Pain Assessment Is Associated with Decreased Duration of Mechanical Ventilation in the Intensive Care Unit

A Post Hoc *Analysis of the DOLOREA Study*

Jean-Francois Payen, M.D., Ph.D.,* Jean-Luc Bosson, M.D., Ph.D.,† Gérald Chanques, M.D.,‡ Jean Mantz, M.D., Ph.D.,§ José Labarere, M.D., Ph.D.,|| for the DOLOREA Investigators#

Background: Critically ill patients frequently experience pain, but assessment rates remain below 40% in mechanically ventilated patients. Whether pain assessment affects patient outcomes is largely unknown.

Methods: As part of a prospective cohort study of mechanically ventilated patients who received analgesia on day 2 of their stay in the intensive care unit (ICU), the investigators performed propensity-adjusted score analysis to compare the duration of ventilator support and duration of ICU stay between 513 patients who were assessed for pain and 631 patients who were not assessed for pain.

Results: Patients assessed for pain on day 2 were more likely to receive sedation level assessment, nonopioids, and dedicated analgesia during painful procedures than patients whose pain was not assessed. They also received fewer hypnotics and lower daily doses of midazolam. Patients with pain assessment had a shorter duration of mechanical ventilation (8 *vs.* 11 days; $P < 0.01$) and a reduced duration of stay in the ICU (13 *vs.* 18 days; $P < 0.01$). In propensity-adjusted score analysis, pain assessment was associated with increased odds of weaning from the ventilator (odds ratio, 1.40; 95% confidence interval, 1.00–1.98) and of discharge from the ICU (odds ratio, 1.43; 95% confidence interval, 1.02–2.00).

Conclusions: Pain assessment in mechanically ventilated patients is independently associated with a reduction in the duration of ventilator support and of duration of ICU stay. This might be related to higher concomitant rates of sedation assessments and a restricted use of hypnotic drugs when pain is assessed.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

This article is accompanied by an Editorial View. Please see: Kumar AB, Brennan TJ: Pain assessment, sedation, and analgesic administration in the intensive care unit. ANESTHESIOLOGY 2009; 111:1187–8.

* Professor, Department of Anesthesiology and Critical Care, Grenoble University Hospital, Grenoble, France. † Professor, Department of Biostatistics, and TIMC-IMAG, UMR-CNRS 5525, Joseph Fourier University, Grenoble, France. ‡ Assistant Professor, Department of Anesthesiology and Critical Care, Montpellier University Hospital, Montpellier, France. § Professor, Department of Anesthesiology and Critical Care, Beaujon University Hospital, Assistance Publique des Hôpitaux de Paris, Clichy, France. || Assistant Professor, Quality of Care Unit, Grenoble University Hospital and TIMC-IMAG, UMR-CNRS 5525, Joseph Fourier University, Grenoble, France. # DOLOREA investigators are listed in the appendix.

EVIDENCE suggests that mechanically ventilated critically ill patients experience stressful, unpleasant, and potentially harmful experiences during their time in intensive care units (ICU). These include pain, fear, sleep deprivation, nightmares, inability to speak, and feelings of isolation and loneliness.[1,2] Such physical and psychological stresses affect quality of life even after the patient's discharge from the ICU.[3,4] Among these adverse experiences, acute pain has emerged as a leading stressor for ICU patients. Nearly 50% of patients interviewed rated their pain intensity as moderate to severe, at rest as well as during procedures.[5–8] This issue becomes more complex for the substantial number of mechanically ventilated ICU patients who are unable to report their pain because of the concomitant use of sedatives (hypnotics) or as a consequence of severe brain damage.

Despite the existence of clinical scoring systems to quantify pain in verbal and nonverbal patients,[9] routine clinical practice seldom applies them. National surveys have studied primarily rates of sedation assessment (consciousness) and sedative use.[10–13] The multicenter patient-based DOLOREA study described current practices in analgesia and sedation use for 1,381 mechanically ventilated patients during their first week in the ICU.[14] We found that only 42% of patients received pain assessments on day 2 (D2) in ICUs, although 90% of patients were concomitantly given opioids.

The extent to which pain assessment and pain control in the ICU influence patient outcomes is largely unknown. One center demonstrated an association between systematically evaluating pain and agitation levels and shorter mechanical ventilation (MV) durations, as well as lower rates of nosocomial infections.[15] We hypothesized that measuring pain levels in patients rendered nonverbal from MV and hypnotic use would lead to higher concomitant rates of sedation assessments and a more appropriate use of both analgesics and sedatives. These changes would in turn reduce the duration of MV

and duration of ICU stay, because inappropriate sedative and analgesic use prolongs both of these criteria.[16–18] A systematic pain assessment for mechanically ventilated patients could thus function as a marker for good clinical practice in the ICU. To verify this hypothesis, we separately analyzed the DOLOREA data as reflecting what was done daily in 44 ICUs. The current study aimed to establish whether an association exists between pain measurements, MV duration, and duration of ICU stay in this cohort of mechanically ventilated patients receiving analgesia on D2 of their ICU stay.

Materials and Methods

Study Design

The prospective, multicenter, observational DOLOREA study was conducted from January 2004 until January 2005, in 43 ICUs in France and 1 ICU in Luxembourg.[14] Patients 15 yr or older were enrolled in the study if admitted to the ICU for a foreseeable duration of MV of more than 24 h. Patients were excluded if they had severe brain injury on admission (defined by a Glasgow Coma Scale score of less than 9), or if MV was delayed for more than 24 h after admission to ICU. For the purpose of this *post hoc* analysis, we excluded from the DOLOREA database those patients who had not received analgesia on D2 of their ICU stay.

Data Management

A detailed description of data collection and quality control procedures is available elsewhere.[14] Briefly, each site had a dedicated individual who entered raw data into an electronic case report form (ClinInfo S.A., Lyon, France). For each patient, a set of variables was collected that included demographic characteristics, illness severity on admission as defined by the Simplified Acute Physiology Score II, and an individual Sequential Organ Failure Assessment score of 3 or 4 (*i.e.*, moderate-to-severe organ failure).[19] For each patient, we also recorded the instrument used to assess sedation and pain levels on D2 of ICU stay, the type of sedative and opioid drug used on D2, the cumulative amounts of these drugs during the previous 24 h, the use of nonopioids and neuromuscular blocking agents on D2, and the management of procedural pain on D2. In patients who were assessed using sedation scales, we defined a deep state of sedation by a Ramsay score of 5 or 6, a Richmond Agitation Sedation Scale score of -5 or -4, or a Sedation Agitation Scale score of 1 or 2. Information about the recruiting sites was collected regarding their resources, the existence of pain control protocols/guidelines, and whether they provided dedicated education for pain and sedation management.

Outcome Definitions

Patients were followed up until death, until ICU discharge, or for 30 days in the ICU. The primary study outcomes included MV duration and duration of ICU stay for survivors. Patients were considered as candidates for weaning from the ventilator if they no longer had a high-grade fever, hemodynamic instability, or severely altered consciousness or if they exhibited adequate oxygenation with an inspired oxygen fraction less than 0.5 and positive end-expiratory pressure less than 5 cm H_2O. Candidates for weaning were switched to pressure support ventilation followed by daily spontaneous breathing trials on a T-piece. The decision to extubate was based on simple bedside tolerance variables, including respiratory rate, arterial oxygen saturation, and the use of accessory respiratory muscles during T-piece trials. This protocol was applied uniformly across all sites.

The secondary study outcomes included mortality rates and, among survivors, the incidence of acquired complications: ventilator-associated pneumonia, gastroduodenal hemorrhage, venous thromboembolism, and colonization of central venous catheters. Ventilator-associated pneumonia was defined by a new parenchymal opacity in the lung on chest radiograph plus at least two of the following three criteria: (1) temperature less than 36°C or greater than 38°C, (2) leukocyte count less than 4,000/ml or greater than 10,000/ml, (3) purulent secretions from the endotracheal tube.[20] Gastroduodenal hemorrhage was defined by esophagogastroduodenoscopy, or by the combination of grossly visible blood from an enterally placed tube and subsequent transfusions of 2 or more units of packed erythrocytes. Thromboembolic events were defined by the presence of a venous thrombosis proven by Doppler ultrasonography or venography, or by the presence of a pulmonary embolism proven by pulmonary angiography, or contrast spiral computed tomography of the thorax. Central venous catheter colonization was defined by the isolation of at least one organism at a concentration of 10^3 or more colony-forming units/ml from a catheter tip culture.[21]

Supplementary Analysis

Clinical practices regarding sedation and analgesia management were also compared between the two groups of patients, *i.e.*, patients assessed for pain *versus* patients not assessed for pain on day 6 (D6) of their ICU stay. Patients were included in the D6 analysis if they had been mechanically ventilated on both D2 and D6, they received analgesia on both D2 and D6, and their allocated group on D2 was the same on D6.

Statistical Analysis

Descriptive statistics included frequencies and percentages for categorical variables, and medians and interquartile range, *i.e.*, 25th and 75th percentiles, for continuous variables. Baseline characteristics were com-

pared using chi-square tests for categorical variables and the nonparametric Kruskal–Wallis test for continuous variables. ICU mortality rates, duration of MV, and duration of ICU stay were compared using discrete time survival logistic hazard models. All observations were censored at 30 days. The duration of MV and the duration of ICU stay were compared among survivors.

Because some patients might have experienced a primary study outcome before pain assessment (*i.e.*, death, weaning from MV, or discharge from the ICU), we used a landmark analysis with prespecified landmarks on D2 of the ICU stay, as before.[22] This landmark analysis minimized the impact of survivor bias by comparing study outcomes of patients with no primary study outcomes on D2.

As individual physician discretion directed pain assessment, unadjusted comparisons of outcomes between patients with and without pain assessment might be confounded by imbalances in baseline characteristics. To address this issue, we performed a propensity score analysis.[23] Conceptually, the propensity score corresponds to the conditional probability of exposure to a treatment given the observed characteristics of a patient. Stratifying on the propensity score tends to balance all observed characteristics that are used to construct the score and, in this way, approximates the conditions of random treatment.[23] In practice, we derived a propensity score for pain assessment on D2 using a full, non-parsimonious logistic regression model that included patient baseline characteristics (age, sex, weight, Simplified Acute Physiology Score II, admission source, Sequential Organ Failure Assessment score 3 or 4 on admission, chronic heart failure, chronic respiratory failure, active cancer, diabetes, regular psychoactive drug use, cirrhosis, chronic renal failure, stroke), ICU characteristics (university affiliated, number of beds ≥ 12, ICU nurse-to-bed ratio > 4, dedicated education, protocol use), treatment with analgesics (morphine, sufentanil, fentanyl, remifentanil, other opioids, paracetamol, nefopam, ketamine, other nonopioids, procedural pain treatment), treatment with sedatives (midazolam, propofol, other sedatives), and treatment with neuromuscular blocking agents. We used a linear spline model to adjust for the confounding effect of age with knots at 40 and 70 yr, and Simplified Acute Physiology Score II with knots at 50 and 75 yr, respectively. The model yielded a *c* statistic of 0.87, indicating a good ability to differentiate between patients with and without pain assessment. Each patient was assigned a propensity score, which ranged from 0.01 to 0.99 and which reflected the conditional probability of pain assessment on D2, given his baseline characteristics. We then stratified patients by quintiles of increasing propensity score. To validate our propensity score adjustment, we checked for the absence of significant residual imbalances in baseline characteristics after adjusting for quintile of propensity score and for adequate overlap of
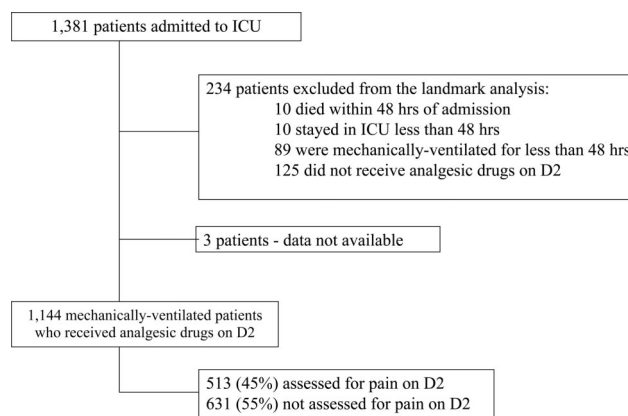
Fig. 1. Patient flow diagram showing the number of identified, excluded, and analyzed patients. D2 = day 2; ICU = intensive care unit.

propensity score between the two groups within each quintile. We then estimated the odds ratios of study outcomes associated with pain assessment on D2 after adjusting for the quintile of propensity score. All *P* values were two-tailed, and $P \leq 0.05$ was considered statistically significant. Analyses were performed using Stata version 9.0 (StataCorp, College Station, TX).

Results

Of the 1,381 patients in the DOLOREA database, 1,144 mechanically ventilated patients satisfied the inclusion criteria for the 48-h landmark analysis. This included patients who were assessed for pain on D2 (n = 513 patients, 45% of the population) and patients who were not assessed for pain on D2 (n = 631 patients, 55% of the population) (fig. 1). Patients had been assessed for pain using the following instruments: the behavioral pain scale[24] (451/513, 49% of patients), the Harris scale[25] (98/513, 19% of patients), the visual analog scale (71/513, 14% of patients), the verbal descriptor scale (64/513, 12% of patients), and the numeric rating scale (24/513, 5% of patients).

Table 1 shows baseline characteristics of the patients. No significant differences were found between the two groups regarding their characteristics, with the exception of age higher than 75 yr, admission source, chronic heart failure, and use of psychoactive drugs. The two groups had comparable illness severity on admission. Patients with pain assessments were more likely to be admitted to university-affiliated sites, to sites with more resources, and to sites with more protocols and dedicated pain education. There was 24-h in-house intensivist coverage for all participating sites.

Forty-eight–hour Landmark Analysis

Although the proportion of patients receiving continuous opioids was comparable between the two groups, patients with pain assessments were more likely to receive fentanyl, higher dosages of sufentanil,

Table 1. Baseline Characteristics of the 1,144 Mechanically Ventilated Patients, Divided According to Their Pain Assessment on Day 2 of the ICU Stay

	Pain Assessment		
	No (n = 631)	Yes (n = 513)	P Value
Age, median (IQR), yr	62 (46–74)	59 (47–73)	0.17
> 75 yr, n (%)	134 (21)	84 (16)	0.04
Female sex, n (%)	216 (34)	172 (33)	0.80
Weight, median (IQR), kg	74 (63–85)	72 (60–83)	0.06
SAPS II,* median (IQR)	44 (31–56)	43 (33–54)	0.40
Admission source, n (%)			< 0.01
Medicine	169 (27)	160 (31)	
Emergency surgery	218 (35)	186 (36)	
Elective surgery	138 (22)	89 (18)	
Trauma	95 (15)	57 (11)	
Others	11 (1)	21 (4)	
SOFA score 3 or 4 on admission,†‡ n (%)			
Respiratory	391 (62)	320 (62)	0.89
Cardiovascular	409 (65)	322 (63)	0.47
Renal	122 (19)	92 (18)	0.54
Neurologic	51 (8)	56 (11)	0.10
Coagulation	59 (9)	36 (7)	0.16
Hepatic	32 (5)	26 (5)	0.99
Patient history,†§ n (%)			
Chronic heart failure	116 (18)	123 (24)	0.02
Chronic respiratory failure	101 (16)	84 (16)	0.87
Active cancer	102 (16)	91 (18)	0.49
Diabetes	99 (16)	75 (15)	0.63
Regular psychoactive drug use	57 (9)	66 (13)	0.04
Cirrhosis	45 (7)	53 (10)	0.05
Chronic renal failure	35 (5)	30 (6)	0.83
Stroke	36 (6)	37 (7)	0.30
ICU characteristics, n (%)			
University affiliated	482 (76)	462 (90)	< 0.01
ICU beds ≥ 12	435 (69)	396 (77)	< 0.01
ICU nurse-to-bed ratio > 4	327 (52)	304 (59)	0.01
Protocol use	172 (27)	349 (68)	< 0.01
Dedicated education	313 (50)	411 (80)	< 0.01

Quantitative data are expressed as median and interquartile range (IQR), *i.e.*, 25th and 75th percentiles.

* Forty-eight missing values. † The number of individual organ failures (Sequential Organ Failure Assessment [SOFA] score 3 or 4) and patient history results exceeds the total number of included patients. ‡ One missing value for renal SOFA score and two missing values for coagulation SOFA score. § Two missing values for cancer, one missing value for diabetes, and one missing value for psychoactive drug use.

ICU = intensive care unit; SAPS = Simplified Acute Physiology Score.

and lower dosages of remifentanil during the previous 24 h (table 2). More patients with pain assessments were treated with nonopioids, such as paracetamol and nefopam, than those without, and they received more often multimodal analgesia in the ICU, *i.e.*, an association of opioids and nonopioids. They were also more likely to have dedicated pain treatment during procedural pain events, such as endotracheal suctioning and mobilization during standard care.

We also noticed markedly different sedation management between the two groups. Patients with pain

Table 2. Analgesia Management and Pain Assessment on Day 2 of the ICU Stay

	Pain Assessment on Day 2		P Value
	No (n = 631)	Yes (n = 513)	
Opioids,* n (%)	600 (95)	474 (92)	0.06
Sufentanil, n (%)	253 (40)	178 (35)	0.06
Median (IQR), $\mu g \cdot kg^{-1} \cdot 24\ h^{-1}$	5.1 (2.8–7.6)	7.6 (4.2–10.9)	< 0.01
Fentanyl, n (%)	179 (28)	184 (36)	< 0.01
Median (IQR), $\mu g \cdot kg^{-1} \cdot 24\ h^{-1}$	43 (30–69)	40 (28–62)	0.40
Morphine, n (%)	94 (15)	60 (12)	0.11
Median (IQR), $mg \cdot kg^{-1} \cdot 24\ h^{-1}$	0.4 (0.3–0.6)	0.4 (0.3–0.8)	0.72
Remifentanil, n (%)	78 (12)	51 (10)	0.20
Median (IQR), $\mu g \cdot kg^{-1} \cdot 24\ h^{-1}$	149 (77–214)	98 (64–145)	0.02
Other opioids,† n (%)	10 (2)	17 (3)	0.05
Nonopioids,*‡ n (%)	184 (29)	217 (42)	< 0.01
Paracetamol, n (%)	153 (24)	185 (36)	< 0.01
Nefopam, n (%)	54 (9)	88 (17)	< 0.01
Ketamine, n (%)	8 (1)	24 (5)	0.01
Others, n (%)	14 (2)	17 (3)	0.25
Opioids + nonopioids, n (%)	153 (24)	181 (35)	< 0.01
Fentanyl + paracetamol, n (%)	46 (7)	25 (5)	0.09
Sufentanil + paracetamol, n (%)	20 (3)	65 (13)	< 0.01
Procedural pain assessment,§ n (%)	24 (4)	348 (68)	< 0.01
Procedural pain treatment,‖ n (%)	106 (17)	134 (26)	< 0.01
Opioids, n (%)	95 (15)	106 (21)	0.01
Nonopioids, n (%)	26 (4)	69 (14)	< 0.01

Drug doses are expressed as median and interquartile range (IQR), *i.e.*, 25th and 75th percentiles.

* Some patients were treated with more than one opioid and/or more than one nonopioid. † Other opioids were tramadol, buprenorphine, nalbuphine, alfentanil. ‡ One missing value for paracetamol and one missing value for other drugs (clonidine, nonsteroidal antiinflammatory). § Two missing values. ‖ Five missing values. The number of patients receiving opioids and nonopioids exceeds the total receiving treatment for procedural pain. Endotracheal suctioning and mobilization were the most frequently reported painful procedures.

ICU = intensive care unit.

assessments on D2 were less likely to receive hypnotic drugs, midazolam in particular, and they received lower daily doses of midazolam (table 3). Of the 928 patients who received hypnotic drugs on D2, those with pain assessments were more likely to be assessed for sedation as well (91% *vs.* 30%; P < 0.01). Sites used the Ramsay scale, the Richmond Agitation–Sedation Scale, the Sedation–Agitation Scale, and other instruments to assess sedation. In patients who were assessed for sedation, the proportion of patients in a deep sedative state was similar between the two groups. Finally, the use of neuromuscular blocking agents was significantly reduced in patients with pain assessment (table 3).

Table 3. Sedation Management, Neuromuscular Blocking Agent Use, and Pain Assessment on Day 2 of the ICU Stay

	Pain Assessment on Day 2		
	No (n = 631)	Yes (n = 513)	P Value
Sedatives,* n (%)	544 (86)	384 (75)	< 0.01
Midazolam, n (%)	411 (65)	295 (57)	< 0.01
Median (IQR), mg · kg^{-1} · 24 h^{-1}	1.5 (0.8–2.6)	1.1 (0.6–2.0)	< 0.01
Propofol, n (%)	133 (21)	86 (17)	0.06
Median (IQR), mg · kg^{-1} · 24 h^{-1}	21 (11–50)	24 (8–40)	0.43
Other sedatives,† n (%)	37 (6)	23 (4)	0.30
Sedation assessment, n/N (%)	162/544 (30)	348/384 (91)	< 0.01
Ramsay	113	153	
SAS	31	45	
RASS	0	68	
Others‡	18	82	
Deep sedative state, n/N (%)	76/162 (47)	170/348 (49)	0.68
NMBAs, n (%)	83 (13)	35 (7)	< 0.01

Drug doses are expressed as median and interquartile range (IQR), *i.e.*, 25th and 75th percentiles.

* Some patients were treated with more than one sedative (hypnotic). † Other sedatives were flunitrazepam (n = 17 patients), levomepromazine (n = 10 patients), cyamemazine (n = 8 patients), sodium gamma-hydroxybutyrate (n = 9 patients), hydroxyzine (n = 5 patients), clorazepate (n = 3 patients), haloperidol (n = 2 patients), pentobarbital (n = 2 patients), loxapine (n = 2 patients), droperidol (n = 1 patient), and tiapride (n = 1 patient). ‡ Other sedation assessment instruments were the Harris scale, Glasgow Coma Scale, Cook Scale, and Bispectral Index.

ICU = intensive care unit; NMBA = neuromuscular blocking agent; RASS = Richmond Agitation–Sedation Scale; SAS = Sedation–Agitation Scale.

Patient Outcome

No significant difference in mortality was found between the two groups of patients, allowing comparisons of MV duration and duration of stay among survivors (table 4). In univariate analysis, patients assessed for pain on D2 had a shorter duration of MV (8 *vs.* 11 days; *P* < 0.01) and duration of ICU stay (13 *vs.* 18 days; *P* < 0.01). While adjusting for quintile of propensity score to rule out all differences in baseline characteristics between the two study groups (data not shown), pain assessment was associated with increased odds of weaning from the ventilator (odds ratio, 1.40; 95% confidence interval, 1.00–1.98) and discharge from the ICU (odds ratio, 1.43; 95% confidence interval, 1.02–2.00). Because MV duration and duration of ICU stay were determined for survivors, the comparisons of ICU- and MV-free days led to the same conclusions between the two study groups (data not shown). A correct overlap of the propensity scores was observed between the two study groups within each quintile (table 5).

Supplementary Analysis

Of the 1,144 patients included in this study, 653 patients were still mechanically ventilated and receiving analgesia on D6. Of these, we excluded 114 because of the absence of MV on D2 (n = 23 patients), the absence of analgesia use on D2 (n = 7 patients), and a crossover between the 2 groups of patients between D2 and D6 (n = 84 patients). No significant differences were found in baseline characteristics for those 84 crossover patients and the 539 analyzed patients (data not shown). The group of patients with pain assessments on D6 included 229 patients (42% of the population), and the group with no pain assessments on D6 included 310 patients (58% of the population). Most of the differences between the two groups of patients regarding pain and sedation management on D2 agreed with those found on D6 (table 6). Patients with pain assessment on D6 were more likely to be assessed for sedation and for procedural pain. Also, they received fewer sedatives and lower daily doses of midazolam compared with patients not assessed for pain. In patients assessed for sedation, the proportion of patients in a deep sedative state was similar between the two groups.

Table 4. Patient Outcomes and Pain Assessment on Day 2 of the ICU Stay

Outcome Measure	Pain Assessment		Unadjusted Odds Ratio (95% CI)*†	P Value	Adjusted Odds Ratio (95% CI)†‡	P Value
	No (n = 631)	Yes (n = 513)				
ICU mortality, n (%)	136 (22)	95 (19)	0.91 (0.58–1.43)	0.69	1.06 (0.76–1.49)	0.71
ICU duration of stay, median (IQR), days	18 (10–30)	13 (7–25)	1.70 (1.29–2.25)	<0.01	1.43 (1.02–2.00)	0.04
Duration of MV, median (IQR), days	11 (6–30)	8 (4–17)	1.87 (1.41–2.48)	<0.01	1.40 (1.00–1.98)	0.05
Ventilator-acquired pneumonia, n (%)	117 (24)	66 (16)	0.61 (0.43–0.85)	<0.01	0.75 (0.48–1.17)	0.21
Thromboembolic events, n (%)	13 (3)	10 (2)	0.91 (0.39–2.09)	0.82	0.68 (0.21–2.24)	0.53
Gastroduodenal hemorrhage, n (%)	8 (2)	4 (1)	0.59 (0.18–1.97)	0.39	—	—
Central venous catheter colonization, n (%)	28 (6)	19 (5)	0.79 (0.44–1.44)	0.45	0.77 (0.34–1.76)	0.54

* Unadjusted odds ratios of intensive care unit (ICU) duration of stay, duration of mechanical ventilation (MV), ventilator-associated pneumonia, thromboembolic events, gastroduodenal hemorrhage, and central venous catheter colonization rates were determined for the 913 patients who were alive at discharge from the ICU. † Odds ratio of ICU mortality, discharge from the ICU, and weaning from the ventilator were estimated using discrete time logistic hazard models. All observations were censored at 30 days. ‡ Odds ratios were adjusted for quintiles of propensity score. Adjusted odds ratios could not be estimated for gastroduodenal hemorrhage because the number of events was too small. Fifty-seven patients with missing data for one or more covariates were excluded from propensity score-adjusted analysis. ICU duration of stay and MV duration were estimated for the 867 survivors with no missing value for covariates.

CI = confidence interval; IQR = interquartile range, *i.e.*, 25th and 75th percentiles.

Table 5. Propensity Score Values and Primary Outcomes According to Pain Assessment on Day 2 of the ICU Stay within Each Quintile

	Quintile of Propensity Score*				
	1	2	3	4	5
No pain assessment on D2					
No. of patients	201	177	147	65	16
Propensity score, median (IQR)	0.05 (0.03–0.08)	0.17 (0.14–0.20)	0.38 (0.32–0.46)	0.66 (0.59–0.72)	0.86 (0.83–0.90)
Pain assessment on D2					
No. of patients	17	40	71	152	201
Propensity score, median (IQR)	0.06 (0.04–0.09)	0.17 (0.14–0.22)	0.44 (0.34–0.50)	0.70 (0.63–0.76)	0.90 (0.86–0.95)
ICU mortality, n (%)					
No pain assessment on D2	40 (20)	37 (21)	30 (20)	19 (29)	2 (12)
Pain assessment on D2	1 (6)	9 (22)	16 (23)	38 (25)	28 (14)
ICU duration of stay, median (IQR), days					
No pain assessment on D2	18 (10–30+)	18 (10–30+)	16 (9–30+)	24 (11–30+)	14 (7–20)
Pain assessment on D2	22 (12–30+)	12 (7–30+)	14 (8–25)	16 (8–29)	12 (7–21)
MV duration, median (IQR), days					
No pain assessment on D2	12 (6–30)	11 (6–30)	10 (6–30+)	16 (7–30)	7 (5–10)
Pain assessment on D2	21 (7–30+)	7 (4–20)	8 (5–18)	11 (6–21)	6 (4–13)

* Fifty-seven patients with missing data for one or more covariates were excluded from propensity score-adjusted analysis. No significant first-order interaction was found between pain assessment and quintile of propensity score for the primary outcomes. Intensive care unit (ICU) duration of stay and mechanical ventilation (MV) duration were estimated for the 867 survivors with no missing value for covariates. All observations were censored at 30 days.

D2 = day 2; IQR = interquartile range, *i.e.*, 25th and 75th percentiles.

Discussion

In this cohort study of mechanically ventilated ICU patients receiving analgesia, pain assessment on D2 of the ICU stay was associated with marked differences in sedation and analgesia management. Such patients had

Table 6. Analgesia, Sedation Management, and Pain Assessment on Day 6 of the ICU Stay

	Pain Assessment on Day 6		P Value
	No (n = 310)	Yes (n = 229)	
Opioids, n (%)	283 (91)	199 (87)	0.10
Sufentanil, n (%)	109 (35)	72 (31)	0.37
Fentanyl, n (%)	87 (28)	69 (30)	0.60
Morphine, n (%)	55 (18)	27 (12)	0.06
Remifentanil, n (%)	33 (11)	23 (10)	0.82
Nonopioids, n (%)	110 (35)	97 (42)	0.10
Procedural pain assessment, n (%)	9 (3)	156 (68)	<0.01
Procedural pain treatment, n (%)	54 (18)	68 (30)	<0.01
Sedatives, n (%)	249 (80)	164 (72)	0.02
Midazolam, n (%)	186 (60)	116 (51)	0.03
Median (IQR), mg · kg^{-1} · 24 h^{-1}	1.7 (0.7–2.7)	1.2 (0.5–2.1)	<0.01
Propofol, n (%)	53 (17)	40 (17)	0.97
Median (IQR), mg · kg^{-1} · 24 h^{-1}	21 (12–37)	20 (11–36)	0.86
Sedation assessment, n/N (%)	68 (27)	152 (93)	<0.01
Deep sedative state, n/N (%)	29/68 (43)	60/152 (40)	0.66
NMBAs, n (%)	25 (8)	17 (7)	0.78

Drug doses are expressed as median and interquartile range (IQR), *i.e.*, 25th and 75th percentiles. Missing values for procedural pain treatments (n = 3), midazolam doses (n = 1) and propofol (n = 5).

ICU = intensive care unit; NMBA = neuromuscular blocking agent.

more frequent sedation level evaluations, fewer hypnotics and neuromuscular blocking agents, lower daily midazolam doses, more nonopioids, and more care for procedural pain than those whose pain was not assessed. Most of these differences still persisted on D6 of the ICU stay. After multiple adjustments for severity factors, pain and sedation medications, and ICU characteristics, these data reveal the use of pain assessments as an independent factor in reducing the MV duration and the duration of ICU stay. Although association does not prove a causal relation, the consistency of the results regarding the types of adjustments and the known effects of sedative use on MV duration suggest a link between pain assessment and patient outcome. Specifically, pain assessment might result in more attention toward pain and sedation management, in a multimodal approach, that in turn might reduce the duration of MV and duration of ICU stay. These findings, drawn from a large database of patient-based current practices, strongly argue in favor of the routine use of dedicated instruments to assess both pain and sedation in mechanically ventilated patients.

Duration of MV and duration of stay in the ICU have become reliable markers for determining the effects of sedatives and analgesics in mechanically ventilated patients.[16–18] Several randomized controlled trials have used these criteria to determine the efficacy of various strategies in optimizing sedation and analgesia: protocol-directed sedation according to consciousness levels,[26,27] sedation-based analgesia,[28,29] daily interruption of sedation,[30–32] combined sedation and ventilator weaning protocol,[33,34] and spontaneous breathing trial during ventilatory support.[35,36] Researchers have also conducted before-and-after studies to determine the impact

of implementing protocols on the duration of MV and duration of ICU stay in single centers.[15,37–40] Common to all of these studies is the repeated measurement of the level of conscious levels—and possibly pain—to achieve the desired target. In routine clinical practice, pain and sedation measurement rates remain unsatisfactory.[10–14] For this reason, we took a different approach to investigating a possible link between clinical practices—assessing pain in a cohort of mechanically ventilated patients—and changes in patient outcome. Despite the well-known limitations of cohort studies compared with randomized controlled trials, cohort studies do provide useful information. In particular, they help to determine the benefits and dangers of medical interventions, provided they respect the guidelines designed to strengthen the quality of reporting in observational studies.[41]

In the ICU, pain can result from several sources, including surgical incisions, traumatic injuries, occult infections, immobility, and ICU procedures.[1,42] Forty-five percent of patients reported moderate to severe pain (visual analog scale > 50 mm) during removal of the endotracheal tube.[43] Pain assessment in verbal patients is straightforward, whereas assessing pain in patients who are unable to communicate presents a great challenge. In the DOLOREA study, self-rating scales increased in use on subsequent days, as the level of hypnotic use decreased and more patients became able to communicate.[14] This resulted in no pain assessment for most nonverbal ICU patients. However, clinical instruments have been developed to address this issue, including the behavioral pain scale[24] and the Critical Care Pain Observation Tool,[44] both of which show good validity and reliability.[9] By using appropriate instruments to systematically assess pain in nonverbal patients, 50% of patients reported moderate to severe pain.[15] Our cohort of mechanically ventilated ICU patients, without severe head injuries, was mostly nonverbal, as 80% received sedatives on D2. We therefore hypothesized that measuring pain in those patients would imply the concomitant use of an instrument for measuring sedation, resulting in possible changes in the drug administration.

In this study, patients assessed for pain were less likely to be treated with hypnotic drugs, and they received 30% smaller daily doses of midazolam in comparison with the patients not assessed for pain. There were marginal differences between the two groups regarding their medical conditions. In addition, daily sedative interruptions were not performed. Although being one means to achieve reduced hypnotic doses, daily sedative interruption is not suitable for all mechanically ventilated patients.[32] Therefore, these differences between the two groups of patients could result from higher sedation assessment rates leading to more restricted sedative use. Previous studies found a 30–50% reduction in the mean daily and cumulative dosages of midazolam after the implementation of an algorithm. Staff repeated pain and sedation measurements every 3 h in the intervention phase to target the sedation level and adjust drug doses accordingly.[38,39] When staff systematically assessed pain and agitation at rest and 30 min after any procedure, the duration of continuous drug infusions was reduced by 30%.[15]

In our cohort of patients, pain assessment was also associated with better procedural pain management and with significant changes in the use of other drugs on D2 (nonopioids, neuromuscular blocking agents), in line with current recommendations.[45–48] Because more than 90% of our patients received opioids in the two groups, it could be postulated that nonopioids were used more often because pain assessment was provided in the group "Yes." Some evidence indicates that nefopam, a centrally acting nonopioid analgesic that inhibits serotonin and norepinephrine reuptake, may reduce postoperative morphine consumption and morphine-related side effects in surgical patients.[49] Although no impact can be inferred from 12% of patients treated with nefopam, this suggests that benefits could be expected from combining the use of nonopioids with opioids in the ICU setting. Our results also indicate that implementing ICU protocols and increasing education about pain and sedation could significantly help caregivers to follow national guidelines.

We found that patients assessed for pain required fewer hypnotics, lower midazolam doses, shorter MV durations by 3 days, and shorter ICU stays by 5 days. The relation between continuous hypnotic infusions and MV duration has been explored by daily sedative interruptions, which resulted in lower daily midazolam doses and, concomitantly, reduced MV durations.[30] Using the concept of sedative interruption, the use of propofol instead of lorazepam (a long-acting benzodiazepine) further reduced MV duration.[50] Both the dose and the type of daily hypnotics can affect MV duration, a statement supported by our findings. The comparable proportion of patients in a deep sedative state (47% *vs.* 49% on D2) indicates that, for those patients assessed for sedation, both groups had similar sedation requirements, thus excluding a potential confounding factor affecting MV duration. This assertion is somewhat hampered by the low proportion of patients assessed for sedation in the group with no pain assessment (30%). Interestingly, few studies have investigated whether the liberal use of opioids has a similar effect on patient outcome. In the study by Kress *et al.*,[30] the shorter MV duration in the intervention group resulted from lower doses of either morphine or midazolam. De Jonghe *et al.*[38] reported no changes in either the daily fentanyl doses or in the duration of fentanyl administration during the intervention phase, which resulted in 5 fewer days of MV. In our study, we found marginal differences in opioid use between the two groups, suggesting that those agents may have a less important role *per se* in the duration of MV than hypnotic drugs. The high concomitant rates of sedation assessments as well as the optimal use of anal-

gesics at rest and during procedures should surely prevent the inappropriate use of hypnotics to treat agitation and other sources of patient discomfort. With a restricted use of hypnotics in sedation-based analgesia, results showed differences in MV duration from opioids with different pharmacologic profiles.[28,29]

The current analysis has several limitations, in addition to those of the DOLOREA study that are discussed elsewhere.[14] First, although we made every effort to adjust for illness severity, treatments, and ICU characteristics, we could not randomly assign pain assessment. We used propensity-adjusted analysis to eliminate imbalances between the groups of patients for measured characteristics of both patients and sites. Apart from the highest quintile, the overlap of propensity scores between the two groups was satisfactory, indicating no imbalances in baseline characteristics. Interestingly, no significant first-order interaction was found (table 5), suggesting that the relation between pain assessment and the shorter duration of MV and duration of ICU stay was homogeneous across the quintiles of propensity scores. However, we could not exclude unrecorded confounding factors that may have influenced patient outcome, as recently pointed out.[51] Our finding that differences in pain and sedation management between the two groups still persisted on D6 gives some reliability to the results found on D2. Second, the odds ratios and their 95% confidence limits for MV duration and duration of ICU stay were close to one in the propensity score-adjusted analysis. Therefore, the data may not be compelling enough to strongly recommend pain assessment as a way of improving ICU patient outcomes. However, an adequately powered randomized controlled trial exploring the impact of pain assessment in the ICU on patient outcomes is ethically impossible to conduct, because pain and sedation assessments are strongly recommended in national guidelines.[45] Third, although we did study individual complications as a matter of routine, we cannot exclude possible interrelations between multiple complications within individuals. Fourth, we did not study the pharmacokinetic interactions between hypnotics and opioids or the pharmacogenetics of opioids that may have influenced the sedative/analgesic drug effects.[52] In particular, there were more elderly patients with no pain assessment, which could explain, in part, findings on MV duration due to their sensitivity to drugs.[53] However, the impact of age was balanced between the two groups with the use of a linear spline model in our adjustments.

In conclusion, our analysis shows an association between assessing pain in mechanically ventilated ICU patients and changes in clinical practice. In particular, staff assessed sedation more frequently and reduced hypnotic use. After adjustments, these changed clinical practices were associated with a shorter duration of MV and a reduced duration of stay in the ICU. Therefore, pain assessment in nonverbal ICU patients, although difficult, must be promoted together with sedation measurements in a multimodal approach, to avoid inappropriate use of hypnotic drugs to treat or mask pain.

References

1. Turner JS, Briggs SJ, Springhorn HE, Potgieter PD: Patients' recollection of intensive care unit experience. Crit Care Med 1990; 18:966–8

2. Rotondi AJ, Chelluri L, Sirio C, Mendelsohn A, Schulz R, Belle S, Im K, Donahoe M, Pinsky MR: Patients' recollections of stressful experiences while receiving prolonged mechanical ventilation in an intensive care unit. Crit Care Med 2002; 30:746–52

3. Schelling G, Stoll C, Haller M, Briegel J, Manert W, Hummel T, Lenhart A, Heyduck M, Polasek J, Meier M, Preuss U, Bullinger M, Schuffel W, Peter K: Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. Crit Care Med 1998; 26:651–9

4. Jones C, Backman C, Capuzzo M, Flaatten H, Rylander C, Griffiths RD: Precipitants of post-traumatic stress disorder following intensive care: A hypothesis generating study of diversity in care. Intensive Care Med 2007; 33:978–85

5. Carroll KC, Atkins PJ, Herold GR, Mlcek CA, Shively M, Clopton P, Glaser DN: Pain assessment and management in critically ill postoperative and trauma patients: A multisite study. Am J Crit Care 1999; 8:105–17

6. Stanik-Hutt JA, Soeken KL, Belcher AE, Fontaine DK, Gift AG: Pain experiences of traumatically injured patients in a critical care setting. Am J Crit Care 2001; 10:252–9

7. Puntillo KA, Wild LR, Morris AB, Stanik-Hutt J, Thompson CL, White C: Practices and predictors of analgesic interventions for adults undergoing painful procedures. Am J Crit Care 2002; 11:415–29

8. Chanques G, Sebbane M, Barbotte E, Viel E, Eledjam JJ, Jaber S: A prospective study of pain at rest: Incidence and characteristics of an unrecognized symptom in surgical and trauma *versus* medical intensive care unit patients. ANESTHESIOLOGY 2007; 107:858–60

9. Li D, Puntillo K, Miaskowski C: A review of objective pain measures for use with critical care adult patients unable to self-report. J Pain 2008; 9:2–10

10. Soliman HM, Melot C, Vincent JL: Sedative and analgesic practice in the intensive care unit: The results of a European survey. Br J Anaesth 2001; 87:186–92

11. Egerod I, Christensen BV, Johansen L: Trends in sedation practices in Danish intensive care units in 2003: A national survey. Intensive Care Med 2006; 32:60–6

12. Mehta S, Burry L, Fischer S, Martinez-Motta JC, Hallett D, Bowman D, Wong C, Meade MO, Stewart TE, Cook DJ: Canadian survey of the use of sedatives, analgesics, and neuromuscular blocking agents in critically ill patients. Crit Care Med 2006; 34:374–80

13. Martin J, Franck M, Sigel S, Weiss M, Spies CD: Changes in sedation management in German intensive care units between 2002 and 2006: A national follow up survey. Crit Care 2007; 11:R124

14. Payen JF, Chanques G, Mantz J, Hercule C, Auriant I, Leguillou JL, Binhas M, Genty C, Rolland C, Bosson JL: Current practices in sedation and analgesia for mechanically ventilated critically ill patients: A prospective multicenter patient-based study. ANESTHESIOLOGY 2007; 106:687–95

15. Chanques G, Jaber S, Barbotte E, Violet S, Sebbane M, Perrigault PF, Mann C, Lefrant JY, Eledjam JJ: Impact of systematic evaluation of pain and agitation in an intensive care unit. Crit Care Med 2006; 34:1691–9

16. 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; 114:541–8

17. Freire AX, Afessa B, Cawley P, Phelps S, Bridges L: Characteristics associated with analgesia ordering in the intensive care unit and relationships with outcome. Crit Care Med 2002; 30:2468–72

18. Arroliga A, Frutos-Vivar F, Hall J, Esteban A, Apezteguia C, Soto L, Anzueto A: Use of sedatives and neuromuscular blockers in a cohort of patients receiving mechanical ventilation. Chest 2005; 128:496–506

19. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996; 22:707–10

20. Cook DJ, Walter SD, Cook RJ, Griffith LE, Guyatt GH, Leasa D, Jaeschke RZ, Brun-Buisson C: Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. Ann Intern Med 1998; 129:433–40

21. Brun-Buisson C, Abrouk F, Legrand P, Huet Y, Larabi S, Rapin M: Diagnosis of central venous catheter-related sepsis: Critical level of quantitative tip cultures. Arch Intern Med 1987; 147:873–7

22. Anderson JR, Cain KC, Gelber RD: Analysis of survival by tumor response. J Clin Oncol 1983; 1:710–9

23. Joffe MM, Rosenbaum PR: Invited commentary: Propensity scores. Am J Epidemiol 1999; 150:327–33

24. Payen JF, Bru O, Bosson JL, Lagrasta A, Novel E, Deschaux I, Lavagne P, Jacquot C: Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med 2001; 29:2258–63

25. Harris CE, O'Donnell C, Macmillan RR, Mostafa SB: Use of propofol by infusion for sedation of patients undergoing haemofiltration: Assessment of the effect of haemofiltration on the level of sedation and on blood propofol concentration. J Drug Dev 1991; 4:37–9

26. Brook AD, Ahrens TS, Schaiff R, Prentice D, Sherman G, Shannon W, Kollef MH: Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med 1999; 27:2609–15

27. Bucknall TK, Manias E, Presneill JJ: A randomized trial of protocol-directed sedation management for mechanical ventilation in an Australian intensive care unit. Crit Care Med 2008; 36:1444–50

28. Breen D, Karabinis A, Malbrain M, Morais R, Albrecht S, Jarnvig IL, Parkinson P, Kirkham AJ: Decreased duration of mechanical ventilation when comparing analgesia-based sedation using remifentanil with standard hypnotic-based sedation for up to 10 days in intensive care unit patients: A randomised trial. Crit Care 2005; 9:R200–10

29. Muellejans B, Matthey T, Scholpp J, Schill M: Sedation in the intensive care unit with remifentanil/propofol *versus* midazolam/fentanyl: A randomized, open-label, pharmacoeconomic trial. Crit Care 2006; 10:R91

30. 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; 342:1471–7

31. Mehta S, Burry L, Martinez-Motta JC, Stewart TE, Hallett D, McDonald E, Clarke F, Macdonald R, Granton J, Matte A, Wong C, Suri A, Cook DJ: A randomized trial of daily awakening in critically ill patients managed with a sedation protocol: A pilot trial. Crit Care Med 2008; 36:2092–9

32. de Wit M, Gennings C, Jenvey WI, Epstein SK: Randomized trial comparing daily interruption of sedation and nursing-implemented sedation algorithm in medical intensive care unit patients. Crit Care 2008; 12:R70

33. Lellouche F, Mancebo J, Jolliet P, Roeseler J, Schortgen F, Dojat M, Cabello B, Bouadma L, Rodriguez P, Maggiore S, Reynaert M, Mersmann S, Brochard L: A multicenter randomized trial of computer-driven protocolized weaning from mechanical ventilation. Am J Respir Crit Care Med 2006; 174:894–900

34. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, Taichman DB, Dunn JG, Pohlman AS, Kinniry PA, Jackson JC, Canonico AE, Light RW, Shintani AK, Thompson JL, Gordon SM, Hall JB, Dittus RS, Bernard GR, Ely EW: 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; 371:126–34

35. Ely EW, Baker AM, Dunagan DP, Burke HL, Smith AC, Kelly PT, Johnson MM, Browder RW, Bowton DL, Haponik EF: Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med 1996; 335:1864–9

36. Putensen C, Zech S, Wrigge H, Zinserling J, Stuber F, Von Spiegel T, Mutz N: Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. Am J Respir Crit Care Med 2001; 164:43–9

37. Brattebo G, Hofoss D, Flaatten H, Muri AK, Gjerde S, Plsek PE: Effect of a scoring system and protocol for sedation on duration of patients' need for ventilator support in a surgical intensive care unit. BMJ 2002; 324:1386–9

38. De Jonghe B, Bastuji-Garin S, Fangio P, Lacherade JC, Jabot J, Appéré-De-Vecchi C, Rocha N, Outin H: Sedation algorithm in critically ill patients without acute brain injury. Crit Care Med 2005; 33:120–7

39. Quenot JP, Ladoire S, Devoucoux F, Doise JM, Cailliod R, Cunin N, Aube H, Blettery B, Charles PE: Effect of a nurse-implemented sedation protocol on the incidence of ventilator-associated pneumonia. Crit Care Med 2007; 35:2031–6

40. Marshall J, Finn CA, Theodore AC: Impact of a clinical pharmacist-enforced intensive care unit sedation protocol on duration of mechanical ventilation and hospital stay. Crit Care Med 2008; 36:427–33

41. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP: STROBE Initiative: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement—Guidelines for reporting observational studies. BMJ 2007; 335:806–8

42. Puntillo KA, Morris AB, Thompson CL, Stanik-Hutt J, White CA, Wild LR: Pain behaviors observed during six common procedures: Results from Thunder Project II. Crit Care Med 2004; 32:421–7

43. Gacouin A, Camus C, Le Tulzo Y, Lavoue S, Hoff J, Signouret T, Person A, Thomas R: Assessment of peri-extubation pain by visual analogue scale in the adult intensive care unit: A prospective observational study. Intensive Care Med 2004; 30:1340–7

44. Gelinas C, Fillion L, Puntillo KA, Viens C, Fortier M: Validation of the critical-care pain observation tool in adult patients. Am J Crit Care 2006; 15:420–7

45. 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, Murray MJ, Peruzzi WT, Lumb PD: Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002; 30:119–41

46. Sauder P, Andreoletti M, Cambonie G, Capellier G, Feissel M, Gall O, Goldran-Toledano D, Kierzek G, Mateo J, Mentec H, Mion G, Rigaud JP, Seguin P: Sédation-analgésie en réanimation (nouveau-né exclu). French Society of Anesthesia and Intensive Care and French-speaking Intensive Care Society. Ann Fr Anesth Reanim 2008; 27:541–51

47. Kress JP, Pohlman AS, Hall JB: Sedation and analgesia in the intensive care unit. Am J Respir Crit Care Med 2002; 166:1024–8

48. Sessler CN, Varney K: Patient-focused sedation and analgesia in the ICU. Chest 2008; 133:552–65

49. Evans MS, Lysakowski C, Tramer MR: Nefopam for the prevention of postoperative pain: Quantitative systematic review. Br J Anaesth 2008; 101:610–7

50. Carson SS, Kress JP, Rodgers JE, Vinayak A, Campbell-Bright S, Levitt J, Bourdet S, Ivanova A, Henderson AG, Pohlman A, Chang L, Rich PB, Hall J: A randomized trial of intermittent lorazepam *versus* propofol with daily interruption in mechanically ventilated patients. Crit Care Med 2006; 34:1326–32

51. Nuttall GA, Houle TT: Liars, damn liars, and propensity scores. ANESTHESIOLOGY 2008; 108:3–4

52. Sia AT, Lim Y, Lim EC, Goh RW, Law HY, Landau R, Teo YY, Tan EC: A118G single nucleotide polymorphism of human μ-opioid receptor gene influences pain perception and patient-controlled intravenous morphine consumption after intrathecal morphine for postcesarean analgesia. ANESTHESIOLOGY 2008; 109:520–6

53. Rivera R, Antognini JF: Perioperative drug therapy in elderly patients. ANESTHESIOLOGY 2009; 110:1176–81

Appendix: DOLOREA Investigators

Joachim Calderon, M.D. (Hôpital Cardiologique, Bordeaux, France), Laurent Beydon, M.D. (Centre Hospitalier Universitaire, Angers, France), Charles Cerf, M.D. (Hôpital Henri Mondor, Créteil, France), Philippe Barbe, M.D. (Centre Hospitalier, Chambéry, France), Stéphane Winnock, M.D. (Centre Hospitalier Universitaire, Bordeaux, France), Jean Hébert, M.D. (Centre Hospitalier Universitaire, Caen, France), Moldi Hamrouni, M.D. (Hôpital Louis Pasteur, Chartres, France), Dominique Guelon, M.D. (Hôpital Gabriel Montpied, Clermont-Ferrand, France), Stéphanie Artigues, M.D. (Hôtel Dieu, Clermont-Ferrand, France), Irène Messant, M.D. (Hôpital Général, Dijon, France), Elsa Brocas, M.D. (Centre Hospitalier Louise Michel, Evry, France), Pierre Lavagne, M.D. (Hôpital Michallon, Grenoble, France), Christiane Hercule, M.D. (Hôpital Cardiovasculaire et Pneumologique Louis Pradel, Lyon, France), Serge Duperret, M.D. (Hôpital Croix Rousse, Lyon, France), Khalid Berrada, M.D. (Hôtel Dieu, Lyon, France), Jean-Michel Grozel, M.D. (Centre Hospitalier Lyon Sud, Lyon, France), Gérald Chanques, M.D. (Hôpital St Eloi, Montpellier, France), Sarah Valette, M.D. (Hôpital Lapeyronie, Montpellier, France), Francine Bonnet, M.D., Laurent Benayoun, M.D. (Hôpital Beaujon, Clichy, France), Adrien Decorps-Declère, M.D. (Hôpital Antoine Beclère, Clamart, France), Jacques Duranteau, M.D. (Hôpital Bicêtre, Le Kremlin-Bicêtre, France), Jean Mantz, M.D., Hervé Quintard, M.D. (Hôpital Bichat Claude Bernard, Paris, France), Jean-Francois Timsit, M.D., Bruno Mourvilliers, M.D. (Hôpital Bichat Claude Bernard, Paris, France), Christian Rathat, M.D. (Hôpital Avicenne, Bobigny, France), Rémy Gauzit, M.D. (Hôpital Jean Verdier, Bondy, France), Andrea Passard, M.D. (Hôpital Ambroise Paré, Boulogne-Billancourt, France), Jean-Paul Perez, M.D. (Hôpital d'Instruction des Armées, Clamart, France), Laurent Dubé, M.D. (Centre Hospitalier Universitaire, Angers, France), Michèle Binhas, M.D. (Hôpital Henri Mondor, Créteil, France), Anne-Claire Lukaszewicz, M.D. (Hôpital Lariboisière, Paris, France), Jean-Luc Leguillou, M.D. (Institut Mutualiste Montsouris, Paris, France), Laurent Jacob, M.D. (Hôpital Saint Louis, Paris, France), Sonia Elmetaoua, M.D. (Hôpital Tenon, Paris, France), Jean-Paul Bleichner, M.D. (Hôpital Ponchaillou, Rennes, France), Igor Auriant, M.D., Gaëlle Demeilliers-Pfister, M.D. (Hôpital Charles Nicolle, Rouen, France), Philippe Mahul, M.D. (Hôpital Nord, St Etienne, France), Guy Freys, M.D. (Hôpital de Hautepierre, Strasbourg, France), Pascale Sanchez, M.D. (Hôpital Purpan, Toulouse, France), Francois Lagarrigue, M.D. (Hôpital Trousseau, Tours, France), Bruno Raynard, M.D. (Institut Gustave Roussy, Villejuif, France), Emmanuelle Nalet, M.D. (Centre Hospitalier de la Région Annecienne, Annecy, France), Marc Feissel, M.D. (Centre Hospitalier Général, Belfort, France), Jérôme Baudot, M.D. (Centre Hospitalier Henri Duffaut, Avignon, France), Marc Klop, M.D. (Clinique Sainte Thérèse, Luxembourg).