patients. Endotracheal Suctioning, Turning, Wound Care And The Presence Of Drains And Lines Are All Painful, And The Behavioural Cues Of Pain May Be Misread As Agitation Or Anxiety, Leading To The Reflex Administration Of A Sedative That Does Not Address The Cause. Validated Behavioural Pain Tools, Applied Regularly, Allow Clinicians To Distinguish Pain From Other Sources Of Distress, And The Guidelines Recommend That Analgesics Be Optimised Before Sedatives Are Added [8]. In Practice This Means That Many Patients Can Be Managed With An Opioid Alone Or With A Small Dose Of A Short-Acting Sedative, With The Sedative Reserved For Those Who Remain Agitated Or Anxious Despite Adequate Analgesia. Ketamine And Inhaled Anaesthetics Have Attracted Interest As Adjuncts Or Alternatives, Particularly Where Opioid Requirements Are High Or Deep Sedation Is Difficult To Achieve, But The Evidence For Their Routine Use In Ventilated Adults Is Much More Limited Than For The Agents Above And They Are Not Considered Further As Primary Strategies Here.

Depth Of Sedation: Deep, Light And Minimal

The Depth Of Sedation Has Emerged As One Of The Most Important Determinants Of Outcome. In A Prospective Cohort Of Ventilated Patients, Deeper Sedation In The First 48 Hours Was An Independent Predictor Of Delayed Extubation And Of Higher Mortality At 180 Days, Even After Adjustment For Severity Of Illness [1]. Observational Data Cannot Establish Causation, Since Sicker Patients Are Sedated More Deeply, But The Finding Has Been Consistent With The Trial Evidence. In A Randomized Comparison, Light Sedation Did Not Worsen The Psychological Outcomes Of Survivors, Which Addressed An Early Concern That Awake Patients Might Suffer More Distressing Memories [15]. These Observations Form The Basis Of The Guideline Recommendation To Prefer Light Sedation [8].

The Most Radical Version Of Light Sedation Is The Avoidance Of Continuous Sedatives Altogether. In The Danish Single-Centre Trial, Patients Assigned To No Sedation, Who Were Managed With Bolus Morphine And A Nursing Culture Accustomed To The Approach, Had A Mean Of 13.8 Ventilator-Free Days In 28 Compared With 9.6 Days For Those Receiving Propofol Followed By Midazolam With Daily Interruption, And A Shorter ICU Stay; However, Agitated Delirium Was More Frequent In The No-Sedation Group (20% Versus 7%) [6]. These Results Are Depicted In Figure 1(B). The Trial Was Unblinded And Single-Centre, And The Unit Had Long Experience Of The Approach, Which Limits Generalisability.

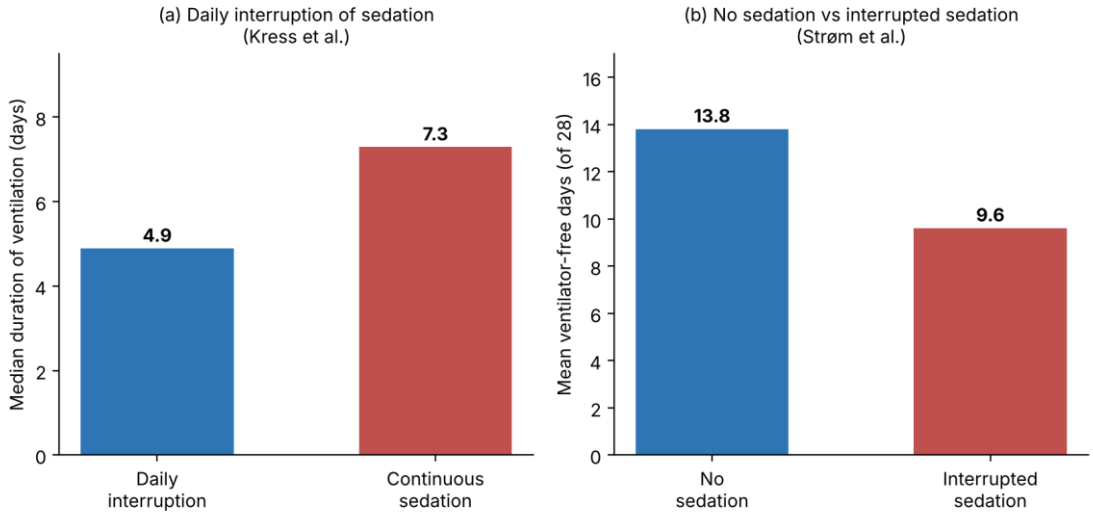


Figure 1. Outcomes in Two Randomized Trials of Reduced Sedation: (A) Median Duration of Ventilation with Daily Interruption versus Continuous Sedation [3]; (B) Mean Ventilator-Free Days with No Sedation versus Interrupted Sedation [6].

The multicentre NONSEDA trial tested the same idea in a broader setting. It compared nonsedation with light sedation and daily interruption and found no significant difference in 90-day mortality, with more agitation requiring intervention in the nonsedation arm

[7]. The reasonable interpretation of the two trials together is that minimal sedation is feasible and does not appear to cause harm in units with adequate staffing and training, and that it may shorten ventilation in some settings, but it has not been shown to improve survival, and it requires a high level of nursing presence, effective analgesia and a tolerance of some agitation. Where those conditions are not met, a strategy of titrated light sedation is likely to be safer.

Deep sedation nevertheless retains a legitimate role. Patients with severe hypoxaemic respiratory failure who require prone positioning or neuromuscular blockade, patients with raised intracranial pressure, those with refractory status epilepticus and those undergoing targeted temperature management may need deeper levels of sedation for limited periods. The important principle is that deep sedation should be a deliberate, documented decision with an indication and a plan for lightening as soon as the indication resolves, rather than a default.

Interruption of Sedation, Protocols and Bundles

The evidence on strategies to limit cumulative sedative exposure is summarised in Table 2. Daily interruption of continuous infusions reduced the median duration of mechanical ventilation from 7.3 to 4.9 days in the original randomized trial [3], as shown in Figure 1(a), and the Awakening and Breathing Controlled trial extended the concept by pairing the interruption with a spontaneous breathing trial, with more ventilator-free days and lower one-year mortality than breathing trials alone [4].

Table 2. Key Trials of Sedation Strategies in Mechanically Ventilated Adults.

Study	Design and population	Comparison	Principal findings
Kress et al. [3]	Randomized trial; 128 patients	Daily interruption vs continuous sedation	Median duration of ventilation 4.9 vs 7.3 days; shorter ICU stay with interruption
Girard et al. [4]	Randomized trial; mechanically ventilated ICU patients	Paired awakening and breathing trial vs breathing trial alone	More ventilator-free days and lower one-year mortality with the paired protocol
Mehta et al. [13]	Randomized trial; protocolised units	Protocol plus daily interruption vs protocol alone	No reduction in time to extubation; higher sedative doses with interruption
Strøm et al. [6]	Randomized trial; 140 patients, single centre	No sedation vs sedation with daily interruption	Ventilator-free days 13.8 vs 9.6; shorter ICU stay; agitated delirium 20% vs 7%
Olsen et al. [7]	Randomized multicentre trial	Nonsedation vs light sedation	No significant difference in mortality; more agitation with nonsedation
Riker et al. [16]	Randomized trial	Dexmedetomidine vs midazolam	Similar time in target range; less delirium and shorter time to extubation with dexmedetomidine; more bradycardia
Shehabi et al. [18]	Randomized trial; 4000 patients	Early dexmedetomidine vs usual care	No difference in 90-day mortality; more bradycardia and hypotension
Hughes et al. [19]	Randomized trial; patients with sepsis	Dexmedetomidine vs propofol	No difference in days alive without delirium or coma

The subsequent trial by Mehta and colleagues is an important qualification. In ICUs that already used a nurse-driven sedation protocol with a light target and preference for bolus dosing, adding daily interruption did not shorten the time to extubation and was associated with higher sedative doses and more nursing workload [13]. A reasonable reading of this finding, together with the earlier protocol trial [5], is that the benefits of interruption are largely achieved by any system that prevents oversedation, and that daily interruption has the greatest effect where practice would otherwise be one of continuous deep sedation. Light targets set by a protocol and applied by trained nurses can replace interruption,

whereas daily interruption can compensate for a lack of such targets.

These findings have been integrated into the ABCDEF bundle, in which spontaneous awakening and breathing trials are combined with attention to pain, choice of sedation, delirium, mobility and family engagement. In a very large multicentre cohort, greater performance of the bundle was associated with higher survival and more days alive without delirium or coma, although residual confounding is likely in an observational study and the bundle as a whole, rather than any single element, is what is being evaluated [14]. The practical lesson is that sedation strategy is best considered as one component of a coordinated approach to ICU care.

From an implementation standpoint, pairing the awakening trial with the breathing trial is not merely a matter of scheduling. It requires the nurse and the respiratory therapist to agree a safety screen for each step, for example the absence of active seizures, of escalating sedative requirement and of myocardial ischaemia before awakening, and adequate oxygenation and haemodynamic stability before a breathing trial. When a patient fails the awakening screen, the reason should be documented and revisited the next day. When the patient passes the awakening trial but fails the breathing trial, sedation should be restarted at a reduced dose rather than at the previous rate, since accumulated drug and recovery of consciousness both change the dose requirement. These details are rarely reported in trials, yet they probably account for a large proportion of the variation in results between units [4], [13].

Choice of Agent: Benzodiazepines, Propofol and Dexmedetomidine

Benzodiazepines have a long track record and are inexpensive, but the evidence has moved against their routine use. In the MENDS trial, patients sedated with dexmedetomidine had more days alive without delirium or coma than those sedated with lorazepam [2]. In the SEDCOM trial, dexmedetomidine produced a similar time within the target sedation range as midazolam but was associated with less delirium and a shorter time to extubation, together with more bradycardia [16]. A systematic review of trials comparing benzodiazepine-based with non-benzodiazepine-based sedation reported that non-benzodiazepine regimens shortened the duration of mechanical ventilation and ICU stay, although the effect on mortality was not demonstrated [20]. A large cohort study found propofol to be associated with more favourable outcomes than benzodiazepines [21]. Taken together with the guidelines [8], these data support the avoidance of benzodiazepines as first-line agents except in specific indications such as alcohol withdrawal, seizures and the need for deep sedation when other agents are inadequate.

The comparison of dexmedetomidine with propofol is less clear-cut. In the MIDEX and PRODEX trials dexmedetomidine was non-inferior to midazolam and to propofol in maintaining the target sedation level, shortened the duration of ventilation compared with midazolam but not propofol, and was accompanied by more bradycardia and hypotension, and the patients were better able to communicate pain and cooperate [17]. The much larger SPICE III trial randomized 4000 ventilated patients to dexmedetomidine as the primary early sedative or to usual care and found no difference in 90-day mortality, with a substantial proportion of patients in the dexmedetomidine arm requiring supplemental sedatives and more bradycardia and hypotension [18]. In patients with sepsis, the MENDS2 trial found no difference in days alive without delirium or coma between dexmedetomidine and propofol [19]. The honest conclusion is that dexmedetomidine and propofol are both acceptable, that neither has been shown to reduce mortality compared with the other, and that the choice may be driven by haemodynamic profile, the desire for a patient who can be roused and cooperate, cost and local availability.

The economics of agent choice deserve explicit mention. Dexmedetomidine is considerably more expensive than propofol and benzodiazepines and is not universally available, which is relevant to health systems with constrained budgets. The more important lever on outcome in these settings is probably process rather than drug: protocolised light sedation, avoidance of continuous benzodiazepine infusions and daily review can be implemented with agents that are widely available, and trials such as that of Mehta and colleagues suggest that a well-run protocol captures much of the benefit [13].

Adverse effects of the preferred agents also need to be anticipated. Dexmedetomidine causes dose-related bradycardia and hypotension, which were more frequent than with comparators in the large trials [17], [18],

and it is therefore best avoided or used cautiously in patients with high-grade heart block or severe haemodynamic instability. Propofol is lipid-based and contributes to caloric load, so triglycerides and pancreatic enzymes should be monitored during prolonged high-dose use, and unexplained metabolic acidosis, rhabdomyolysis or cardiac dysfunction in a patient receiving high-dose propofol should prompt consideration of propofol infusion syndrome. Benzodiazepines, when they are used, should be given at the lowest effective dose and preferably as intermittent boluses, since continuous infusion promotes accumulation [10]. These considerations illustrate that agent choice is not only a question of outcomes in trials but also of the safety profile in the individual patient.

Delirium, Cognition and Long-Term Outcomes

Delirium is common in ventilated patients and is associated with longer stay, higher mortality and long-term cognitive impairment. Systematic screening using CAM-ICU [12] together with measurement of depth of sedation using the RASS [11] permits distinction between sedation-related unresponsiveness and delirium. Trial evidence indicates that choice of sedative influences delirium. Lorazepam exposure led to fewer days alive without delirium or coma than dexmedetomidine [2], and midazolam produced more delirium than dexmedetomidine [16]. By contrast, comparisons of dexmedetomidine and propofol have shown similar delirium outcomes [19], which suggests that avoidance of benzodiazepines, rather than selection of a specific alternative, is the key point.

Long-term outcomes extend beyond mortality. Many survivors of critical illness experience persistent cognitive impairment, anxiety, depression and symptoms of post-traumatic stress. The concern that light sedation might increase distressing memories has not been confirmed in trials [15], and lighter strategies are theoretically attractive because they permit early mobilisation and engagement of the family. The cohort evidence in support of a bundled approach is encouraging [14]. However, long-term follow-up is an infrequent outcome in sedation trials, and the evidence for a direct effect of any specific sedation strategy on long-term cognitive or psychological outcome remains limited.

Non-pharmacological measures complement the choice of sedative. Early mobilisation, which becomes practical only when sedation is light, has been identified as an important component of the bundle [14]. Promotion of sleep through reduction of night-time noise and light, clustering of care and avoidance of unnecessary overnight interventions can reduce reliance on sedatives and may lower the risk of delirium. Involving the family, who can provide reorientation and reassurance, is an additional measure with little cost. Clear communication with patients who are awake but intubated, using writing boards, gesture or picture charts, is both humane and a means of detecting unrecognised pain or distress. These measures are particularly relevant in resource-limited settings, where they are inexpensive and are not dependent on access to costly drugs.

Special Populations and Settings

The strategies discussed above were studied principally in general medical and surgical ICU populations, and several groups require individual consideration. In acute respiratory distress syndrome, deeper sedation is often required during the initial period of lung-protective ventilation, prone positioning or neuromuscular blockade, but should be lightened as soon as the physiological indication resolves. In neurocritical care, sedation serves therapeutic purposes such as control of intracranial pressure and treatment of seizures, and neurological examination requires periodic lightening of sedation. In older patients, the susceptibility to delirium and the altered pharmacokinetics of sedatives strengthen the case for avoiding benzodiazepines and for using the lowest effective doses. In patients with sepsis, agents with less haemodynamic effect may be preferred, although propofol and dexmedetomidine have been compared directly with comparable delirium outcomes [19].

Resource-limited settings pose a different set of challenges. The nurse-to-patient ratio, availability of validated assessment tools, access to newer drugs and the training of staff all influence the feasibility of strategies that were developed in well-resourced units. A minimal-sedation protocol, for example, depends on sufficient nursing presence to manage agitation safely, and implementing it without these conditions may risk unplanned extubation and removal of lines [7]. In such settings, a pragmatic approach that is built on a validated sedation scale, an explicit light

target, intermittent bolus dosing, avoidance of continuous benzodiazepine infusion and daily review may be the most achievable way of capturing the main benefits of the evidence [5], [13]. Local audit and context-specific research are needed.

Specific points are worth emphasising for such units. First, it is better to introduce one element of change at a time, beginning with the measurement of sedation depth using a validated scale, since many units discover that patients are deeper than clinicians had intended once they begin to measure. Second, intermittent bolus dosing of a short-acting agent guided by the target score is a low-technology means of avoiding accumulation. Third, the avoidance of long-term continuous benzodiazepine infusion can be achieved without new drugs [20]. Fourth, nurse-led titration within defined limits has been shown to be effective, and empowering nursing staff to adjust sedation within the protocol is both effective and economical [5]. Finally, because most trials reviewed here were conducted in well-resourced centres, clinicians in other environments should view the findings as hypotheses to be tested locally, using audit, rather than as guarantees of benefit.

A Framework for Sedation Strategy

The synthesis suggests that sedation decisions are best approached as a structured sequence, shown in Figure 2. This framework is a conceptual synthesis by the authors of the reviewed evidence and is not a substitute for clinical judgement or local protocols. The sequence begins with the assessment and treatment of pain and the setting of an explicit target and indication for sedation, consistent with the analgesia-first approach recommended by the guidelines [9], [8]. The second step is to ask whether deep sedation is clinically required, for example for severe hypoxaemic respiratory failure, intracranial hypertension or status epilepticus. If it is, deep sedation is used at the lowest effective dose, with a documented indication, and is reassessed daily with early de-escalation. If it is not, the target is light sedation, or no sedation where the unit has the staffing and experience to support it [6], [7]. The agent of choice is propofol or dexmedetomidine, with benzodiazepines reserved for specific indications [8], [16]. In every case a daily structured review should include an awakening and breathing trial [4], delirium screening [12], early mobilisation and family engagement [14].

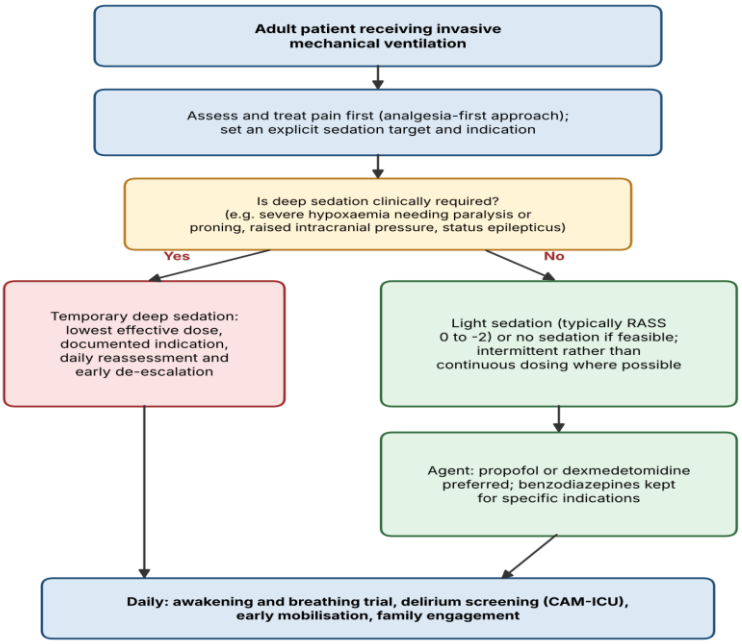


Figure 2. Proposed Stepwise Framework for Sedation Strategy in Mechanically Ventilated Adults (Conceptual Synthesis by the Authors).

The framework is intentionally agent-agnostic where the evidence is balanced. It does not prescribe a choice between propofol and dexmedetomidine, since large trials have not shown a difference in mortality [18], [19], and recommends that this decision be based on

patient factors, haemodynamics and resources. It also avoids prescribing the use of daily interruption in units that already have effective protocols, in recognition of the findings of Mehta and colleagues [13].

Implementation and Quality Indicators

Translating the evidence into practice requires more than the publication of guidelines. Experience from units that have adopted sedation protocols suggests that three elements are critical. The first is a clear local protocol that specifies the target RASS range, the analgesic and sedative agents of choice, the criteria for deeper sedation and the daily review process, developed jointly by physicians, nurses and pharmacists [8], [5]. The second is training and competency assessment in the use of the sedation and delirium scales, since a protocol is only as reliable as the scores that drive it [11], [12]. The third is a cycle of audit and feedback, in which the unit monitors its own performance and responds to deviations.

Several indicators are practical for such audit. The proportion of ventilator-days on which a documented sedation target was set, and the proportion on which the recorded score was within the target range, measure adherence to the protocol. The proportion of patients receiving continuous benzodiazepine infusions measures adoption of agent recommendations. The proportion of eligible patients who undergo an awakening and breathing trial each day, the frequency of delirium screening, the rate of unplanned extubation and the median time from intubation to first mobilisation measure the wider bundle [14]. Because deeper sedation tends to be associated with poorer outcomes [1], units may also wish to track the proportion of time spent at deep sedation levels in patients without a documented indication for them. Reporting these metrics back to the bedside team on a regular basis is a low-cost means of sustaining change.

Strengths, Limitations and Implications for Research

The strength of this review is the evaluation of the principal sedation strategies within a single framework, linked to guideline recommendations. Its limitations should be acknowledged. As a narrative review it is susceptible to selection bias despite a defined search approach and eligibility criteria, and it does not generate new pooled estimates. Strategy trials cannot be blinded to clinicians, and the control arms vary widely, from deep continuous sedation to protocolised light sedation, so that the apparent benefit of an intervention depends on what it is compared with. Several influential trials were conducted in single centres with unusually experienced staff [6]. Outcome definitions, particularly of delirium and of sedation depth, differ between studies. Some of the long-term associations rest on observational data [1], [21], [14]. The framework proposed is based on synthesis and has not been prospectively validated.

Several research priorities follow. Trials of sedation strategies in low- and middle-income settings, using drugs and staffing that are available there, are needed. The optimal management of patients who need deep sedation for physiological reasons, including its duration and the role of alternative agents, requires further study. Comparative studies should report long-term cognitive, psychological and functional outcomes. Finally, implementation research is needed on how to embed protocolised light sedation and bundles into routine practice, and on the cost-effectiveness of newer agents.

CONCLUSION

Sedation in mechanically ventilated adults should be regarded as a titrated therapy with an explicit target and a regular review, rather than as an automatic accompaniment to ventilation. The best-supported approach combines an analgesia-first strategy, light rather than deep sedation, a protocol or daily process that prevents accumulation of sedatives, and the preferential use of propofol or dexmedetomidine rather than benzodiazepines [8], [3], [4]. Minimal or no sedation is feasible in well-staffed units and may shorten ventilation, but it has not been shown to improve survival and is accompanied by more agitation [6], [7]. Dexmedetomidine and propofol appear to give comparable long-term results [18], [19], so the choice between them should be individualised. Deep sedation remains appropriate for specific physiological indications but should be time-limited. Research in resource-limited settings, on patients needing deep sedation and on long-term outcomes is the most pressing need.

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The authors declare that they have no known financial or personal conflicts of interest that could have appeared to influence the work reported in this article.

Informed Consent
Informed consent was not applicable, as this review analysed published literature and did not involve human participants or identifiable patient data.

Ethical Approval
Ethical approval was not required for this narrative review, since it did not involve human participants, patient records or animals.

Data Availability
No new datasets were generated or analysed. All data discussed are available in the cited published sources.

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