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

Timothy D Girard, John P Kress, Barry D Fuchs, Jason W W Thomason, William D Schweickert, Brenda T Pun, Darren B Taichman, Jan G Dunn, Anne S Pohlman, Paul A Kinniry, James C Jackson, Angelo E Canonico, Richard W Light, Ayumi K Shintani, Jennifer L Thompson, Sharon M Gordon, Jesse B Hall, Robert S Dittus, Gordon R Bernard, E Wesley Ely

Lancet 2008; 371: 126–34

See **Comment** page 95

Department of Medicine (A E Canonico MD) **and Saint Thomas Research Institute** (J G Dunn RN), **Saint Thomas Hospital, Nashville, TN, USA; Department of Medicine, Division of Allergy, Pulmonary, and Critical Care Medicine** (T D Girard MD, J W W Thomason MD, B T Pun RN, J C Jackson PsyD, Prof R W Light MD, Prof G R Bernard MD, Prof E W Ely MD), **Center for Health Services Research** (T D Girard, J C Jackson, S M Gordon PsyD, Prof R S Dittus MD, E W Ely), **and Department of Biostatistics** (A K Shintani PhD, J L Thompson MPH), **Vanderbilt University School of Medicine, Nashville, TN, USA; VA Tennessee Valley Geriatric Research, Education and Clinical Center (GRECC), VA Service, Department of Veterans Affairs Medical Center, Tennessee Valley Healthcare System, TN, USA** (S M Gordon, R S Dittus, E W Ely); **Department of Medicine, Section of Pulmonary and Critical Care, University of Chicago, Chicago, IL, USA** (J P Kress MD, W D Schweickert MD, A S Pohlman RN, Prof J B Hall MD); **and Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA** (B D Fuchs MD, D B Taichman MD, P A Kinniry MD)

Summary

Background Approaches to removal of sedation and mechanical ventilation for critically ill patients vary widely. Our aim was to assess a protocol that paired spontaneous awakening trials (SATs)—ie, daily interruption of sedatives—with spontaneous breathing trials (SBTs).

Methods In four tertiary-care hospitals, we randomly assigned 336 mechanically ventilated patients in intensive care to management with a daily SAT followed by an SBT (intervention group; n=168) or with sedation per usual care plus a daily SBT (control group; n=168). The primary endpoint was time breathing without assistance. Data were analysed by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00097630.

Findings One patient in the intervention group did not begin their assigned treatment protocol because of withdrawal of consent and thus was excluded from analyses and lost to follow-up. Seven patients in the control group discontinued their assigned protocol, and two of these patients were lost to follow-up. Patients in the intervention group spent more days breathing without assistance during the 28-day study period than did those in the control group (14·7 days *vs* 11·6 days; mean difference 3·1 days, 95% CI 0·7 to 5·6; p=0·02) and were discharged from intensive care (median time in intensive care 9·1 days *vs* 12·9 days; p=0·01) and the hospital earlier (median time in the hospital 14·9 days *vs* 19·2 days; p=0·04). More patients in the intervention group self-extubated than in the control group (16 patients *vs* six patients; 6·0% difference, 95% CI 0·6% to 11·8%; p=0·03), but the number of patients who required reintubation after self-extubation was similar (five patients *vs* three patients; 1·2% difference, 95% CI –5·2% to 2·5%; p=0·47), as were total reintubation rates (13·8% *vs* 12·5%; 1·3% difference, 95% CI –8·6% to 6·1%; p=0·73). At any instant during the year after enrolment, patients in the intervention group were less likely to die than were patients in the control group (HR 0·68, 95% CI 0·50 to 0·92; p=0·01). For every seven patients treated with the intervention, one life was saved (number needed to treat was 7·4, 95% CI 4·2 to 35·5).

Interpretation Our results suggest that a wake up and breathe protocol that pairs daily spontaneous awakening trials (ie, interruption of sedatives) with daily spontaneous breathing trials results in better outcomes for mechanically ventilated patients in intensive care than current standard approaches and should become routine practice.

Introduction

A third of patients in intensive care worldwide are mechanically ventilated.[1] Although instituted to save lives, mechanical ventilation is nearly universally accompanied by the administration of large doses of sedatives;[2] together these interventions are associated with significant morbidity.[3–6] Efforts to reduce the duration of mechanical ventilation in intensive-care populations via ventilator weaning protocols and sedation protocols can improve clinical outcomes.[7–9] Unfortunately, only a few patients are managed with these strategies since there is ongoing disagreement among health-care professionals with regard to benefits and risks and because weaning protocols and sedation protocols are viewed as separate concerns—often handled in a cumbersome fashion by different members of the patient-care team (eg, sedation by nurses and ventilator weaning by respiratory therapists and physicians). Since the process of discontinuing ventilatory support is affected by heavy use of sedatives, there is an unmet need to combine approaches to sedation and ventilator weaning and to optimise their management.

Numerous randomised trials support the use of ventilator weaning protocols that include daily spontaneous breathing trials (SBTs) as their centrepiece; such protocols are standard of care, having reduced the duration of mechanical ventilation in diverse populations of patients with acute respiratory failure.[7,10–14] Recent clinical trials, seeking to identify ways to manage sedation that might also facilitate earlier extubation, have shown that both intermittent use of sedatives and spontaneous awakening trials (SATs)—ie, daily interruption of sedatives—can reduce the duration of mechanical ventilation without compromising patient comfort or

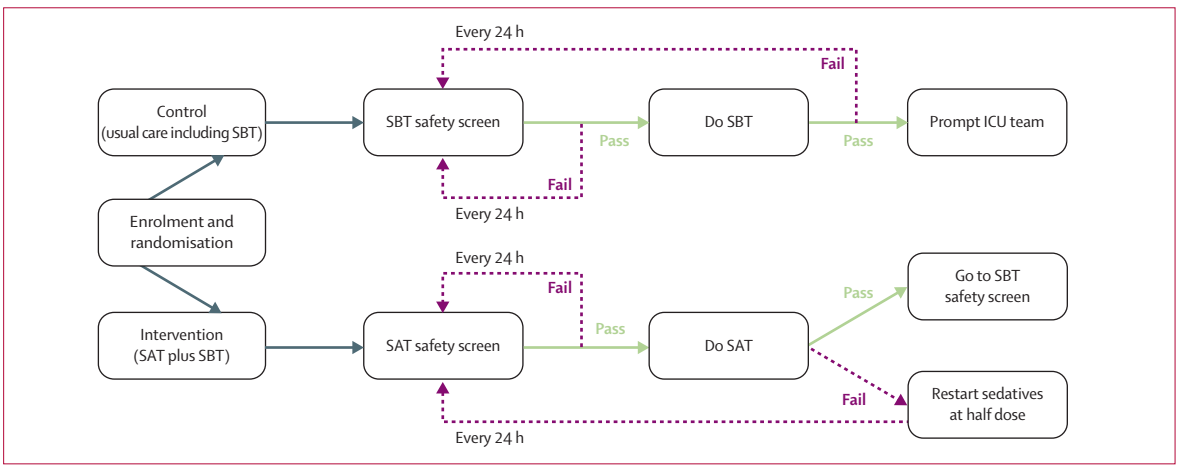

Figure 1: **Treatment protocols**
ICU=intensive-care unit. SAT=spontaneous awakening trial. SBT=spontaneous breathing trial.

Correspondence to:
Dr Timothy D Girard, Division of Allergy, Pulmonary, and Critical Care Medicine, Center for Health Services Research, 6th Floor MCE 6110, Vanderbilt University School of Medicine, Nashville, TN 37232-8300, USA
timothy.girard@vanderbilt.edu

safety.[8,9,15] The paucity of additional evidence supporting the routine use of SATs, however, as well as anecdotal concerns regarding patient safety and agitation, have led to limited use of this sedation strategy. Whereas some intensive-care practitioners report only lightly sedating patients during most of their time on the ventilator, less than half of practitioners worldwide have implemented daily interruption of sedatives—eg, 34% in Germany,[16] 40% in Canada,[17] and 40% in the USA.[18,19] Also, proponents of patient-targeted sedation strategies argue that titration of sedatives according to patients' needs produces outcomes equivalent to those resulting from a protocol that promotes daily SATs.[20,21]

To test our hypothesis that routine SATs improve patient outcomes when combined with routine SBTs, we undertook the Awakening and Breathing Controlled (ABC) trial, a multicentre, randomised controlled trial in which we assessed the efficacy and safety of a protocol of daily SATs paired with SBTs versus a standard SBT protocol in patients receiving patient-targeted sedation as part of usual care.

Methods

Patients

We recruited participants at four large medical centres: Saint Thomas Hospital (Nashville, TN, USA), University of Chicago Hospitals (Chicago, IL, USA), Hospital of the University of Pennsylvania (Philadelphia, PA, USA), and Penn Presbyterian Medical Center (Philadelphia). Vanderbilt Coordinating Center (Nashville, TN, USA) supervised the trial; a Vanderbilt investigator was available 24 h a day to answer questions and respond to reports of adverse events.

Study personnel screened all patients in intensive care every day to identify adult patients (≥18 years old) who required mechanical ventilation for 12 h or more. Patients receiving full ventilatory support and those whose support was being weaned were eligible. Patients were excluded from enrolment for the following reasons: admission after cardiopulmonary arrest, continuous mechanical ventilation for 2 weeks or longer, moribund state (ie, death was perceived to be imminent), withdrawal of life support, profound neurological deficits (eg, large stroke or severe dementia), or current enrolment in another trial.

The institutional review boards at each participating centre approved the study protocol, and written informed consent was obtained from participants or their authorised surrogates.

Procedures

Patients were randomly assigned in a 1:1 manner to management with paired SAT and SBT protocols (the intervention group) or usual care, including patient-targeted sedation and an SBT protocol (the control group). A computer-generated, permuted-block randomisation scheme was stratified according to study centre by a Vanderbilt biostatistician. Each assignment was designated on a tri-folded piece of paper enclosed in a consecutively numbered, sealed, opaque envelope. After informed consent was obtained, before data were collected, the appropriate envelope was opened by local study personnel.

According to each study centre intensive-care unit's usual practice of care, physicians and nurses managed all patients with patient-targeted sedation, titrating sedative and analgesic doses to maintain the level of arousal and comfort deemed clinically appropriate for each patient. Each intensive-care unit used a validated sedation scale to monitor depth of sedation. Beginning the morning after enrolment, intensive-care nurses and respiratory therapists or study personnel managed patients according to the study protocols. Figure 1 displays the steps in each study protocol.

In accordance with the SBT protocol, patients in the control group were assessed every morning with an SBT

safety screen. Patients passed the screen if they had adequate oxygenation (oxygen saturation [SpO_2] ≥88% on a fraction of inspired oxygen [F_iO_2] ≤50% and a positive end-expiratory pressure [PEEP] ≤8 cm H_2O), any spontaneous inspiratory effort in a 5-min period, no agitation, no evidence of myocardial ischaemia in the previous 24 h, no significant use of vasopressors or inotropes (dopamine or dobutamine ≥5 μg/kg per min, norepinephrine ≥2 μg/min, or vasopressin or milrinone at any dose), and no evidence of increased intracranial pressure. Patients who failed the screen were reassessed the following morning.

Patients who passed underwent an SBT: ventilatory support was removed, and the patient was allowed to breathe through either a T-tube circuit or a ventilatory circuit with continuous positive airway pressure of 5 cm H_2O or pressure support ventilation of less than 7 cm H_2O.[22] No change was made in F_iO_2 or PEEP during the SBT. Patients failed the SBT if they developed a respiratory rate of more than 35 or less than eight breaths per min for 5 min or longer, hypoxaemia (SpO_2 <88% for ≥5 min), abrupt changes in mental status, an acute cardiac arrhythmia, or two or more signs of respiratory distress, including tachycardia (>130 bpm), bradycardia (<60 bpm), use of accessory muscles, abdominal paradox, diaphoresis, or marked dyspnoea. Patients who failed the SBT were ventilated immediately with the ventilator settings used before the trial. Patients passed the SBT if they did not develop any failure criteria during a 120-min trial. If the SBT was successful, the patients' physicians were notified verbally. Study personnel did not participate in decisions to extubate patients.

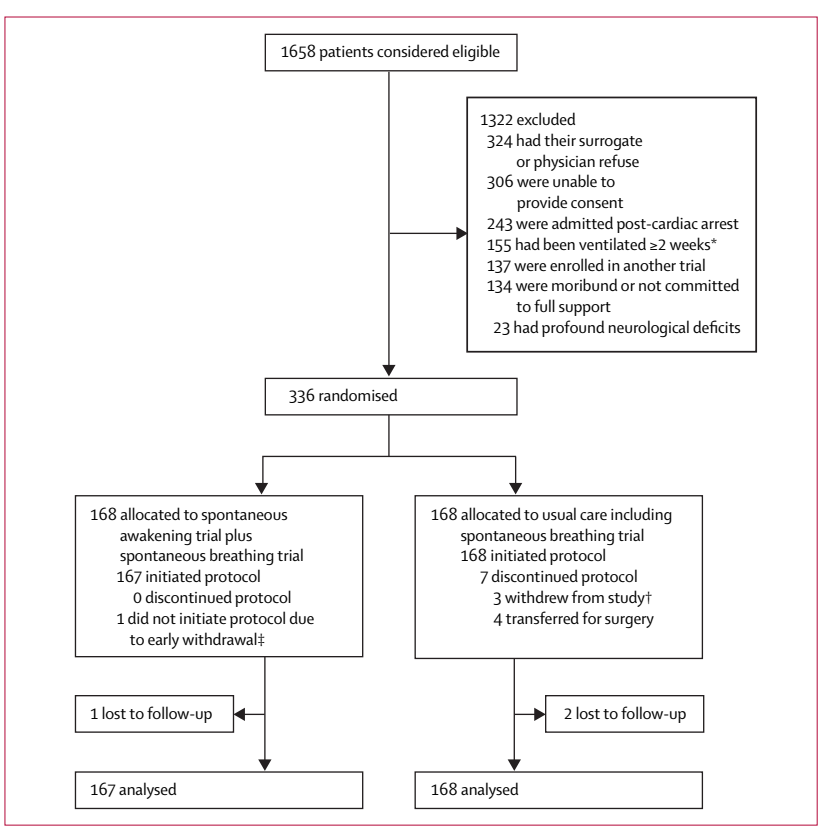

Figure 2: **Trial profile**
*Patients who were excluded because of ≥2 weeks of mechanical ventilation were transferred from other intensive-care units after periods of prolonged mechanical ventilation. †Withdrew from the study: discontinued the study protocol but allowed study personnel to track study outcomes, which were included in analysis. ‡One person was excluded from analysis due to study withdrawal by the surrogate immediately after randomisation, before any data collection.

In accordance with the SAT protocol, patients in the intervention group were assessed every morning with an SAT safety screen. SATs were prescribed by protocol only for patients in the intervention group, although patients in the control group were not prevented from undergoing SATs if the managing clinician felt that they were indicated. Patients passed the screen unless they were receiving a sedative infusion for active seizures or alcohol withdrawal, were receiving escalating sedative doses due to ongoing agitation, were receiving neuromuscular blockers, had evidence of active myocardial ischaemia in the previous 24 h, or had evidence of increased intracranial pressure. Patients who failed the screen were reassessed the following morning.

Patients who passed the screen underwent an SAT: all sedatives and analgesics used for sedation were interrupted. Analgesics needed for active pain were continued. Patients were monitored by intensive-care staff or study personnel for up to 4 h. Patients passed the SAT if they opened their eyes to verbal stimuli or tolerated sedative interruption for 4 h or more without exhibiting failure criteria. Patients failed the SAT if they developed sustained anxiety, agitation, or pain, a respiratory rate of more than 35 breaths per min for 5 min or longer, an SpO_2 of less than 88% for 5 min or longer, an acute cardiac dysrhythmia, or two or more signs of respiratory distress, including tachycardia, bradycardia, use of accessory muscles, abdominal paradox, diaphoresis, or marked dyspnoea. When patients failed an SAT, intensive-care staff restarted sedatives at half the previous dose and then titrated the medications to achieve patient comfort. Patients who passed the SAT were immediately managed with the SBT protocol.

The primary endpoint was defined a priori as the number of days patients were breathing without assistance (ventilator-free days) during the 28-day study period, which began at the time of enrolment. Patients who died during the study period were assigned 0 ventilator-free days.[23] A period of unassisted breathing began with extubation (or removal of ventilatory support for patients with tracheostomies) if the period of unassisted breathing lasted at least 48 consecutive hours. Secondary endpoints included time to discharge from the intensive-care unit and from the hospital, all-cause 28-day mortality, 1-year survival, and duration of coma and delirium.

Trained study personnel did neurological assessments every day with two well-validated instruments: level of

arousal was assessed with the Richmond agitation-sedation scale (RASS),[24,25] and delirium was diagnosed with the confusion assessment method for the intensive-care unit (CAM-ICU).[26–28] Duration of coma was defined as the number of days in the study period that patients had no response to verbal or physical stimulation (RASS –5) or responded to physical or painful stimulation with movement but without eye opening (RASS –4). Duration of delirium was defined as the number of days in the study period during which patients were CAM-ICU positive and were not comatose.

Patients were followed up from enrolment until death or discharge, and survivors were followed up for vital status until 1 year after enrolment using the hospitals' electronic record systems, telephone calls, in-person visits, and a commercial version of the Social Security Death Master File.[29]

Study personnel monitored patients for adverse events during the trial and reported all serious, unexpected, and study-related adverse events to an independent data and safety monitoring board. Self-extubation and reintubation were tracked as safety endpoints. The data and safety monitoring board reviewed two interim analyses of adverse events after enrolment of 30 and 100 patients. No interim analysis of efficacy was done.

Statistical analysis

On the basis of a pilot database, we expected a mean of 12·9 (SD 10·4) ventilator-free days in the control group. Thus, we calculated that a sample size of 334 patients would be needed to detect a 25% increase in ventilator-free days to 16·1 days within the intervention group with 80% power and a two-sided significance level of 0·05.[30]

Data were analysed with an intention-to-treat approach. We used χ^2 tests to compare categorical variables between the study groups, and the Wilcoxon-Mann-Whitney two-sample rank-sum test to compare continuous variables, including the primary endpoint. We also used bootstrapping with 2000 samples to calculate a non-parametric 95% CI for the difference in mean ventilator-free days, because the variable had an unusual distribution.[31] Specifically, we calculated the difference in mean ventilator-free days in each of 2000 samples randomly generated from the original data using resampling with replacement and determined the 95% CI using the 2·5 and 97·5 percentiles of the results of these calculations.

To compare the effects of the two treatment protocols on length of stay in the intensive-care unit and in the hospital, we used time-to-event analyses. Patient data were censored at time of death. Medians and IQRs were obtained with Kaplan-Meier analyses, and the log-rank test was used to assess the effect of the treatment protocols. Kaplan-Meier analysis and the log-rank test were also used to assess the effect of the treatment protocols on 1-year survival; patients were censored at the time of last contact alive or at 1 year from enrolment, whichever was first. The unadjusted hazard ratio (HR) of death up to 1 year was obtained with Cox proportional hazards regression. We assessed the proportional hazards assumption by examining scaled Schoenfeld's partial residuals[32] for the independent variable included in the model; no violation of the assumption was detected. To

	Intervention group (n=167)	Control group (n=168)
Age (years)	60 (48 to 71)	64 (51 to 75)
Sex (female)	77 (46%)	83 (49%)
APACHE II score	26 (21 to 33)	26·5 (21 to 31)
SOFA score	9 (6 to 11)	8 (6 to 11·5)
Diagnosis on admission to intensive care		
Sepsis/acute respiratory distress syndrome	79 (47%)	87 (52%)
Myocardial infarction/congestive heart failure	22 (13%)	29 (17%)
Chronic obstructive pulmonary disease/asthma	17 (10%)	12 (7%)
Altered mental status	18 (11%)	12 (7%)
Hepatic or renal failure	9 (5%)	5 (3%)
Malignancy	3 (2%)	2 (1%)
Alcohol withdrawal	1 (1%)	1 (1%)
Other*	18 (11%)	20 (12%)
RASS on first study day	–4 (–5 to –2)	–4 (–5 to –2)
Sedation before enrolment		
Benzodiazepines (mg)†	8 (4 to 34)	10 (2 to 41)
Opiates (μg)‡	815 (184 to 4380)	850 (142 to 4685)
Propofol (mg)	5102 (2340 to 9720)	3248 (1455 to 7420)
Time from admission to enrolment (days)	2·2 (1·1 to 3·9)	2·2 (1·1 to 3·9)

Data are n (%) or median (IQR). APACHE II=acute physiology and chronic health evaluation II. RASS=Richmond agitation-sedation scale. SAT=spontaneous awakening trial. SBT=spontaneous breathing trial. SOFA=sequential organ failure assessment. *Including gastrointestinal bleeding, metabolic disarray, haemoptysis, pulmonary embolism, and status epilepticus. †Expressed in lorazepam equivalents.[34] ‡Expressed in fentanyl equivalents.[34]

Table 1: **Baseline characteristics**

	Intervention group (n=167)	Control group (n=168)	p value
Underwent an SAT	150 (90%)*	0 (0%)	<0·0001
Sedatives held before any SBT	150 (90%)*	52 (31%)	<0·0001
Underwent an SBT	136 (81%)†	146 (87%)†	0·17
Benzodiazepine use post-enrolment			
Patients treated	120 (72%)	111 (66%)	0·25
Total dose (mg)‡	20 (5–93)	39 (8–213)	0·02
Average daily dose (mg)‡	2 (0–8)	3 (1–17)	0·12
Opiate use post-enrolment			
Patients treated	130 (78%)	128 (76%)	0·87
Total dose (μg)§	2662 (431–9875)	3700 (772–16 306)	0·07
Average daily dose (μg)§	327 (49–891)	301 (69–1555)	0·28
Propofol use post-enrolment			
Patients treated	117 (70%)	115 (69%)	0·88
Total dose (mg)	8950 (3070–17 159)	8380 (2250–18 980)	0·90
Average daily dose (mg)	1230 (431–2070)	987 (373–2158)	0·40

Data are n (%) or median (IQR). SAT=spontaneous awakening trial. SBT=spontaneous breathing trial. *17 patients in the intervention group never passed an SAT safety screen or underwent an SAT. †22 patients in the control group and 31 in the intervention group never passed an SBT safety screen or underwent an SBT. ‡Expressed in lorazepam equivalents.[34] §Expressed in fentanyl equivalents.[34]

Table 2: **Protocol adherence and sedative use**

	Intervention group (n=167)	Control group (n=168)	p value
Ventilator-free days*			
Mean	14·7 (0·9)	11·6 (0·9)	0·02
Median	20·0 (0 to 26·0)	8·1 (0 to 24·3)	
Time to discharge (days)			
From intensive care	9·1 (5·1 to 17·8)	12·9 (6·0 to 24·2)	0·01
From hospital	14·9 (8·9 to 26·8)	19·2 (10·3 to NA)†	0·04
28-day mortality	47 (28%)	58 (35%)	0·21
1-year mortality	74 (44%)	97 (58%)	0·01
Duration of brain dysfunction (days)			
Coma	2 (0 to 4)	3 (1 to 7)	0·002
Delirium	2 (0 to 5)	2 (0 to 6)	0·50
RASS at first successful SBT	−1 (−3 to 0)	−2·5 (−4 to 0)	0·0001
Complications			
Any self-extubation	16 (10%)	6 (4%)	0·03
Self-extubation requiring reintubation‡	5 (3%)	3 (2%)	0·47
Reintubation‡	23 (14%)	21 (13%)	0·73
Tracheostomy	21 (13%)	34 (20%)	0·06

Data are mean (SD), n (%), or median (IQR). RASS=Richmond agitation-sedation scale. SAT=spontaneous awakening trial. SBT=spontaneous breathing trial. *Ventilator-free days from study day 1 to 28. †Greater than 25% of patients in the SBT group remained in the hospital at study day 28. ‡Reintubation within 48 hours of extubation.

Table 3: **Main outcomes**

assess for an interaction between study centre and treatment with respect to the primary endpoint, we included an interaction term in a proportional odds logistic regression model with ventilator-free days as the dependent variable. We used R (version 2.4 patched) for all statistical analyses.[33] An independent biostatistician re-analysed the final dataset and verified all our results.

This study is registered with ClinicalTrials.gov, number NCT00097630.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

1658 patients were considered eligible for enrolment between October, 2003, and March, 2006. We enrolled and randomised 336 of these individuals (figure 2). 168 patients were randomly assigned to each group. Seven (4%) patients in the control group discontinued the protocol: surrogates withdrew three patients from the study, and four patients were transferred to another service not participating in the trial. No patient in the intervention group discontinued the protocol; a surrogate withdrew one patient before protocol initiation or any data collection, and this patient was excluded from analyses.

The two groups were similar at baseline (table 1). On day 1, 87 (52%) patients in the control group and 94 (56%) patients in the intervention group were comatose. Before enrolment, the two groups were treated with similar doses of benzodiazepines and opiates, although patients in the intervention group received more propofol (p=0·02). Propofol dose before enrolment, however, was not associated with study outcomes (data not shown).

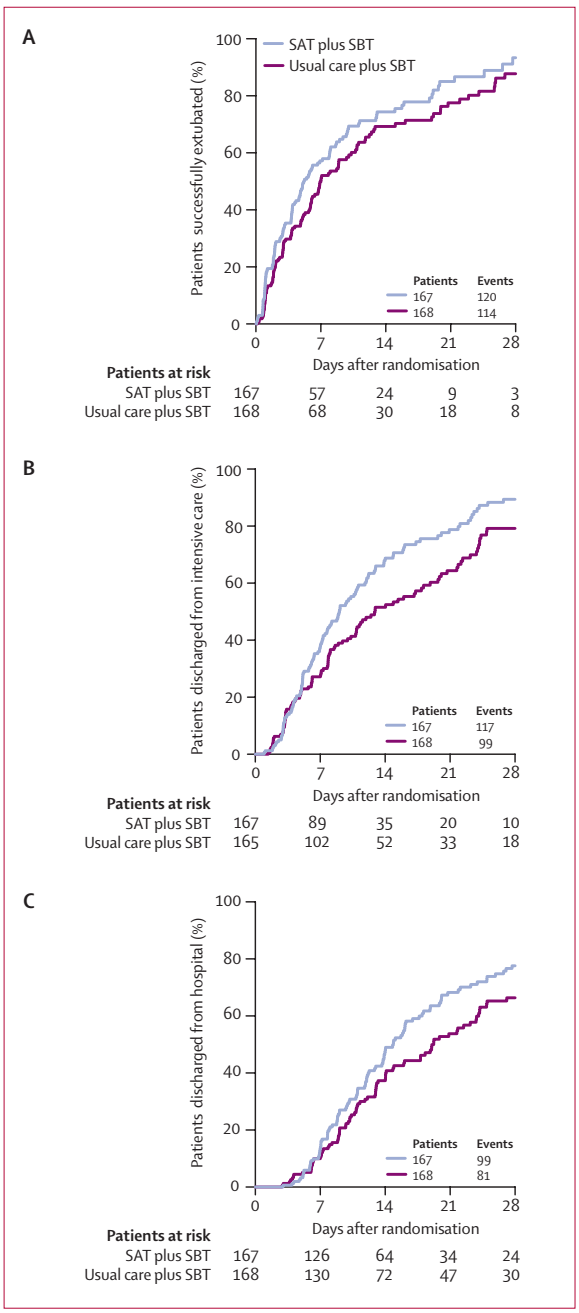

Figure 3: **Probability of successful extubation (A), discharge from intensive care (B), and hospital discharge (C) during the first 28 days after randomisation**

Events indicate total number of successful extubations (A), discharges from intensive care (B), and discharges from the hospital (C) in each treatment group during the 28 days from enrolment.

150 (90%) patients in the intervention group passed an SAT safety screen; these patients underwent 895 SATs (table 2). Analgesics were continued for pain during 132 (15%) of these SATs. Clinicians discontinued the sedatives administered to 52 (31%) patients in the control group before at least one SBT (table 2). The number of patients in each group treated with benzodiazepines, opiates, or propofol was similar, as was the cumulative dose of propofol (table 2). The cumulative benzodiazepine dose was higher in the control group than in the intervention group. Only 45 (27%) patients in the control group and 31 (18%) patients in the intervention group received haloperidol (p=0·07).

Patients in the intervention group spent more days breathing without assistance than those in the control group (3·1 mean ventilator-free days difference, 95% CI 0·7–5·6; p=0·02; table 3). Additionally, the intervention protocol resulted in discharge about 4 days earlier from both intensive care and from the hospital (table 3 and figure 3). There was no significant interaction between study centre and treatment with respect to the number of ventilator-free days (data not shown).

The duration of coma was significantly shorter in the intervention group than in the control group, whereas the duration of delirium was similar between the two groups (table 3). Of the assessable patients, delirium occurred in 124 (74%) in the intervention group and 119 (71%) in the control group (p=0·66).

Patients in the two treatment groups progressed to the point of passing an SBT at the same rate (median number of days to first passed SBT 3·8 [IQR 1·1–14·0] days in the intervention group *vs* 3·9 [1·0–11·8] days in the control group; p=0·49). Patients in the intervention group, however, were more alert than were those in the control group on the day they first passed an SBT safety screen (median RASS –2 [IQR –3 to 0] *vs* –3 [–4 to –1]; p=0·0003) and an SBT (–1 [–3 to 0] *vs* –2·5 [–4 to 0]; p=0·0001). 59 (54%) of the 109 patients in the intervention group who ever passed an SBT were extubated on the day they first passed an SBT compared with 49 (40%) of the 124 patients in the control group (14·6% difference, 95% CI 1·0–26·0; p=0·03).

Analysis of 1-year survival showed that, at any instant during the year after enrolment, patients managed with the SAT plus SBT strategy were 32% less likely to die than were patients in the control group (HR 0·68, 95% CI 0·50 to 0·92; p=0·01; figure 4). For every seven patients treated with the SAT plus SBT protocol, one life was saved (number needed to treat 7·4, 95% CI 4·2–35·5).

Tracheostomies, which no patient had at enrolment, were placed in 21 (13%) patients in the intervention group and in 34 (20%) of those in the control group (absolute risk reduction 7·6%, 95% CI –0·3% to 15·6%; p=0·06). Median time to tracheostomy placement was similar in the two groups (12·7 [IQR 5·9–13·4] days in the intervention group *vs* 12·9 [8·0–18·1] days in the control group; p=0·32).

More patients in the intervention group self-extubated than in the control group (6·0% difference, 95% CI 0·6–11·8; p=0·03; table 3). Only five individuals in the intervention group self-extubated, however, during or within 12 h of an SAT. Also, five patients in the intervention group required reintubation within 48 h of self-extubation,

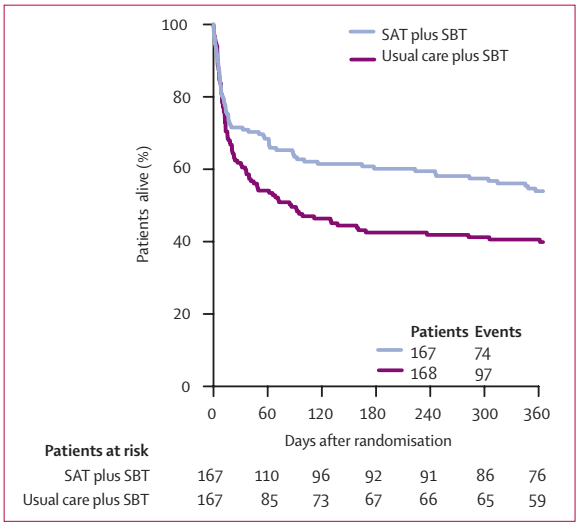

Figure 4: **Survival at 1 year**
Events indicate the number of deaths in each group in the year after enrolment.

	Intervention group	Control group	p value
SAT			
Total	895	0	
Passed	837 (94%)	NA	NA
Opened eyes to verbal stimuli	731 (82%)	NA	NA
Tolerated SAT for ≥4 h	106 (11%)	NA	NA
Failed*	58 (7%)	NA	NA
Anxiety, agitation, or pain	42 (5%)	NA	NA
Signs of respiratory distress	25 (3%)	NA	NA
Tachypnoea	20 (2%)	NA	NA
Hypoxaemia	12 (1%)	NA	NA
Dysrhythmia	1 (0%)	NA	NA
SBT			
Total	603	948	
Passed	319 (53%)	492 (52%)	0·70
Failed*	284 (47%)	456 (48%)	..
Tachypnoea	221 (37%)	351 (37%)	0·75
Signs of respiratory distress	125 (37%)	217 (23%)	0·27
Hypoxaemia	33 (6%)	51 (5%)	0·98
Abrupt change in mental status	13 (2%)	17 (2%)	0·64
Bradypnoea	8 (1%)	19 (2%)	0·31
Dysrhythmia	15 (3%)	9 (1%)	0·02

Data are n (%). NA=not applicable. SAT=spontaneous awakening trial. SBT=spontaneous breathing trial. *Some patients had more than one reason for failure.

Table 4: **Results of the spontaneous awakening trials and spontaneous breathing trials**

compared with three patients in the control group (1·2% difference, 95% CI –5·2% to 2·5%; p=0·47). The overall rate of reintubation was similar between the two groups (1·3% difference, 95% CI –8·6% to 6·1%; p=0·73).

Patients in the intervention group failed 201 (18%) of the 1140 SAT safety screens that were done, most often due to agitation, which was noted during 151 (13%) safety screens. An SAT was done after 895 (95%) of the 939 SAT safety screens that were passed. Patients passed 837 (94%) of these SATs. Patients who failed SATs most often did so due to anxiety, agitation, or pain, which occurred only during 42 (5%) SATs (table 4).

Two-thirds of all SBT safety screens were passed (647 [66%] of 983 screens done in the intervention group *vs* 1036 [65%] of 1599 in the control group; p=0·59), and half of all SBTs were passed by patients in both groups (table 4). The most common reasons for SBT failure in both groups were tachypnoea and other signs of respiratory distress. Patients failed a small number of SBTs in both groups due to acute dysrhythmias; this occurred more frequently in patients in the intervention group (1·6% difference, 95% CI 0·3–3·2; p=0·02). None of these dysrhythmias were deemed to be serious, since none resulted in clinically adverse sequelae other than termination of the SBT.

Discussion

Our results show that a paired sedation and ventilator weaning protocol consisting of daily SATs plus SBTs resulted in patients spending more time off mechanical ventilation, less time in coma, and less time in intensive care and the hospital, and the protocol improved 1-year survival compared with usual care. This wake up and breathe strategy was effective and was associated with few adverse events in a diverse population in intensive care in both community and university hospitals.

Respiratory failure and mechanical ventilation frequently result in anxiety and pain.[35,36] Thus, clinicians use sedatives and analgesics to alleviate patient discomfort, decrease oxygen consumption, facilitate nursing care, and ensure patient safety.[37] These medications, however, are associated with adverse effects, including oversedation,[38] delirium,[5] and prolongation of mechanical ventilation.[6] The most appropriate pattern and dose of administration is often difficult to determine, and many intensive-care practitioners have the perception that their patients are not oversedated, even though observational studies in Europe[2] and the USA[38] found that nearly half of intensive-care patients are deeply sedated and unarousable.

In 2000, Kress and colleagues[9] reported that a protocol of daily SATs reduced duration of mechanical ventilation and length of stay in intensive care. This study showed that SATs are safe; self-extubation,[9] intensive-care-related complications,[39] myocardial ischaemia,[40] and post-traumatic stress disorder[41] did not occur more frequently in patients managed with daily SATs than in those managed without SATs. Kress and colleagues' trial was limited, however, being a single-centre trial that did not mandate daily SBTs. Because of the absence of a multicentre trial supporting the efficacy of SATs and persistent concerns regarding the safety of this sedation strategy, most intensive-care patients are not managed with routine SATs; intensive-care practitioners often opt instead for individualised, patient-targeted sedation.[16–19]

In the current investigation, daily SATs reduced the likelihood of oversedation so that patients were neurologically ready for extubation once their respiratory failure had improved. Patients in the intervention group were more alert than were patients in the control group on first passing both an SBT safety screen and SBT. Thus, these patients were more likely to be extubated shortly after first passing a breathing trial. Accompanying this earlier neurological recovery in the intervention group was a higher rate of self-extubation. Since these events did not result in more reintubations, the patients were apparently ready to come off the ventilator earlier than the intensive-care team had expected. Self-extubation within the intervention group did not substantially affect the results of the trial; after excluding all patients who self-extubated, the difference in ventilator-free days between treatment groups remained significant (data not shown).

In both the current trial and that by Kress and colleagues,[9] patients managed with daily SATs were treated with less total benzodiazepine medication than were patients who did not undergo SATs, a difference in drug dose that was considerable over the entire stay in intensive care but small on any given day of treatment. Total propofol doses, however, were similar between groups in both studies, suggesting that a reduction in drug dose was not the sole factor leading to improved outcomes. The pattern of administration is apparently an important factor; the interruption of a sedative infusion—during the wake up component of the SAT plus SBT protocol—probably facilitates a decline in plasma drug concentration and reduces the likelihood of drug accumulation.

Major strengths of the ABC trial included the parallel format of the SAT plus SBT protocol, which includes specific safety screens and failure criteria, making it easy to replicate; participation by intensive-care staff, including nurses and respiratory therapists; use of patient-target sedation and an SBT protocol in both groups; assessment of coma and delirium with validated and reliable instruments; and a multicentre study design with enrolment in both open and closed intensive-care units. Also, the liberal SBT safety screen criteria used (F_IO_2 ≤50% and PEEP ≤8 cm H_2O) facilitated the observation that many patients might be ready to breathe without assistance sooner than previously expected. Likewise, the simple criteria for passing an SAT were part of an SAT plus SBT protocol that was easy to implement yet effective. The

format of the SAT plus SBT protocol (ie, linkage of SATs and SBTs) should facilitate its use, making the typical practice of devising and implementing sedation protocols and ventilator weaning protocols as independent constructs unnecessary, thereby avoiding emphasis on one or the other depending on local strengths and personnel. Lastly, the patients and critical care communities that participated in the ABC trial were heterogeneous, greatly enhancing the generalisability of these findings.

Several limitations should be noted. Research personnel and intensive-care staff were not blinded to patient allocation because blinding is not possible in a study of this kind. Knowledge of group allocation can bias study results, so we randomly assigned patients to treatment groups, managed patients in both groups with formal protocols, followed well-defined outcomes, and used a statistical analysis plan designed a priori. Although each participating intensive-care unit used patient-targeted sedation strategies, we did not mandate the use of a specific sedation protocol in the control group or particular short-acting or long-acting sedatives in either group but—to compare the SAT plus SBT protocol with usual care—allowed clinicians to use their judgment with regard to the most appropriate medications and levels of sedation for individual patients. A detailed description of sedation practices used to manage patients in the control group is therefore not available except that sedative doses were recorded. By chance, patients in the intervention group received more propofol before enrolment than did those in the control group, whereas benzodiazepine and opiate doses were similar between groups. Although increased propofol doses before enrolment in the intervention group might have biased the results against showing improved outcomes in the intervention group, our analysis indicated that pre-enrolment propofol dose was not associated with study outcomes. Because we did not track the time spent executing the SAT plus SBT protocol, we cannot report the amount of personnel time needed to implement this intervention. The protocol was designed to be done by bedside nurses and respiratory therapists during the course of routine care, and it was implemented largely by clinical staff during the trial. Lastly, we did not enrol surgical patients because of their potential need for continuous analgesia; thus, the wake up and breathe protocol should be tested separately in a surgical intensive-care population.

At any instant during the year following enrolment, patients managed with the wake up and breathe protocol were about a third less likely to die than were patients in the control group. Patients with more severe critical illness, who tend to have prolonged stays in intensive care—ie, those who accrue the largest cumulative exposure to sedative medications—could receive the greatest benefit from management with the SAT plus SBT strategy, but we are limited in our ability to draw such conclusions since no data exist to elucidate the mechanism of the observed survival benefit.

In conclusion, our results suggest that use of a so-called wake up and breathe protocol that pairs daily spontaneous awakening trials (ie, interruption of sedatives) with daily spontaneous breathing trials for the management of mechanically ventilated patients in intensive care results in better outcomes than current standard approaches and should become routine practice.

Contributors

JWWT and EWE conceived the trial. TDG, JPK, BDF, JWWT, BTP, DBT, JCJ, AKS, SMG, JBH, RSD, GRB, and EWE participated in study design. TDG, JPK, BDF, JWWT, WDS, BTP, DBT, JGD, ASP, PAK, JCJ, AEC, RWL, and EWE recruited patients and collected data, and TDG, AKS, JLT, and EWE analysed the data. All authors participated in interpretation of results. TDG drafted the manuscript, and all authors contributed to the critical review and revision of the manuscript. All authors have seen and approved the final version of the manuscript.

Conflict of interest statement

EWE has received grant support or honoraria from Pfizer, Hospira, Lilly, and Aspect Medical. All other authors declare that they have no conflict of interest.

Acknowledgments

We thank the Saint Thomas Foundation (Nashville, TN, USA), the National Institutes of Health (AG001023, HL007123, and RR024975), the Veterans Affairs Tennessee Valley Geriatric Research, Education, and Clinical Center (GRECC), the Hartford Geriatrics Health Outcomes Research Scholars Award Program, and the Vanderbilt Physician Scientist Development Program for financial support. We thank the ABC trial study personnel at University of Chicago Hospitals (Joseph Levitt, Celerina Nigos, Stacey Sandbo, and Ajeet Vinayak), Hospital of the University of Pennsylvania (Megan Carr-Lettieri, Joan Hoch, and Edward Tollok), and Penn Presbyterian Medical Center (Hernan Alvarado Jr, Sandra Kaplan, William E Laury, and Jennifer Shin); the members of the data and safety monitoring board (Daniel W Byrne, Brian W Christman, and John H Newman); Frank E Harrell Jr for his expert statistical guidance; Daniel W Byrne for independently verifying all statistical results; and the staff of the intensive care units at Saint Thomas Hospital, the University of Chicago Hospitals, the Hospital of the University of Pennsylvania, and Penn Presbyterian Medical Center for their invaluable participation in the ABC trial.

References

1 Esteban A, Anzueto A, Frutos F, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA* 2002; **287:** 345–55.

2 Payen JF, Chanques G, Mantz J, et al. Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. *Anesthesiology* 2007; **106:** 687–95.

3 Cook DJ, Walter SD, Cook RJ, et al. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. *Ann Intern Med* 1998; **129:** 433–40.

4 Pinhu L, Whitehead T, Evans T, Griffiths M. Ventilator-associated lung injury. *Lancet* 2003; **361:** 332–40.

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:** 21–26.

6 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:** 541–48.

7 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:** 1864–69.

8 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:** 2609–15.

9 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:** 1471–77.

10 MacIntyre NR, Cook DJ, Ely EW Jr, et al. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. *Chest* 2001; **120:** 375S–95S.

11 Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. *N Engl J Med* 1995; **332:** 345–50.

12 Kollef MH, Shapiro SD, Silver P, et al. A randomized, controlled trial of protocol-directed versus physician-directed weaning from mechanical ventilation. *Crit Care Med* 1997; **25:** 567–74.

13 Marelich GP, Murin S, Battistella F, Inciardi J, Vierra T, Roby M. Protocol weaning of mechanical ventilation in medical and surgical patients by respiratory care practitioners and nurses: effect on weaning time and incidence of ventilator-associated pneumonia. *Chest* 2000; **118:** 459–67.

14 Lellouche F, Mancebo J, Jolliet P, et al. A multicenter randomized trial of computer-driven protocolized weaning from mechanical ventilation. *Am J Respir Crit Care Med* 2006; **174:** 894–900.

15 Carson SS, Kress JP, Rodgers JE, et al. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. *Crit Care Med* 2006; **34:** 1326–32.

16 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.

17 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:** 374–80.

18 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.

19 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:** 556–57.

20 Heffner JE. A wake-up call in the intensive care unit. *N Engl J Med* 2000; **342:** 1520–22.

21 Hong JJ, Mazuski JE, Shapiro MJ. Daily interruption of sedative infusions in critically ill patients. *N Engl J Med* 2000; **343:** 814–15.

22 Esteban A, Alia I, Gordo F, et al. Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. *Am J Respir Crit Care Med* 1997; **156:** 459–65.

23 Schoenfeld DA, Bernard GR. 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:** 1772–77.

24 Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond agitation-sedation scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002; **166:** 1338–44.

25 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:** 2983–91.

26 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:** 2703–10.

27 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:** 1370–79.

28 Ely EW, Pun BT. The Confusion assessment method for the ICU (CAM-ICU) training manual. http://www.icudelirium.org/delirium/CAM-ICUTraining.html (accessed Sept 20, 2006).

29 Anon. Social security death index. http://ssdi.rootsweb.com (accessed July 3, 2007).

30 Dupont WD, Plummer WD. PS power and sample size program available for free on the Internet. *Controlled Clin Trials* 1997; **18:** 274.

31 Efron B, Tibshirani RJ. An introduction to the bootstrap. New York, NY: Chapman & Hall/CRC, 1993.

32 Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika* 1982; **69:** 239–41.

33 Ihaka R, Gentleman R. R: a language for data analysis and graphics. *J Comput Graph Stat* 1996; **5:** 299–314.

34 Wilson WC, Smedira NG, Fink C, McDowell JA, Luce JM. Ordering and administration of sedatives and analgesics during the withholding and withdrawal of life support from critically ill patients. *JAMA* 1992; **267:** 949–53.

35 Novaes MA, Knobel E, Bork AM, Pavao OF, Nogueira-Martins LA, Ferraz MB. Stressors in ICU: perception of the patient, relatives and health care team. *Intensive Care Med* 1999; **25:** 1421–26.

36 Puntillo KA. Pain experiences of intensive care unit patients. *Heart Lung* 1990; **19:** 526–33.

37 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:** 119–41.

38 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:** 393–401.

39 Schweickert WD, Gehlbach BK, Pohlman AS, Hall JB, Kress JP. Daily interruption of sedative infusions and complications of critical illness in mechanically ventilated patients. *Crit Care Med* 2004; **32:** 1272–76.

40 Kress JP, Vinayak AG, Levitt J, et al. Daily sedative interruption in mechanically ventilated patients at risk for coronary artery disease. *Crit Care Med* 2007; **35:** 365–71.

41 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:** 1457–61.