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# Perceptions and practices regarding delirium, sedation and analgesia in critically ill patients: a narrative review

*Percepções e práticas sobre delirium, sedação e analgesia em pacientes críticos: uma revisão narrativa*

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## ABSTRACT

A significant number of landmark studies have been published in the last decade that increase the current knowledge on sedation for critically ill patients. Therefore, many practices that were considered standard of care are now outdated. Oversedation has been shown to be hazardous, and light sedation and no-sedation protocols are associated with better patient outcomes. Delirium is increasingly recognized as a major form of acute brain dysfunction that is associated with higher mortality, longer duration of mechanical ventilation and longer lengths of stay in the intensive care unit and hospital. Despite all the

available evidence, translating research into bedside care is a daunting task. International surveys have shown that practices such as sedation interruption and titration are performed only in the minority of cases. Implementing best practices is a major challenge that must also be addressed in the new guidelines. In this review, we summarize the findings of sedation and delirium research over the last years. We also discuss the gap between evidence and clinical practice and highlight ways to implement best practices at the bedside.

**Keywords:** Sedation; Delirium; Benzodiazepines; Propofol; Analgesics, opioid; Dexmedetomidine; Critical illness

## INTRODUCTION

Sedation is commonly used in the intensive care unit (ICU), mainly in mechanically ventilated patients, to promote comfort, facilitate patient-ventilator interaction, and prevent self-harm.<sup>(1)</sup> In addition, deep sedation is often employed to reduce anxiety and promote amnesia in mechanically ventilated patients. Additionally, deep sedation allows healthcare practitioners to provide patient care in the ICU. However, the unrestricted administration of sedatives is frequently associated with oversedation,<sup>(2)</sup> which has been shown to increase the duration of mechanical ventilation and the lengths of ICU and hospital stays.<sup>(2-4)</sup> Over the past years, several studies were published that questioned the notion of deep sedation as standard of care.<sup>(2,3,5,6)</sup> Oversedation is associated with prolonged mechanical ventilation, longer ICU length of stay (LOS), increased delirium rates and increased mortality.<sup>(7,8)</sup>

Delirium is a frequent and severe form of acute brain dysfunction and is a major source of concern in critical care. Studies over the past

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ten years have clearly demonstrated an association between delirium and increased mortality, duration of mechanical ventilation, and hospital LOS.<sup>(9)</sup> Moreover, benzodiazepines, which were the most frequently used sedative drugs in ICU patients, were also associated with transitioning to delirium.<sup>(10)</sup> Despite the substantial evidence, these results have not been applied to clinical practice.<sup>(11-13)</sup> Surveys performed in different countries have shown conflicting results between ICU physicians' and nurses' perceptions of care and actual bedside practice.<sup>(14,15)</sup> In the present article, we present a narrative, non-systematic review to discuss the main advances in sedation research over the past 10 years and their impact on the care of critically ill patients.

### Sedation guidelines

In 2002, the Society of Critical Care Medicine published its Guidelines for Sedation and Analgesia in Critical Care Adults.<sup>(16)</sup> These guidelines established a sedation goal that should be regularly reassessed for the individual patient with the systematic use of a validated sedation scale. Regarding the use of sedatives, the guidelines recommended benzodiazepines, namely lorazepam, as the first-line drug. It was recommended that midazolam be used for acutely agitated patients but only for short durations (48-72 hours). After this period, lorazepam was recommended for continuous or intermittent intravenous sedation. Propofol was suggested for neurosurgical patients or in other situations where rapid awakening was desirable. Dexmedetomidine was only briefly mentioned, and no recommendation for its use could be made at that time due to the lack of major studies in critically ill patients. Incorporating the findings of Kress et al.<sup>(2)</sup> and Kollef et al.,<sup>(7)</sup> these guidelines also recommended titration of the sedative dose to achieve an individual goal or a daily awakening strategy and the use of a sedation protocol.

Because most of the literature examining delirium in ICU patients is recent,<sup>(17)</sup> delirium is only briefly discussed in the 2002 sedation guidelines, which only emphasizes the need for routine assessment of delirium and the use of haloperidol as the drug of choice for delirium treatment.

### Randomized controlled trials to decrease sedative exposure

Since the 2002 Guidelines for Sedation and Analgesia were published, sedation research has grown substantially, as seen in the graphic showing the exponential growth in PubMed citations over the last decade (Figure 1);<sup>(17)</sup> some pivotal studies are highlighted in figure 2. In 2000, Kress et al. showed that daily interruption of sedation reduced the duration of mechanical ventilation (4.9 versus 7.3 days;  $p=0.004$ ) and also reduced ICU LOS (6.4 versus 9.9 days;  $p=0.02$ ).<sup>(2)</sup> The impressive findings of this single-center study led to recommendations for "daily awakening" in the 2002 Guidelines.<sup>(17)</sup> Subsequently, Girard et al. performed a confirmatory multicenter study that compared daily awakening paired with a spontaneous breathing trial with the standard sedation care paired with a spontaneous breathing trial. Patients who underwent the intervention had decreased ICU (ICU LOS 9.1 versus 12.9 days;  $p=0.01$ ) and hospital (hospital LOS 14.9 versus 19.2 days;  $p=0.04$ ) lengths of stay.<sup>(5)</sup> There were more self-extubation events in the intervention group; however, the rates of reintubation were comparable. Interestingly, the intervention group showed improved 1-year survival (HR 0.68, 95% CI 0.50 to 0.92;  $p=0.01$ ), representing a number needed to treat (NNT) of 7. This study certainly represents a major achievement over any contemporary critical care intervention trial. Recent data demonstrate that patients managed with protocolized sedation strategies do not benefit from the addition of daily sedation interruption because their durations of MV and ICU stays were unchanged.<sup>(18)</sup>

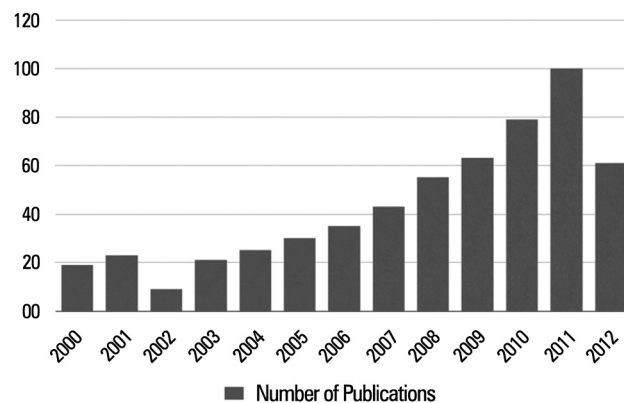


Figure 1 - Sedation and delirium research over the past 12 years.

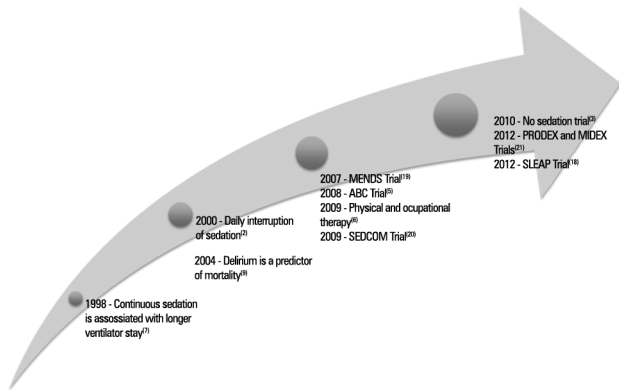


Figure 2 - Major sedation and delirium studies.

More recently, physical and occupational therapy coupled with daily interruption of sedation was compared with the use of daily interruption of sedation alone. Patients in the physical therapy group were more likely to return to an independent status at hospital discharge (59% versus 35%,  $p=0.02$ ; odds ratio 2.7 [95% CI 1.2-6.1]), had a shorter duration of delirium (2.0 days, IQR 0.0-6.0 versus 4.0 days, 2.0-8.0;  $p=0.02$ ), and had more ventilator-free days (23.5 versus 21.1 days,  $p=0.05$ ).<sup>(6)</sup>

Subsequently, Strom et al. evaluated the impact of a “no-sedation protocol” on the outcomes of mechanically ventilated patients. Patients were randomized to no-sedation (only morphine bolus as needed) or sedation (propofol for 48 hours, midazolam thereafter plus morphine bolus as needed) with daily awakening. In this single-center study, the intervention group had significantly more days without ventilation (mean difference, 4.2 days; 95% CI 0.3-8.1;  $p=0.019$ ) as well as shorter stays in the intensive care unit (HR 1.86, 95% CI 1.05-3.23;  $p=0.031$ ) and hospital (3.57, 1.52-9.09;  $p=0.004$ ).<sup>(3)</sup> Interestingly, the control group was already managed with the best evidence-based care to date, which makes the results even more impressive. Regarding the controversies surrounding daily suspension of sedation and protocolized sedation, it was previously shown that daily sedation interruption does not add to protocolized sedation strategies, insofar as the sedation goals are met.<sup>(18)</sup>

Substantial progress has also been made regarding the occurrence of delirium and sedation choice. Since the early 2000s, delirium was recognized as prevalent and was associated with worse outcomes in ICU patients. In a landmark prospective cohort study, Ely et al. demonstrated that delirium was independently associated with 6-month mortality in mechanically

ventilated patients (adjusted HR, 3.2; 95% confidence interval [CI], 1.4-7.7;  $p=0.008$ ).<sup>(9)</sup> Since then, studies have demonstrated the association of different sedative drugs with the occurrence and severity of delirium.<sup>(9,10)</sup> Benzodiazepine exposure was associated with delirium transitioning in several studies. Pandharipande et al. demonstrated that lorazepam was an independent risk factor for daily transition to delirium (odds ratio, 1.2; 95% confidence interval, 1.1-1.4;  $p=0.003$ ) in a dose-dependent manner.<sup>(10)</sup> However, similar results were not obtained for propofol or fentanyl.<sup>(9)</sup> Other studies corroborate this finding. In a 1-day point-prevalence multicenter study involving 104 ICUs in 11 countries, Salluh et al. found that delirium was associated with increased mortality and ICU LOS and that, among sedatives, midazolam was associated with a diagnosis of delirium.<sup>(8)</sup>

In 2007, a randomized controlled trial termed the MENDS study tested the hypothesis that a benzodiazepine-sparing sedation strategy could reduce the occurrence of acute brain dysfunction in mechanically ventilated patients.<sup>(19)</sup> Patients in the dexmedetomidine group spent more time at a targeted level of sedation (80% versus 67%;  $p=0.04$ ) and had more days without delirium or coma (7.0 versus 3.0 days;  $p=0.01$ ), mainly due to reduced incidence of coma (63% versus 92%;  $p<0.001$ ). Two years later, the SEDCOM study compared the efficacy and safety of dexmedetomidine versus midazolam in medical/surgical patients who were expected to remain on mechanical ventilation for more than 24 hours.<sup>(20)</sup> The secondary end-points were prevalence and duration of delirium. Dexmedetomidine was comparable to midazolam for achieving a targeted sedation; however, patients in the dexmedetomidine group had less delirium (54% versus 76.6%,  $p<0.001$ ) and less time to extubation (3.7 versus 5.6 days,  $p=0.01$ ), although the ICU length of stay was similar in both groups. Interestingly, the main outcomes examined in MIDEX and PRODEX (non-inferiority trials comparing dexmedetomidine to midazolam and propofol) were the proportion of time in light-to-moderate sedation (RASS scores between 0 and -3) and the duration of mechanical ventilation.<sup>(21)</sup> Dexmedetomidine was comparable to midazolam and propofol for achieving light-to-moderate long-term sedation; however, it reduced the length of mechanical ventilation compared with midazolam (123 versus 164 hours;  $p=0.03$ ) but not when compared with propofol

(97 versus 118 hours;  $p=0.24$ ). In both studies, there was no difference in the number of patients who needed to be sedated due to delirium, although the incidence of delirium was evaluated only once at 48 hours after stopping the sedative drugs.<sup>(21)</sup> Taken together, the results of these studies suggest that benzodiazepines are associated with increased risk of acute brain dysfunction, and interventions that reduce benzodiazepine use can improve relevant clinical outcomes in mechanically ventilated critically ill patients.

Progress in sedation research over the last decade was reflected in the 2013 guidelines for sedation, analgesia and delirium endorsed by the Society of Critical Care Medicine, as shown in table 1.

**Table 1 - Major differences between the 2002 and 2013 sedation guidelines**

Topics	2002	2013
Number of recommendations	28	33
Pain assessment	Numeric rating scale (NRS)	Behavioral pain scale (BPS) and the Critical care pain observation tool (CPTO)
Sedation goal	A sedation goal should be implemented	Light sedation is the goal for the majority of patients
Sedation assessment	Validated sedation scale (SAS, MAAS or VICS)	Most validated sedation scale (RASS or SAS)
Sedation strategy	Use of sedation protocols	Either daily interruption of sedation or light target level of sedation
Sedation selection	Lorazepam is the drug of choice for most patients	Preference for non-benzodiazepine sedatives
Delirium risk factor	None	Benzodiazepine use
Delirium prevention	None	Early mobilization is recommended

### Current use of sedation: perception and practices of healthcare practitioners

Several surveys were published in the last decade that focused on the practice of sedation worldwide<sup>(12,22,23)</sup> (Table 2). Although the majority of these studies report self-perception, some audits were performed as well, and they reveal startling differences between physicians' statements and actual clinical practice.

In 2001, Soliman et al. published the largest sedation survey in Europe, which included 647 ICU physicians distributed in 16 countries. These authors reported that morphine and fentanyl were equally employed

for opioid-based analgesia (33% each) followed by sufentanil (23%). The most frequently used sedative drug was midazolam (63%) followed by propofol (35%), and lorazepam was infrequently used (<0.5%).<sup>(23)</sup> In 2009, Tanios et al. performed a survey of 904 critical care practitioners (60% physicians, 14% nurses and 12% pharmacists) in the United States. According to the current guidelines, the most frequently used sedative agents were lorazepam and midazolam, and propofol was selected as the first-choice sedative by only 13-26% of responders. Morphine was primarily used for analgesia.<sup>(22)</sup> Patel et al. surveyed 1384 health care practitioners (70% physicians, 23% nurses and 1.6% respiratory therapists) in North America about sedation. In that study, benzodiazepines (84%) and propofol (81%) were the most commonly used sedative agents.<sup>(24)</sup>

In contrast, an Australian-New Zealand survey performed in 2010 with critical care physicians and nurses showed that midazolam and propofol were equally used (50% each) as the sedation drug of choice, and again, morphine was used as the first choice for analgesia (67%) followed by fentanyl (13%).<sup>(15)</sup> These findings may be indicative of a cultural difference regarding the approach to sedation.

Regarding the adherence to daily interruption of sedation, the results also varied significantly across countries. However, adherence was generally low, varying from 14% in Malaysia<sup>(25)</sup> and 15% in Nordic countries<sup>(26)</sup> to 31% in Denmark<sup>(27)</sup> and 34% in Germany.<sup>(28)</sup> Patel et al. reported that the majority of respondents (76%) had a written policy on spontaneous awakening trials. However, less than half of the health care practitioners evaluated (44%, 446/1019) performed spontaneous awakening trials on more than half of the ICU days.<sup>(24)</sup> Recently, Australia-New Zealand<sup>(15)</sup> and UK surveys<sup>(29)</sup> revealed higher levels of self-reported sedation interruption (62 and 78%, respectively). A study comparing sedation interruption in ICUs in Germany showed that from 2002 to 2006, there was a 34% increase (23 to 45% of ICUs) in the implementation of sedation interruption.<sup>(30)</sup> Unfortunately, despite evidence of the dangers of continuous sedation and oversedation, the practice of sedation interruption has not yet been implemented in most ICUs, creating a large evidence-to-practice gap.

The use of written sedation protocols is strongly encouraged as a way to promote a consistent approach to individually targeted sedation, but it also varies in different countries. Martin et al. reported a 21%



**Table 2** - Summary of surveys dealing with sedation that have been published in the last decade

Study	Year	Site of study	Number of respondents	Healthcare worker evaluated (%)	Daily interruption of sedation (%)	Sedation protocol (%)	Sedation scale (%)	Sedation goal (%)
Murdoch et al. <sup>(31)</sup>	2000	England	255	Physicians	Not reported	Yes (27)	Yes (67)	Not reported
Soliman et al. <sup>(23)</sup>	2001	Europe	647	Physicians	Not reported	Not reported	Yes (43)	Not reported
Guldbrand et al. <sup>(26)</sup>	2004	Nordic countries	88	Not reported	Yes (15)	Yes (41)	Yes (53)	Not reported
Martin et al. <sup>(28)</sup>	2006	Germany	305	Physicians	Not reported	Not reported	Not reported	Not reported
Egerod et al. <sup>(27)</sup>	2006	Denmark	82	Physicians (47.5), nurses (52.5)	Not reported	Yes (physicians-23/nurses-9)	Yes (nurses-30/physicians-44)	Not reported
Martin et al. <sup>(30)</sup>	2007	Germany	220	Physicians	Yes (34% increase from 2002 to 2006)	Yes (46)	Yes (46)	Not reported
Ahmad et al. <sup>(25)</sup>	2007	Malaysia	37	Physicians	Yes (14)	Yes (35)	Yes (35)	Not reported
Mehta et al. <sup>(14)</sup>	2007	Canada	88	Nurses	Not reported	Not reported	Not reported	Not reported
Reschreiter et al. <sup>(29)</sup>	2008	UK	192	Not reported	Yes (78)	Yes (80)	Yes (88.1)	Not reported
Patel et al. <sup>(24)</sup>	2009	United States	1,384	Physicians (70), nurses (23.2), respiratory therapists (1.6)	Yes (76)	Yes (71)	Yes (88)	Not reported
Tanios et al. <sup>(22)</sup>	2009	United States	904	Physicians (60%), nurses (14), pharmacists (12)	Yes (40)	Yes (64)	Not reported	Not reported
Salluh et al. <sup>(32)</sup>	2009	Brazil	1,015	Physicians	Yes (31.7)	Yes (52.7)	Yes (88.3)	Yes (37.2)

frequency of use in German ICUs,<sup>(28)</sup> whereas other authors showed a 27% use in the UK<sup>(31)</sup> and a 33% use in Denmark.<sup>(27)</sup> Patel et al. reported that 29% of respondents did not have a written sedation protocol.<sup>(24)</sup> Earlier surveys reported an increasing trend in using sedation protocols, ranging from 52% in Germany<sup>(28)</sup> to 80% in the UK.<sup>(31)</sup> The Ramsay scale appeared to be the most commonly used scale for sedation assessment in the various surveys.<sup>(28-31)</sup>

In Brazil, a study published in 2009 with 1015 critical care physicians found that midazolam and fentanyl were the most frequently used sedative agents (97.8 and 91.5%, respectively) followed by propofol (55%).<sup>(32)</sup> Only 52.7% of respondents reported using a sedation protocol in their ICUs. Approximately 62.8% of physicians reported not discussing sedation targets in daily rounds, and 68.3% did not practice sedation interruption at all.

### Changing sedation practices and critical care culture: a major challenge

Implementing change in clinical routines is complex and labor intensive. Sedation audits in the ICU reveal a different reality from that which is reported by surveys.

In an audit performed in 1,381 adult patients admitted to 44 ICUs in France, Payen et al. reported that midazolam was the most commonly used sedative agent (70%) followed by propofol (20%).<sup>(11)</sup> Opioid-based analgesia was implemented mainly with sufentanil (40%) and fentanyl (35%). A large proportion of patients underwent deep sedation (40-50%), and regular assessment for sedation and analgesia was significantly lower than the use of sedatives and opioids. None of the ICUs performed sedation interruption, and procedural analgesia was infrequently used (less than 25% of patients). In a Canadian study that included 52 ICUs, Burry et al. reported that sedative and analgesia interruptions were performed only 20% and 9% of the time, respectively. These authors also found that only 8% of patients underwent sedative dose adjustment based on the use of a validated sedation scale.<sup>(33)</sup>

The impact of clinical trials on current practice is low overall, and there are many plausible explanations. Gaps in the dissemination of knowledge, skepticism about the cost-effectiveness of the practice (cost being perceived as financial resources and effort), doubts about personnel and equipment support and applicability to an

individual setting are frequently cited as major barriers to implementing new practices.<sup>(34)</sup> Tanios et al. reported that the three most common reasons that prevented multidisciplinary teams from adopting sedation scales were no physician order (35%), lack of nursing support (11%), and fear of oversedation (7%). The main reasons that prevented teams from adopting daily interruption of sedation were lack of nurse acceptance (22%), concern about risk of patient-initiated device removal (19%), and inducement of either respiratory compromise (26%) or patient discomfort (13%).<sup>(22)</sup> In another study, O'Connor and Bucknall found that nurses were more likely to believe that daily interruption of sedation would increase their workload.<sup>(15)</sup> In the same study, when asked about other factors that could influence sedation management, physicians and nurses alike cited level of experience and education and support from staff. Other factors cited by nurses were staffing level and pressure for beds, whereas physicians most often cited unit culture ("a quiet patient is a good patient"). Cost is also an important issue in clinical decision-making, being cited by 52% of ICU physicians in the UK<sup>(27)</sup> and 64% in Maghreb.<sup>(35)</sup>

New guidelines for sedation and analgesia in critical care will incorporate these changes; however, guideline publishing is not enough to translate good evidence into good bedside practice.<sup>(34)</sup> Carey et al. suggested that guidelines should focus not only on the best evidence available but also on planning strategies for its best implementations and pilot studies for evaluating implementation plans.<sup>(36)</sup> Gesme and Wiseman have also advocated for a leadership role and an organizational culture that support change to help implement the best practices.<sup>(37)</sup> However, studies have shown that even complex quality improvement strategies may be successfully implemented in the ICU setting.<sup>(38,39)</sup>

## CONCLUSION

Despite all the available evidence, best sedation practices are still heterogeneous and insufficiently implemented worldwide. It is imperative to address the obvious gap between research and practice. More data are needed to help establish the best implementation strategies and help provide the best care to all patients admitted in the intensive care unit.

## RESUMO

Durante a última década, foi publicado um número significativo de estudos fundamentais que aumentaram o conhecimento atual sobre a sedação em pacientes criticamente enfermos. Desse modo, muitas das práticas até então consideradas como padrão de cuidado são hoje obsoletas. Foi demonstrado que a sedação excessiva é perigosa, e que protocolos com sedação leve ou sem sedação se associaram a melhores desfechos dos pacientes. O *delirium* vem sendo cada vez mais reconhecido como uma forma importante de disfunção cerebral associada com mortalidade mais alta, maior duração da ventilação mecânica e maior permanência na unidade de terapia intensiva e

no hospital. Apesar de todas as evidências disponíveis, a tradução da pesquisa para o cuidado ao pé do leito é uma tarefa hercúlea. Foi demonstrado, por levantamentos internacionais, que práticas como interrupção e titulação da sedação só são realizadas em uma minoria dos casos. O estabelecimento das melhores práticas é um tremendo desafio que deve também ser contemplado nas novas diretrizes. Nesta revisão, resumimos os achados de estudos a respeito de sedação e *delirium* nos anos recentes e discutimos a distância entre a evidência e a prática clínica, assim como as formas de estabelecer as melhores práticas ao pé do leito.

**Descritores:** Sedação; Delírio; Benzodépinas; Propofol; Analgésicos opióides; Dexmedetomidina; Estado terminal

## REFERENCES

1. Mehta S, McCullagh I, Burry L. Current sedation practices: lessons learned from international surveys. *Anesthesiol Clin*. 2011;29(4):607-24.
2. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342(20):1471-7.
3. Strøm T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet*. 2010;375(9713):475-80.
4. Gupta K, Gupta VK, Jayashree M, Singhi S. Randomized controlled trial of interrupted versus continuous sedative infusions in ventilated children. *Pediatr Crit Care Med*. 2012;13(2):131-5. Erratum in *Pediatr Crit Care Med*. 2012;13(3):373. Muralindharan, Jayashree [corrected to Jayashree, Muralindharan].
5. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371(9607):126-34.

6. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009;373(9678):1874-82.
7. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. *Chest*. 1998;114(2):541-8.
8. Salluh JI, Soares M, Teles JM, Ceraso D, Raimondi N, Nava VS, Blasquez P, Ugarte S, Ibanez-Guzman C, Centeno JV, Laca M, Grecco G, Jimenez E, Arias-Rivera S, Duenas C, Rocha MG; Delirium Epidemiology in Critical Care Study Group. Delirium epidemiology in critical care (DECCA): an international study. *Crit Care*. 2010;14(6):R210.
9. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. 2004;291(14):1753-62.
10. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology*. 2006;104(1):21-6.
11. Payen JF, Chanques G, Mantz J, Hercule C, Auriant I, Leguillou JL, et al. Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. *Anesthesiology*. 2007;106(4):687-95; quiz 891-2.
12. Mehta S, Burry L, Fischer S, Martinez-Motta JC, Hallett D, Bowman D, Wong C, Meade MO, Stewart TE, Cook DJ; Canadian Critical Care Trials Group. Canadian survey of the use of sedatives, analgesics, and neuromuscular blocking agents in critically ill patients. *Crit Care Med*. 2006;34(2):374-80.
13. Rhoney DH, Murry KR. National survey of the use of sedating drugs, neuromuscular blocking agents, and reversal agents in the intensive care unit. *J Intensive Care Med*. 2003;18(3):139-45.
14. Mehta S, Meade MO, Hynes P, Filate WA, Burry L, Hallett D, et al. A multicenter survey of Ontario intensive care unit nurses regarding the use of sedatives and analgesics for adults receiving mechanical ventilation. *J Crit Care*. 2007;22(3):191-6.
15. O'Connor M, Bucknall T, Manias E. Sedation management in Australian and New Zealand intensive care units: doctors' and nurses' practices and opinions. *Am J Crit Care*. 2010;19(3):285-95.
16. Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, Chalfin DB, Masica MF, Bjerke HS, Coplin WM, Crippen DW, Fuchs BD, Kelleher RM, Marik PE, Nasraway SA Jr, Murray MJ, Peruzzi WT, Lumb PD; Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists (ASHP), American College of Chest Physicians. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med*. 2002;30(1):119-41. Erratum in *Crit Care Med*. 2002;30(3):726.
17. Morandi A, Watson PL, Trabucchi M, Ely EW. Advances in sedation for critically ill patients. *Minerva Anesthesiol*. 2009;75(6):385-91.
18. Mehta S, Burry L, Cook D, Fergusson D, Steinberg M, Granton J, Herridge M, Ferguson N, Devlin J, Tanios M, Dodek P, Fowler R, Burns K, Jacka M, Olafson K, Skrobik Y, Hébert P, Sabri E, Meade M; SLEAP investigators; Canadian Critical Care Trials Group. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. *JAMA*. 2012;308(19):1985-92. Erratum in *JAMA*. 2013;309(3):237.
19. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA*. 2007;298(22):2644-53.
20. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, Whitten P, Margolis BD, Byrne DW, Ely EW, Rocha MG; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA*. 2009;301(5):489-99.
21. Jakob SM, Ruokenem E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, Bratty JR, Takala J; Dexmedetomidine for Long-Term Sedation Investigators. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA*. 2012;307(11):1151-60.
22. Tanios MA, de Wit M, Epstein SK, Devlin JW. Perceived barriers to the use of sedation protocols and daily sedation interruption: a multidisciplinary survey. *J Crit Care*. 2009;24(1):66-73.
23. Soliman HM, Mélot C, Vincent JL. Sedative and analgesic practice in the intensive care unit: the results of a European survey. *Br J Anaesth*. 2001;87(2):186-92.
24. Patel RP, Gambrell M, Speroff T, Scott TA, Pun BT, Okahashi J, et al. Delirium and sedation in the intensive care unit: survey of behaviors and attitudes of 1384 healthcare professionals. *Crit Care Med*. 2009;37(3):825-32.
25. Ahmad N, Tan CC, Balan S. The current practice of sedation and analgesia in intensive care units in Malaysian public hospitals. *Med J Malaysia*. 2007;62(2):122-6.
26. Gulbrandsen P, Berggren L, Bratlebø G, Mälstam J, Rönholm E, Winsö O; Scandinavian Critical Care Trials Group. Survey of routines for sedation of patients on controlled ventilation in Nordic intensive care units. *Acta Anaesthesiol Scand*. 2004;48(8):944-50.
27. Egerod I, Christensen BV, Johansen L. Trends in sedation practices in Danish intensive care units in 2003: a national survey. *Intensive Care Med*. 2006;32(1):60-6.
28. Martin J, Franck M, Fischer M, Spies C. Sedation and analgesia in German intensive care units: how is it done in reality? Results of a patient-based survey of analgesia and sedation. *Intensive Care Med*. 2006;32(8):1137-42.
29. Reschreiter H, Maiden M, Kapila A. Sedation practice in the intensive care unit: a UK national survey. *Crit Care*. 2008;12(6):R152.
30. Martin J, Franck M, Sigel S, Weiss M, Spies C. Changes in sedation management in German intensive care units between 2002 and 2006: a national follow-up survey. *Crit Care*. 2007;11(6):R124.
31. Murdoch S, Cohen A. Intensive care sedation: a review of current British practice. *Intensive Care Med*. 2000;26(7):922-8.
32. Salluh JI, Dal-Pizzol F, Mello PV, Friedman G, Silva E, Teles JM, Lobo SM, Bozza FA, Soares M; Brazilian Research in Intensive Care Network. Delirium recognition and sedation practices in critically ill patients: a survey on the attitudes of 1015 Brazilian critical care physicians. *J Crit Care*. 2009;24(4):556-62.
33. Burry L, Perreault M, Williamson D, Cook D, Wog Z, Rodrigues H, et al. A prospective evaluation of sedative, analgesic, anti-psychotic and paralytic practices in Canadian mechanically ventilated adults. *Am J Respir Crit Care Med*. 2009;179:A5492.
34. Shojania KG, McDonald KM, Wachter RM, Owens DK, editors. Closing the quality gap: a critical analysis of quality improvement strategies. (Vol. 1: Series Overview and Methodology). Rockville, MD: Agency for Healthcare Research and Quality (US); 2004.
35. Kamel S, Tahar M, Nabil F, Mohamed R, Mhamed Sami M, Mohamed SB. [Sedative practice in intensive care units results of a Maghrebien survey]. *Tunis Med*. 2005;83(11):657-63. French.
36. Carey M, Buchan H, Sanson-Fisher R. The cycle of change: implementing best-evidence clinical practice. *Int J Qual Health Care*. 2009;21(1):37-43.
37. Gesme D, Wiseman M. How to implement change in practice. *J Oncol Pract*. 2010;6(5):257-9.
38. Scales DC, Dainty K, Hales B, Pinto R, Fowler RA, Adhikari NK, et al. A multifaceted intervention for quality improvement in a network of intensive care units: a cluster randomized trial. *JAMA*. 2011;305(4):363-72.
39. Doig GS, Simpson F, Finfer S, Delaney A, Davies AR, Mitchell I, Dobb G; Nutrition Guidelines Investigators of the ANZICS Clinical Trials Group. Effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial. *JAMA*. 2008;300(23):2731-41.