Reducing ICU Delirium

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Disclosures

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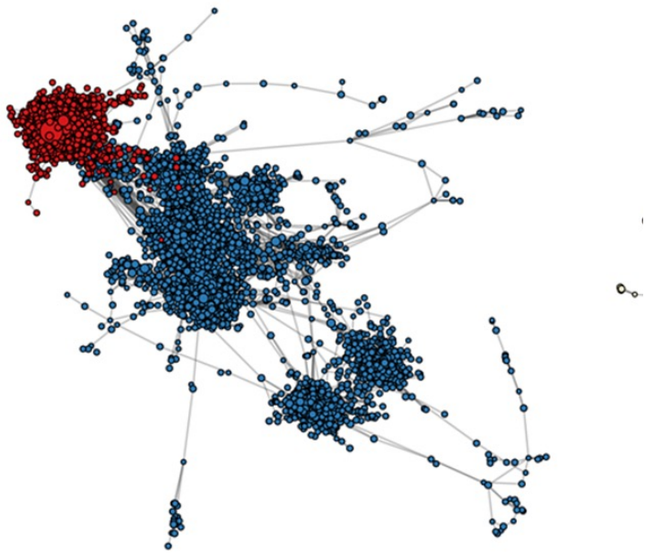
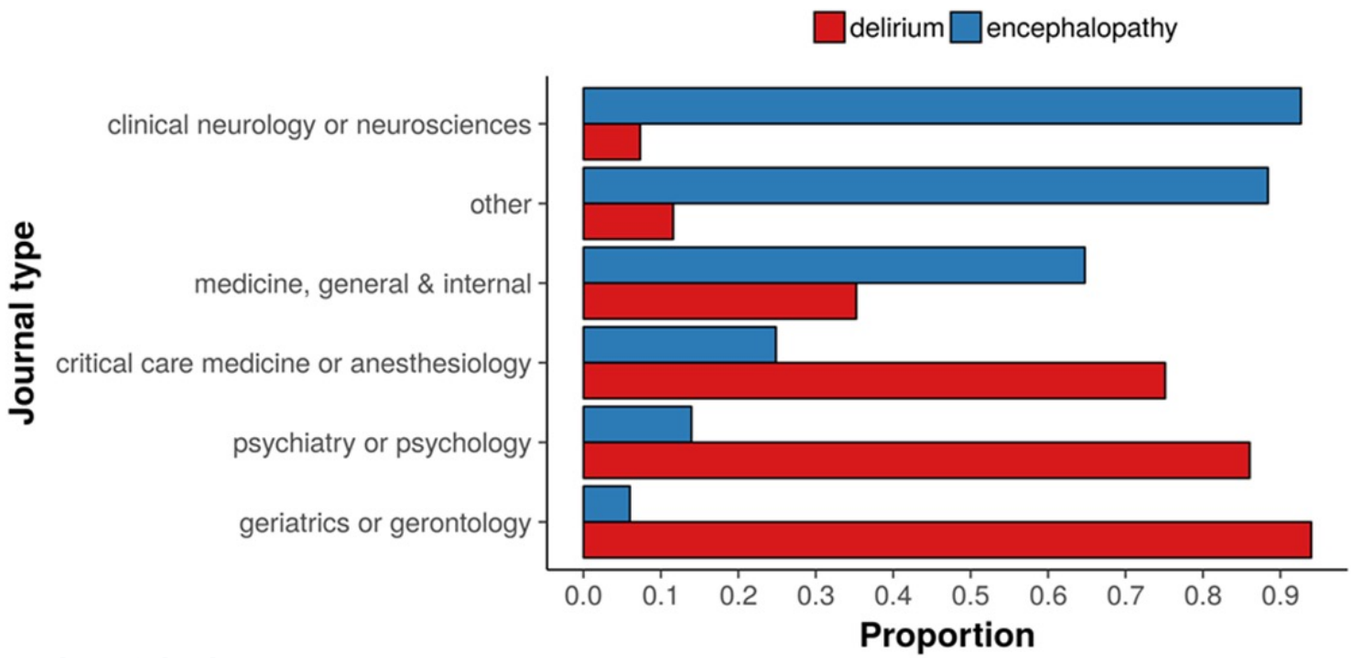
- Haisco Pharma

WHAT'S NEW IN INTENSIVE CARE

Updated nomenclature of delirium and acute encephalopathy: statement of ten Societies

Arjen J. C. Slooter[1*], Wim M. Otte[2], John W. Devlin[3,4], Rakesh C. Arora[5,6], Thomas P. Bleck[7], Jan Claassen[8], Matthew S. Duprey[3,4], E. Wesley Ely[9,10], Peter W. Kaplan[11], Nicola Latronico[12], Alessandro Morandi[13,14], Karin J. Neufeld[15], Tarek Sharshar[16], Alasdair M. J. MacLullich[17] and Robert D. Stevens[18]





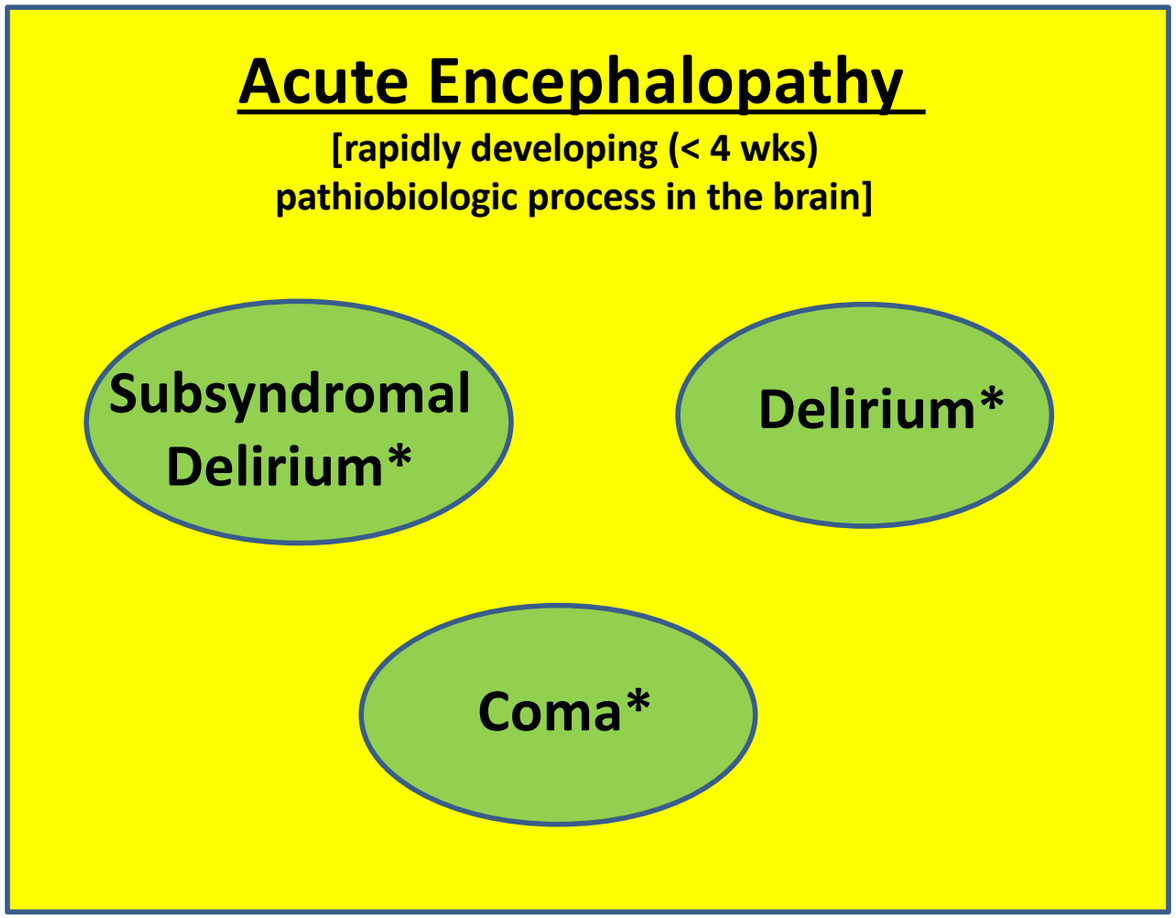
PubMed Search 1990-2018:

n=5,709 delirium–titled n=13,156 encephalopathy-titled

Only n=13 had both in title

N=7 Delphi Rounds

Preferred Terms



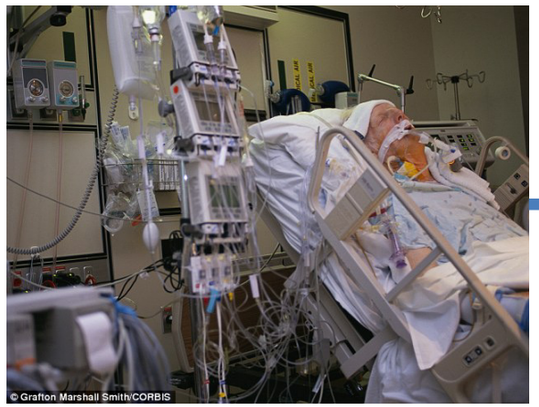
**Clinical sequelae of acute encephalopathy*

Terms that *Should Not* be Used as a Replacement for Acute Encephalopathy or Delirium

- Acute Confusional State
- Acute Brain Dysfunction
- Acute Brain Failure
- Altered Mental Status

Slooter AJC, Otte W, Devlin JW, et al, Intensive Care Med 2020

Prevalence of delirium in critically ill older adults 50-70%



ICU Survivorship

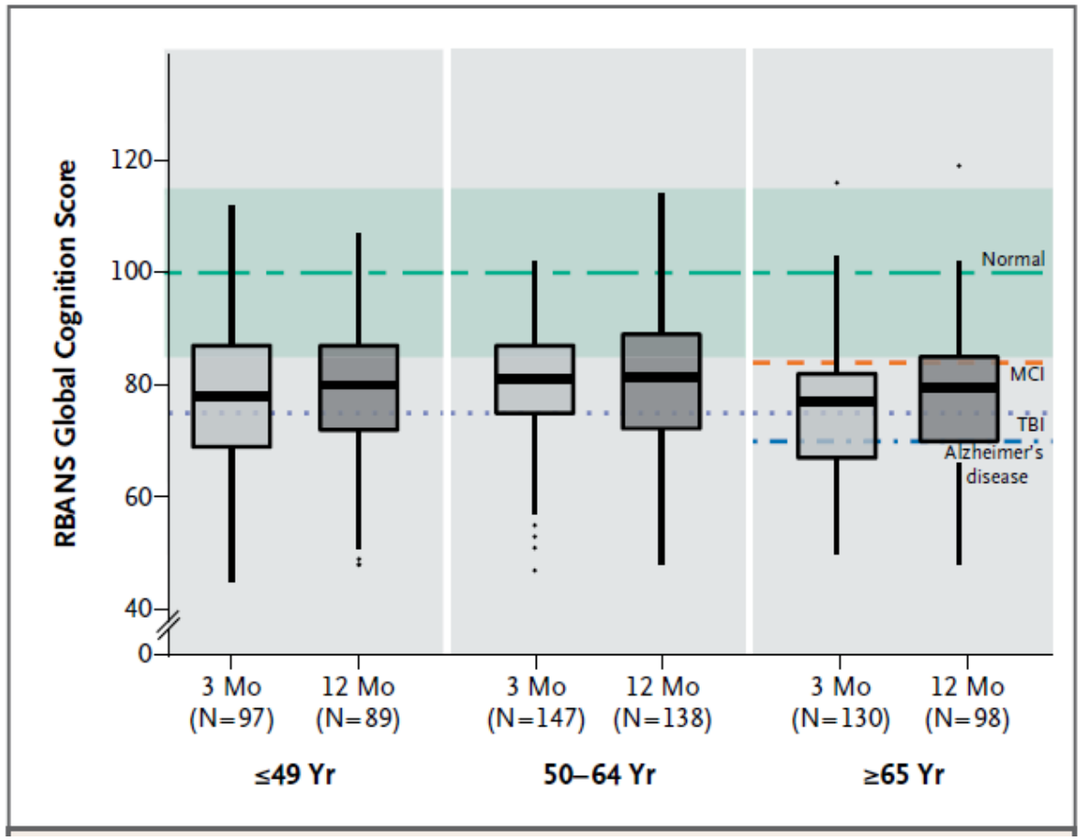
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Cognitive Impairment after Critical Illness

N=826 critically ill adults

- Age = 61 [41-71]
- Apache II = 25 [19-31]
- Medical 68%
- Mech Ventilation =91%
- Delirium = 74 % for 4 [2-7] days
- Coma = 63% for 3 [2-6] days
- Benzodiazepine = 62%
- Propofol = 52%
- Dexmedetomidine = 13%
- Opioids = 78%



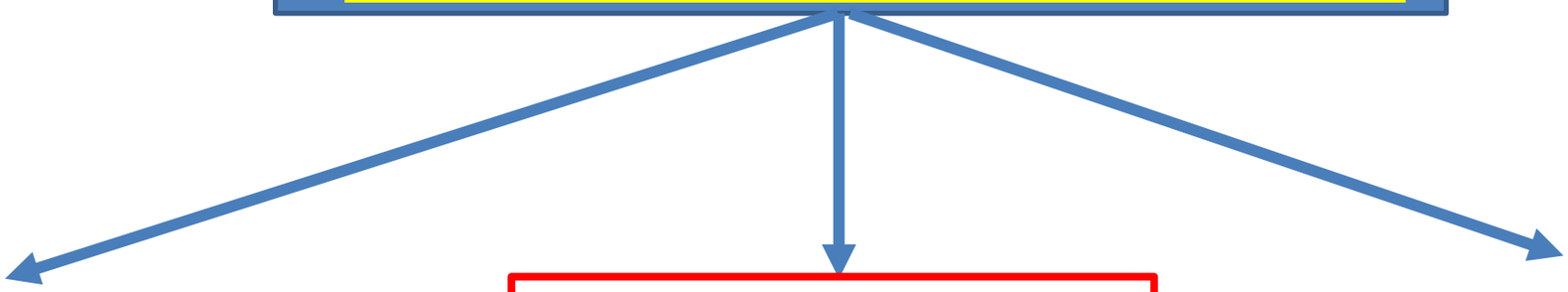
A longer duration of delirium was independently associated with:

a) worse global cognition at 3 months (P=0.001) and 12 months (P=0.004)

b) worse executive function at 3 months (P=0.004) and 12 months (P=0.007)

Pandharipande PP, Girard TD, Jackson JC, et al. New Engl J Med 2013; 369:1306

Post-intensive care syndrome (PICS)

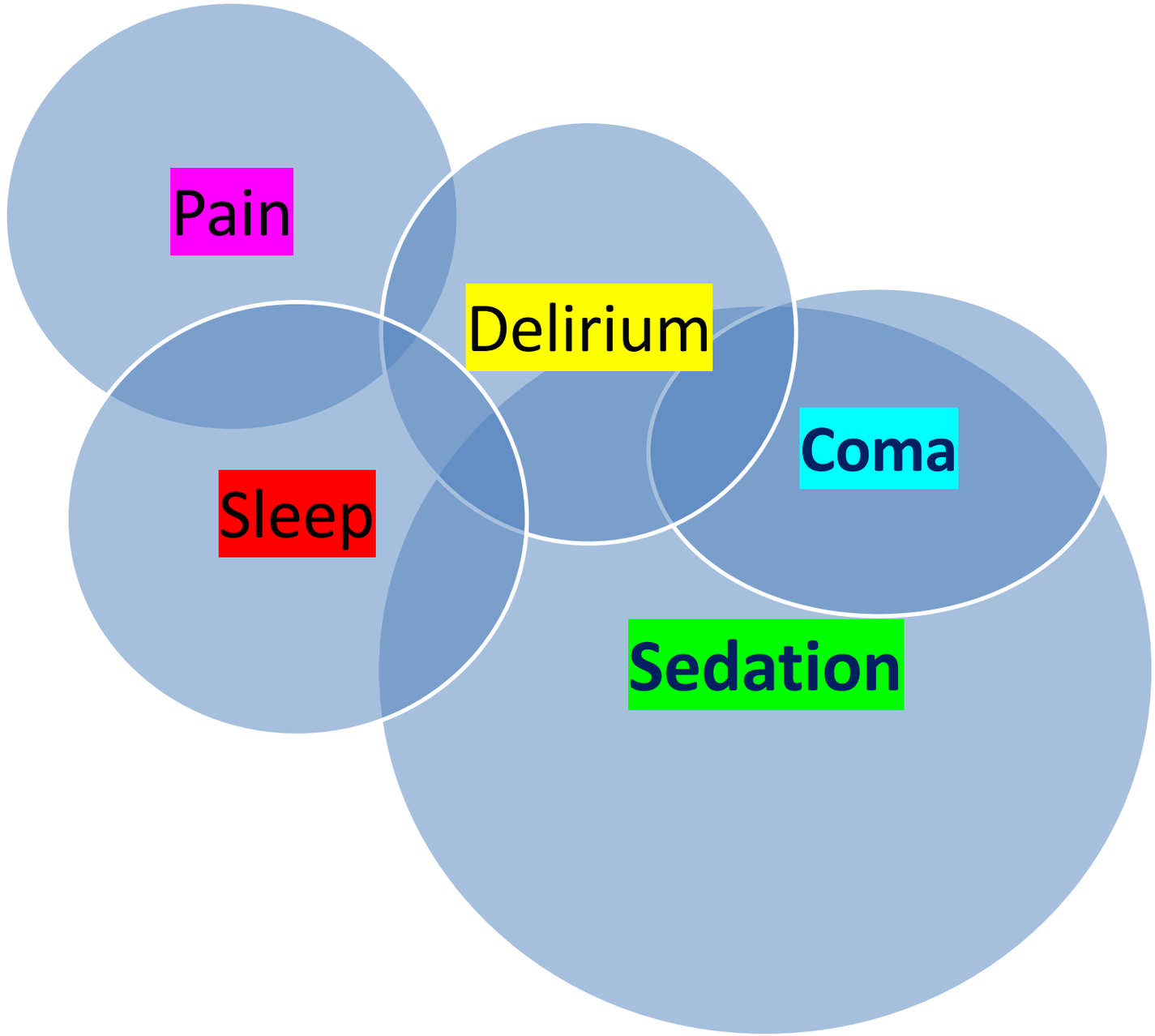


Psychological Symptoms
- Anxiety
- Depression
- PTSD
- Sleep problems

Cognitive Symptoms
- Executive function
- Memory
- Attention
- Visual-spatial
- Mental processing speed

Physical Symptoms
- Breathing difficulties
- Weakness and balance problems
- Neuromuscular impairment
- Pain or numbness

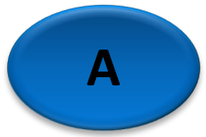
Herridge MS, Cheung AM, Tansey CM, et al: et al, N Engl J Med 2003; 348:682
Krumholz HM, N Engl J Med 2013; 368:100
Iwashyna TJ, Ely EW, Smith DM, et al: JAMA 2010; 304:1787
Fan E, Dowdy DW, Colantuoni E, et al: Crit Care Med 2014; 42:849
Needham DM, Wozniak AW, Hough CL, et al: Am J Respir Crit Care Med 2014:42:849
Parker AM, Srichiaroenchai T, Raparla S, et al: Crit Care Med 2015; 43:1121
Marra A, Pandharipande PP, Girdard TD, et al: Crit Care Med 2018; 46:1393.


Pain
Delirium
Coma
Sleep
Sedation

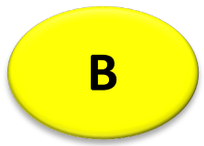
Four Key Strategies to Reduce ICU Delirium

1. Screen critically ill adults regularly and reliably for delirium.
2. Recognize and reduce modifiable risk factors for delirium.
3. Focus on non-pharmacologic interventions known to reduce delirium that may include use a multimodal protocol (e.g., ABCDEF bundle).
4. Generally, avoid pharmacologic interventions to reduce delirium in most patients.

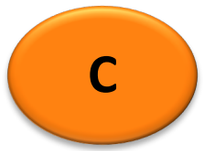
ABCDEF Bundle Elements



Assess, Prevent and manage Pain

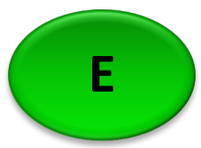


Both SAT and SBT



Choice of Analgesia and Sedation

Delirium: Assess, Prevent and Manage



Early Mobility and Exercise

Family Engagement and Empowerment

Vasilevskis EE, et al. *Chest*. 2010;138(5):1224-1233.
Davidson JE, et al. *Am Nurse Today*. 2013;8(5):32-38.

Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults

Brenda T. Pun, DNP, RN, FCCM[1]; Michele C. Balas, PhD, RN, CCRN-K, FCCM, FAAN[2,3]; Mary Ann Barnes-Daly, MS, RN, CCRN-K, DC[4]; Jennifer L. Thompson, MPH[5]; J. Matthew Aldrich, MD[6]; Juliana Barr, MD, FCCM[7,8]; Diane Byrum MSN, RN, CCRN-K, CCNS, FCCM[9]; Shannon S. Carson, MD[10]; John W. Devlin, PharmD, FCCM[11]; Heidi J. Engel, PT, DPT[12]; Cheryl L. Esbrook, OTR/L, BCPR[13]; Ken D. Hargett, MHA, FAARC, FCCM[14]; Lori Harmon, RRT, MBA, CPHQ[15]; Christina Hielsberg, MA[15]; James C. Jackson, PsyD[1]; Tamra L. Kelly, BS, RRT, MHA[4]; Vishakha Kumar, MD, MBA[15]; Lawson Millner, RRT[16]; Alexandra Morse, PharmD[4]; Christiane S. Perme, PT, CCS, FCCM[14]; Patricia J. Posa, BSN, MSA, CCRN-K[17]; Kathleen A. Puntillo, PhD, RN, FCCM, FAAN[18]; William D. Schweickert, MD[19]; Joanna L. Stollings, PharmD, FCCM[20]; Alai Tan, PhD[2]; Lucy D'Agostino McGowan, PhD[21]; E. Wesley Ely, MD, MPH, FCCM[1,22]

Pun, B; Balas, M; Barnes-Daly, MA *Crit Care Med* 2019

ICU Liberation Collaborative - Methods

- **Collaborative Overview**
  - 68 academic, community and VA ICUs
  - 20 months
  - Operationalized the bundle (with flexibility)
  - Operationalized the daily benchmarks for each element
  - Each Site: Interprofessional Executive Team
  - Education and Support Provided:
    - In Person Meetings
    - Coaching Calls
    - Peer Benchmarking
    - Online materials
    - Resource Sharing

Pun B, et al. *Crit Care Med.* 2019; 47:3-14


Family Member
Intensivist
Advanced Practice Provider
Critical Care Nurse
Critical Care Pharmacist
Respiratory Care Practitioner
Physical and Occupational Therapists
Dietician
Social Worker
Case Manager
Spiritual Care Provider
Nursing Asissant
Non-Intensivist Physician
Speech & Language Pathologist
Patient

Bundle Performance

ABCDEF bundle performance (our main exposure) was evaluated in two ways:

1. Complete performance:
- patient received every eligible bundle element on any given day

2. Proportional performance
- percentage of eligible bundle elements performed on any given day

Pun B, et al. *Crit Care Med.* 2019; 47:3-14

Relationship Between Degree of Bundle Performance and Outcomes

We explored the association between complete and proportional ABCDEF bundle performance and the three sets of outcomes:

*All models were adjusted for a minimum of 18 a priori-determined potential confounders.

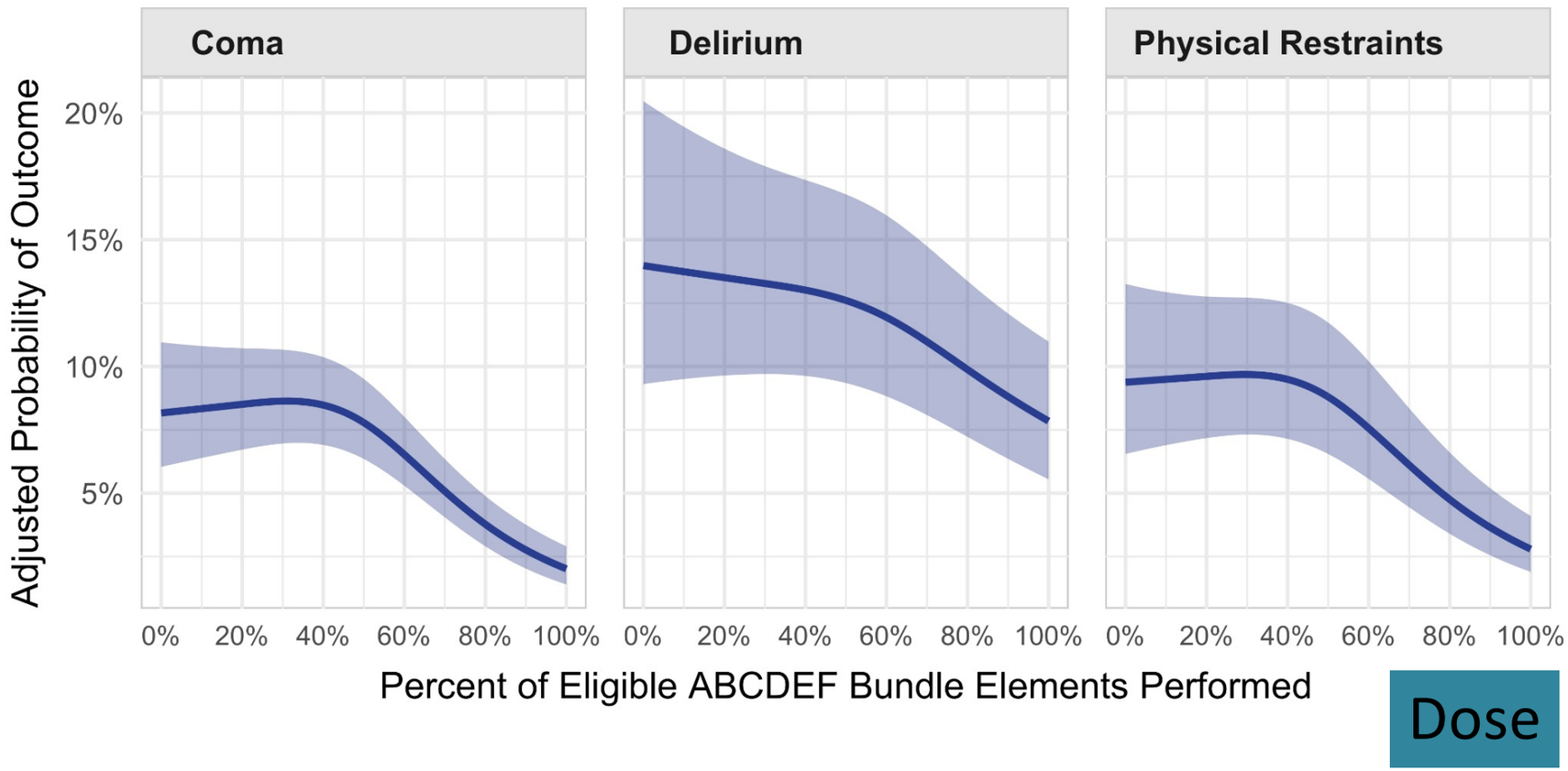
Pun, B; Balas, M; Barnes-Daly, MA et al. *Crit Care Med* 2019

TABLE 2. Outcomes for Patients With Complete (vs Incomplete) ABCDEF Bundle Performance: Data are Adjusted Hazard Ratios (AHRs) and Adjusted Odds Ratios (AORs)

Outcomes	Complete Bundle Performance	*p* Value
Patient-Related Outcomes	**AHR (95% CI)**	
ICU discharge[a]	1.17 (1.05–1.30)	< 0.004
Hospital discharge[b]	1.19 (1.01–1.40)	< 0.033
Death[c]	0.32 (0.17–0.62)	< 0.001
Symptom-Related Outcomes[d]	**AOR (95%CI)**	
Mechanical ventilation	0.28 (0.22–0.36)	< 0.0001
Coma	0.35 (0.22–0.56)	< 0.0001
Delirium	0.60 (0.49–0.72)	< 0.0001
Significant pain	1.03 (0.88–1.21)	0.7000
Physical restraints	0.37 (0.30–0.46)	< 0.0001
System-Related Outcomes	**Adjusted OR (95%CI)**	
ICU readmission[e]	0.54 (037–0.79)	< 0.001
Discharge destination[f]	0.64 (0.51–0.80)	< 0.001

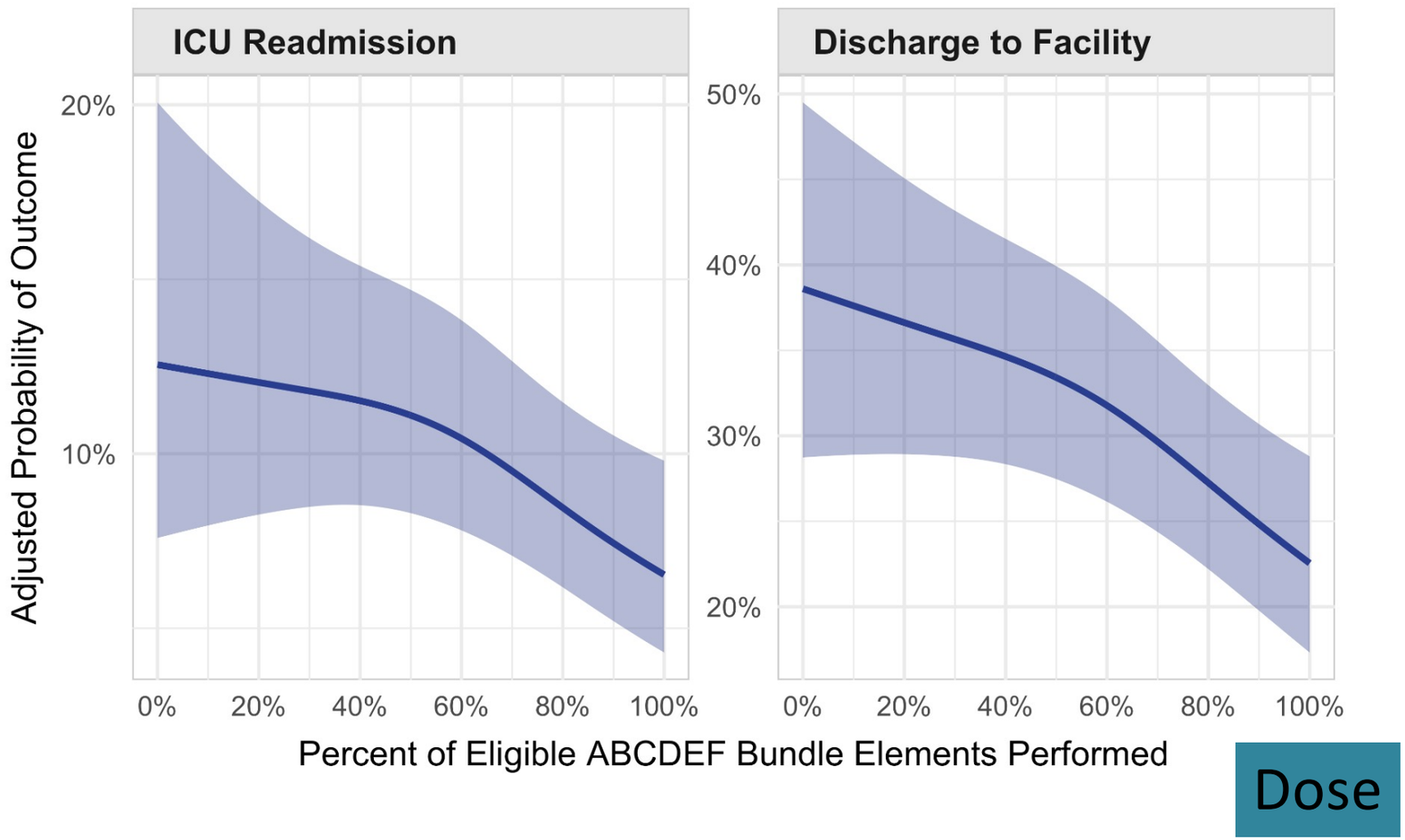
Pun, B; Balas, M; Barnes-Daly, MA et al. *Crit Care Med* 2019

Results: Symptom-Related Outcomes



Pun B, et al. *Crit Care Med.* 2019; 47:3-14

Results: System-Related Outcomes



Pun, et al. *Crit Care Med.* 2019; 47:3-14

Narrative Review

Critical Care Explorations

OPEN

Strategies to Optimize ICU Liberation (A to F) Bundle Performance in Critically Ill Adults With Coronavirus Disease 2019

John W. Devlin, PharmD, MCCM[1]; Hollis R. O'Neal Jr, MD, MS[2]; Christopher Thomas , MD[2]; Mary Ann Barnes Daly, MS, RN, CCRN[3]; Joanna L. Stollings, PharmD, FCCM[4,5]; David R. Janz, MD, MS[6]; E. Wesley Ely, MD, MS, FCCM[5,7]; John C. Lin, MD[8]

A Assess, Prevent and Manage Pain

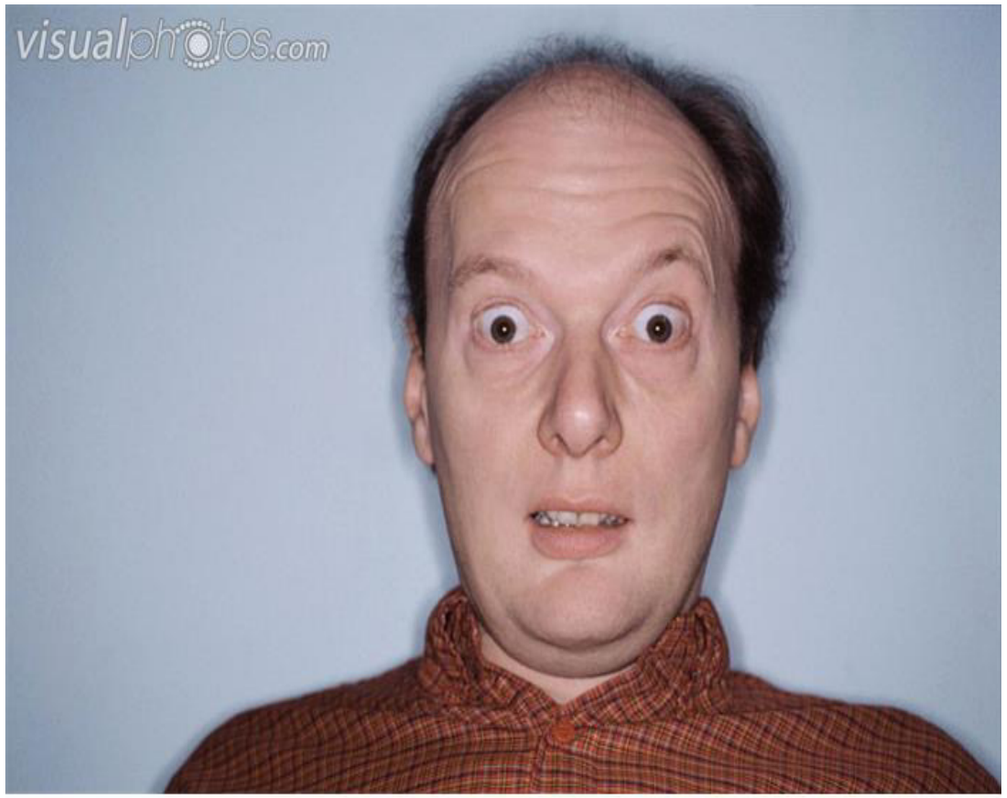
1. Assessment
   - Use a valid assessment tool every 4 hours

2. Prevention
   - Anticipate pain (e.g., risk factors; procedures)

3. Management of Pain
   - Treat pain before using a sedative

Patient Wakefulness is Important!

We recommend that sedative medications should be titrated to maintain a light rather than deep level of sedation in adult ICU patients, unless clinically contraindicated (+1B).



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

↑ Patient communication

↓ Delirium

↑ Ability to screen for delirium

↑ Spontaneous breathing trial

↑ Early mobilization

↓ PTSD

↓ Risk for sedative ADEs

B Both Spontaneous Breathing Trial/Spontaneous Breathing Trial

1. Establish clear 24 sedation goal
   - Evaluate sedation every 4 hours with RASS or SAS
2. Work with night nurses to maintain wakefulness
   - Sedation ≠ Good Sleep
   - Deep sedation/coma in am should be a “never event”
3. Consider q2h sedative protocol
   - Preferred by RNs over SATs
4. SBT safety screens and SBT attempts

C

Choice of Analgesia and Sedation

1. Administer opioid and/or sedative boluses before initiating an infusions
   - Evaluate the continued need for opioid/sedative infusions daily
2. Consider Non-opioid Analgesics
   - Multimodal protocol useful in surgical patients
3. Revaluate opioid/analgesic and sedative choices daily
   - Use of the same sedative from intubation to extubation rarely optimal

Opioid Use Increases the Risk of Delirium in Critically Ill Adults Independently of Pain

Matthew S. Duprey[1], Sandra M. A. Dijkstra-Kersten[2,3], Irene J. Zaal[2,3], Becky A. Briesacher[1], Jane S. Saczynski[1], John L. Griffith[4], John W. Devlin[1,5], and Arjen J. C. Slooter[2,3,6]

Multinomial model on transitions of daily mental status conditional on opioid exposure

Mental Status		Opioid Exposure	Adjusted Odds ratio*^		P value
Day t	Day t+1				
Awake without delirium	Awake without delirium	No	reference		
Awake without delirium	Delirium	Yes	1.45	(1.24-1.69)	<0.001
Awake without delirium	Delirium	10mg MEQ#	1.24	(1.15-1.39)	<0.001

*adjusted for time-fixed covariables: admission category (medical, surgical, trauma), age, gender, Acute Physiology and Chronic Health Evaluation (APACHE) IV Score, body mass index, Charlson Comorbidity Index

^adjusted for time-varying covariables on day t: day of ICU admission, modified Sequential Organ Failure Assessment score (without neurologic component), use of mechanical ventilation, use of a benzodiazepine, presence of severe pain

#adjusted odds ratio represents the odds for a 1 log-fold increase in morphine equivalent dose

Odds for delirium remained stable across study years and age groups, was observed in both medical and surgical patients, and was not dependent on the degree of pain present on the day preceding a transition to delirium.

***Severe pain was inversely associated with a transition to delirium (OR 0.72; 95% CI 0.53-0.97).**

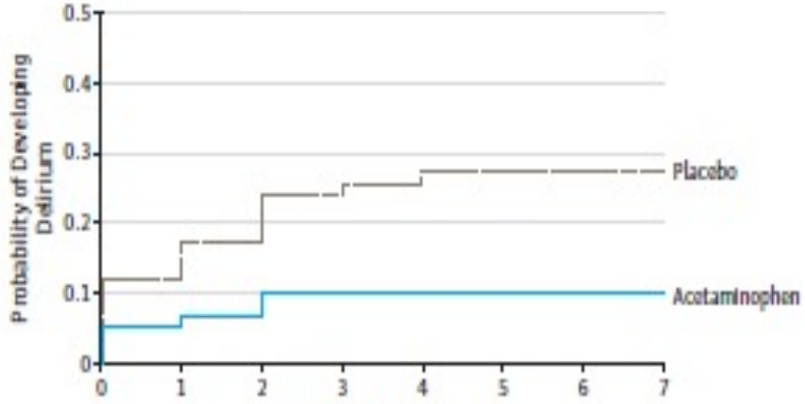
Duprey MS, Dijkstra-Kersten S, Zaal IJ, et al. Am J Respir Crit Care Med 2021; 204:566-571

JAMA | Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Intravenous Acetaminophen vs Placebo Combined With Propofol or Dexmedetomidine on Postoperative Delirium Among Older Patients Following Cardiac Surgery

The DEXACET Randomized Clinical Trial

B Analgesic: acetaminophen vs placebo



Outcomes	Analgesic				Sedative			
	Acetaminophen (n = 60)	Placebo (n = 60)	Difference (95% CI)	*P* Value	Dexmedetomidine (n = 59)	Propofol (n = 61)	Difference (95% CI)	*P* Value
MoCA score[b]								
Baseline, median (IQR)	24.0 (22.0 to 26.0)	23.5 (20.4 to 26.0)	0.5 (−1 to 2)	.39	24.0 (21.0 to 26.0)	24.0 (21.0 to 26.0)	0 (−1 to 1)	.84
Discharge, median (IQR)	24.0 (21.0 to 26.0)	24.0 (20.0 to 26.0)	0 (−1 to 2)	.29	24.0 (21.0 to 25.0)	24.0 (21.0 to 26.0)	0 (−2 to 1)	.55
Change from baseline, median (IQR)	0.0 (−2.0 to 1.0)	−0.4 (−2.0 to 1.0)	0.4 (−1.0 to 1.0)	.82	0.0 (−1.6 to 1.0)	−0.9 (−2.0 to 1.2)	0.9 (−1.0 to 1.0)	.82
48-h Postoperative medication administration								
Total morphine equivalent administered, median (IQR), μg[c]	10 082.5 (7524.0 to 15 090.0)	12 609.0 (10 076.0 to 20 141.5)	−2530 (−5064 to −22)	.03	10 110.0 (5113.0 to 15 075.0)	12 612.5 (10 052.5 to 20 067.5)	−2567 (−5094 to −26)	.03

Subramaniam B, Sharkar P, Shaefi S, et al JAMA. 2019 Feb 19;321(7):686-696.

Intensive Care Med (2015) 41:2130–2137
DOI 10.1007/s00134-015-4063-z

ORIGINAL

Irene J. Zaal
John W. Devlin
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Arendina W. van der Kooi
David S. Y. Ong
Olaf L. Cremer
Rolf H. Groenwold
Arjen J. C. Slooter

Benzodiazepine-associated delirium in critically ill adults

- N=1112 critically adults were included
- Among the 5299 (53.7 %) observation days patients were awake without delirium, 562 (11 %) transitions to delirium occurred the next day.

Mental status		Exposure	Adjusted odds ratio[a,b,c]	*p* value
Day *t*	Day *t* + 1			
Awake without delirium	Awake without delirium	No	Reference	
Awake without delirium	Delirium	Yes[d]	1.04 (1.02–1.05)	<0.001

Relative Risk for each 5 mg BZ administered in midazolam equivalents

Midazolam infusion 3 mg/hr = 72mg/24 hours……72/5 = 14.4 x 4% = 57.6% chance of transitioning from awake and no delirium to delirium the next day.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexmedetomidine or Propofol for Sedation in Mechanically Ventilated Adults with Sepsis

	Dexmedetomidine N=214	Propofol N=208	Difference
Baseline			
Age	59 [48, 68]	60 [50, 68]	NS
APACHE-II	27 [21, 32]	27 [22, 32]	NS
Medical	64%	65%	NS
RASS score ≥ -2 at randomization	49%	46%	NS
Outcomes			
Days without delirium or coma at 14 d* median [95% CI]	10.7 [8.5, 12.5]	10.8 [8.7, 12.6]	NS
Ventilator-free days at 28 days* median [95% CI]	23.7 [20.5, 25.4]	24.0 [20.9, 25.4]	NS
Mortality at 90 days*	38%	39%	NS
Telephone Interview for Cognitive Status (TICS) at 6 mo.%	40.9 [33.6, 47.1]	41.4 [34.0, 47.3]	NS

***Multivariable adjustment for n=16 variables; % age-adjusted**

Hughes CG, Mailloux PT, Devlin JW, et al. New Engl J Med 2021; 384(15):1424-1436.

ADVENTURES IN SOUND

WL 106

COLUMBIA

lp

DELIRIUM IN HI-FI

Recorded somewhere in France

ELSA POPPING and her PIXIELAND BAND

ADVENTURES IN SOUND

D Delirium: Assess, Prevent and Manage

1. **Assess for Delirium every RN shift with CAM-ICU or ICDSC**
   - **Ensure patients are maximally awake before CAM-ICU screening**
   - **Delirium assessments should be documented/reported on rounds**
   - **All ICU clinicians should be trained on proper CAM-ICU use**

2. **Evaluate patients for new risk factors for delirium daily**

Risk Factors

Question:
Which predisposing and precipitating risk factors are associated with delirium occurrence (i.e., incidence, prevalence, or daily transition), delirium duration, or severity in critically ill adults?

Rationale: 68 studies published from 2000-2015

- Evaluated critically ill adults for delirium using multivariable analysis or randomization to evaluate variables as potential risk factors

Ungraded Statement:

For the following risk factors, ***strong evidence*** indicates these are associated with delirium in critically ill adults:
***Modifiable*: drug-induced coma, benzodiazepine use, opioid use, ICU severity of illness, and blood transfusions**
Non-modifiable: greater age, dementia, pre-ICU emergency surgery or trauma, greater baseline APACHE-II score

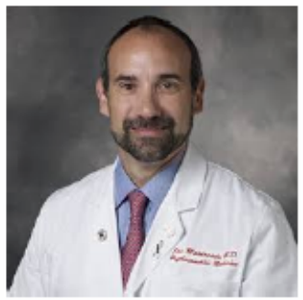
Devlin JW, et al. Crit Care Med 2018; 46 (9); e825-873

Dr. DRE:

***Important to use a standardized approach to mitigate delirium risk factors on a daily basis during ICU rounds**

Diseases	New onset sepsis/infection Worsening organ dysfunction Worsening hypoxemia Dehydration
DRug Removal	Sedative de-escalation e.g., SATs Reduce benzodiazepines and opioids Stop/reduce psychoactive meds
Environment	Immobilization Sleep disruption Noise/light Hearing aids/glasses

Pharmacologic Intervention

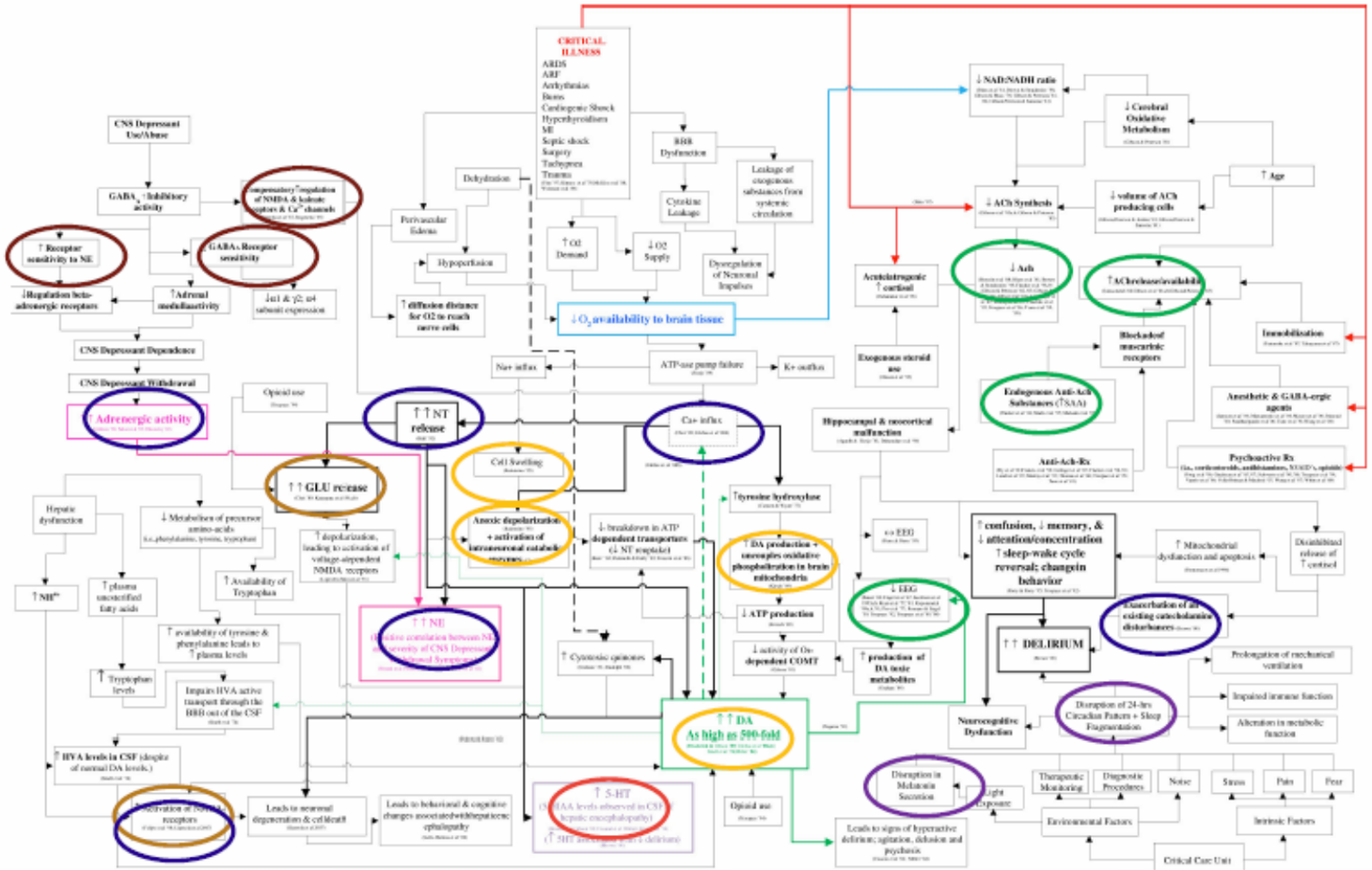


Maldonado, *Crit Care Clin* 2008

GABA-Inhibition

Dopamine Antagonists

Cholinergic Enhancement



NMDA Antagonists

5HT3 Antagonists

Alpha-2 Agonists

Melatonin Agonists

Statin Use for Delirium Prevention

- Acute neuroinflammation is a key nidus for delirium development; the pleiotropic effects of statins may reduce delirium
- Cohort studies suggest patient's taking a statin at the time of ICU admission have reduced ICU delirium

Page VJ et al. AJRCCM; 2014: 1898:666
Morandi A et al. Crit Care Med 2014; 42:1899-1909

Evaluation of early administration of simvastatin in the prevention and treatment of delirium in critically ill patients undergoing mechanical ventilation (MoDUS): a randomised, double-blind, placebo-controlled trial

Valerie J Page, Annalisa Casarin, E Wesley Ely, Xiao Bei Zhao, Ciara McDowell, Lynn Murphy, Daniel F McAuley

- Simvastatin 80mg daily vs. placebo in critically ill adults with or without delirium
- Days alive with delirium or coma in the 14 days after randomization not different (5.7[5.1](Sim) vs. 6.1[5.2] days, p=0.66)

Paige VJ et al. Lancet Respir Med 2017; 2016; 5:727

Rosuvastatin versus placebo for delirium in intensive care and subsequent cognitive impairment in patients with sepsis-associated acute respiratory distress syndrome: an ancillary study to a randomised controlled trial

Dale M Needham, Elizabeth Colantuoni, Victor D Dinglas, Catherine L Hough, Amy W Wozniak, James C Jackson, Peter E Morris, Pedro A Mendez-Tellez, E Wesley Ely, Ramona O Hopkins

- Rosuvastatin 20mg daily vs. placebo in critically ill adults with ARDS with or without delirium
- % of ICU days with delirium not different (HR=1.14; 95% CI 0.92,1.41; p=0.22)
- % of patients with cognitive impairment at 6 months not different (HR=0.93; 95% CI 0.39, 2.22; p=0.87)

Needham DM et al. Lancet Respir Med 2016; 4:203

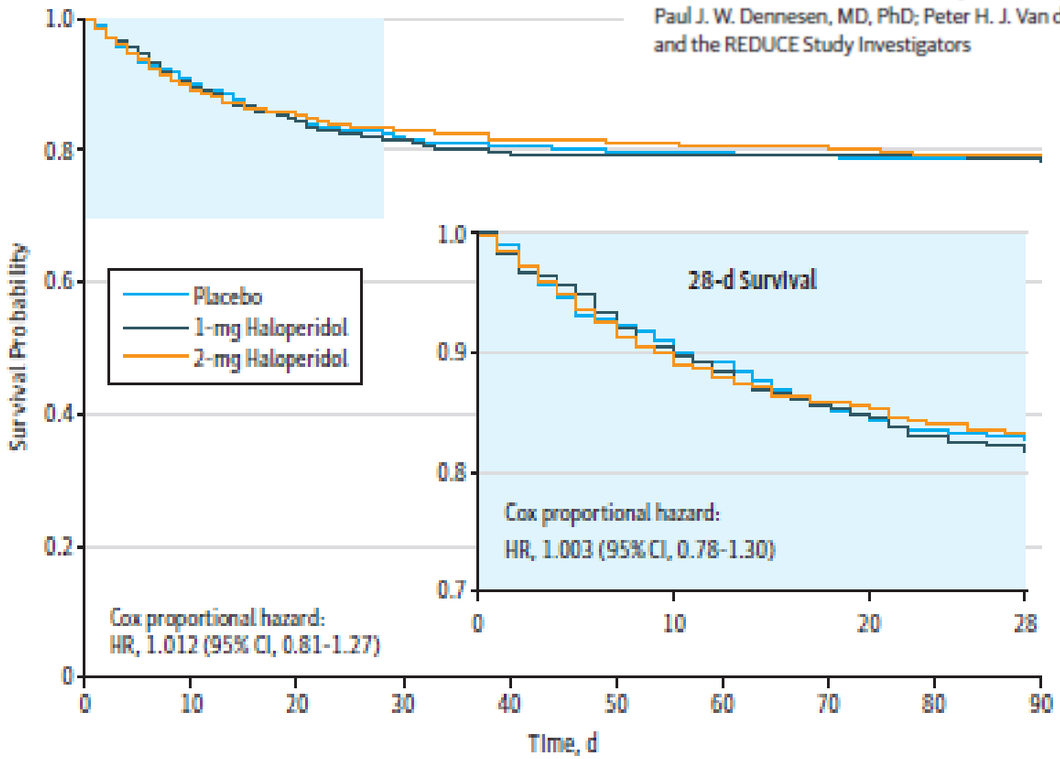
No difference in delirium incidence between haloperidol (1 mg IV q6h or 2mg IV q6h) and placebo

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Haloperidol on Survival Among Critically Ill Adults With a High Risk of Delirium
The REDUCE Randomized Clinical Trial

Mark van den Boogaard, PhD; Arjen J. C. Slooter, MD, PhD; Roger J. M. Brüggemann, PharmD, PhD; Lisette Schoonhoven, PhD; Albertus Beishuizen, MD, PhD; J. Wytze Vermeijden, MD, PhD; Danie Pretorius, MD; Jan de Koning, MD; Koen S. Simons, MD; Paul J. W. Dennesen, MD, PhD; Peter H. J. Van der Voort, MD, PhD; Saskia Houterman, PhD; J. G. van der Hoeven, MD, PhD; Peter Pickkers, MD, PhD; and the REDUCE Study Investigators

Figure 2. Survival Analysis at 28 and 90 Days



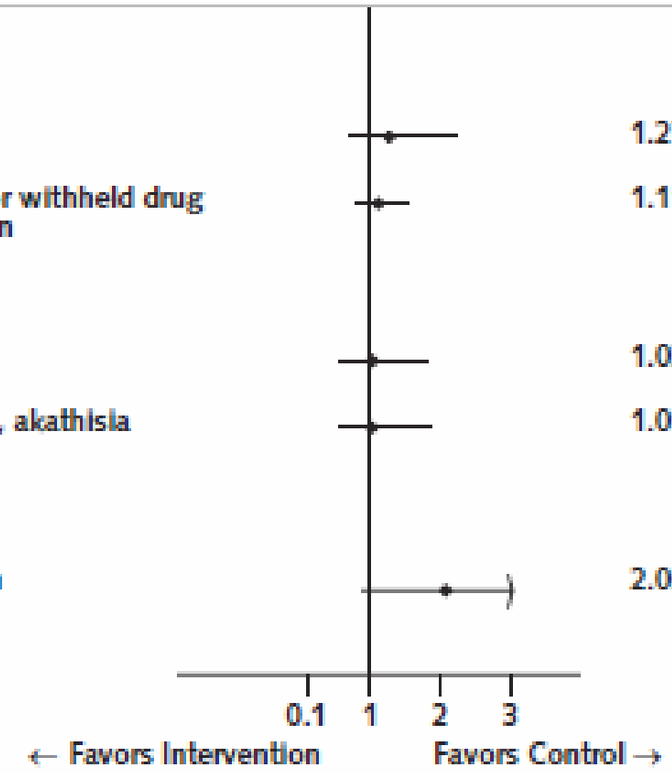
No. at risk										
Placebo	707	644	600	580	571	565	563	559	557	556
1-mg Haloperidol	350	317	297	285	279	278	278	278	277	276
2-mg Haloperidol	732	658	627	609	599	595	591	589	582	579

For the 28-day end point, follow-up for the 1-mg haloperidol group was a median of 28 days (interquartile range [IQR], 28-28 days); for the 2-mg group, 28 days (IQR, 28-28 days); and for the placebo group, 28 days (IQR, 28-28 days). For the 90-day end point, follow-up for the 1-mg haloperidol group was 90 days (IQR, 90-90 days), for the 2-mg haloperidol group, 90 days (IQR, 90-90 days); and for the placebo group, 90 days (IQR, 90-90 days).

Van den Boorgard M, et al. JAMA 2018; 319(7):680-691

Figure 2. Meta-analysis of difference in the incidence of adverse events in studies evaluating effect of antipsychotics.

Comparison	Studies, *n* (*N*)	Study Population	Outcome	Pooled RR (95% CI)*
Cardiac effects				
Haloperidol vs. placebo	6 (2653)	At risk for delirium	Arrhythmias	1.27 (0.72–2.21)
Haloperidol vs. placebo	7 (2721)	At risk for delirium	QTc prolonged >500 ms or withheld drug owing to QTc prolongation	1.11 (0.80–1.55)
Neurologic effects				
Haloperidol vs. placebo	8 (3276)	At risk for delirium	Extrapyramidal symptoms	1.02 (0.58–1.79)
Haloperidol vs. placebo	4 (2069)	Critically ill patients	Extrapyramidal symptoms, akathisia	1.01 (0.56–1.83)
Sedation				
Haloperidol vs. placebo	4 (881)	At risk for delirium	Somnolence, oversedation	2.05 (0.86–4.85)



RR = relative risk; QTc = corrected QT interval.
* I^2 for all the meta-analysis was 0.0%.

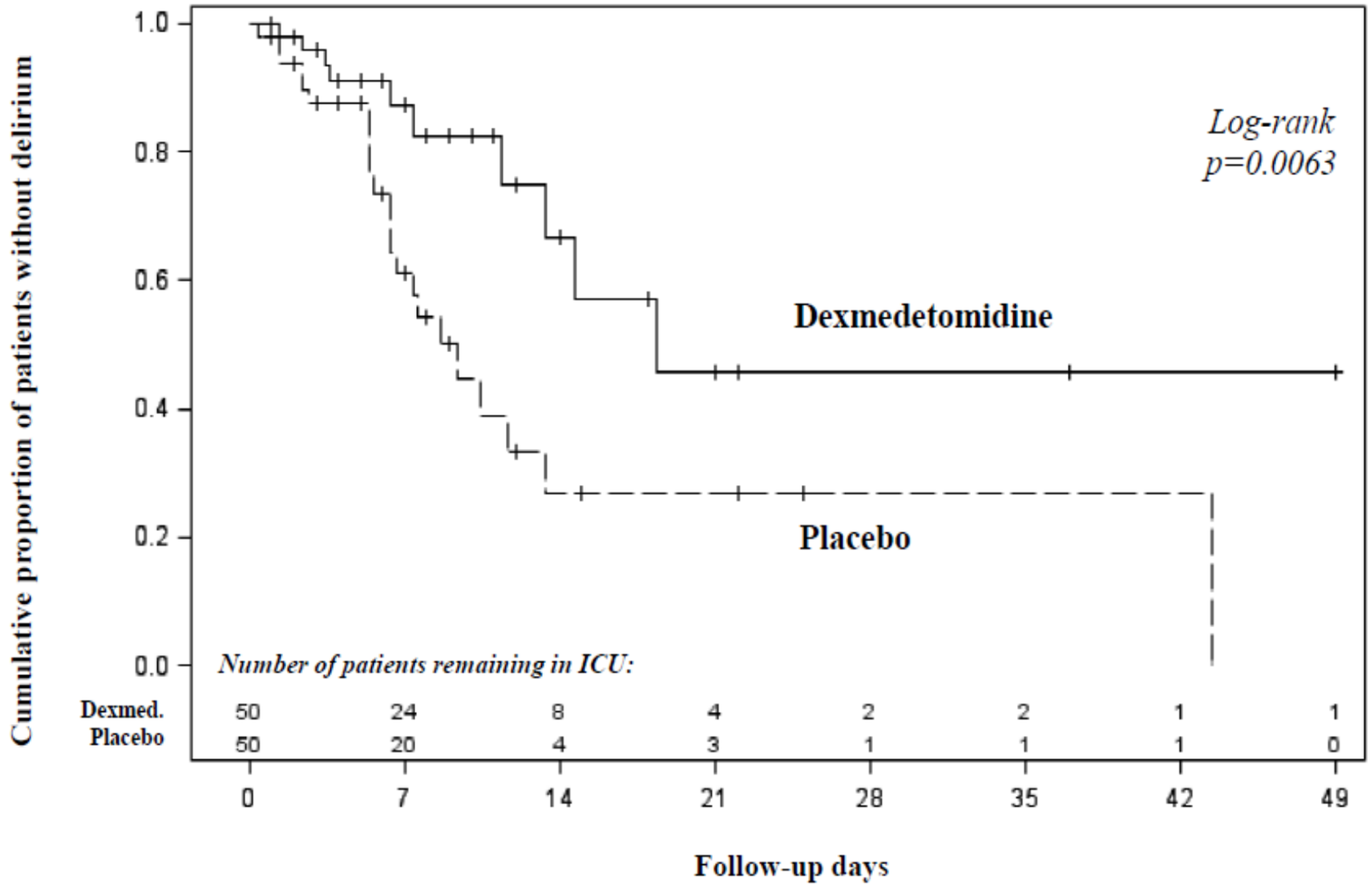
Oh ES et al. Ann Intern Med 2019

Delirium Pharmacological Prevention

Recommendation:
We suggest **NOT** using haloperidol, an atypical antipsychotic, dexmedetomidine, a statin, or ketamine to ***prevent*** delirium in **all** critically ill adults (Conditional recommendation, very low to low quality of evidence)

Devlin JW, et al. Crit Care Med 2018; 46 (9); e825-873

Low-dose Nocturnal Dexmedetomidine Prevents ICU Delirium: A Randomized, Placebo-Controlled trial



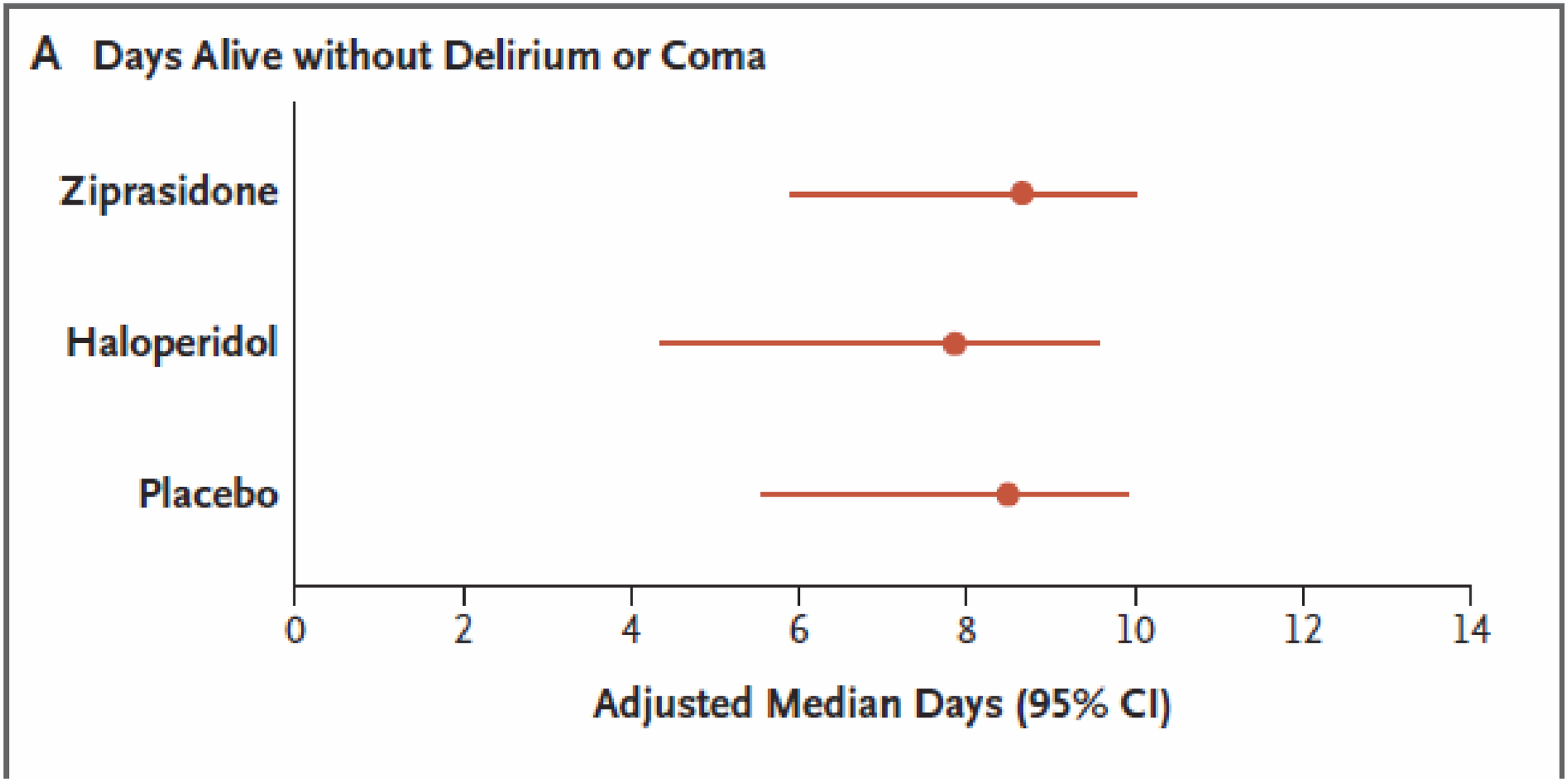
No difference in LEEDS Sleep Score between groups

Skrobik Y, Duprey M, Hill NS, Devlin JW. AJRCCM 2018

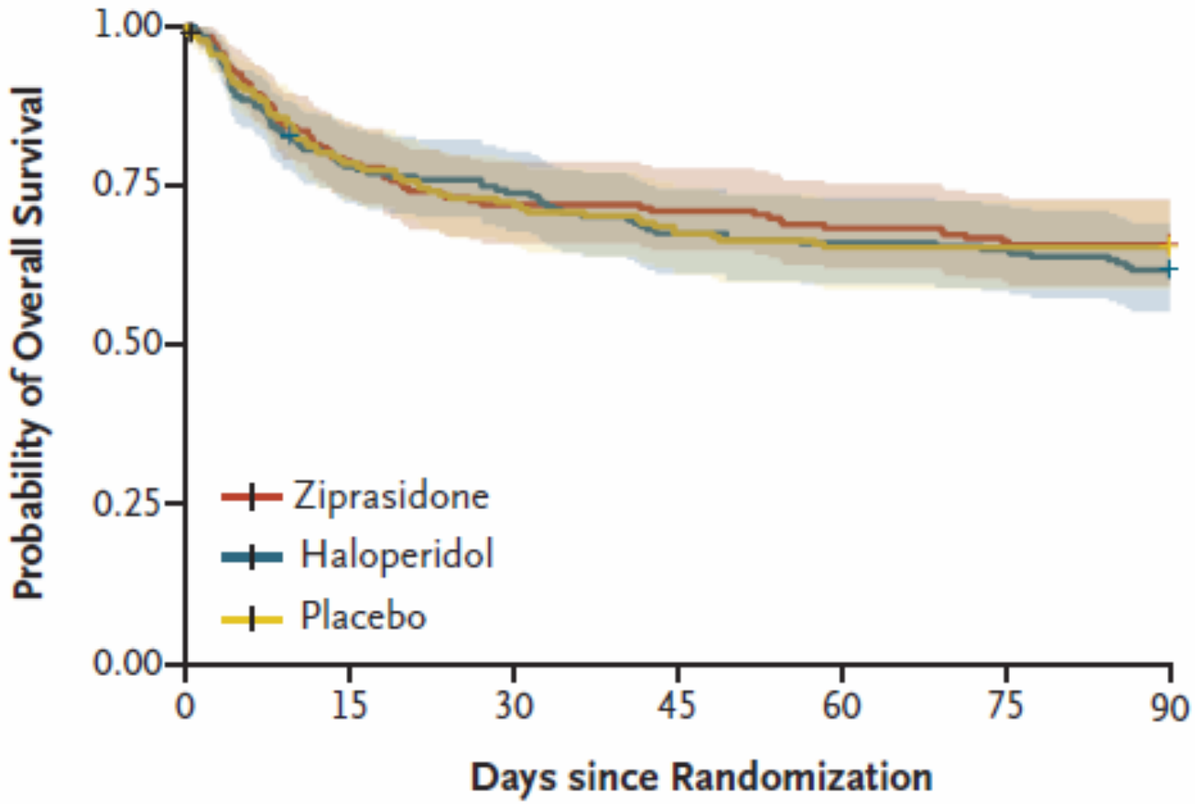
Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness

T.D. Girard, M.C. Exline, S.S. Carson, C.L. Hough, P. Rock, M.N. Gong, I.S. Douglas, A. Malhotra, R.L. Owens, D.J. Feinstein, B. Khan, M.A. Pisani, R.C. Hyzy, G.A. Schmidt, W.D. Schweickert, R.D. Hite, D.L. Bowton, A.L. Masica, J.L. Thompson, R. Chandrasekhar, B.T. Pun, C. Strength, L.M. Boehm, J.C. Jackson, P.P. Pandharipande, N.E. Brummel, C.G. Hughes, M.B. Patel, J.L. Stollings, G.R. Bernard, R.S. Dittus, and E.W. Ely, for the MIND-USA Investigators*

Girard TD et al. N Engl J Med 2018; 379:2506



Girard TD et al. N Engl J Med 2018; 379:2506



No. at Risk (cumulative no. of deaths)

Ziprasidone	190 (0)	150 (40)	137 (53)	135 (55)	130 (60)	126 (64)	125 (65)
Haloperidol	192 (0)	149 (42)	141 (50)	129 (62)	126 (65)	124 (67)	118 (73)
Placebo	184 (0)	143 (39)	132 (50)	123 (59)	119 (63)	119 (63)	119 (63)

Figure 3. Effects of Haloperidol, Ziprasidone, and Placebo on 90-Day Survival.

Girard TD et al. N Engl J Med 2018; 379:2506

Antipsychotic vs. None (Treatment)

Rationale, includes:

- **No benefit for any critical outcomes**
- **Not Routinely (vs. Never) given that patients with fear, anxiety or agitation not-related to pain may still benefit from a short-course of antipsychotic therapy**
- **Unnecessary continuation causes significant morbidity & cost**

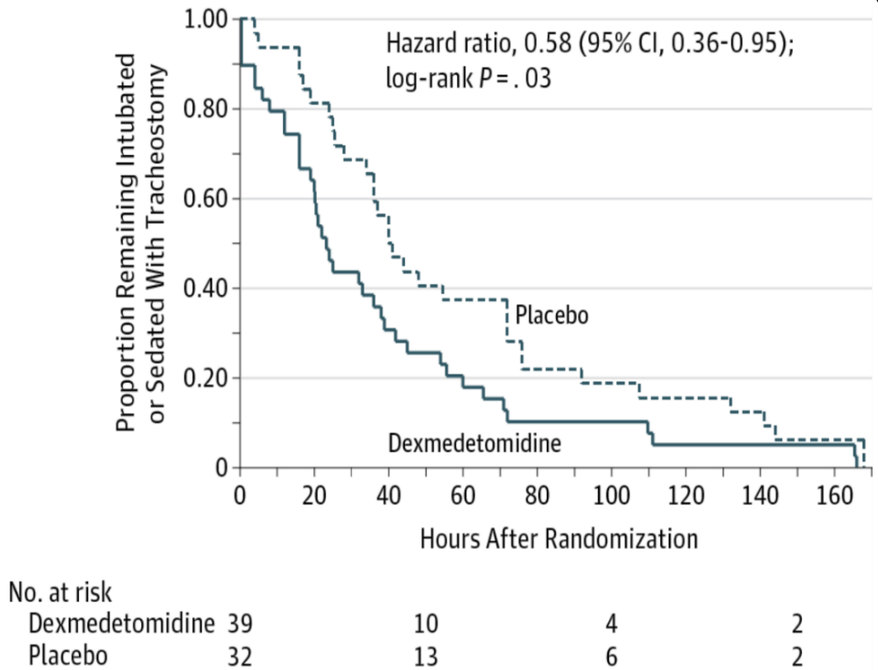
Recommendation:
We ***suggest NOT*** routinely using haloperidol and atypical antipsychotic to treat delirium (conditional recommendation, low quality of evidence).

Devlin JW, et al. Crit Care Med 2018; 46 (9); e825-873

Dexmedetomidine vs. Placebo (Treatment)

Rationale: 1 RCT (71 pts)

- Significant increase in ventilator-free hours
  - Mean Difference 17 hrs (95% CI, 4 to 33 hrs); very low quality



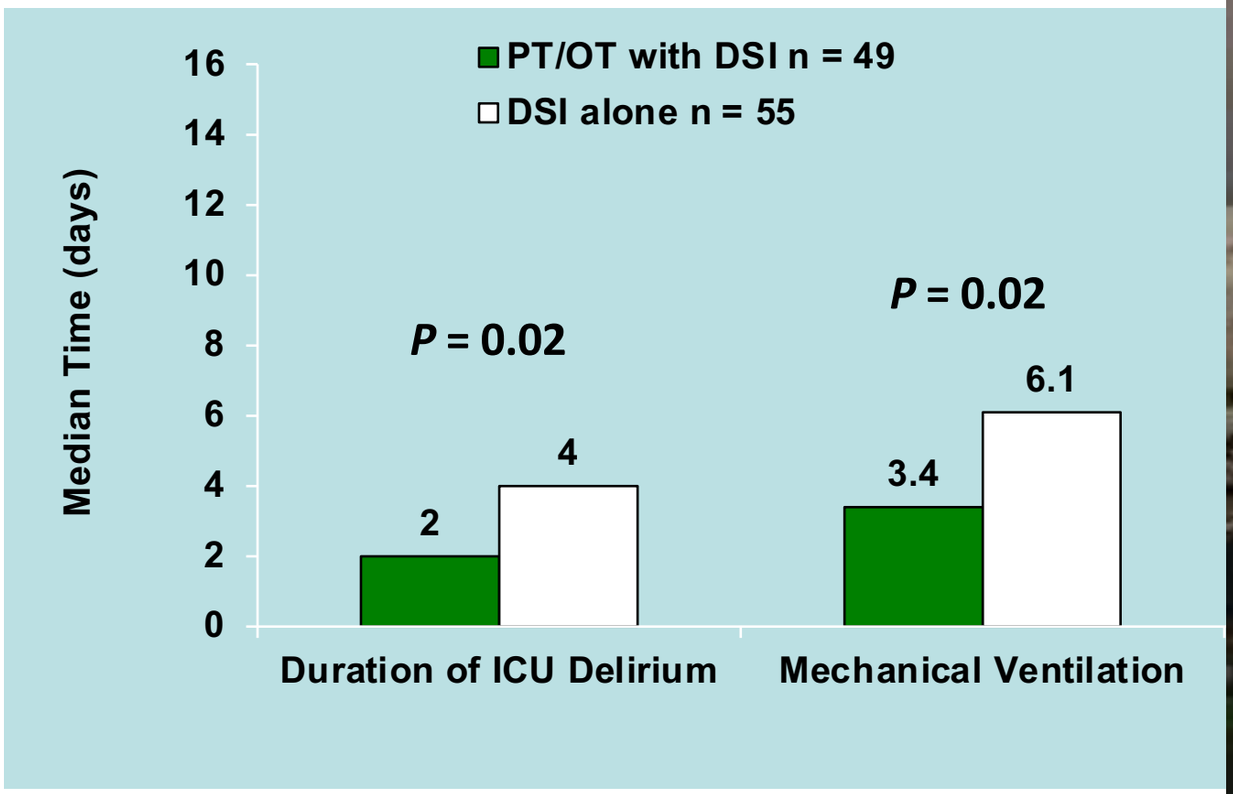
Important Study Limitations

- 21,500 intubated patients screened to enroll 71
- Alcohol withdrawal patients not excluded
- Study terminated early because lack of funding
- Many patients did not receive opioids
  - was some of the agitation pain-related?
- No effect on ICU/Hospital LOS

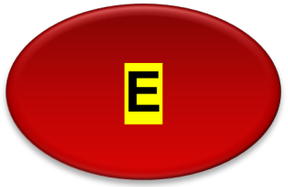
Recommendation:

We ***suggest*** using dexmedetomidine for delirium in mechanically ventilated adults **where agitation is precluding weaning/extubation** (conditional recommendation, low quality of evidence).

Early Mobilization



Schweickert WD, et al. *Lancet*. 2009;373(9678):1874-1882.



Early Mobilization and Rehabilitation

1. Screen Every ICU Patient Daily for Rehabilitation/Mobility
   - PT ideal for screening
   - RN, RT, RN assistants (and family) can deliver the mobilization
   - In bed rehabilitation will benefit patient
2. Ensure consensus re: Mobilization Start/Stop Criteria.
3. Start mobilization efforts in 1-2 ICU beds and then slowly expand
4. Mobility RCTs show early mobility is far more effective than late mobility

F Family Engagement and Empowerment

1. Attempt to involve, engage and empower patients and families to be active participants in ICU Care
2. The best way for this to be done remains unclear
3. While family participation in ICU rounds is ideal; it is often NOT feasible.

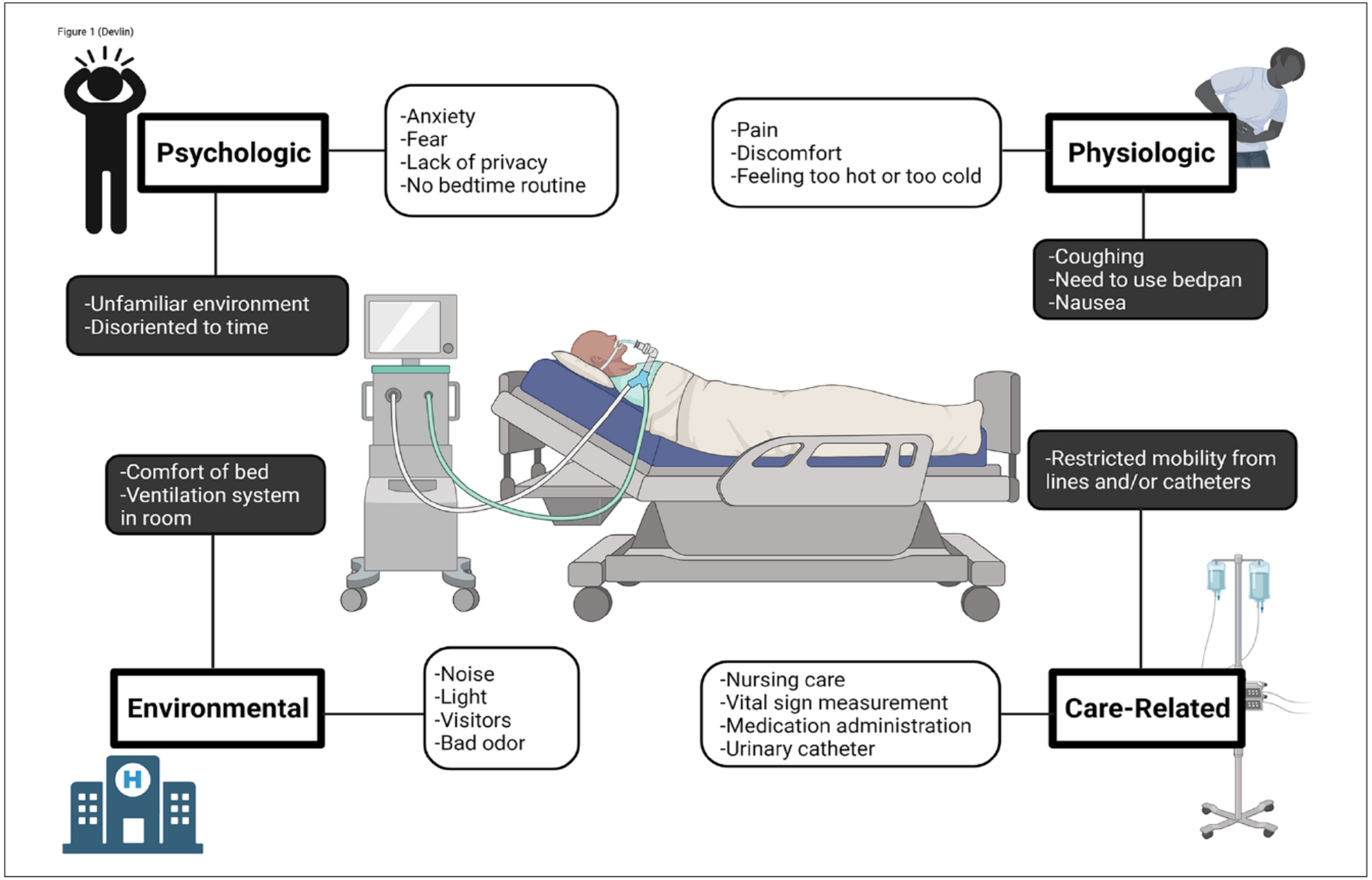


Figure 1. Intensive care unit factors known to influence sleep quality.[a]

[a]Rounded boxes shaded in white: modifiable factors; rounded boxes shaded in black: nonmodifiable factors.

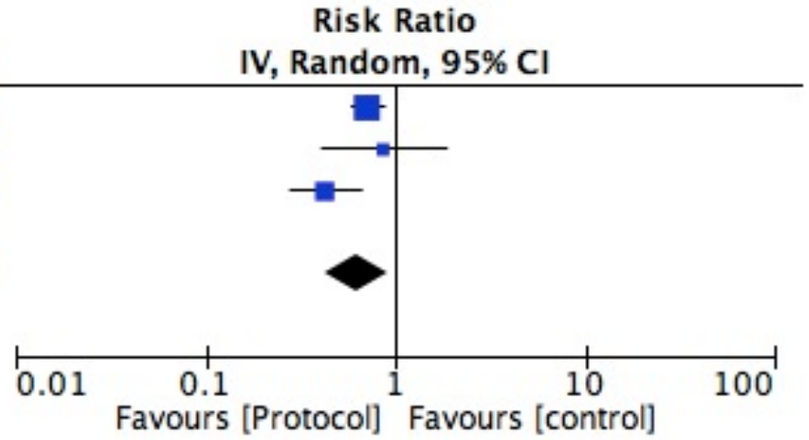
Honarmond K, Rafay H, Le J, Mohan, S, Rochwerg B, Devlin JW, et al. A systematic review of risk factors for sleep disruption in critically ill adults. Crit Care Med 2020; 48(7):1066-1074.

Evidence: Sleep Promoting Protocol

Study or Subgroup	Protocol Events	Protocol Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Kamdar 2013	86	175	76	110	49.3%	0.71 [0.58, 0.87]
Lee 2012	6	13	8	15	17.6%	0.87 [0.41, 1.84]
Patel 2014	24	171	55	167	33.0%	0.43 [0.28, 0.65]
Total (95% CI)		**359**		**292**	**100.0%**	**0.62 [0.42, 0.91]**
Total events	116		139			

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 5.04$, df = 2 (P = 0.08); $I^2 = 60\%$

Test for overall effect: Z = 2.44 (P = 0.01)



Delirium prevalence: RR: 0.62; 95% CI, 0.42 to 0.91 (for n=3 before-after studies)

<u>Recommendation:</u>

We suggest using a sleep-promoting, multicomponent protocol in critically ill adults (conditional recommendation, low quality evidence).

Sleep-Promotion Bundle Development, Implementation, and Evaluation in Critically Ill Adults: Roles for Pharmacists

Annals of Pharmacotherapy
1–11

DOI: 10.1177/10600280211048494

Patricia R. Louzon, PharmD, BCPS, BCCCP[1],
Mojdeh S. Heavner, PharmD, BCPS, BCCCP[2],
Kyle Herod, PharmD[3], Ting Ting Wu, PharmD, BCCCP[4,5],
and John W. Devlin, PharmD, BCCCP, MCCM[4,5]

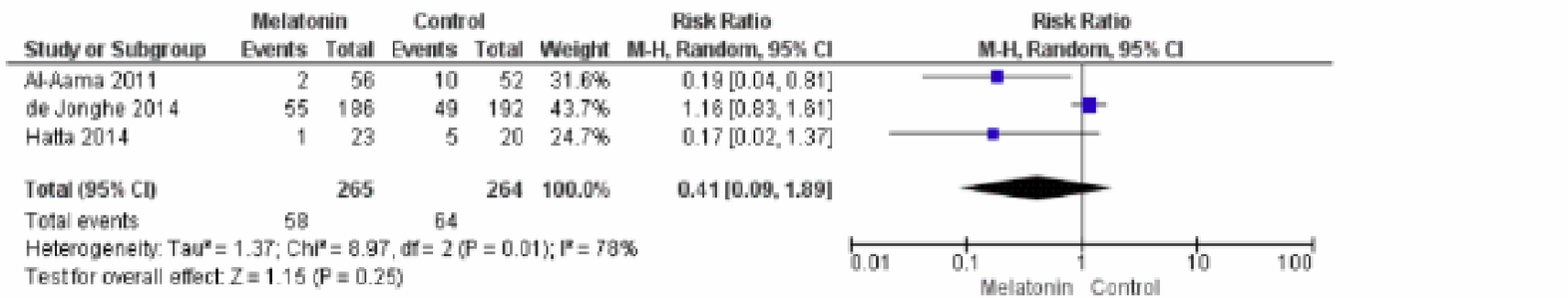
Synthesis: Nine studies (3 randomized, 1 quasi-experimental, 5 before-and-after) were identified. Bundle elements varied and were primarily focused on nonpharmacological interventions designed to be performed during either the day or night; only 2 studies included a medication-based strategy. Five studies were associated with reduced delirium; 2 studies were associated with improved total sleep time and 2 with improved patient-perceived sleep. Pharmacists were involved directly in 4 studies. **Relevance to Patient Care and Clinical Practice:** Sleep improvement bundles are recommended for use in all critically ill adults; specific bundle elements and ICU team member roles should be individualized at the institution/ICU level. Pharmacists can help lead bundle development efforts and routinely deliver key elements. **Conclusions:** Pharmacists can play an important role in the development and implementation of ICU sleep bundles. Further research regarding the relative benefit of individual bundle elements on relevant patient outcomes is needed.

Melatonin to Improve Sleep

Rationale:

- 3 small RCT (n=60), 3-10 mg HS
- Only evaluated, lower, acuity patients with chronic respiratory failure
- No clear improvements in sleep or reduced delirium

Figure 6. Forest plot of comparison: 4 Prophylactic melatonin versus placebo, outcome: 4.1 Incident delirium.



- While relatively safe and low cost, not FDA regulated.

Recommendation:

We make no recommendation regarding the use of melatonin to improve sleep in critically ill adults (no recommendation, very low quality of evidence).

Devlin JW, et al. Crit Care Med 2018; 46 (9); e825-873

Ramelteon to Reduce Delirium?

Results of Three Randomized, Placebo-Controlled Trials

	Population	Dose	Method of delirium assessment	Use of other delirium reduction efforts?	Delirium Incidence		Difference, 95% CI	Comments
					Ramelteon	Placebo		
Hatta et al. JAMA Psych 2014	Delirium-free older medical adults: floor (64%); ICU-not intubated (36%)	8mg ghs	Psych using DSMV daily	Multimodal – non pharm protocol	1/33 (3%)	4/34 (12%)	RR= 0.09; 0.01-0.69	Delirium occurrence primary outcome Results between ICU and floor patients NR
Nishimura M et al. Crit Care Med 2018	Delirium-free critically ill adults (mostly medical; 40% intubated; AP2 score mean=24)	8mg ghs up to 2d after ICU admit	CAM-ICU by bedside nurse q4h	NR	11/45 (24%)	20/43 (47%)	OR=2.69; 1.09, 6.65)	Duration of ICU stay was primary outcome Coma NR Delirium reduction strategies NR
Jaiswal SJ et al. Crit Care Med 2019	Delirium-free adults admitted to the ICU after elective pulmonary thomboendarectomy (average age=57)	8mg qhs starting night before surgery	CAM-ICU twice daily by physician member of research team	Other than daily SAT/SBT NR	22/58 (40%)	19/59 (32%)	RR=0.80; 0.5, 1.4)	No difference in ICU LOS Patients who died assigned outcome of delirium + No difference in delirium occurrence in patient subgroup > 65 yrs

Medication Overload: America's Other Drug Problem

How the drive to prescribe is harming older adults

LOWN INSTITUTE

Antipsychotic Continuation Beyond ICU Discharge

Study	Design	Patients Studied	ICU to Floor n (%)	Floor to Discharge n (%)*
Jasiak et al. J Pharm Pract. 2013;26(3):253	Single-center, retrospective	59	28/59 (47)	20/28 (71)
Rowe et al. J Crit Care. 2015;30:1283	Single-center, retrospective	341	n/a	82/341 (24)
Flurie et al. Am J Health-Syst Pharm. 2015;72(suppl 3):S133	Single-center, retrospective	87	23/87 (26)	9/23 (39)
Kram et al. J Crit Care. 2015;30:814	Single-center, retrospective	133	112/133 (84)	38/112 (34)
Gilbert et al. J Intensive Care Med. 2016. DOI: 10.1177/0885066615622424	Single-center, retrospective	161	85/161 (53)	54/85 (64)
Marshall et al. J Crit Care. 2016;33:119	Single-center, retrospective	3,119	n/a	642/3,119 (21)
			248/440 (56%)	**845/3,708 (23%)**

Devlin JW, et al. Crit Care Med 2018; 46 (9); e825-873

Four Key Strategies to Reduce ICU Delirium

1. Screen critically ill adults regularly and reliably for delirium.
2. Recognize and reduce modifiable risk factors for delirium.
3. Focus on non-pharmacologic interventions known to reduce delirium that may include use a multimodal protocol (e.g., ABCDEF bundle).
4. Generally, avoid pharmacologic interventions to reduce delirium in most patients.

Case of RS – ICU day #2

- RS is a 72 year old female who remains in the Surgical ICU POD #2 after emergent surgical repair of a leaking 3 inch abdominal aortic aneurysm.
- HR =110, BP = 98/63, RR = 20
- CPOT= 2, RASS = -3, CAM-ICU = negative
- Mechanically ventilated: SIMV =14, TV 500, FiO2 = 40%, PEEP=5
- Tolerating tube feeds at 20 mL/hr
- Receiving fentanyl 25-50 mcg IVP q4h prn pain, propofol @ 30 mcg/kg min, and haloperidol 1mg IV q6h
- She has not left the bed since she arrived in the emergency department.
- Prior to admission she enjoyed bridge and golfed weekly in a women's golf league.

What is the most important intervention to make in RS's care at this time?

a. Increase haloperidol to 2mg IV q6h as this is the dose shown in the REDUCE RCT (JAMA 2018) to prevent delirium and reduce 28-d mortality.

b. Hold her propofol to reach a RASS = 0 and conduct an SBT screen.

c. Hold her propofol to reach a RASS = 0 and try to mobilize her out of bed.

d. Given she is in pain, a known risk factor for delirium, start a continuous IV fentanyl infusion @ 50 mcg/hr.

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