

Implementing the 2013 ICU Pain, Agitation, and Delirium Guidelines: Opportunities for Pharmacists to Lead Interdisciplinary Change



Management of Pain, Agitation, and Delirium in Critically Ill Adults: A Decade of Change

Gilles L. Fraser, Pharm.D., FCCM
Professor, Tufts University School of Medicine
PGY2 Critical Care Residency Program Director
Clinical Pharmacist, Critical Care
Maine Medical Center
Portland, Maine



Discussion Outline

- **Greater concern for outcomes after ICU discharge**
- Importance of pain evaluation
- Analgosedation
- Wakefulness is an important therapeutic goal
- Upgrade use of propofol and dexmedetomidine
- Downgrade use of benzodiazepines
- Delirium assessment and nonpharmacological prevention strategies

What We've Learned: Goals for Our ICU Patients

- THEN: Survival and discharge
- NOW: Don't fix patients and break them at the same time
 - Complications extend beyond hospital discharge
 - Delirium = 10%
 - Long-term (1 year) cognitive impairment ~ 30%
 - Similar to traumatic brain injury or early Alzheimer's disease
 - PTSD ~15%
- FUTURE: Modifiable risk factors?

– Pandharipande P et al. N Engl J Med 2013; 369:1306

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Pain and/or Discomfort Should ALWAYS Be
Considered a Cause of ICU Agitation

"Mundane/routine" aspects of ICU care are the most
troublesome for patients

1990
63% remembered moderate to severe pain
Puntillo KA. Heart Lung. 1990; 19:526-33.



2007
50% remembered unmet analgesic needs
Gelinas C. Intensive Crit Care Nurs. 2007; 23:298-303.

There has been little progress in improving patient comfort in the ICU despite 17
years of focused attention on pain as an important clinical issue

ICU Pain and Discomfort

- Why is this so difficult for caregivers?
 - What is routine to us is hardly routine to the patient
 - Lack of appreciation for how poorly we assess pain
 - Gold standard for pain assessment = NRS
 - Unable to communicate with intact motor function?
 - Use validated behavioral pain scales
 - CPOT and BPS

NRS = numerical rating scale

Payen JF et al. Crit Care Med. 2001; 29:2258-63.
Gelinas C et al. Am J Crit Care. 2006; 15:420-7.
Payen JF et al. Anesthesiology. 2009; 111:1308-16.

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Newly Validated Pain Scales for Nonverbal ICU Patients

- Behavioral Pain Scale (BPS)
 - Evaluates facial expression, upper limb movement, and compliance with ventilator
- Critical-Care Pain Observation Tool (CPOT)
 - Evaluates all of the above plus muscular tension and vocalization if not intubated
- Scales do NOT consider vital sign changes!!
- Systematic use decreases....
 - Moderate to severe pain
 - Time on the ventilator and in the ICU
 - Amount of sedatives administered

Payen JF et al. *Crit Care Med.* 2001; 29:2258-63.
Gelinas C et al. *Am J Crit Care.* 2006; 15:420-7.
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New Paradigm: Analgesia-Based “Sedation”

- Also known as analgo-sedation or analgesia-first (A-1) sedation
- Acknowledges that discomfort is a common cause of agitation
- Any opioid useful... typically rapid onset and offset
- ~ 50% will require additional sedative agents

Clinical Practice Pearl: This is one way to limit avoidable serious adverse reactions from sedatives (immunomodulation, death, delirium, metabolic acidosis, hemodynamic derangement, etc).

Strom T et al. *Lancet.* 2010; 375:475-80.

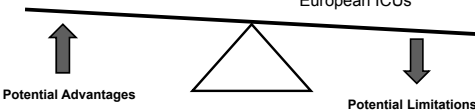
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"Analgo-sedation" Is Not Appropriate

- Drug/substance withdrawal (except opiates)
 - Replenish substance or alternative when appropriate
- Drug-induced agitation
 - Serotonin syndrome (linezolid, SSRIs)
 - Neuroleptic malignant syndrome
 - Delirium (benzodiazepines, meperidine, diphenhydramine, corticosteroids, etc)
 - Confusion (cefepime, quinolones, digoxin)
- Any agitation associated with a clear and reversible etiology

Finding the Balance with Analgo-sedation

- Pain and discomfort are a common cause for agitation
- Avoid potential sedative-related adverse events:
 - immunomodulation
 - death (e.g., PRIS)
 - delirium
 - metabolic acidosis
 - hemodynamic derangement
- ICU LOS, ventilator time, delirium, VAP, mortality, and cost of care NOT consistently reduced
- May interfere with respiratory drive, gastric motility, nutrition
- Potential for withdrawal symptoms when stopped
- Rigorously evaluated only in European ICUs





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Deep Sedation

- Greater than 40% patients are more deeply sedated than desired
- Drug-induced coma present during 32% of patient evaluations
 - Yet only 2.6% of clinicians rate these patients as “oversedated”

Does This Matter?

Weinert C et al. *Crit Care Med.* 2007; 35:393-401.
Payen JF et al. *Anesthesiology.* 2007; 106:687-95.

Avoiding Coma Improves Outcome

- Facilitates participation in care: pulmonary toilet, repositioning, early mobility
- Allows more accurate assessments of pain and delirium
- Reduces
 - Mechanical ventilation time (28-57%)
 - ICU length of stay (30-47%)
 - Neurodiagnostic testing (67%)
- Limits the post-intensive care syndrome?
 - Delirium?
 - PTSD?
 - Long-term cognitive impairment?

Treggiari MM et al. *Crit Care Med.* 2009; 37:2527-34.
Barr J et al. *Crit Care Med.* 2013; 41(9 Suppl 1):S99-115.
Fraser GL, Riker RR. *Crit Care Med.* 2007; 35:635-7.

Sedation Management

- Light sedation for most patients (B)
 - Allows wakefulness: respond purposefully to at least three commands
 - RASS and SAS for sedation assessment
 - Light sedation = RASS -1 or -2; SAS 3
- Use protocol with daily sedation interruption or that targets light level of sedation (1B)

Barr J et al. *Crit Care Med.* 2013; 41(9 Suppl 1):S99-115.

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Audience Polling Question

Which of the following has been shown in studies to be an outcome of maintaining mechanically ventilated adult patients at a light (rather than deep) level of sedation?



A greater incidence of post-traumatic stress disorder.



A greater incidence of patient-initiated device removal (e.g., self-extubation).



A shorter duration of mechanical ventilation.



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Sedation Management

- Sedation strategies with non-benzodiazepines may be preferred since they are associated with improved clinical outcomes (2B)
 - Ventilator time
 - ICU time
 - Delirium?
- No effect on mortality

Fraser GL et al. *Crit Care Med*. 2013; 41(9 Suppl 1):S30-8.
Barr J et al. *Crit Care Med*. 2013; 41(9 Suppl 1):S99-115.

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Benzodiazepines

- Good
 - GABA agonist withdrawal
 - Anxiety
 - Intermittent agitation
 - Hemodynamic instability?
 - Seizures
 - Deep sedation and when amnesia is beneficial
- And sometimes they are indeed the devil's handiwork

Barr J et al. *Crit Care Med.* 2013; 41:263-306.

Benzodiazepine Use Impacts Outcome

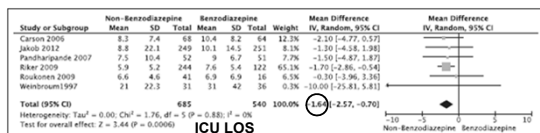


Figure 4. Forest plot for ICU length of stay. Nonbenzodiazepine sedative use was associated with a significantly shorter ICU length of stay compared with benzodiazepine sedative use. df = degrees of freedom.

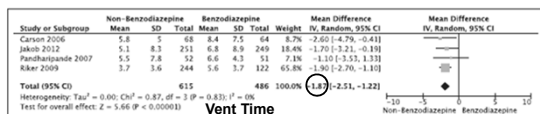


Figure 5. Forest plot for duration of mechanical ventilation. Nonbenzodiazepine sedative use was associated with a significantly shorter duration on mechanical ventilation compared with benzodiazepine sedative use. df = degrees of freedom.

Fraser GL et al. *Crit Care Med.* 2013; 41(9 Suppl 1): S30-8. Used with permission.

See enlargement p. 24

Propofol

- Pharmacology: GABA agonist
- Pharmacokinetics/dynamics: onset 1-2 min, duration 10 min
- Benefits
 - Rapid onset & offset
 - Allows easy dose titration to goal and facilitates daily sedation evaluation
 - When compared to benzodiazepines, results in shorter time on mechanical ventilation and in the ICU
 - Hypnotic and antiemetic
 - Can be used for intractable seizures and elevated intracranial pressures

Carson SS et al. *Crit Care Med.* 2006; 34:1326-32.

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Propofol Concerns

- Not reliably amnestic, especially at low doses
- NO analgesia!
- Hypotension
- Hypertriglyceridemia; lipid source (1.1 kcal/mL)
 - Monitor triglycerides twice weekly
- Respiratory depression
- Propofol-Related Infusion Syndrome (PRIS)
 - Low frequency adverse reaction with very high risk for death

Riker RR et al. *Pharmacotherapy*. 2005;25(5 Pt 2):8S-18S.
Roberts RJ et al. *Crit Care*. 2009; 13(5):R169.

Dexmedetomidine

Competing Concerns

Use Dex

- Less time on the ventilator
- No interference with resp drive
- Less delirium
- Sympatholysis can be helpful

Don't Use Dex

- Econotoxicity
- Hemodynamic derangement
- Not for deep sedation
 - No amnestic properties

Helpful Hints

- If you wouldn't treat a patient with a beta-blocker, don't use dex
- Withdrawal tachycardia and hypertension unusual
- Econotoxicity = HUGE!

Pandharipande PP et al. *JAMA*. 2007;298:2644-53.
Riker RR et al. *JAMA*. 2009; 301:489-99.

Sedation Costs

- MMC sedative costs/DAY in a 90-kg patient
 - Dexmedetomidine 1.4 mcg/kg/hr = \$1000
 - Propofol 60 mcg/kg/min = \$53
 - Midazolam 5 mg/hr = \$13
 - Clonidine 0.2 mg q 6 hr = \$0.36

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Why Systematically Assess Delirium?

- Any data suggesting that this reduces delirium prevalence?
 - No!
- Any data suggesting that this reduces its severity?
 - No!
- So why bother?
 - Prompts timely identification of clinically relevant reversible causes ...infections, etc
 - Prompts scrutiny of drug therapy

Can ICU Delirium Be Prevented?

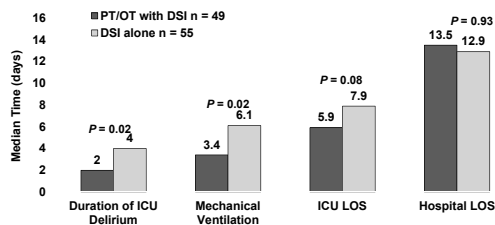
- Nonpharmacologic:
- Early mobilization
- Return to independent functional status
 - 59% vs. 35% ($p=0.02$)



Schweickert WD et al. *Lancet*. 2009;373(9678):1874-82.

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Early Mobilization



- ↑ quality of life
- ↑ physical function
- ↑ peripheral, respiratory muscle strength

Schweickert WD et al. *Lancet*. 2009;373(9678):1874-82.
Needham DM et al. *Arch Phys Med Rehabil*. 2010; 91:536-42.

See enlargement p. 24

Delirium Management?

- Correct inciting factor and offer nonpharmacologic interventions
- Control symptoms?
 - Unclear if standard antipsychotic treatment reduces duration & severity of symptoms
 - Benzodiazepines?
 - For delirium due to drug/alcohol withdrawal
 - Dexmedetomidine?
 - Preferable to benzodiazepines in most delirious patients
- No treatment FDA approved

Riker RR et al. *JAMA*. 2009; 301:489-99.
Reade MC et al. *Crit Care*. 2009; 13:R75.

Translation Into Practice

Assumes that
1) primary causes for pain, agitation, and delirium are addressed
2) non-pharm management options are in place including adjustment of vent settings
3) patient behaviors are troublesome and/or pose a risk

Step 1 → Assess and treat pain

- Routinely assess pain in all ICU patients using self-report if possible (NRS)
 - Evaluate at light levels of sedation
- For patients with intact motor function, but unable to self-report, assess pain with BPS or CPOT
- Preemptively treat procedural pain
- Opiates may be preferred especially if an analgesia-first approach is used.

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Translation Into Practice

Assumes that

- 1) primary causes for pain, agitation, and delirium are addressed
- 2) non-pharm management options are in place including adjustment of vent settings
- 3) patient behaviors are troublesome and/or pose a risk

Step 2

Assess delirium and the
need for sedation

- Assessment for delirium and agitation/sedation should be routine for all ICU patients
 - Use CAM-ICU or ICDSC assessment tools for delirium when patients are wakeful
 - Use RASS or SAS assessment tools for sedation
 - Use protocols and checklists to facilitate sedation management
- Target the lightest level of sedation possible



Successful Pharmacist-driven PAD Guideline Implementation Strategies

John W. Devlin, Pharm.D., FCCP, FCCM
Professor of Pharmacy
Northeastern University
Scientific Staff and Critical Care Pharmacist
Division of Pulmonary, Critical Care and Sleep
Medicine
Tufts Medical Center
Boston, Massachusetts



Pharmacist-Driven PAD Optimization Strategies

- **Interdisciplinary approach: differing perspectives**
- Optimizing patient wakefulness strategies
- Boosting delirium recognition
- Minimizing antipsychotic use
- Reflection of current and past PAD efforts
- Leading PAD quality improvement efforts

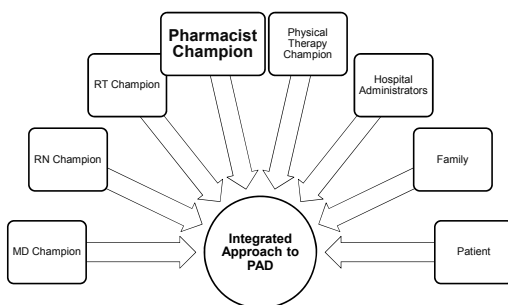
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PAD Interdisciplinary Team

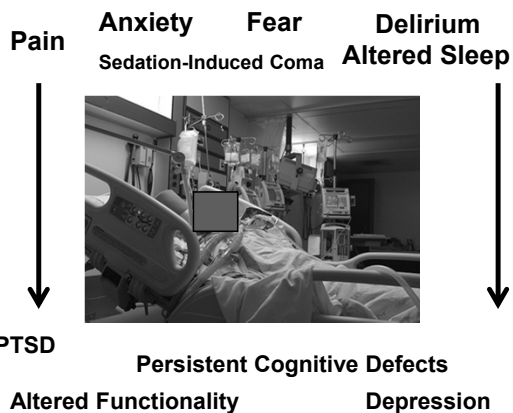


Courtesy J Barr, MD

PAD Interdisciplinary Team

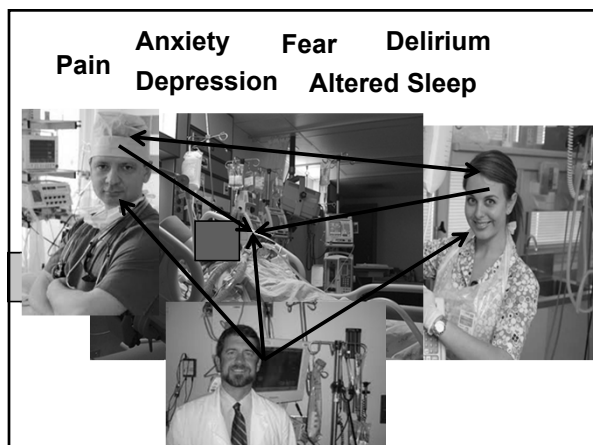


Courtesy J Barr, MD



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**Adapting ICU Pain, Sedation and Delirium
Evidence to the ICU Bedside:
It's all about perspective**





**Pharmacist-Driven PAD
Optimization Strategies**

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Patient Wakefulness is Important!

- ↑ Patient communication
- ↓ Delirium
- ↑ Delirium screening
- ↑ Spontaneous breathing trial
- ↑ Early mobilization
- ↓ PTSD
- ↓ Risk for sedative ADEs

Impact of a Combined SAT-SBT Strategy on Patient Outcomes

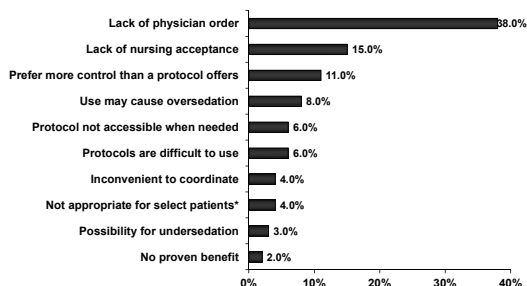
Outcome	SBT	SAT+SBT	P-value
Ventilator-free days	12	15	0.02
Coma, days	3	2	0.002
Time-to-event, days			
Successful extubation	7	5	0.05
ICU discharge	13	9	0.01
Hospital discharge	19	15	0.04

Compliance with SAT and SBT components of protocol in this controlled study was ≥ 90%

SAT = Spontaneous Awakening Trial
SBT = Spontaneous Breathing Trial

Girard TD et al. *Lancet*. 2008; 371:126-34.

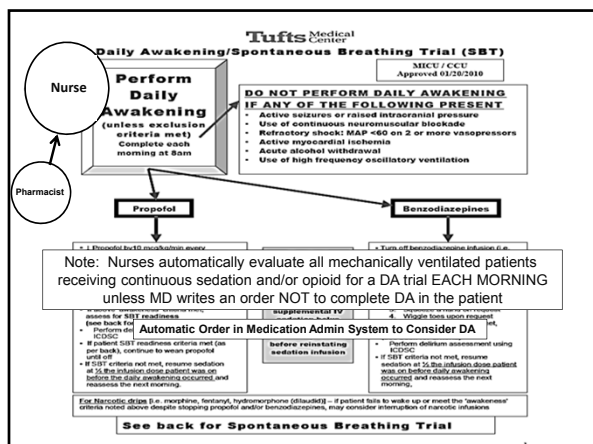
Perceived Barriers to Use of Daily Sedation Interruption (DSI): Engaging the Bedside RN is the Key!



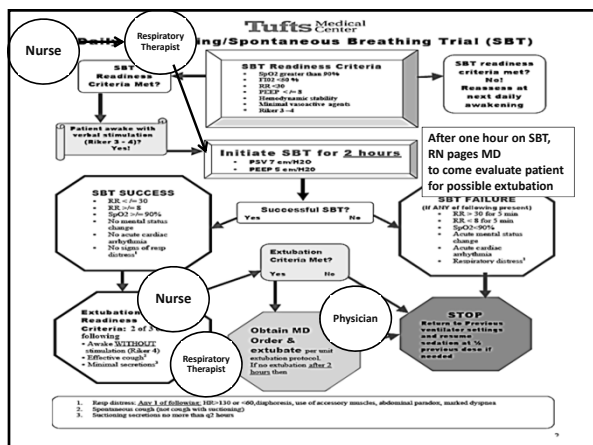
Tanios MA et al. *J Crit Care*. 2009; 24:66-73.

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See enlargement p. 25



See enlargement p. 26

Reduction in Administration of Continuous IV Benzodiazepine and Opioid Therapy in Acute Lung Injury Patients Reduces Incidence of Coma

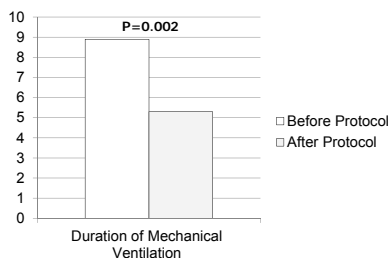
	Before New Sedation Protocol N=120	After New Sedation Protocol n=82	P value
Narcotic infusion*	74%	33%	< 0.001
Benzodiazepine infusion *	70%	22%	< 0.001
Median RASS score	-4 (-5 to -2)	-1.5 (-3, 0)	<0.001
Comatose*	65%	23%	< 0.001

*% of MICU patients

Hager DN et al. Crit Care Med. 2013; 41:1435-42.

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Impact of a Clinical Pharmacist-Enforced ICU Sedation Protocol



Marshall J et al. *Crit Care Med.* 2008; 36:427-33.



Audience Polling Question

Which of the following has been shown to reduce sedation-associated coma in the ICU?



Decreased use of IV sedation infusions



Daily sedation interruption/awakening



Each of the above



Pharmacist-Driven PAD Optimization Strategies

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- **Boosting delirium recognition**
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- Reflection of current and past PAD efforts
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Strategies to Boost Delirium Recognition in the ICU

- Sedation assessment (i.e., SAS or RASS) should be occurring regularly and reliably
- Need buy-in from both nurse and physician managers
- Education
 - Both didactic (e.g., classroom/web) and at bedside
- Both nurses and pharmacists can deliver this education
- - Deliver education to all nurses (i.e., both day and night shift), physicians, and pharmacists
- Ensure that clinicians are comfortable with "not being able to evaluate" components of delirium at certain times
- Documentation of delirium evaluation
- Mandatory discussion of delirium evaluation during daily rounds

SAS=Sedation-Agitation Scale
RASS=Richmond Agitation-Sedation Scale

Devlin JW et al. *Best Pract Res Clin Anaesthesiol.* 2012; 26:385-93.

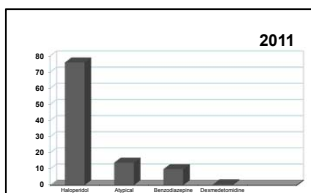
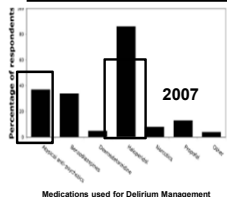


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Use of Antipsychotic Therapy to Treat Delirium Remains High in American ICUs

2002	Drug	No.	%
	Antipsychotics	634	70
	Haloperidol	603	66
	Atypical antipsychotics	34	4



Ely EW et al. *Crit Care Med.* 2004; 32:106-12.
Patel RP et al. *Crit Care Med.* 2009; 37:825-32.
Devlin JW et al. *Ann Pharmacother.* 2011; 45:1217-29.

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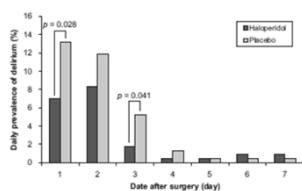
Many False Perceptions by U.S. Critical Care Pharmacists Regarding Antipsychotic Use for Delirium in the ICU

	Frequently or always used in a patient with agitated delirium (%)	Published RCT demonstrating benefit (%)	Labeled by the FDA for delirium treatment (%)
Haloperidol	87	42	34
Quetiapine	59	40	8
Lorazepam	47	3	3
Dexmedetomidine	25	33	8

Devlin JW et al. *Ann Pharmacother*. 2011; 45:1217-29.

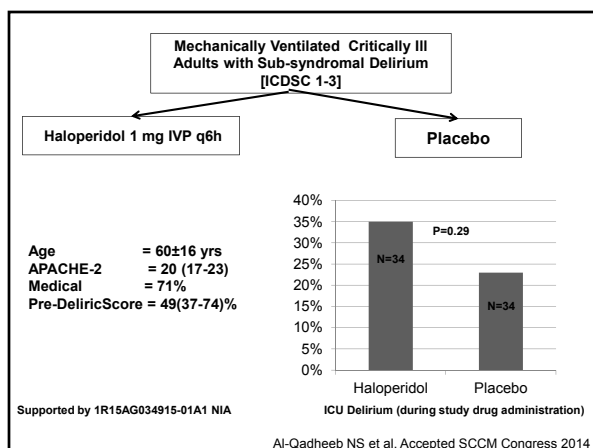
Low-Dose IV Haloperidol Prevents Delirium in Low-Acuity SICU Patients

	Haloperidol 1.7 mg IV over 12 hrs (n=229)	Placebo (n=228)	P-value
Age	74.0 ± 5.8	74.4 ± 7.0	0.50
APACHE-2	8.7 ± 3.0	8.6 ± 2.8	0.58
Intubated (%)	78.6	77.6	0.80



Wang W et al. *Crit Care Med*. 2012; 40: 731-9. Used with permission.

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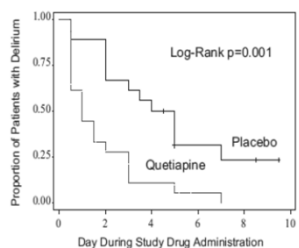
HOPE-ICU Study:

- Mechanically ventilated ICU patients randomized within 72 hrs of ICU admission (regardless of delirium or coma status) to receive:
- Haloperidol 2.5 mg IV q8h or placebo for up 14 days or until ICU discharge or coma and delirium-free x 2 days

	Haloperidol n=71	Placebo n=70	P value
Days alive, delirium-free, and coma-free in the first 14 days	5 (0-10)	6 (0-11)	0.53
Days in delirium in the first 14 days	5 (2-8)	5(1-8)	0.99
Ventilator-free days	21 (0-25)	17 (0-25)	0.88

Page VJ et al. *Lancet Respir Dis.* 2013 Aug 21. Epub ahead of print.

Efficacy and safety of quetiapine in critically ill patients with delirium. A prospective, multicenter, randomized, double-blind, placebo-controlled pilot study



Devlin JW et al. *Crit Care Med.* 2010; 38:419-27. Used with permission.

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MIND USA STUDY

Patients requiring either MV, NPPV or in shock who are CAM-ICU+
N=947 patients at n=14 USA centers

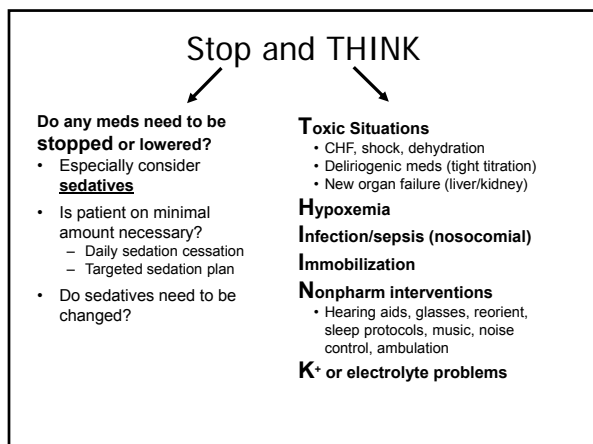
Haloperidol
10 mg IV q12h


Ziprasidone
20 mg IV q12h

Placebo
10 mL q12h

Period spent delirium-free and coma-free 14 days after randomization

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Audience Polling Question

Which of the following is MOST true about the role of haloperidol for either the prevention or treatment of delirium in the ICU?

☐ Haloperidol is approved by the FDA for the treatment of delirium in the ICU.

☐ Haloperidol has been shown in one randomized, controlled trial to prevent delirium in severely ill ICU patients.

☐ Neither of the above



Pharmacist-Driven PAD Optimization Strategies

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- **Reflection of current and past PAD efforts**
- Leading PAD quality improvement efforts

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Perceived vs. Actual Practice

- Survey of 85 ICUs where a sedation protocol was used (24-hr practice snapshot)
 - *Sedation protocols used in 50%*
- Sedation interruption reported in 66% ICUs
 - *Performed in 36% patients*
- Delirium monitoring reported in 25% ICUs
 - *Performed in 10% of patients*

Gill KV et al. *Ann Pharmacother.* 2012; 46:1331-9.

Reflection of Current Practices Important

- Consider past PAD-related successes and failures
- Do you screen for pain with a non-verbal scale?
- Is sedation assessment regular and reliable?
- How many intubated patients receive continuous IV sedation?
- Is a light level of sedation being targeted?
- Is DA-SBT protocol in place?
- Is delirium being screened for?
- Has early mobilization been tried?
- What are the barriers for you to change YOUR daily PAD practices?
- What are the barriers preventing change to YOUR ICU's PAD practices?

****SCCM 2013 PAD guidelines are ONLY guidelines****

**Controlling pain, agitation and delirium in the ICU
requires an individualized approach for most patients**



Implementing the 2013 ICU Pain, Agitation, and Delirium Guidelines: Opportunities for Pharmacists to Lead Interdisciplinary Change



Pharmacist-Driven PAD Optimization Strategies

- Interdisciplinary approach: differing perspectives
- Optimizing patient wakefulness strategies
- Boosting delirium recognition
- Minimizing antipsychotic use
- Reflection of current and past PAD efforts
- **Leading PAD quality improvement efforts**

Performance Management

What Is the ABCDE Bundle?

- (AB) Awakening and Breathing coordination
- (C) Choice of sedative
- (D) Delirium identification and management
- (E) Exercise

Vasilevskis EE et al. CHEST. 2010; 138:1224–33.

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Impact of a ICU Sedation Protocol Incorporating Many PAD Guideline Recommendations

- Pain assessment and treatment first
- Maintenance 24/7 of patients in an awake/slightly sleepy state
- Use of continuous sedation infusions
- Minimal use of benzodiazepines
- Early delirium recognition and treatment

Parameter	Before-Protocol N=604	After-Protocol N=610	P value
RASS	-0.4	-0.4	0.9
No exposure to benzodiazepines	39%	45%	<0.03
Lorazepam equivalents	3.8	2.3	0.05
ICDSC=0	32%	41%	0.002
Discharged to home	45%	52%	0.02

Skrobik Y et al. *Anesth Analg*. 2010; 111:451-63.

Facilitating Knowledge Transfer to the Bedside

- Use clinical practice guidelines as a model
- Develop protocols for managing PAD
- Develop “order sets” based on institution-specific protocols
- Create “bundles” for implementing essential components of practice guidelines
- Consider daily rounding pharmacist or quality checklist with these elements
- Offer real time clinical decision support

Marshall J et al. *Crit Care Med*. 2008; 36:427-33.
DuBose JJ et al. *J Trauma*. 2008; 64:22-7.

Benchmarking PAD Guidelines Performance Improvement

	Pain	Agitation	Delirium
Assess	% of time patients evaluated for pain ≥4x per shift	% of time sedation assessed ≥4x per shift	% of time delirium assessments are performed every shift
Treat	% of time pain treatment administered within 30 minutes of significant pain	% of sedation assessments where patients are over sedated (e.g. RASS ≤ 2)	% of time benzodiazepines are administered to patients with agitated delirium
Prevent	% of time patients receive pre-procedural analgesia	% of failed attempts at SBTs due to oversedation (i.e., lack of daily interruption)	% of patients receiving early mobility

Barr J et al. *Crit Care Med*. 2013;41:263-306.

Benzodiazepine Use Impacts Outcome

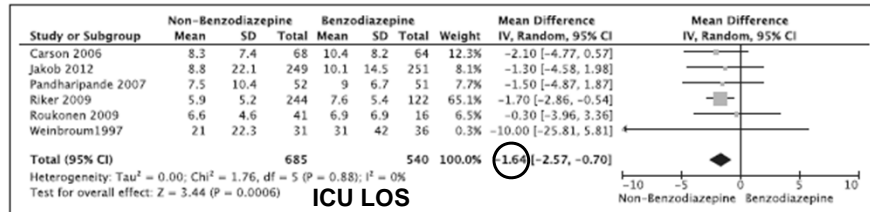


Figure 4. Forrest plot for ICU length of stay. Nonbenzodiazepine sedative use was associated with a significantly shorter ICU length of stay compared with benzodiazepine sedative use. df = degrees of freedom.

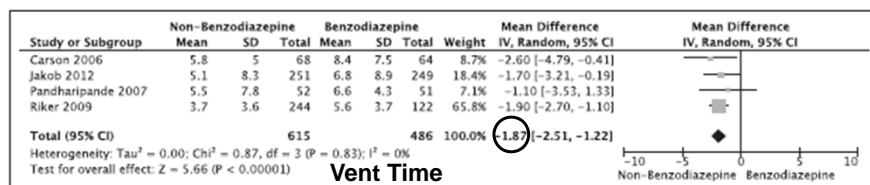
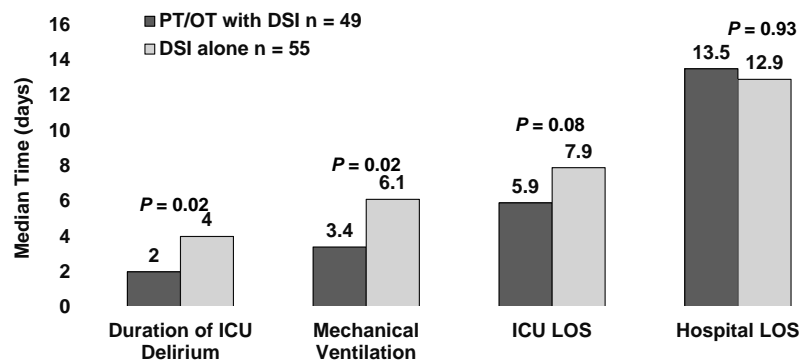


Figure 5. Forrest plot for duration of mechanical ventilation. Nonbenzodiazepine sedative use was associated with a significantly shorter duration on mechanical ventilation compared with benzodiazepine sedative use. df = degrees of freedom.

Fraser GL et al. *Crit Care Med*. 2013; 41(9 Suppl 1): S30-8. Used with permission.

Early Mobilization

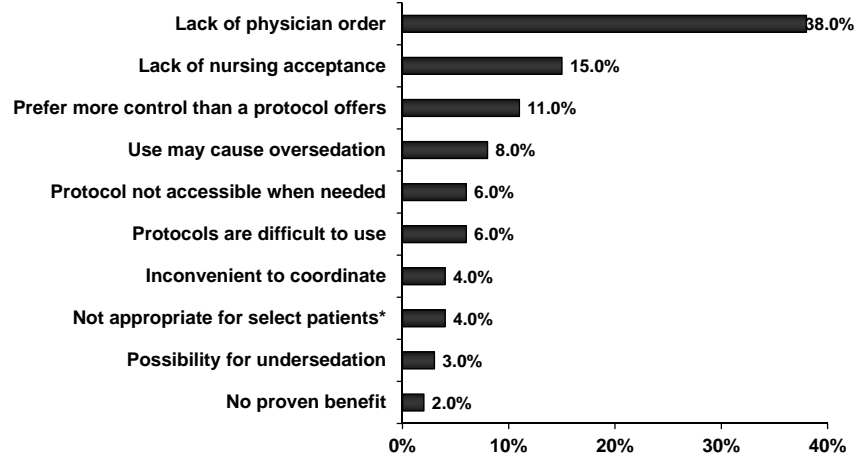


- ↑ quality of life
- ↑ physical function
- ↑ peripheral, respiratory muscle strength

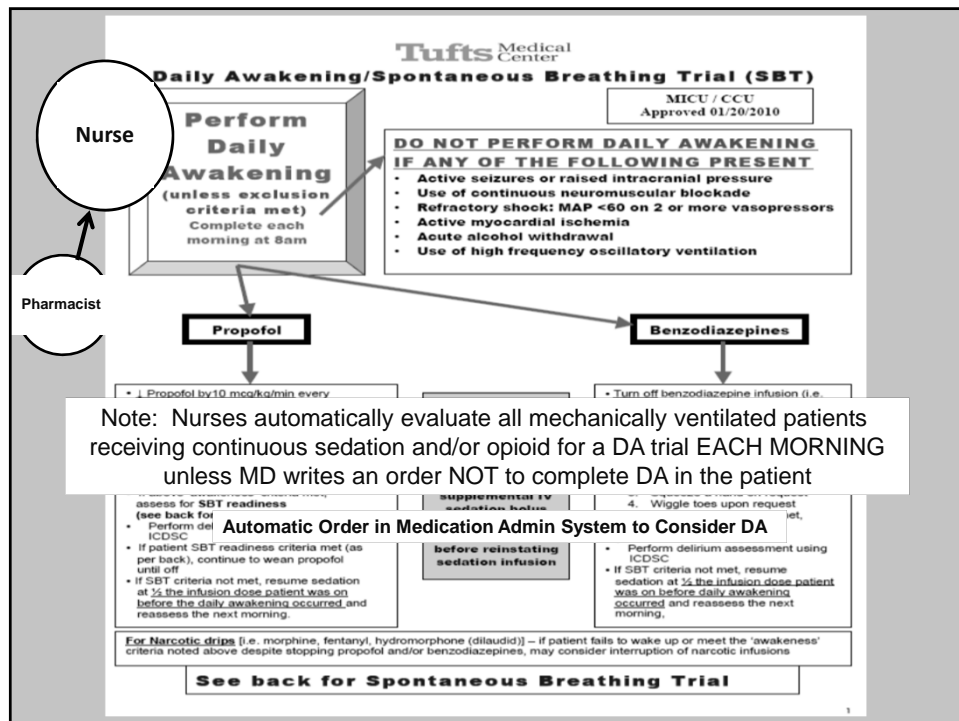
Schweickert WD et al. *Lancet*. 2009;373(9678):1874-82.
Needham DM et al. *Arch Phys Med Rehabil*. 2010; 91:536-42.

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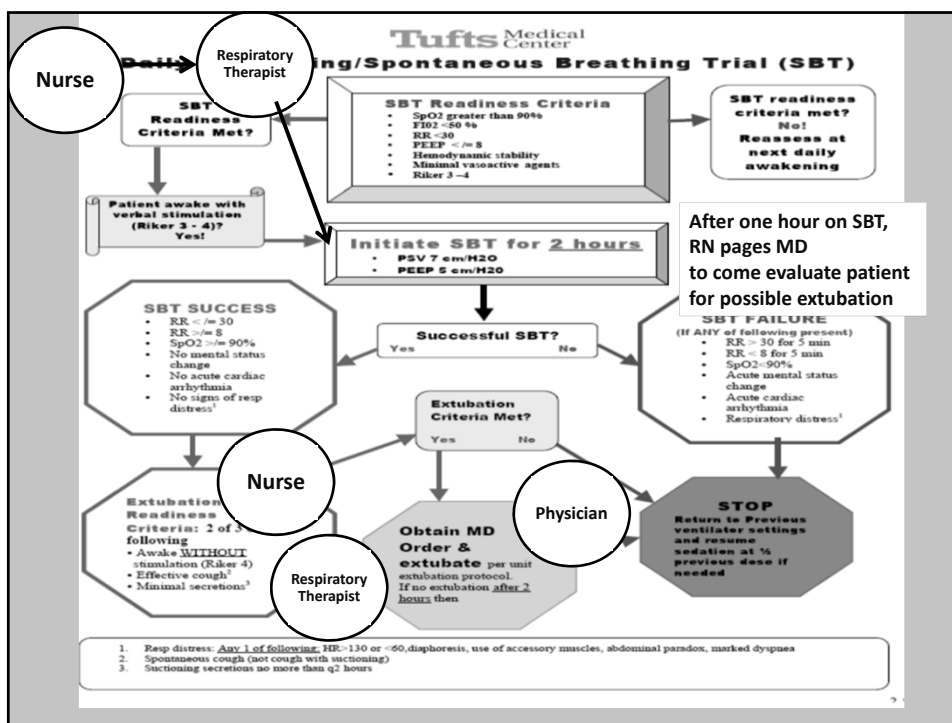
Perceived Barriers to Use of Daily Sedation Interruption (DSI): Engaging the Bedside RN is the Key!



Tanios MA et al. *J Crit Care*. 2009; 24:66-73.



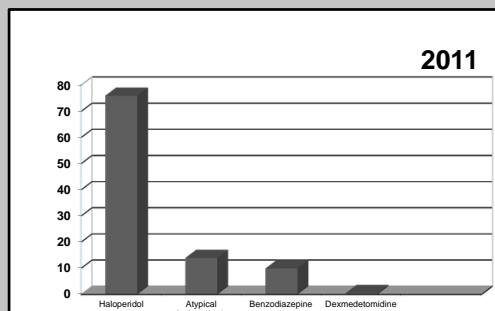
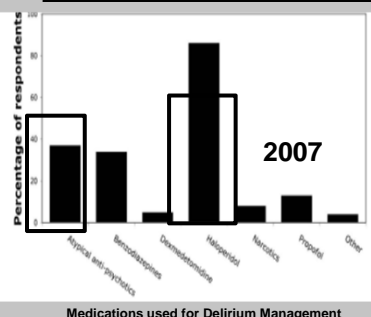
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Use of Antipsychotic Therapy to Treat Delirium Remains High in American ICUs

Table 4. Medication used by healthcare professionals to treat delirium in the intensive care unit

2002	Drug	No.	%
Antipsychotics		634	70
Haloperidol		603	66
Atypical antipsychotics		34	4



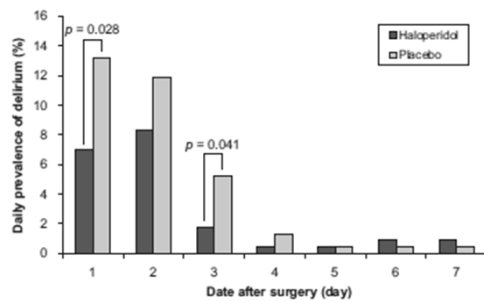
Ely EW et al. *Crit Care Med.* 2004; 32:106-12.

Patel RP et al. *Crit Care Med.* 2009; 37:825-32.

Devlin JW et al. *Ann Pharmacother.* 2011; 45:1217-29.

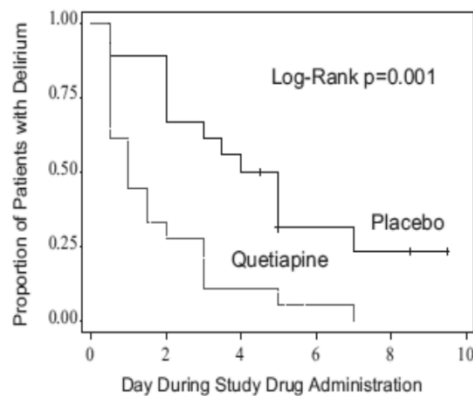
Low-Dose IV Haloperidol Prevents Delirium in Low-Acuity SICU Patients

	Haloperidol 1.7 mg IV over 12 hrs (n=229)	Placebo (n=228)	P-value
Age	74.0 ± 5.8	74.4 ± 7.0	0.50
APACHE-2	8.7 ± 3.0	8.6 ± 2.8	0.58
Intubated (%)	78.6	77.6	0.80



Wang W et al. *Crit Care Med.* 2012; 40: 731-9. Used with permission.

Efficacy and safety of quetiapine in critically ill patients with delirium. A prospective, multicenter, randomized, double-blind, placebo-controlled pilot study



Devlin JW et al. *Crit Care Med.* 2010; 38:419-27. Used with permission.