Effect of Sedation With Dexmedetomidine vs Lorazepam on Acute Brain Dysfunction in Mechanically Ventilated Patients: The MENDS Randomized Controlled Trial

Pratik P. Pandharipande; Brenda T. Pun; Daniel L. Herr; et al.

JAMA. 2007;298(22):2644-2653 (doi:10.1001/jama.298.22.2644)

http://jama.ama-assn.org/cgi/content/full/298/22/2644

Effect of Sedation With Dexmedetomidine vs Lorazepam on Acute Brain Dysfunction in Mechanically Ventilated Patients

The MENDS Randomized Controlled Trial

Pratik P. Pandharipande, MD, MSCI
Brenda T. Pun, RN, MSN, ACNP
Daniel L. Herr, MD
Mervyn Maze, MB, ChB
Timothy D. Girard, MD, MSCI
Russell R. Miller, MD, MPH
Ayumi K. Shintani, MPH, PhD
Jennifer L. Thompson, MPH
James C. Jackson, PsyD
Stephen A. Deppen, MA, MS
Renee A. Stiles, PhD
Robert S. Dittus, MD, MPH
Gordon R. Bernard, MD
E. Wesley Ely, MD, MPH

Context Lorazepam is currently recommended for sustained sedation of mechanically ventilated intensive care unit (ICU) patients, but this and other benzodiazepine drugs may contribute to acute brain dysfunction, ie, delirium and coma, associated with prolonged hospital stays, costs, and increased mortality. Dexmedetomidine induces sedation via different central nervous system receptors than the benzodiazepine drugs and may lower the risk of acute brain dysfunction.

Objective To determine whether dexmedetomidine reduces the duration of delirium and coma in mechanically ventilated ICU patients while providing adequate sedation as compared with lorazepam.

Design, Setting, Patients, and Intervention Double-blind, randomized controlled trial of 106 adult mechanically ventilated medical and surgical ICU patients at 2 tertiary care centers between August 2004 and April 2006. Patients were sedated with dexmedetomidine or lorazepam for as many as 120 hours. Study drugs were titrated to achieve the desired level of sedation, measured using the Richmond Agitation-Sedation Scale (RASS). Patients were monitored twice daily for delirium using the Confusion Assessment Method for the ICU (CAM-ICU).

Main Outcome Measures Days alive without delirium or coma and percentage of days spent within 1 RASS point of the sedation goal.

Results Sedation with dexmedetomidine resulted in more days alive without delirium or coma (median days, 7.0 vs 3.0; $P=.01$) and a lower prevalence of coma (63% vs 92%; $P<.001$) than sedation with lorazepam. Patients sedated with dexmedetomidine spent more time within 1 RASS point of their sedation goal compared with patients sedated with lorazepam (median percentage of days, 80% vs 67%; $P=.04$). The 28-day mortality in the dexmedetomidine group was 17% vs 27% in the lorazepam group ($P=.18$) and cost of care was similar between groups. More patients in the dexmedetomidine group (42% vs 31%; $P=.61$) were able to complete post-ICU neuropsychological testing, with similar scores in the tests evaluating global cognitive, motor speed, and attention functions. The 12-month time to death was 363 days in the dexmedetomidine group vs 188 days in the lorazepam group ($P=.48$).

Conclusion In mechanically ventilated ICU patients managed with individualized targeted sedation, use of a dexmedetomidine infusion resulted in more days alive without delirium or coma and more time at the targeted level of sedation than with a lorazepam infusion.

Trial Registration clinicaltrials.gov Identifier: NCT00095251

JAMA. 2007;298(22):2644-2653 www.jama.com

SEDATIVE AND ANALGESIC MEDICATIONS are routinely administered to mechanically ventilated patients to reduce pain and anxiety and to allow patients to tolerate invasive procedures in the intensive care unit (ICU).[1] Unfortunately, these medications may increase mechanical ventilation time and ICU length of stay[2] and potentiate the risk of developing acute brain dysfunction, ie, delirium and coma.[3-6] Because delirium is an independent risk factor for prolonged length of stay, greater neuropsychological dysfunction, and increased mortality,[7-10] efforts must be made to reduce this manifestation of organ dysfunction within the context of providing adequate sedation for patients.

Lorazepam is currently recommended by the Society of Critical Care Medicine (SCCM) in its clinical practice guidelines[1] for the sustained sedation of mechanically ventilated ICU patients. Although recent trials have shown that protocols with patient-targeted se-

Author Affiliations are listed at the end of this article.
Corresponding Author: Pratik P. Pandharipande, MD, MSCI, 526 MAB, 1211 21st Ave S, Nashville, TN 37212 (pratik.pandharipande@vanderbilt.edu).
Caring for the Critically Ill Patient Section Editor: Derek C. Angus, MD, MPH, Contributing Editor, *JAMA*.

dation and the daily interruption of sedatives improve patient outcomes,[11-14] no study to date has compared benzodiazepine drugs with novel sedative medications that act on different central nervous system receptors in reducing brain organ dysfunction (delirium and coma) and providing efficacious sedation. This presents an unmet need for scientific study given that sedative and analgesic medications are a potentially modifiable risk factor for delirium.[3-6]

Although the mechanisms by which benzodiazepine drugs predispose patients to delirium remain unproven, these drugs may cause brain dysfunction via activation of γ-aminobutyric acid ($GABA_A$) central nervous system receptors[15] that alter levels of potentially deliriogenic neurotransmitters, such as dopamine, serotonin, acetylcholine, norepinephrine, and glutamate.[16-18] Dexmedetomidine, a highly selective α_2-adrenergic receptor agonist that acts at the locus ceruleus and spinal cord to produce both sedation and analgesia, is a viable yet understudied alternative to GABA-mimetic sedatives.[19] With recent pilot data suggesting that sedation with dexmedetomidine reduces rates of delirium,[20] we designed and conducted the MENDS (Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction) study to test the hypothesis that dexmedetomidine, when compared with benzodiazepine drugs, reduces the duration of delirium and coma while effectively sedating mechanically ventilated ICU patients.

METHODS

This was an investigator-initiated study in which the authors obtained an Investigational New Drug approval from the US Food and Drug Administration (FDA). This approval permitted the study of dexmedetomidine for longer than the current 24-hour FDA-labeled indication for use in the ICU and at doses as great as 1.5 µg/kg per hour, ie, higher than doses currently approved by the FDA (≤0.7 µg/kg per hour). The institutional review boards at Vanderbilt University Medical Center, Nashville, Tennessee, and Washington Hospital Center, Washington, DC, approved this study.

Patients

The study inclusion criteria were adult medical and surgical ICU patients requiring mechanical ventilation for longer than 24 hours. Patients were excluded due to neurological disease (previous stroke, cerebral palsy, etc) that would confound the diagnosis of delirium, active seizures, Childs-Pugh class B or C liver disease, moribund state with planned withdrawal of life support, family or physician refusal, alcohol abuse, active myocardial ischemia, second- or third-degree heart block, severe dementia, benzodiazepine dependency, pregnancy or lactation, and severe hearing disabilities or inability to understand English to allow delirium evaluations. Patients who met inclusion criteria and no exclusion criteria were enrolled in the study after informed consent was obtained from patients or their authorized surrogates. Patients for whom surrogate consent was obtained were asked again to provide informed consent once they were determined to be competent. At enrollment, patient surrogates were interviewed to assess baseline cognitive abilities using the validated Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).[21]

Randomization and Baseline Data Collection

Patients were randomized using computer-generated, permuted block randomization (known only to the investigational pharmacists) and stratified by site to receive sedation with either dexmedetomidine or lorazepam. Detailed information of sedative and analgesic medications administered to the patients prior to randomization was collected at the time of enrollment, as were baseline demographics and severity of illness data. Per FDA request, a baseline electrocardiogram was performed and endocrine levels were drawn including cortisol, adrenocorticotrophic hormone, leutinizing hormone, prolactin, and testosterone prior to the start of the study drug infusion.

Study Drug Administration

All patients and study personnel, except for the investigational pharmacist, were blinded to study drug assignment. We chose lorazepam as our control-group sedative because it is the sedative of choice for long-term sedation in critically ill patients, per SCCM guidelines.[1] We used infusion instead of bolus dosing to preserve the blinding and to minimize potential adverse effects. The study drug was prepared in clear bags containing either dexmedetomidine (prepared for a final concentration of 0.15 µg/kg per mL) or lorazepam (1 mg/mL). The study drug infusion was started at 1 mL/h (0.15 µg/kg per hour dexmedetomidine or 1 mg/h lorazepam) and titrated by the bedside nurse to a maximum of 10 mL/h (1.5 µg/kg per hour dexmedetomidine or 10 mg/h lorazepam) to achieve the sedation goal set by the patient's medical team using the Richmond Agitation-Sedation Scale (RASS).[22,23] The study drug was infused as needed until extubation or for the maximum time allowed by the FDA (120 hours) and infusions could be discontinued at any time if patient was at sedation target. Patients who were mechanically ventilated beyond the 120-hour study drug period were then sedated according to the standard practice of the particular ICU. Apparent pain was treated by the nurses with intermittent doses of fentanyl based on physiological parameters, such as changes in blood pressure, heart rate, and respiratory rate, in addition to facial expressions, limb movement, and ventilator synchrony. Additionally, if 10 mL/h of the study drug did not result in adequate sedation or if patients required frequent intermittent doses of fentanyl for pain, a continuous infusion of fentanyl was permitted. If a patient experienced sudden and urgent levels of agitation that had the potential to cause harm to the patient or staff, a propofol bolus of 25 to 50 mg was allowed, while the study drug or fentanyl infusions were titrated upwards. No open label use of either study drug or other benzodiazepine drugs was permitted in the protocol during the study drug period. The decision to perform daily cessation of sedatives[11] and spontaneous breathing trials[24] was considered part of the managing teams' protocol

and not mandated as part of the study protocol.

Primary and Secondary Outcomes

The primary outcome of interest was delirium-free and coma-free days, defined as the days alive without delirium or coma. Additionally, we evaluated efficacy of the 2 sedation regimens in achieving clinically individualized target sedation goals. Secondary outcomes of the study included lengths of stay with ventilation, in the ICU, and in the hospital, along with neuropsychological testing after ICU discharge, 28-day mortality, and 12-month survival from enrollment. In the MENDS study, ventilator-free days were calculated as the number of days alive and not using mechanical ventilation over a 28-day period.[25]

Assessing Delirium and Coma

Delirium was measured until hospital discharge or for 12 days using the Confusion Assessment Method for the ICU (CAM-ICU),[9,26,27] a well-validated instrument for diagnosing delirium in ventilated and nonventilated ICU patients. Patients were categorized as having delirium if they had a RASS score of minus 3 or greater (ie, RASS –3, –2, –1, 0, etc; ie, responsive to verbal stimulus) and a positive CAM-ICU. The CAM-ICU is considered positive with feature 1 (acute onset of mental status change or fluctuation of mental status), feature 2 (inattention), and either feature 3 (disorganized thinking), or feature 4 (altered level of consciousness) symptoms.

Coma was defined as a RASS score of minus 4 (responsive only to physical stimulus) or minus 5 (unresponsive to physical stimulus). Both the RASS and the CAM-ICU instruments are described in more depth at http://www.icudelirium.org. Duration of delirium was calculated as the number of days patients were CAM-ICU-positive during a 12-day evaluation period and was initially registered as the primary outcome in http://www.clinicaltrials.gov. Shortly thereafter and prior to enrollment of any patient, we decided to use the composite end point of delirium-free and coma-free days as our primary end point. This event-free outcome takes into account the contribution of delirium, coma, and death and is the best outcome measure of the improvement in the duration of normal cognitive status (devoid of delirium and coma). We chose delirium-free and coma-free days over delirium-free days because the latter outcome would not account for the contribution of coma, a major category of abnormal brain function that might (we hypothesized) be differentially contributed to by one study drug vs the other. Thus for this study, a delirium-free and coma-free days end point represented the number of days in a 12-day period after enrollment, during which patients were alive without delirium or coma. This duration was chosen to account for acute brain organ dysfunction 1 week beyond the maximum study drug period of 120 hours.

Assessing Level and Efficacy of Sedation

Efficacy of the study drug was defined as the ability to achieve a sedation score within 1 point of the desired goal sedation level. Sedation level was assessed using the RASS,[22,23] a highly reliable and well-validated sedation scale for use within patients over time in the ICU. To measure the desired sedation goal of the managing team, both the physician goal RASS scores and the nurse goal RASS scores were recorded twice daily at the time of the study assessments. The 2 sets of RASS data were collected to account for differences in nurses' and physicians' sedation goals for each patient.[28-30] The physician goal RASS score was obtained from the daily ordered sedation goal in the computerized physician order-entry system. The nurse goal was identified each day by asking bedside nurses to identify their sedation goal. Detailed data regarding hourly study drug infusion and fentanyl administration were also collected prospectively.

Post-ICU Follow-Up

Patients underwent neuropsychological testing within 72 hours of ICU discharge, as long as they were CAM-ICU negative. Testing included the Mini Mental State Examination[31] and the Trails-B test,[32] administered by the research nurses. The Mini Mental State Examination is a global assessment tool that assesses orientation to time and place, registration and recall of 3 words, attention and calculation, and language and visual construction. The Trails-B is a test of visual conceptual and visuomotor tracking (involves motor speed and attention functions).

Patients were observed in the hospital from enrollment until discharge or death, and survivors were observed for vital status until 1 year after enrollment, using the hospitals' electronic record systems and a commercial version of the Social Security Death Master File.[33]

Safety Monitoring

Hematological and blood chemistry data ordered by the medical team, as well as vital signs such as blood pressure, heart rate, heart rhythm, temperature, and oxygen saturations were recorded daily for 21 days or until hospital discharge. The cardiac safety profile included electrocardiograms and serum troponins on study days 2, 4, and 2 days after study drug discontinuation. Cortisol, adrenocorticotropic hormone, luteinizing hormone, prolactin and testosterone, which were measured at enrollment, were also measured 2 days after the study drug was discontinued. Similarly, serum bilirubin and glutamate pyruvate transaminase were measured on study days 2, 4, and 1 week after discontinuing the study drug to evaluate possible changes in liver function due to the different sedative regimens.

Adverse Event Monitoring

Self-extubation and removal of catheters or other medical devices were tracked as safety end points. Additionally, study personnel monitored patients for clinical adverse events daily during the trial, and investigators assessed the seriousness of all adverse events, determining whether or not a patient's medical team thought that any event was related to either study drug or study procedures. Investigators reported all serious, unexpected, and study-related adverse events within 7

days of occurrence to an independent data and safety monitoring board and the institutional review board. The data and safety monitoring board and the FDA reviewed 1 interim analysis of all the safety data independently after enrollment of 26 patients. No interim evaluation of efficacy was conducted.

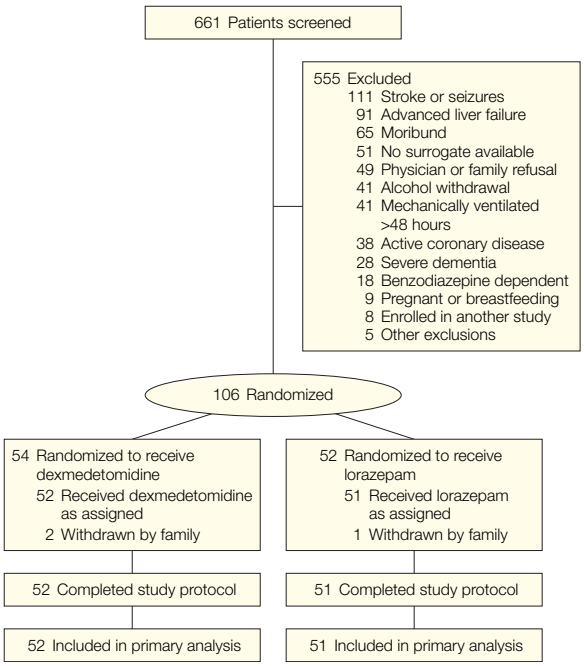
Cost Evaluation

Total costs were obtained from Vanderbilt University Medical Center's cost-accounting system for the 90 patients who were enrolled there. Cost data were not available for the Washington Hospital Center patients. Vanderbilt University Medical Center uses a procedural-based cost-accounting methodology that sums activity at the department level and distributes indirect and other fixed costs by weighting activity according to the procedures' relative value units. Each individual item that a patient used and was billed by the financial system, was then standardized to the cost of the item or service in fiscal year 2006. If no match could be made between the financial activity in a previous year and a similar item or service in 2006, the cost of the item in the year that the charge was generated was used. Study drug cost data were determined by using the actual number of vials used by each patient, multiplied by the actual cost to purchase and administer that drug to the patient. Costs for the hospitalization, outside the study drug cost, were calculated separately by department to reflect total costs for pharmacy, respiratory therapy (including ventilator cost), as well as ICU and total hospital care.

Sample Size Calculation

The primary outcome variable for analysis was delirium-free and coma-free days, defined as the number of days out of a 12-day period following enrollment, during which patients were alive without delirium or coma. Our pilot data indicated that ICU patients had a mean (SD) of 5.54 (4.37) delirium-free and coma-free days and a median (interquartile range) of 5 (1-9.5) days. Because this variable is skewed, sample size for this study was based on transformed delirium and coma-free days and was estimated to detect a 30% increase (ie, improvements) in delirium-free and coma-free days by the intervention. To achieve 80% analytical power to detect the difference, the study required 48 patients in each group at 2-sided 5% significance level.

Figure 1. Screening, Enrollment, and Randomization



Three patients were withdrawn by family after giving informed consent and after randomization but prior to study drug administration and were excluded from analysis since no data collection was permitted.

Statistical Analysis

Data were analyzed using an intention-to-treat approach. Continuous data were described using median and interquartile range, and categorical data using frequencies and proportions. We used Pearson χ^2 tests to compare categorical variables between the 2 study groups and Wilcoxon rank-sum tests to compare continuous variables, including the primary outcome variable, delirium-free and coma-free days. Time-to-event analyses were used to compare the effects of the 2 sedation regimens on 28-day mortality, 12-month mortality, and ICU and hospital lengths of stay. Kaplan-Meier survival curves were used for graphical presentation of these time-to-event analyses and log-rank statistics were used to assess the effects of the 2 sedation regimens. For the 28-day mortality analyses, patients were censored at the time of last contact alive or at 28 days from enrollment, whichever was first. For the 12-month mortality analyses, patients were censored at the time of last contact alive or at 365 days from enrollment, whichever was first. Censoring for ICU or hospital discharge analyses occurred at time of death or study withdrawal. Two-sided *P* values of .05 or less were considered to indicate statistical significance. All analyses were completed using version 2.4 of R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Enrollment

From August 2004 to April 2006, we screened 661 consecutive mechanically ventilated patients and enrolled 106 patients. FIGURE 1 shows the reasons for exclusion. Three patients were

withdrawn from the study by family following informed consent and randomization but prior to study drug administration. No data were collected from these patients who were, therefore, excluded from the analysis. Analysis included 103 patients with 52 patients randomized to the dexmedetomidine group and 51 patients to the lorazepam group. All randomized patients completed the study protocol and were observed throughout their hospitalization or until study day 21.

Table 1. Baseline Demographics of Patients Sedated With Dexmedetomidine vs Lorazepam[a]

Variable	Dexmedetomidine (n = 52)	Lorazepam (n = 51)	*P* Value
Age, y	60 (49 to 65)	59 (45 to 67)	.97
Men, No. (%)	30 (58)	23 (45)	.20
Severity of illness assessment scores			
APACHE II	29 (24 to 32)	27 (24 to 32)	.75
SOFA	10 (8 to 12)	9 (7 to 11)	.15
IQCODE at enrollment	3 (3 to 3)	3 (3 to 3)	.31
ICU type, No. (%)			.78
Medical ICU	37 (71)	35 (69)	
Surgical ICU	15 (29)	16 (31)	
Preenrollment history			
Total lorazepam exposure, mg	0.25 (0 to 4.25)	0 (0 to 3.0)	.69
Mechanical ventilator support prior to enrollment, h	22 (14 to 35)	17 (8 to 27)	.18
RASS score at enrollment	–3 (–4 to –1)	–4 (–4 to –1)	.21
Admission diagnosis, No. (%)			
Sepsis/acute respiratory distress syndrome	19 (37)	20 (39)	.78
Pulmonary (other)[b]	12 (23)	11 (22)	.85
Malignancies	4 (8)	4 (8)	.98
Airway/ear, nose and throat (otolaryngeal surgery)	3 (6)	1 (2)	.32
Acute lung injury	2 (4)	3 (6)	.63
Chronic obstructive pulmonary disease	2 (4)	2 (4)	.98
Cardiogenic shock	2 (4)	0 (0)	.16
Hemorrhagic shock	1 (2)	1 (2)	.99
Renal failure	1 (2)	0 (0)	.32
Other[c]	6 (10)	9 (17)	.38

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; SOFA, Sequential Organ Failure Assessment.
[a] Median (interquartile range) unless otherwise noted.
[b] Pulmonary (other) included admissions due to pulmonary hypertension, cystic fibrosis, hemoptysis, pulmonary embolism, and pulmonary fibrosis.
[c] Includes admission diagnoses due to gastric and colonic surgery, orthopedic surgery, urological surgery, vascular surgery, and cardiac surgery; reasons other than sepsis; and adult respiratory distress syndrome.

Table 2. Outcomes in Mechanically Ventilated Patients Sedated With Dexmedetomidine vs Lorazepam[a]

Outcome Variable	Dexmedetomidine (n = 52)	Lorazepam (n = 51)	*P* Value
Duration of brain organ dysfunction, d			
Delirium-free and coma-free[b]	7 (1-10)	3 (1-6)	.01
Delirium-free[b]	9 (5-11)	7 (5-10)	.09
Coma-free[b]	10 (9-12)	8 (5-10)	<.001
Delirium	2.5 (1-5)	4 (1-5)	.71
Coma	2 (0-3)	3 (2-5)	.003
Prevalence of brain organ dysfunction, No. (%)[c]			
Delirium or coma	45 (87)	50 (98)	.03
Delirium	41 (79)	42 (82)	.65
Coma	33 (63)	47 (92)	<.001
Other clinical outcomes			
Mechanical ventilator-free, d[d]	22 (0-24)	18 (0-23)	.22
Intensive care unit length of stay, d	7.5 (5-19)	9 (6-15)	.92
28-Day mortality, No. (%)	9 (17)	14 (27)	.18

[a] Median (interquartile range) unless otherwise noted.
[b] Indicates the number of days alive without stated dysfunction from study days 1 to 12.
[c] Prevalence is used to describe the rates of brain organ dysfunction instead of incidence because preintensive care unit delirium or coma status could not be determined. Prevalence represents the occurrence of brain organ dysfunction at any time during the 12-day assessment period.
[d] Indicates the number of days alive, breathing without mechanical ventilator assistance, from study day 1 to 28.

Baseline Characteristics

The 2 groups were similar at baseline with respect to demographics, severity of illness, comorbid conditions, and ICU admission diagnoses (TABLE 1). Median time from onset of mechanical ventilation to enrollment was 22.1 hours in the dexmedetomidine group and 16.7 hours in the lorazepam group ($P=.18$). Median lorazepam use prior to enrollment was similar in the dexmedetomidine and lorazepam groups ($P=.69$).

Clinical Outcomes

The major clinical outcomes are shown in TABLE 2. Dexmedetomidine patients had more days alive without delirium or coma (median, 7 vs 3; $P=.01$) (FIGURE 2). About 30% fewer patients experienced coma in the dexmedetomidine group than in the lorazepam group (63% vs 92%; $P<.001$). Nonsignificant differences were noted between the dexmedetomidine and lorazepam groups in 28-day mortality (17% vs 27%; $P=.18$) (FIGURE 3) and ventilator-free days (22 vs 18 days alive and free of mechanical ventilation; $P=.22$). A higher but nonsignificant percentage of patients in the dexmedetomidine group (42% vs 31%; $P=.61$) were able to complete post-ICU neuropsychological testing. The time from enrollment to testing was 2.5 days earlier in the dexmedetomidine group (7 vs 9.5 days), which reflected an earlier return to delirium-negative cognitive state in those patients. In the dexmedetomidine vs lorazepam groups, the median Mini-Mental State Examination scores (assessing global cognitive function) were 28 vs 27 ($P=.23$) and Trails-B scores (assessing motor speed and attention functions) corrected for age and level of education were 18 vs 19 ($P=.75$).

The 12-month time to death in the dexmedetomidine vs the lorazepam group was 363 vs 188 days, respec-

tively. The likelihood of dying at 12 months was similar between groups (hazard ratio, 0.8; 95% confidence interval, 0.5-1.4; $P = .48$).

Efficacy of Sedation

The median infusion rate for dexmedetomidine was 0.74 µg/kg per hour (interquartile range, 0.39 µg/kg per hour-1.04 µg/kg per hour); and for lorazepam was 3 mg per hour (interquartile range, 2.2 mg per hour-6 mg per hour). Patients sedated with dexmedetomidine spent more time at the level of sedation targeted by both nurses and physicians than patients sedated with lorazepam (TABLE 3 and FIGURE 4). The median administered fentanyl dose was 575 µg per day in the dexmedetomidine group vs 150 µg per day in the lorazepam group ($P = .006$), and this difference was more notable when patients had deeper sedation goals (FIGURE 5). Seven patients in the dexmedetomidine group were administered propofol boluses for perceived dangerous agitation or for procedure-related sedation, while 4 patients in the lorazepam group received propofol. There was no difference in administration of antipsychotic medications during the study (Table 3).

Safety Evaluation

TABLE 4 outlines the safety parameters assessed during the course of the study. Patients in the dexmedetomidine and lorazepam groups had comparable measures of blood pressure and vasoactive drug use during the study. Patients in the dexmedetomidine group had a higher incidence of sinus bradycardia (heart rate <60/min) than the lorazepam patients, although only 1 patient from each group had an episode of heart rate of lower than 40 beats/min. Neither of these was associated with hemodynamic compromise, yet both were treated with glycopyrolate. There were 4 self-extubations in the dexmedetomidine group vs 2 in the lorazepam group. Of the 4 self-extubations in the dexmedetomidine group, 3 required immediate reintubation and both patients in the lorazepam group had to be reintubated. Patients in the dexmedetomidine group had a nonsignificant increase in the incidence of atrial fibrillation, with 3 patients developing atrial fibrillation, vs none in the lorazepam group. There were no statistical differences in the laboratory values of troponin, serum bilirubin, serum glutamate pyruvate transaminase, cortisol, adrenocorticotropic hormone, luteinizing hormone, testosterone, and prolactin at any time during the study (all P values >.30).

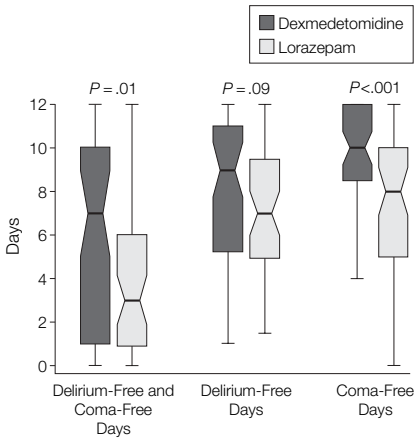
Cost of Care

The median calculated cost for the study drug in the dexmedetomidine group was $4675 and for lorazepam was $2335. The net costs were balanced between the dexmedetomidine and the lorazepam groups with regard to overall pharmacy, respiratory, ICU, and hospital costs (TABLE 5). The median total hospital cost was approximately $22 500 higher in the dexmedetomidine group (not statistically significant), although the majority of this difference was due to costs prior to enrollment and randomization to study drug.

COMMENT

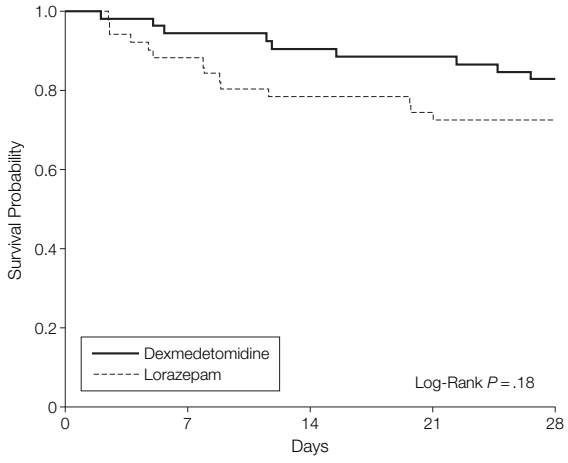
In this double-blind, randomized controlled trial, sustained sedation with dexmedetomidine resulted in 4 more days alive without delirium or coma and significantly more time at the desired level of sedation as compared with lorazepam administered by intravenous infusion. For decades, benzodiazepine drugs, acting on $GABA_A$ receptors, have been the most commonly prescribed

Figure 2. Delirium-Free and Coma-Free Days During Study



Horizontal bars indicate median; error bars indicate the most extreme data point (no more than 1.5 × the interquartile range [IQR]); upper and lower limits of the boxes indicate IQR; upper and lower limits of the notches indicate (1.58 × IQR)/square root of n; side notches allow assessment of significance in difference between the 2 medians. If the notches do not overlap, the 2 groups' medians are significantly different at the $\alpha = .05$ level. Calculations are based on the formula given in Chambers et al.[34] Delirium-free and coma-free days is a composite score to assess duration of being alive and without delirium or coma over a 12-day evaluation period (1 week beyond the maximum 120-hour study drug protocol).

Figure 3. Time to Death Within 28 Days of Enrollment for All Patients



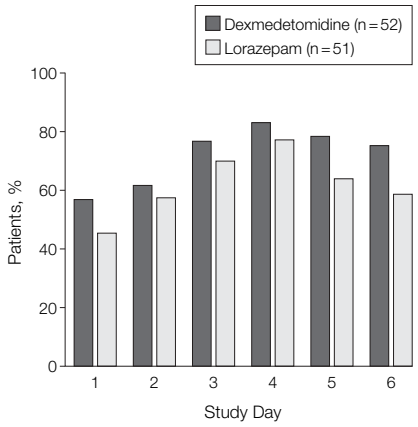
Probability of survival during first 28 days after enrollment.

Table 3. Efficacy of Sedation With Dexmedetomidine vs Lorazepam[a]

Variable	Dexmedetomidine (n = 52)	Lorazepam (n = 51)	*P* Value
Outcome			
Received study drug, d	5 (2-6)	4 (2-6)	.52
RASS score within 1 point of nurse goal, % (IQR)[b]	80 (58-100)	67 (48-83)	.04
RASS score within 1 point of physician goal, % (IQR)[b]	67 (50-85)	55 (8-67)	.008
Sedated deeper than nurse goal RASS score, % (IQR)[c]	15 (0-33)	33 (11-48)	.01
Oversedated on study drug, d	1 (0-2.2)	2 (1-3.5)	.01
Other drugs received during study			
Median fentanyl, µg/d	575 (140-2206)	150 (0-922)	.006
Any antipsychotics, No. (%)	24 (46)	18 (35)	.26
Any propofol, No. (%)	7 (13)	4 (8)	.36
Received antipsychotics, d	0 (0-5)	0 (0-3)	.32

Abbreviations: IQR, interquartile range; RASS, Richmond Agitation-Sedation Scale.
[a] Median (IQR) unless otherwise noted.
[b] The nurse and physician goal RASS score outcomes indicate the percentage of days while on study drug when patients were either at goal or within 1 RASS point of the stated goal.
[c] Percentage of days the RASS scores were 2 or more points deeper than the nurse goal for RASS score.

Figure 4. Percentage of Patients by Study Day Who Were Within 1 Point of the RASS Sedation Goal While Receiving Study Drug



Percentage of patients within 1 point of the nurse target (goal) Richmond Agitation-Sedation Scale (RASS) sedation score (physician data similar). On any given day, dexmedetomidine-treated patients had a 4% to 17% greater likelihood of being at the target sedation score than lorazepam-treated patients. Patients in the study were permitted to be administered the study drug for 120 hours (5 days). Some patients received the study drug until day 6, which reflects enrollment and start of study drug late on day 1 and required drug infusion until day 6, for completion of 120 hours of study drug use.

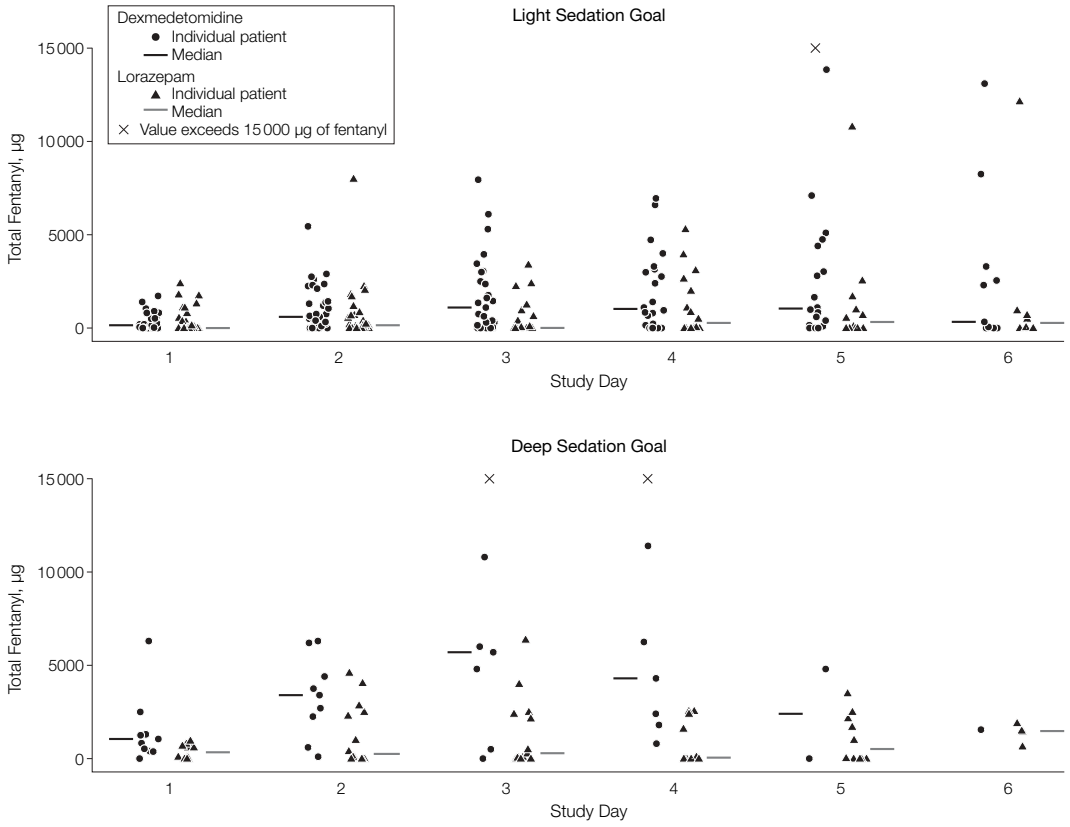
medications for providing anxiolysis and sedation for critically ill patients, and lorazepam continues to be mentioned in current clinical practice guidelines as the drug of choice by which to provide sustained sedation for mechanically ventilated patients.[1,35] Recent studies, however, have shown that benzodiazepine drugs increase the risk for development of delirium,[3-6] which is an independent predictor of higher 6-month mortality, length of stay, and cost of care.[7,8,10] The MENDS trial is the first double-blind randomized controlled trial in mechanically ventilated, general medical and surgical ICU patients to evaluate an alternative sedation paradigm using dexmedetomidine, an α_2-receptor agonist that spares the $GABA_A$ receptors. Despite the higher cost of dexmedetomidine, as compared with lorazepam, the benefits of sustained sedation with this agent were realized with comparable overall pharmacy, respiratory, ICU and hospital costs.

Several small trials have examined the effect of dexmedetomidine on postoperative delirium and found that it attenuates postoperative delirium in adults and children.[20,36,37] Maldonado et al[20] reported in abstract form that 8% of cardiac surgical patients who were randomized to sedation with dexmedetomidine developed postoperative delirium compared with 50% of those sedated with propofol or midazolam, supporting the hypothesis that alpha$_2$ receptor agonists may lead to less delirium than $GABA_A$ receptor agonists.

Benzodiazepine drugs and propofol have high affinity for $GABA_A$ receptors,[15] of which activation can alter levels of numerous neurotransmitters believed to be deliriogenic.[16-18] In addition to altering neurotransmitter concentrations, benzodiazepine drugs impair the quality of sleep via slow-wave sleep suppression, thus, possibly contributing to delirium.[18,38] Unlike benzodiazepine drugs and propofol, which act directly at the level of the tuberomammilary nucleus and the venterolateral preoptic nucleus,[39,40] dexmedetomidine acts at the level of the locus ceruleus, with a different neurotransmitter profile and preserves slow-wave (deep nonrapid eye movement) sleep in its neuronal pathway.[40] Future studies that formally measure depth, duration, and quality of sleep within the context of randomized controlled trials comparing sedation regimens, may provide a better understanding of the differential effects of sedative medications on brain dysfunction.

The MENDS trial adds substantially to the available safety data regarding infusion of dexmedetomidine to critically ill patients.[19] We accomplished this through working within the context of an FDA Investigational New Drug approval for this study, thereby allowing us to test dexmedetomidine at as much as twice the approved maximum dose and as much as 5 times longer than the currently approved, yet impractical and limiting, 24-hour infusion period. Dexmedetomidine can cause both hypotension, especially in volume-depleted patients, and hypertension via central and peripheral α_2-receptor activation, respectively.[19] In our study, these adverse effects were similar in patients treated with either dexmedetomidine or lorazepam. Sinus bradycardia (mediated by central α_2-receptor activation or by dexmedetomidine's vagomimetic action)[19] was more common among patients in the dexmedetomidine group, but only 1 patient in each study group was treated with glycopyrolate for bradycardia, and there were no cases of hemodynamic compromise due to bradycardia in either group. No significant differences according to study group were observed in the postinfusion concentrations of random cortisol, adrenocorticotrophic hormone, testosterone, luteinizing

Figure 5. Fentanyl Dose While Receiving Study Drug According to Depth of Target Sedation



The median fentanyl dose was 575 µg/d in the dexmedetomidine group vs 150 µg/d in the lorazepam group ($P = .006$), and this difference in dosage was more notable when patients were more deeply sedated than when patients were lightly sedated. Deep sedation was defined as a Richmond Agitation-Sedation Scale (RASS) target score of –3 and deeper (–4 and –5); light sedation, as a Rass target score of –2 and lighter (–1, 0, etc). Patients were permitted to be administered the study drug for 120 hours.

hormone, or prolactin, and no evidence was found of study drug-induced cardiac or hepatic toxicity.

Several strengths and limitations unique to this new area of critical care research warrant discussion. The use of delirium and coma as a primary outcome is possibly unprecedented in the realm of critical care literature. The availability of new, reliable, and valid instruments by which to measure these components of organ dysfunction has made such studies possible, and this trial ushers in a new line of investigation to inform our care of the critically ill patient. In ensuing years, there will no doubt be an evolution in thinking about the best way to construct studies to measure brain organ dysfunction. In this study, we chose the number of days alive without delirium or coma as the out-

Table 4. Safety Outcomes With Dexmedetomidine vs Lorazepam[a]

Safety Variable While Receiving Study Drug	Dexmedetomidine (n = 52)	Lorazepam (n = 51)	*P* Value
Blood pressure history			
Lowest systolic blood pressure, mm Hg	96 (88-105)	97 (88-102)	.60
Lowest diastolic blood pressure, mm Hg	48 (44-55)	49 (44-54)	.91
Ever systolic blood pressure <80 mm Hg, No. (%)	13 (25)	10 (20)	.51
Hypotensive, d	0 (0-0.2)	0 (0-0)	.51
Vasoactive drug history			
Days received	0 (0-2)	0 (0-3)	.72
Number of vasoactive drugs/d[b]	0 (0-0.6)	0 (0-1)	.55
Ever vasoactive drugs increased, No. (%)	15 (29)	18 (35)	.48
Vasoactive drugs were increased, d	0 (0-1)	0 (0-1)	.73
Heart rate/rhythm, No. (%)			
Ever sinus bradycardia, <60/min	9 (17)	2 (4)	.03
Heart rate <40/min	1 (2)	1 (2)	.99
Ever sinus tachycardia, >100/min	36 (69)	37 (73)	.71
Ever atrial fibrillation	3 (6)	0 (0)	.08
Seizures, No. (%)	2 (4)	1 (2)	.57
Self-extubations, No. (%)	4 (8)	2 (4)	.41

[a] Measured during 120-hour study drug protocol. Median (interquartile range) unless otherwise noted.
[b] Reported as the median of the average number of vasoactive drugs that the patients were administered daily in each group.

Table 5. Costs of Care in Patients Sedated With Dexmedetomidine and Patients Sedated With Lorazepam[a]

Total Cost	Cost, Median (Interquartile Range), US $		*P* Value
	Dexmedetomidine (n = 45)	Lorazepam (n = 45)	
Pharmacy	27 460 (15 710-46 430)	20 660 (9840-42 270)	.15
Respiratory care	3530 (2170-6940)	2920 (2070-5830)	.35
Intensive care unit	61 400 (37 300-108 200)	59 500 (35 900-83 000)	.32
Hospital	101 400 (64 500-148 900)	78 900 (44 000-12 4600)	.18

[a] Costs (not charges) were calculated from patients enrolled only at Vanderbilt University Medical Center. See the "Methods" section for an explanation of the hospital cost-accounting system.

come measure that we believed would best demonstrate improvement in the duration of normal cognitive status (devoid of delirium and coma).

Pain management and monitoring is another limitation of all studies in critical care that must be considered in light of the fact that dexmedetomidine (as opposed to lorazepam) is known to have analgesic qualities. Investigations in intubated ICU patients share a difficulty in assessing pain using nonverbal cues. Pain was assessed in the MENDS study by the nurses, not by an objective scale, but using physiological cues such as blood pressure, heart rate, and respiratory rate in addition to facial expressions, limb movement, and ventilator synchrony (the standard of care in the participating ICUs). In our study, patients treated with dexmedetomidine received more fentanyl than those treated with lorazepam. It is possible that because patients treated with dexmedetomidine spent less time delirious and comatose, that they were more capable of communicating the need for analgesia to nurses. Conversely, and we believe more likely, fentanyl was used for its sedating properties, a hypothesis supported by the high fentanyl doses among patients in the dexmedetomidine group during periods when deep sedation goals were recorded. While we cannot say exactly why higher fentanyl doses were delivered in the dexmedetomidine group, both of the previously mentioned explanations can be explored through future studies by allowing higher doses of dexmedetomidine (offering potentially more sedative and analgesic effects if needed).

Regulatory oversight is imperative when studying a drug for new uses. In designing MENDS, the FDA stipulated that dexmedetomidine be administered no longer than 120 hours. Patients requiring sedation longer than 120 hours were treated with lorazepam or midazolam according to each ICU's usual protocol. Despite this limitation, superior outcomes were observed among patients treated with dexmedetomidine, but this effect may have been diluted by not maintaining separation of groups beyond the stipulated period. We chose lorazepam as the control sedative agent based on current clinical practice guidelines for long-term sedation and its recommendation for use in delirium,[1,35,41] but did not permit bolus dosing during the study drug infusion period to ensure study blinding and prevent potential for serious bradycardia and hypotension due to rapid boluses of dexmedetomidine. This protocol constraint, which was designed to optimize patient safety, could have led to a higher probability of oversedation in the lorazepam group. In our estimation, however, the impact of a randomized, double-blind investigation outweighed the probability that bolus dosing of lorazepam would have reduced oversedation. This was supported by the fact that nearly 70% of the times, patients in the lorazepam group were at their sedation goal. We suspect this number is much higher than the number seen in most critical care practices, and yet it was statistically inferior to that of the dexmedetomidine group.

The MENDS study was conducted in 2 busy tertiary medical centers, which included a broad range of patients in both medical and surgical ICUs. We believe our admission diagnoses represent demographics of most busy ICUs, but that these data may not apply to trauma, neurological, and burn ICUs. Additionally, the results of this trial are not uniformly applicable to sedatives other than lorazepam, eg, the shorter-acting GABA-agonist, propofol.

Another area for research is the role of antipsychotics in the prevention of acute brain dysfunction. Presently, antipsychotic medications are recommended for the treatment of delirium in the ICU by current clinical practice guidelines[1,35,41]; however, this recommendation is not supported by level 1 evidence specific to ventilated ICU patients, although there are ongoing randomized, placebo-controlled trials in this area. Additionally, future trials should compare dexmedetomidine with mandated daily interruption of sedation, a practice decision that was the responsibility of the individual managing teams during this investigation, and while recommended, known to be used in the minority of mechanically ventilated patients throughout the world during this investigation.[42-44]

CONCLUSION

In this double-blind, randomized controlled trial, dexmedetomidine was more effective than lorazepam for achieving sustained sedation of mechanically ventilated medical and surgical ICU patients. Dexmedetomidine-treated ICU patients had 4 more days alive and without delirium or coma, significantly higher accuracy at meeting the stated sedation goals, and no added cost of care, as measured using data obtained at the largest enrolling site.

Author Affiliations: Department of Anesthesiology/Division of Critical Care (Dr Pandharipande), Department of Medicine, Center for Health Services Research (Drs Girard, Stiles, Jackson, Dittus, and Ely), and Division of Allergy/Pulmonary/Critical Care Medicine (Ms Pun and Drs Girard, Miller, Bernard, and Ely), Department of Biostatistics (Dr Shintani and Ms Thompson), Department of Accreditation and Standards (Mr Deppen), Vanderbilt University Schools of Medicine and Nursing, Nashville, Tennessee; the VA Tennessee Valley Geriatric Research, Education and Clinical Center (GRECC), Nashville, Tennessee (Drs Jackson, Dittus, and Ely); Department of Surgery and Surgical Critical Care at Washington Hospital Center, Washington, DC (Dr Herr); and the Department of An-

aesthetics, Pain Medicines, and Intensive Care, Imperial College London, London, England (Dr Maze).
Author Contributions: Drs Pandharipande and Ely had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Pandharipande, Pun, Maze, Girard, Shintani, Jackson, Deppen, Stiles, Dittus, Bernard, and Ely.
Acquisition of data: Pandharipande, Pun, Herr, Girard, Miller, Jackson, Deppen, Stiles, and Ely.
Analysis and interpretation of data: Pandharipande, Pun, Herr, Maze, Girard, Miller, Shintani, Thompson, Jackson, Deppen, Stiles, Dittus, Bernard, and Ely.
Drafting of the manuscript: Pandharipande, Pun, Herr, Maze, Girard, Miller, Shintani, Thompson, and Ely.
Critical revision of the manuscript for important intellectual content: Pandharipande, Herr, Maze, Girard, Jackson, Deppen, Stiles, Dittus, Bernard, and Ely.
Statistical analysis: Shintani and Thompson.
Administrative, technical, or material support: Jackson.
Study supervision: Pandharipande, Herr, and Ely.
Financial Disclosures: Drs Pandharipande, Herr, Maze, and Girard and Ms Pun have received research grants or honoraria from Hospira Inc. Dr Ely has received research grants and honoraria from Hospira, Inc, Pfizer, and Eli Lilly, and a research grant from Aspect Medical Systems. The other authors report no financial disclosures.
Funding/Support: This investigator-initiated study was aided by receipt of study drug and an unrestricted research grant for laboratory and investigational studies from Hospira Inc. Dr Pandharipande is the recipient of the ASCCA-FAER-Abbott Physician Scientist Award and the Vanderbilt Physician Scientist Development Award. Dr Girard is supported by the Hartford Geriatrics Health Outcomes Research Scholars Award Program and the Vanderbilt Physician Scientist Development Program. Dr Ely is supported by the VA Clinical Science Research and Development Service (VA Merit Review Award) and a grant from the National Institutes of Health (AG0727201).
Role of the Sponsor: Hospira Inc (Lake Forest, Illinois) provided dexmedetomidine as well as funds for safety laboratory studies and electrocardiograms (requested by the FDA). Hospira Inc had no role in the design or conduct of the study; in the collection, analysis, and interpretation of the data; in the preparation, review, or approval of this manuscript; or in the publication strategy of the results of this study. These data are not being used to generate FDA label changes for this medication, but rather to advance the science of sedation, analgesia, and brain dysfunction in critically ill patients.

REFERENCES

1. Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med*. 2002; 30(1):119-141.
2. 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):541-548.
3. Marcantonio ER, Juarez G, Goldman L, et al. The relationship of postoperative delirium with psychoactive medications. *JAMA*. 1994;272(19):1518-1522.
4. Dubois MJ, Bergeron N, Dumont M, Dial S, Skrobik Y. Delirium in an intensive care unit: a study of risk factors. *Intensive Care Med*. 2001;27(8):1297-1304.
5. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology*. 2006;104(1):21-26.
6. Pandharipande P, Constable B, Cotton B, et al. Prevalence and risk factors of delirium in surgical and trauma ICU patients. *J Trauma*. In press.
7. Ely EW, Gautam S, Margolin R, et al. The impact of delirium in the intensive care unit on hospital length of stay. *Intensive Care Med*. 2001;27(12):1892-1900.
8. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. 2004;291 (14):1753-1762.
9. Lin SM, Liu CY, Wang CH, et al. The impact of delirium on the survival of mechanically ventilated patients. *Crit Care Med*. 2004;32(11):2254-2259.
10. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y. Incidence, risk factors and consequences of ICU delirium. *Intensive Care Med*. 2007;33(1):66-73.
11. 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):1471-1477.
12. Kress JP, Gehlbach B, Lacy M, Pliskin N, Pohlman AS, Hall JB. The long-term psychological effects of daily sedative interruption on critically ill patients. *Am J Respir Crit Care Med*. 2003;168(12):1457-1461.
13. Brook AD, Ahrens TS, Schaiff R, et al. Effect of a nursing implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med*. 1999; 27(12):2609-2615.
14. Brattebø 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(7350):1386-1389.
15. Mihic SJ, Harris RA. GABA and the GABAA receptor. *Alcohol Health Res World*. 1997;21(2): 127-131.
16. van der Mast RC. Delirium: the underlying pathophysiological mechanisms and the need for clinical research. *J Psychosom Res*. 1996;41(2):109-113.
17. van der Mast RC. Pathophysiology of delirium. *J Geriatr Psychiatry Neurol*. 1998;11(3):138-145.
18. Pandharipande P, Ely EW. Sedative and analgesic medications: risk factors for delirium and sleep disturbances in the critically ill. *Crit Care Clin*. 2006; 22(2):313-327.
19. Maze M, Scarfini C, Cavaliere F. New agents for sedation in the intensive care unit. *Crit Care Clin*. 2001; 17(4):881-897.
20. Maldonado JR, van der Starre PJ, Wysong A. Postoperative sedation and the incidence of ICU delirium in cardiac surgery patients [abstract A465, presented at the American Society of Anesthesiologists 2003 Session, October 13-17, 2003, San Francisco, California]. *Anesthesiology*. 2003;99:A465.
21. Jorm AF, Scott R, Cullen JS, MacKinnon AJ. Performance of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) as a screening test for dementia. *Psychol Med*. 1991;21(3):785-790.
22. Sessler CN, Gosnell M, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care patients. *Am J Respir Crit Care Med*. 2002;166(10):1338-1344.
23. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA*. 2003;289(22):2983-2991.
24. Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med*. 1996;335(25):1864-1869.
25. Schoenfeld DA, Bernard GR; ARDS Network. Statistical evaluation of ventilator free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. *Crit Care Med*. 2002; 30(8):1772-1777.
26. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the confusion assessment method for the intensive care unit (CAM-ICU). *Crit Care Med*. 2001;29(7):1370-1379.
27. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA*. 2001;286(21): 2703-2710.
28. Weinert CR, Chlan L, Gross C. Sedating critically ill patients: factors affecting nurses' delivery of sedative therapy. *Am J Crit Care*. 2001;10(3):156-167.
29. Slomka J, Hoffman-Hogg L, Mion LC, Bair N, Bobek MB, Arroliga AC. Influence of clinicians' values and perceptions on use of clinical practice guidelines for sedation and neuromuscular blockade in patients receiving mechanical ventilation. *Am J Crit Care*. 2000; 9(6):412-418.
30. Weinert CR, Calvin AD. Epidemiology of sedation and sedation adequacy for mechanically ventilated patients in a medical and surgical intensive care unit. *Crit Care Med*. 2007;35(2):393-401.
31. Folstein MF, Folstein SE, McHugh P. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12(3):189-198.
32. Spreen O, Strauss E. *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. 2nd ed. New York, NY: Oxford University Press; 1998.
33. Social Security Death Index. http://ssdi.rootsweb.com. Accessed November 16, 2007.
34. Chambers JA, Cleveland WS, Tukey PA. *Graphical Methods for Data Analysis (The Wadsworth Statistics/Probability Series)*. Pacific Grove, CA: Duxbury Press; 1983:62.
35. Young C, Knudsen N, Hilton A, Reves JG. Sedation in the intensive care unit. *Crit Care Med*. 2000; 28(3):854-866.
36. Ibacache ME, Munoz HR, Brandes V, Morales AL. Single-dose dexmedetomidine reduces agitation after sevoflurane anesthesia in children. *Anesth Analg*. 2004;98(1):60-63.
37. Levänen J, Makela ML, Scheinin H. Dexmedetomidine premedication attenuates ketamine-induced cardiostimulatory effects and postanesthetic delirium. *Anesthesiology*. 1995;82(5):1117-1125.
38. Bourne RS, Mills GH. Sleep disruption in critically ill patients: pharmacological considerations. *Anaesthesia*. 2004;59(4):374-384.
39. Nelson LE, Guo TZ, Lu J, Saper CB, Franks NP, Maze M. The sedative component of anesthesia is mediated by GABA(A) receptors in an endogenous sleep pathway. *Nat Neurosci*. 2002;5(10):979-984.
40. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M. The α_2-adrenoceptor agonist dexmendetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. *Anesthesiology*. 2003; 98(2):428-436.
41. Wijdicks EFM. *Neurologic Complications of Critical Illness*. New York, NY: Oxford University Press; 2002.
42. Mehta S, Burry L, Fischer S, et al. Canadian survey of the use of sedatives, analgesics, and neuromuscular blocking agents in critically ill patients. *Crit Care Med*. 2006;34(2):374-380.
43. Tanios MA, Devlin JW, Epstein SK. Perceived barriers to implementing strategy of daily interruption of sedative in the intensive care unit for critically ill patients. *Proc Am Thorac Soc*. 2005;2:A793.
44. Devlin JW, Tanios MA, Epstein SK. Intensive care unit sedation: waking up clinicians to the gap between research and practice. *Crit Care Med*. 2006; 34(2):556-557.