ICU Strategies to Improve Cognitive Function after Critical Illness

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Northeastern University
Bouvé College *of* Health Sciences
School *of* Pharmacy

Disclosures

Research Funding:

NIA
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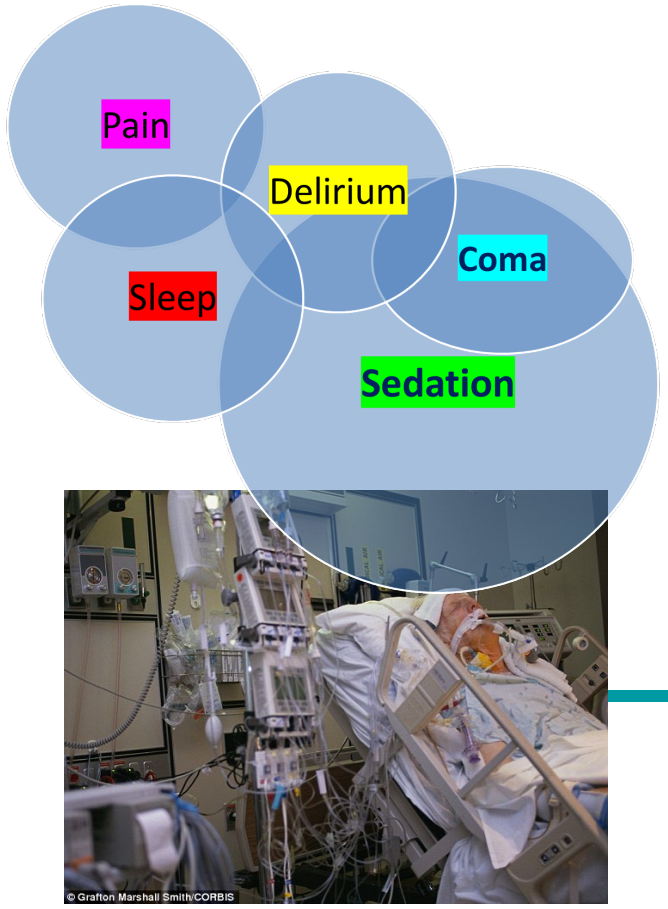


ICU Survivorship

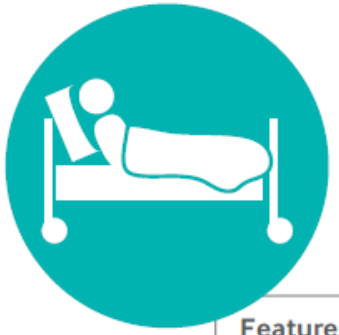
Cognitive Impairment/ Dementia

ICU Delirium

- **Prevalence: 20-70%**
  - Broad range driven by variability in predisposing and precipitating factors between patients
    - Severity of illness is a key driver of daily occurrence
- **Associated with:**
  - Substantial distress to patients, families and caregivers
  - Increased short- and long-term mortality
  - Prolonged mechanical ventilation and ICU/hospital length of stay
    - Increased healthcare costs
  - **Reduced long-term cognitive decline (dementia)**

Devlin JW et al. PADIS Crit Care Med 2018

Risk Factors for ICU Delirium



Features of acute illness
- Severity of illness
- Mechanical ventilation
- Delirium previous day
- Polytrauma
- Emergency surgery
- Metabolic acidosis
- Coma

- Organ failure

- Temperature/fever
- Medical admission
- Kidney function/failure
- Acute respiratory disease
- Anemia
- Bilirubin
- Urea
- Hypo/hypernatremia

Patient or host factors
- Age
- Dementia
- Hypertension

- Alcohol use
- Nicotine use
- ASA physical status
- Cardiac disease

Environmental or iatrogenic factors
- Deep sedation

- Medication

- Room without light
- Loss of day-night cues

Lack of exercise

Potentially Modifiable Factors

Wilcox ME, et al. BMJ 2021;373:n1007

Select Studies of Delirium and Long-Term Cognitive Outcomes in Patients with Critical Illness

Date	Characteristic	Study cohort	Primary outcome	Results
Girard et al, 2010	Prospective cohort	126 medical ICU patients; mechanically ventilated	Cognitive outcome at 3 and 12 months	Duration of delirium independently associated with long term cognitive outcomes
Van den Boogaard et al, 2012	Prospective cohort	1292 patients; 272 with delirium and 1020 without delirium	Cognitive failure questionnaire at 18 months	Duration of delirium associated with long term cognitive impairment
Pandharipande et al, 2013	Prospective cohort	821 patients with respiratory failure or shock in medical or surgical ICU	Cognitive outcome at 3 and 12 months	Days of delirium in hospital associated with worse global cognition and executive function at 3 and 12 months
Wolters et al, 2017	Prospective cohort	567 one year survivors from medical-surgical ICU	Cognitive failures questionnaire at 1 year	Days delirious independently associated with greater self-reported cognitive problems
Mitchell et al, 2018	Prospective cohort	148 medical or surgical ICU survivors	Repeatable Battery for the Assessment of Neuropsychological Status and Trails Making Tests at 3 and 6 months	ICU delirium associated with impaired information processing speed and executive function at 6 months follow-up

Wilcox ME, et al. BMJ 2021;373:n1007

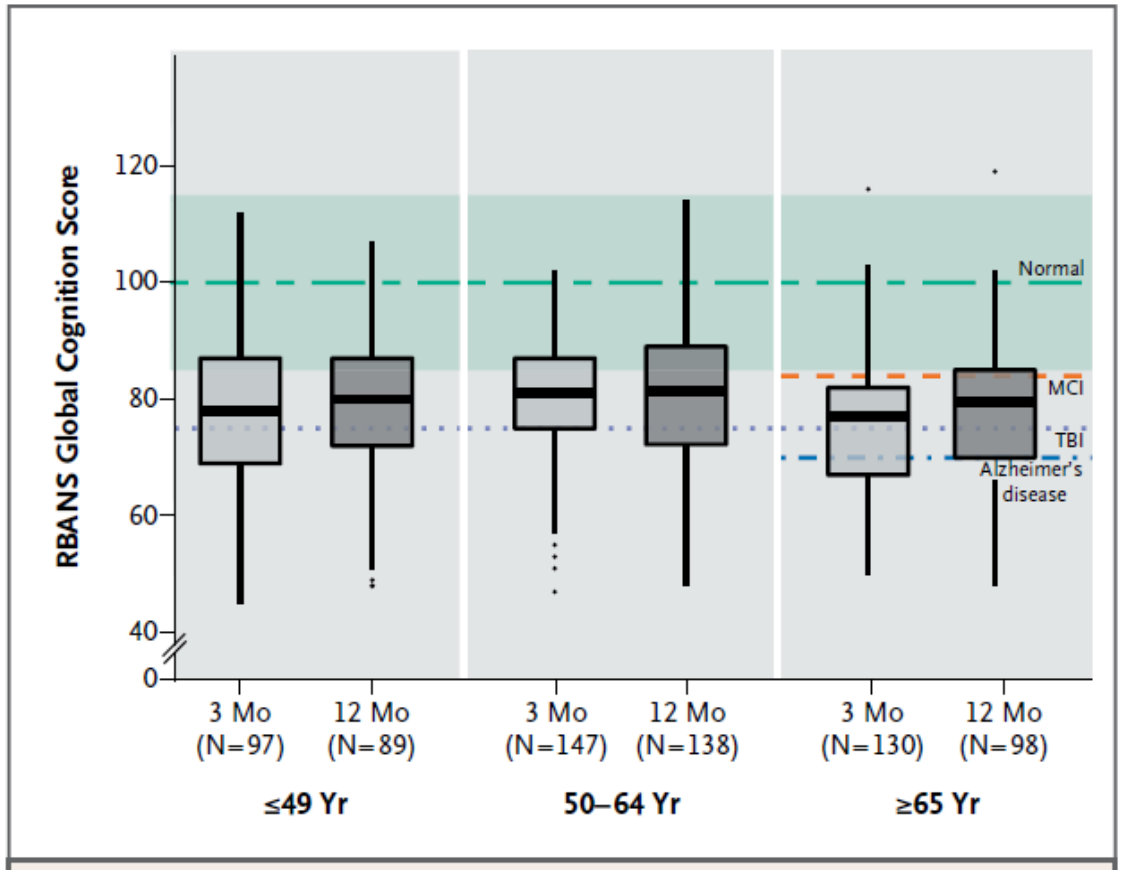
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Cognitive Impairment after Critical Illness

N=826 critically ill adults:

- Age = 61 [41-71]
- APACHE II score = 25 [19-31]
- Medical 68%
- Mechanical ventilation = 91%
- Delirium = 74 % for duration of 4 [2-7] days
- Coma = 63% for 3 [2-6] days
- Benzodiazepine = 62%
- Propofol = 52%
- Dexmedetomidine = 13%
- Opioids = 78%



Pandharipande PP, et al. N Engl J Med 2013; 369:1306

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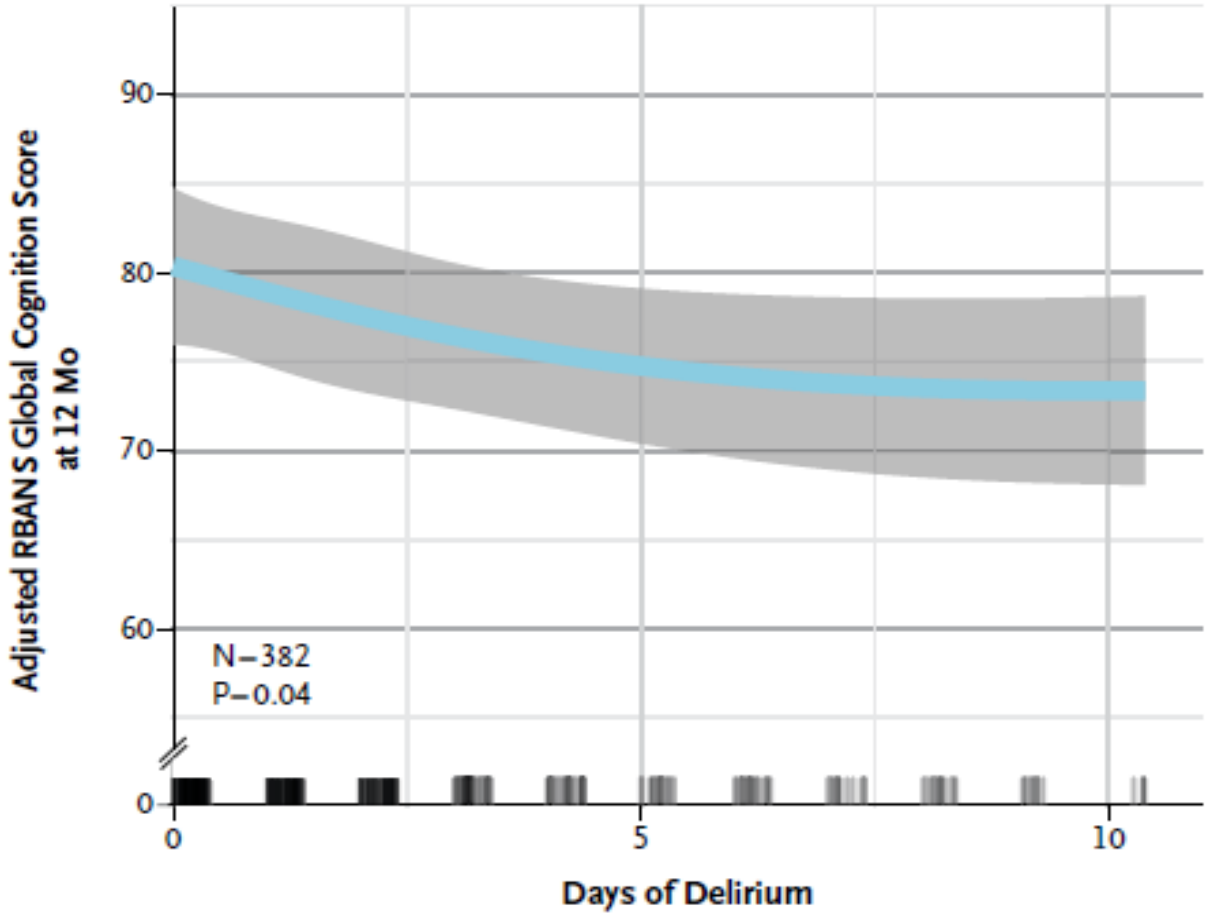
Long-Term Cognitive Impairment after Critical Illness



A Longer Duration of Delirium was Independently Associated with Worse Global Cognition at:

- 3 months (P=0.001)
- 12 months (P=0.004)

Pandharipande PP, et al. N Engl J Med 2013; 369:1306

Is there a Causal Link between ICU Delirium and Dementia?

Postulated explanations for an association between delirium and dementia

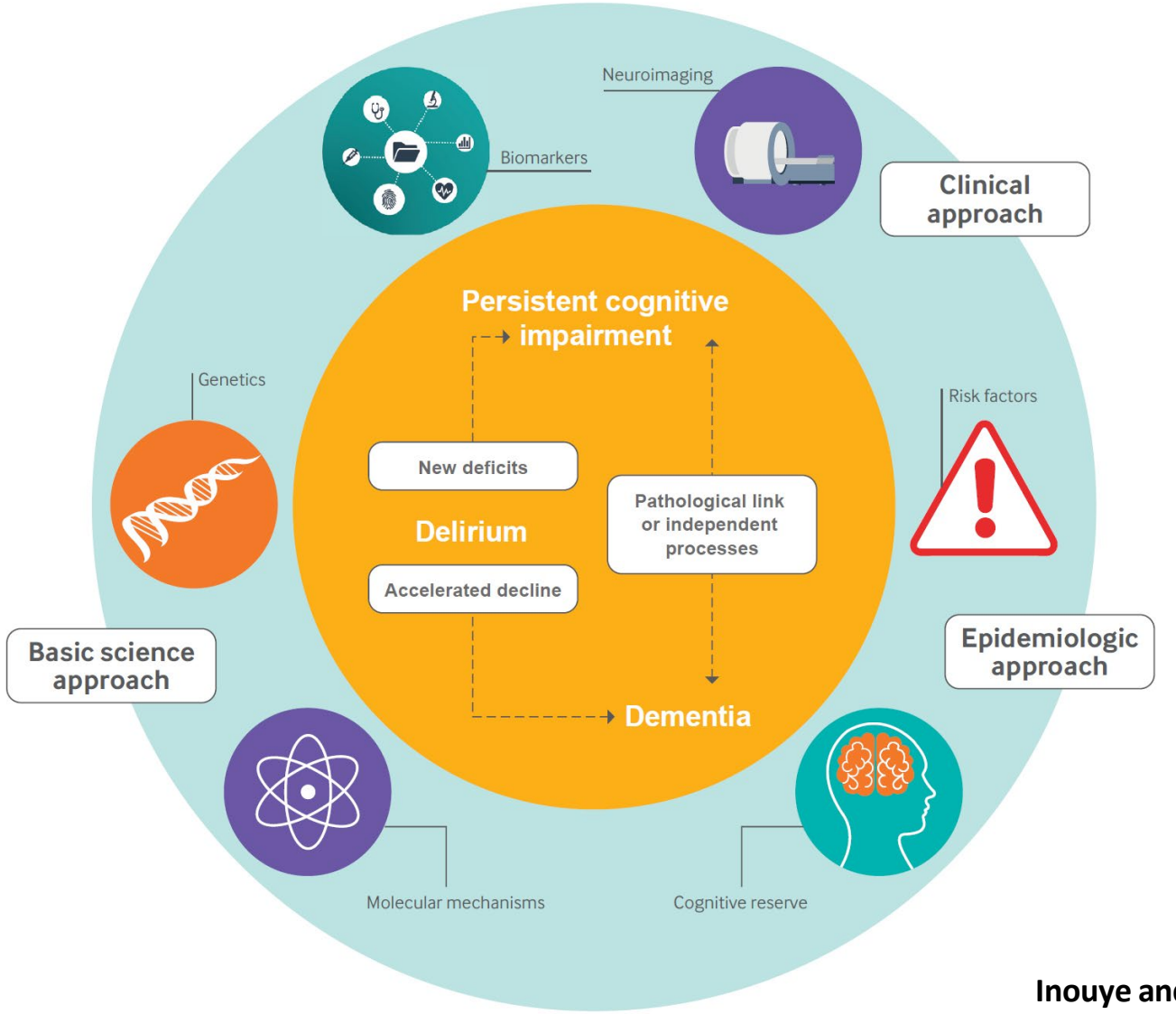
1. Delirium itself **causes** dementia

2. Delirium is a **marker** of vulnerability to dementia

3. Delirium is an **intermediate factor** in the development of dementia

Fong T, et al. Lancet Neurol 2015

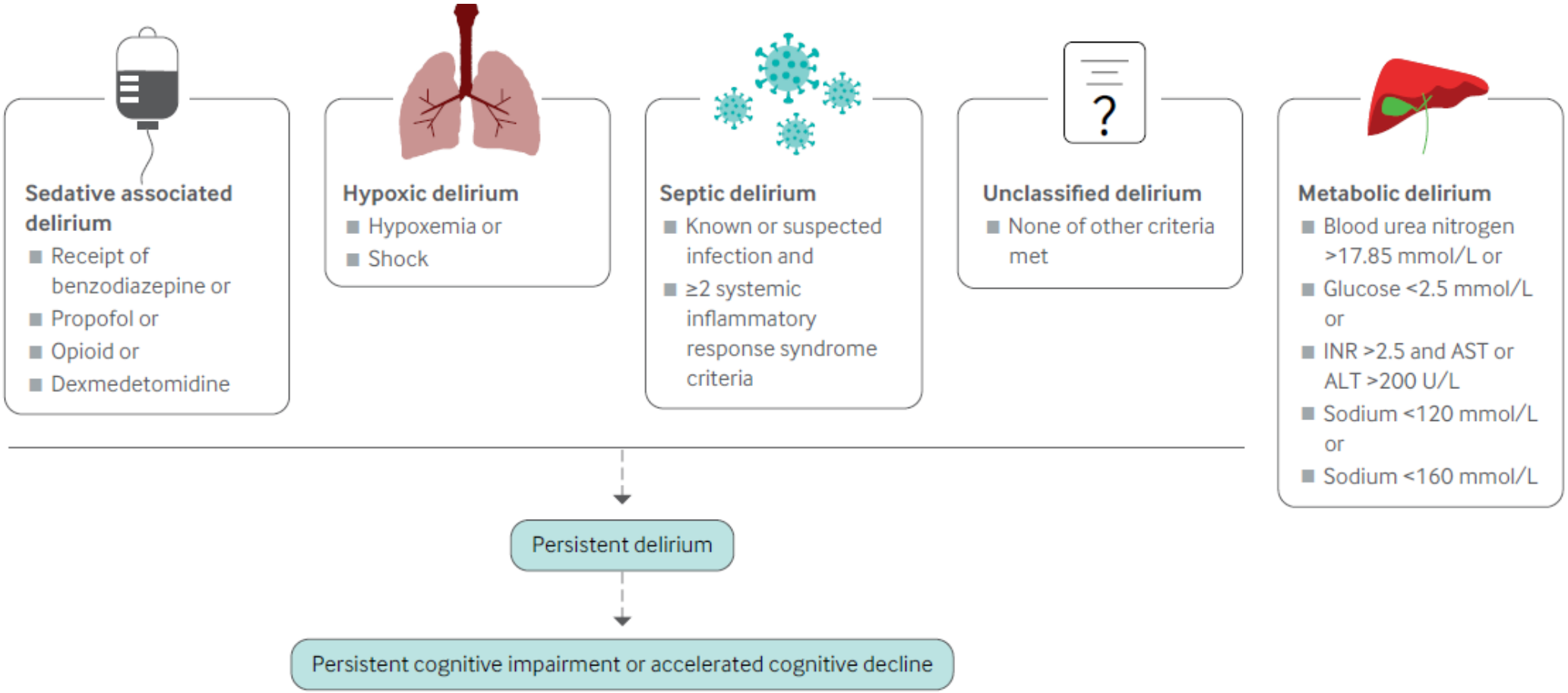
Conceptual framework for exploring inter-relationship between delirium and long-term cognitive impairment and between delirium and acceleration of dementia



Inouye and Ferrucci. *J Gerontol A Biol Sci Med Sci* 2006

Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study

Timothy D Girard, Jennifer L Thompson, Pratik P Pandharipande, Nathan E Brummel, James C Jackson, Mayur B Patel, Christopher G Hughes, Rameela Chandrasekhar, Brenda T Pun, Leanne M Boehm, Mark R Elstad, Richard B Goodman, Gordon R Bernard, Robert S Dittus, E W Ely



Girard TD, et al. *Lancet Respir Med* 2018;6:213-22.

Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study

Adjusted for n=11 relevant baseline and daily variables

Timothy D Girard, Jennifer L Thompson, Pratik P Pandharipande, Nathan E Brummel, James C Jackson, Mayur B Patel, Christopher G Hughes, Rameela Chandrasekhar, Brenda T Pun, Leanne M Boehm, Mark R Elstad, Richard B Goodman, Gordon R Bernard, Robert S Dittus, E W Ely

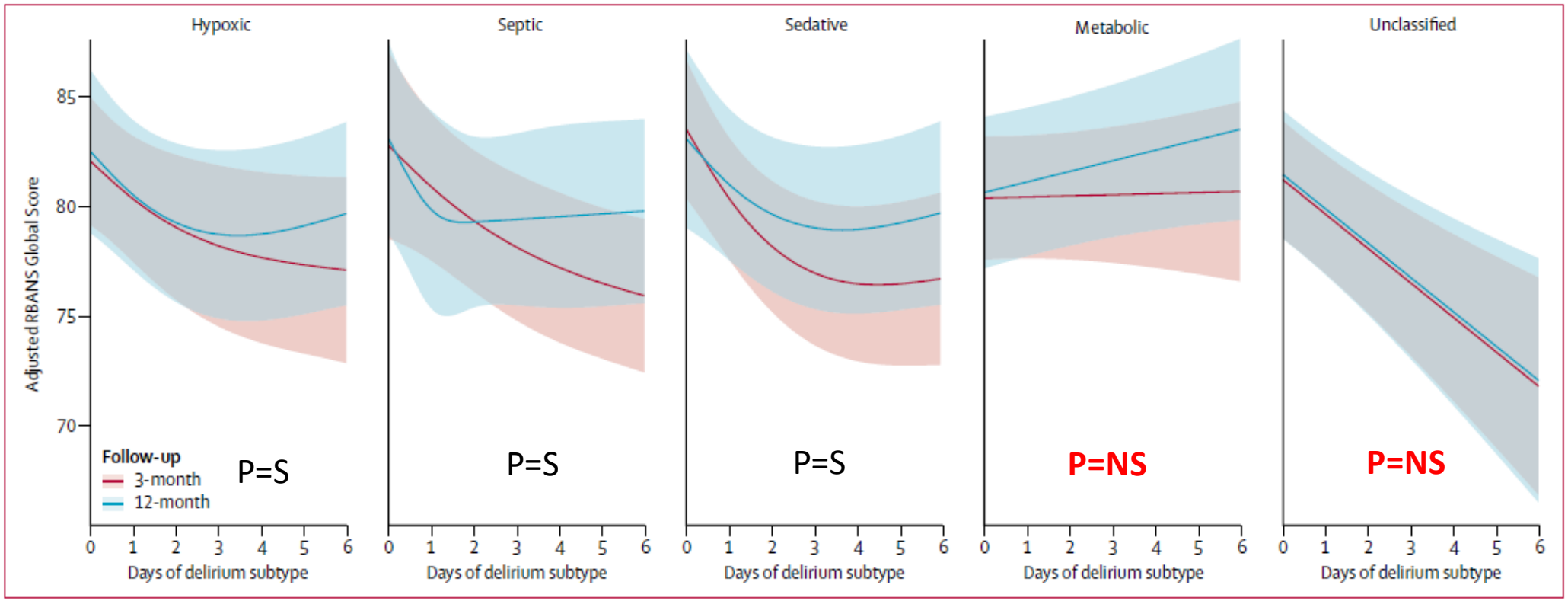


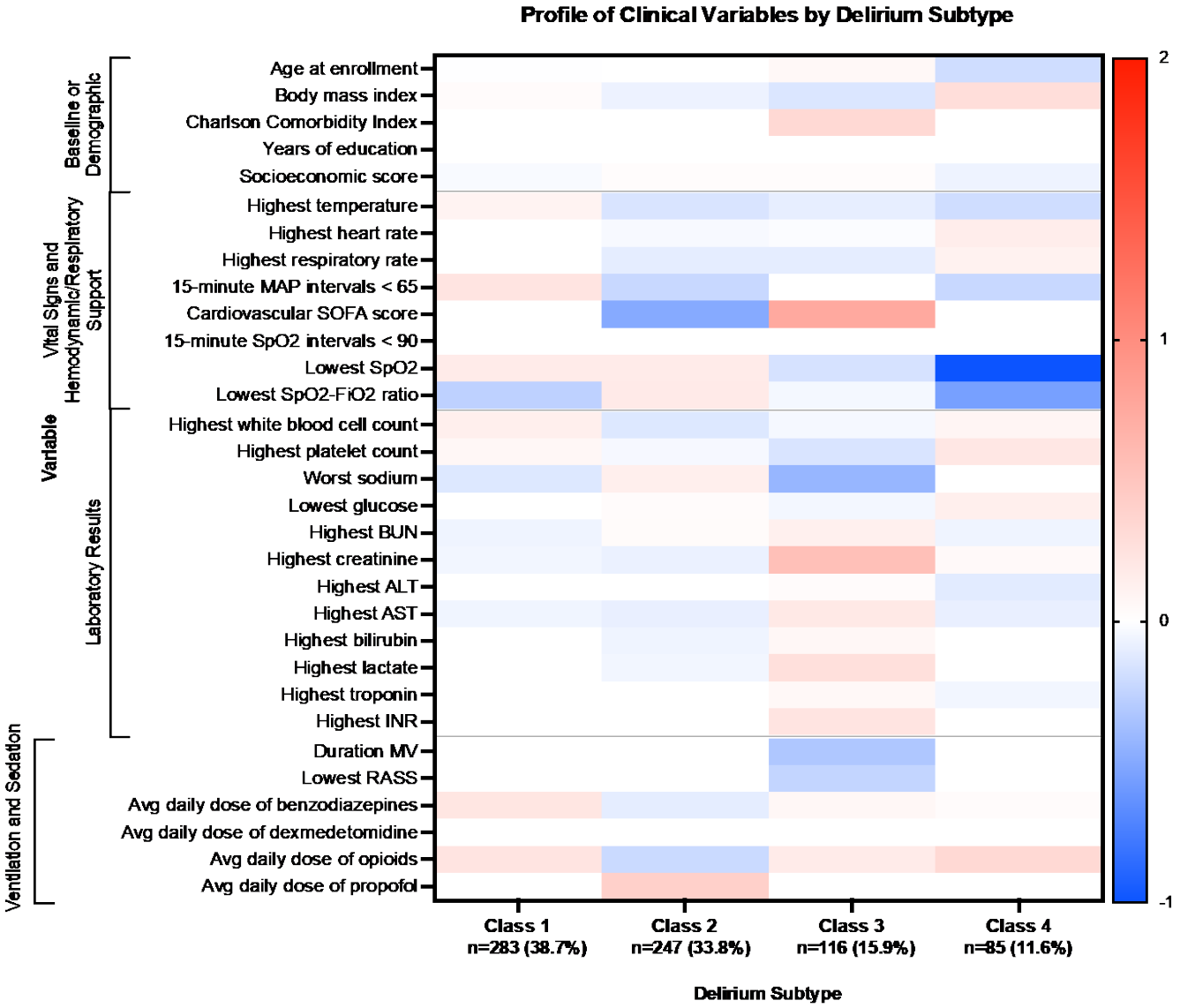
Figure 2: **Associations between duration of delirium phenotypes and global cognition scores at 3-month and 12-month follow-up**
Each line graph shows the association between the duration of a delirium phenotype (on the x-axis) and global cognitive performance on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) at 3 months (red lines, with the 95% CI represented by red shading) and 12 months (blue lines, with the 95% CI represented by blue shading) after hospital discharge.

Girard TD, et al. *Lancet Respir Med* 2018;6:213-22.

Data-derived subtypes of delirium during critical illness

Kelly M. Potter,[a,*] Jason N. Kennedy,[a] Chukwudi Onyemekwu,[b] Niall T. Prendergast,[b] Pratik P. Pandharipande,[c,e] E Wesley Ely,[d,e,f] Christopher Seymour,[a] and Timothy D. Girard[a,d]

Fig. 2: Heat map of the profile of clinical variables by delirium subtype for the final four-class model. The values of the variables in the figure are scaled to the median (indicated by 0 on the y-axis) and interquartile range. The heat map is shaded according to the value of each variable among the four data-derived delirium subtypes. Values represent a relative increase (red) or decrease (blue) from the median of the variable in



eBioMedicine 2024;100:104942

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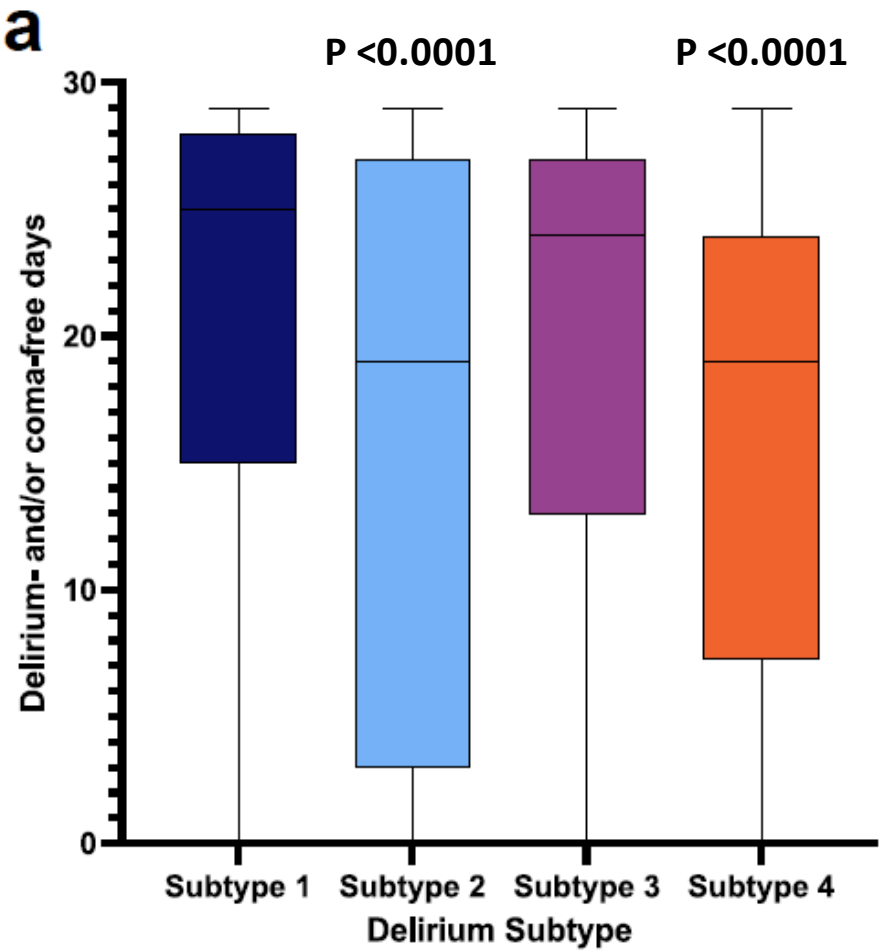
Delirium and Coma-Free Days



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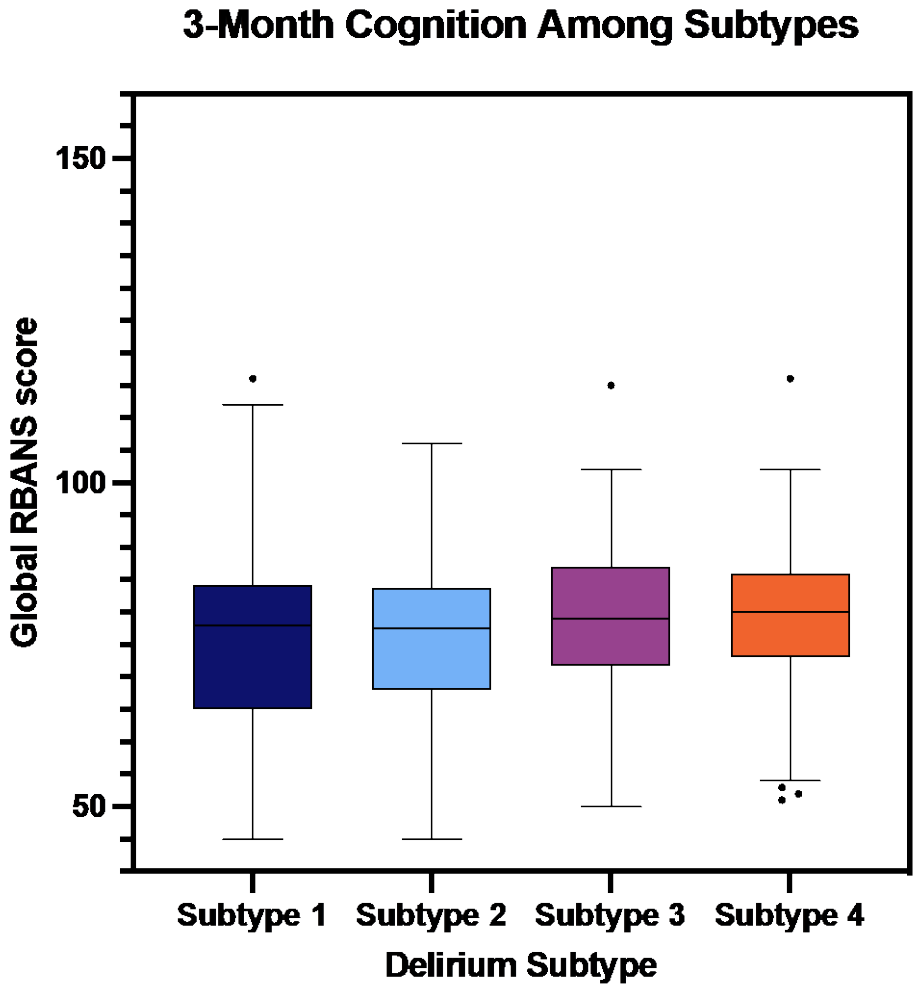
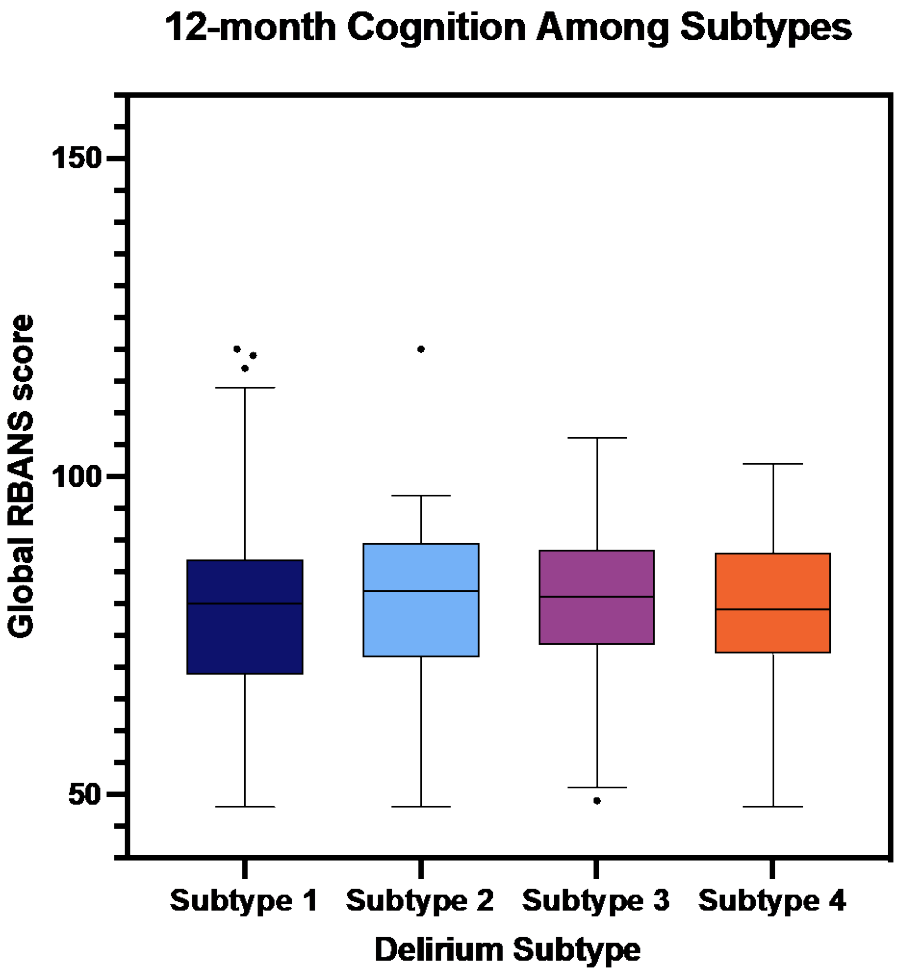
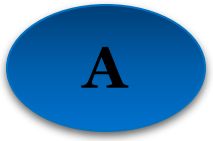




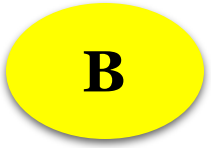
eFigure 10. At 3- and 12-month follow up, all data-derived delirium subtypes were affected by clinically significant cognitive impairment. However, the severity of cognitive impairment was not different by subtype (3-month: p=0.26, 12-month: 0.80).

eBioMedicine 2024;100:104942

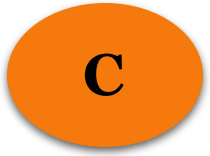
ABCDEF Bundle Elements



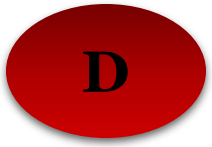
Assess, Prevent and manage Pain



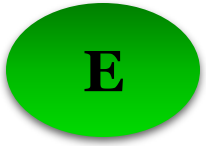
Both SAT and SBT



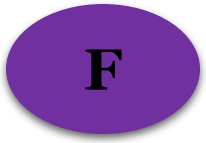
Choice of Analgesia and Sedation



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]

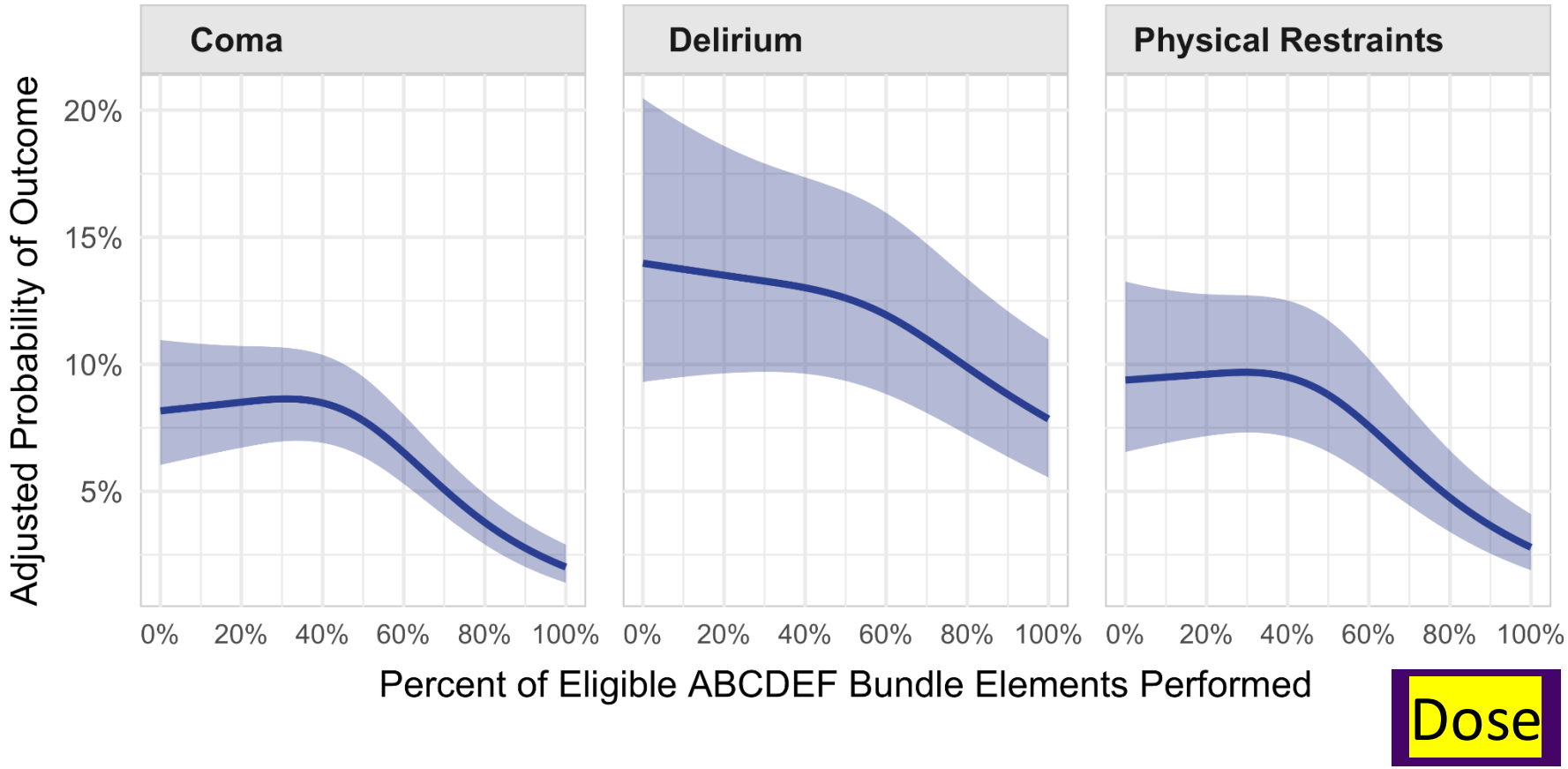
Pun B; Balas M; Barnes-Daly MA et al: *Crit Care Med* 2019

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



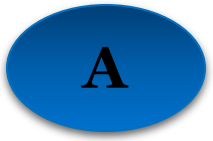
Pun B, et al. *Crit Care Med.* 2019; 47:3-14

Does Daily Use of the ABCDEF Bundle Improve Long-Term Cognitive Cognition?

Does Daily Use of the ABCDEF Bundle Improve Long-Term Cognitive Cognition?

Not Sure Yet……

ABCDEF Bundle Elements



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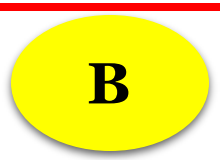

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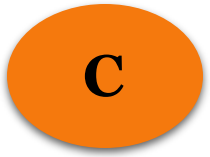

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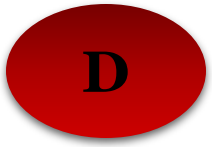

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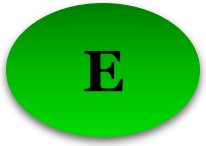

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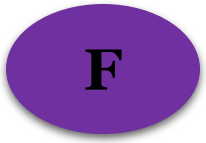

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Vasilevskis EE, et al. *Chest*. 2010;138(5):1224-1233.
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Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and 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

Outcome*	SBT	SAT+SBT	*P*-value
Ventilator-free days	12	15	0.02
Time-to-Event, days			
Successful extubation, days	7.0	5	0.05
ICU discharge, days	13	9	0.02
Hospital discharge, days	19	15	0.04
Death at 1 year, n (%)	97 (58%)	74 (44%)	0.01
Days of brain dysfunction			
Coma	3.0	2.0	0.002
Delirium	2.0	2.0	0.50

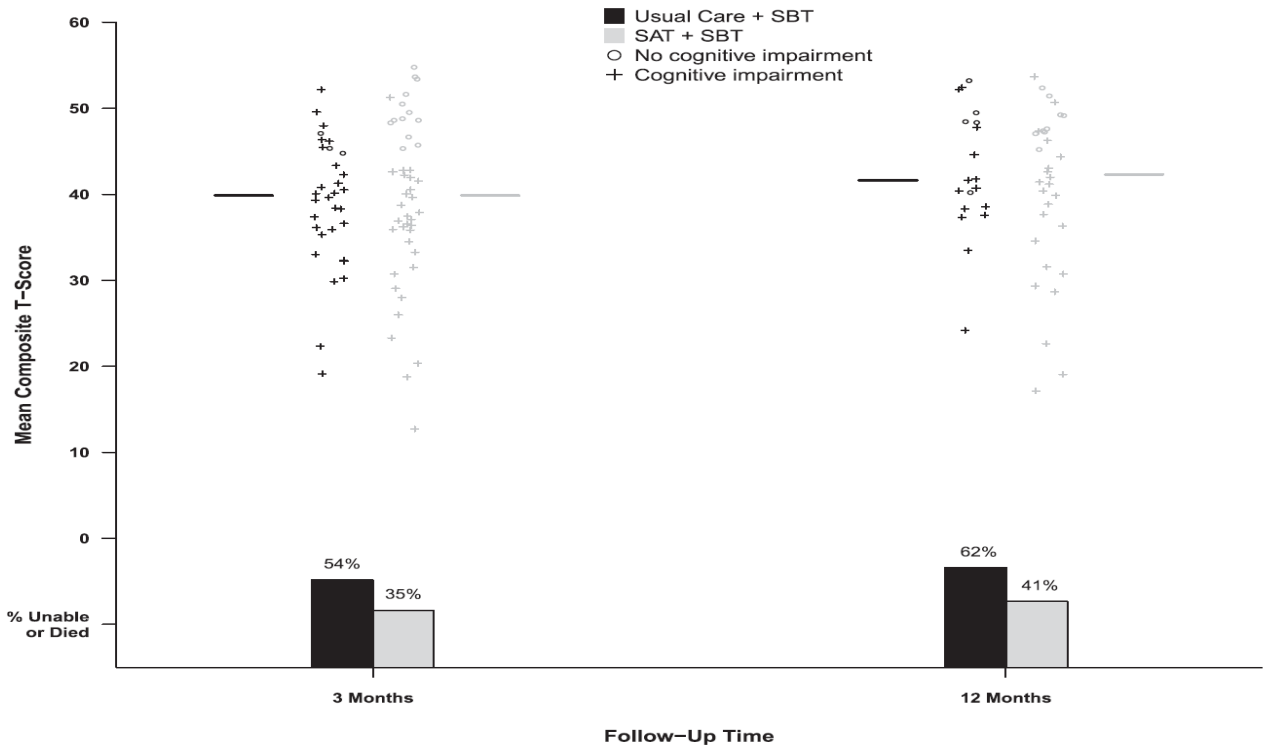
Girard TD, et al. *Lancet*. 2008;371:126-134.

Long-term Cognitive and Psychological Outcomes in the Awakening and Breathing Controlled Trial

James C. Jackson[1,2,3,4], Timothy D. Girard[1,2,5], Sharon M. Gordon[2,5], Jennifer L. Thompson[6], Ayumi K. Shintani[6], Jason W. W. Thomason[7], Brenda T. Pun[1], Angelo E. Canonico[8], Janet G. Dunn[9], Gordon R. Bernard[1], Robert S. Dittus[2,5], and E. Wesley Ely[1,2,6]

TABLE 3. LONG-TERM OUTCOMES

	3-mo Follow-up			12-mo Follow-up		
Outcome	Intervention	Control	*P* Value	Intervention	Control	*P* Value
Cognitive						
Composite T-score	40 (36–47)	40 (36–45)	0.80	42 (36–47)	42 (38–48)	0.61
Impaired, %	70	91	0.03	72	70	0.89



Am J Respir Crit Care Med 2010;182:183-191

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nonsedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients

	Non-sedation group No sedation; IVP opioid prn for pain/agitation Goal RASS=0 + ABCDE bundle N=354	Sedation group Continuous sedation to reach RASS=-3 to -2 0-48hrs = propofol; ≥ 48 hrs midazolam + ABCDE bundle N=356	Difference
Days free from coma/delirium within 28 days, median [IQR]	27 [21-28]	26 [22-28]	NS

Olsen HT, et al N Engl J Med 2020; 382:1103

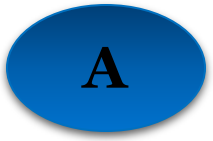
Evaluation of 6 month Post-ICU Cognition Between Non-Sedation and Sedation Groups

	Non-sedation group	Sedation group	Difference
Cognitive Function* %	***N=42***	***N=47***	
Occurrence of Delirium in the ICU	29 (69%)	45 (96%)	0.002
Duration of Delirium in the ICU	1 [0,6] days	5 [2, 11] days	< 0.001
Severe cognitive impairment	16 (38%)	17 (26%)	NS

***baseline demographic parameters not different between two study groups**
% only 1 of the 8 Study Centers

Nedergaard HK, Jensen HI, Stylsvig M, et al. Acta Anesth 2020; 64:1136

ABCDEF Bundle Elements



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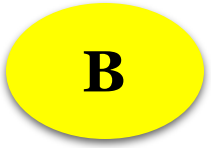

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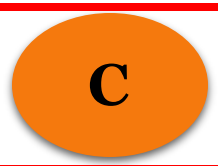
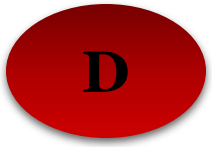
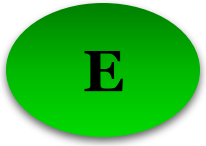


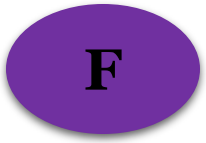
Choice of Analgesia and Sedation



Delirium: Assess, Prevent and Manage



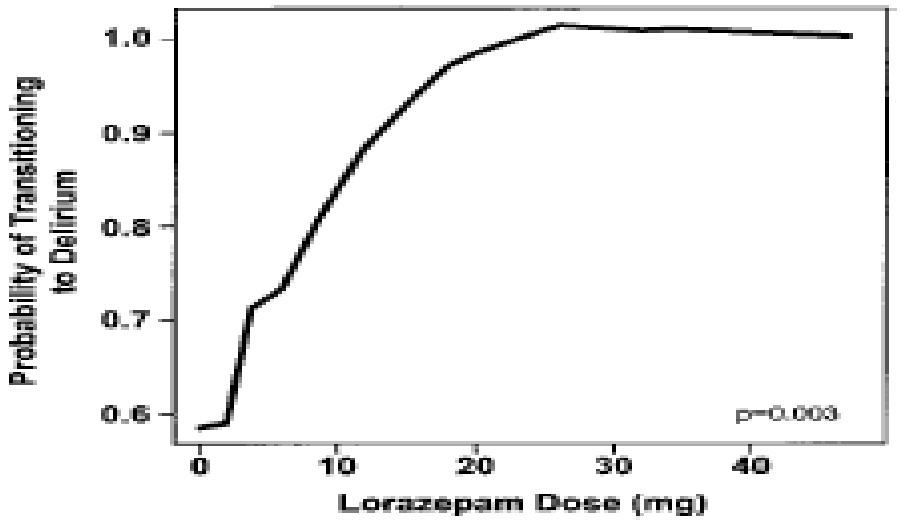
Early Mobility and Exercise



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.

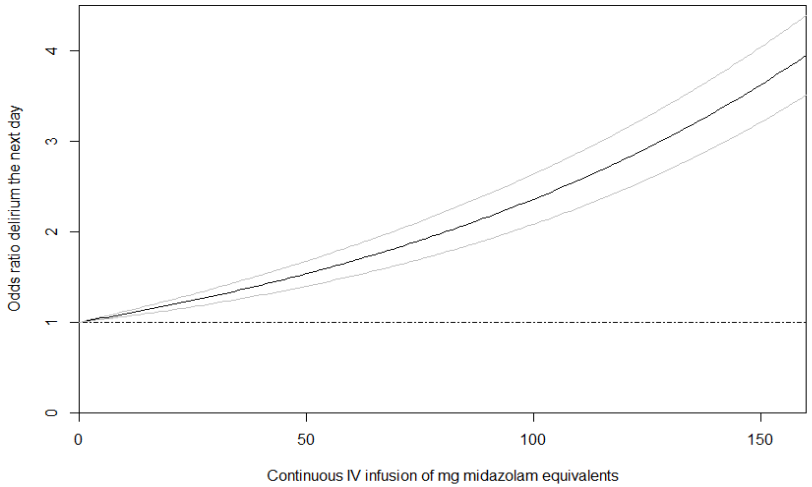
Lorazepam



OR = 1.20 (95% CI 1.1, 1.4)
***per every 1mg of lorazepam**

Pandharipande P, et al Anesthesiology 2006; 104:21

Midazolam



OR = 1.04 (95% CI 1.02, 1.05)
***per every 5mg of midazolam**

3 mg/hr = 72mg/24 hours

72/5 = 14.4 x 4% = 57.6% chance of having delirium the next day.

Zaal I, Devlin JW et al. Intensive Care 2015; 41:2130

Choice of Sedative

Recommendation:

We **suggest** using **either** propofol or dexmedetomidine over benzodiazepines for sedation in critically ill mechanically ventilated adults (conditional recommendation, low quality of evidence).

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

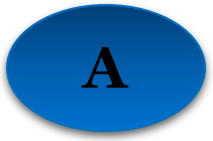
Dexmedetomidine or Propofol for Sedation in Mechanically Ventilated Adults with Sepsis

	Dexmedetomidine N=214	Propofol N=208	Difference
APACHE-II	27 [21, 32]	27 [22, 32]	
Medical	64%	65%	
Moderate-Severe ARDS	26%	29%	
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
Telephone Interview for Cognitive Status (TICS) at 6 mo.	40.9 [33.6, 47.1]	41.4 [34.0, 47.3]	NS
RASS score while receiving study sedation	-2 [-3 to -1]	- 1.9 [-3 to -0.9]	NS
Daily adherence to all ABCDE bundle elements	86%	85%	NS

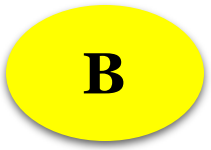
*Multivariable adjustment for n=16 variables

Hughes CG, Mailloux PT, Devlin JW, et al. New Engl J Med (Feb 2 2021)

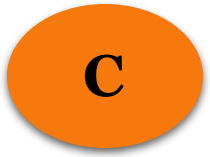
ABCDEF Bundle Elements



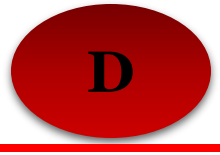
Assess, Prevent and manage Pain



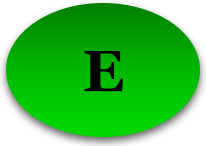
Both SAT and SBT



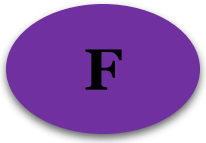
Choice of Analgesia and Sedation



Delirium: Assess, Prevent and Manage



Early Mobility and Exercise



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Davidson JE, et al. *Am Nurse Today*. 2013;8(5):32-38.

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**

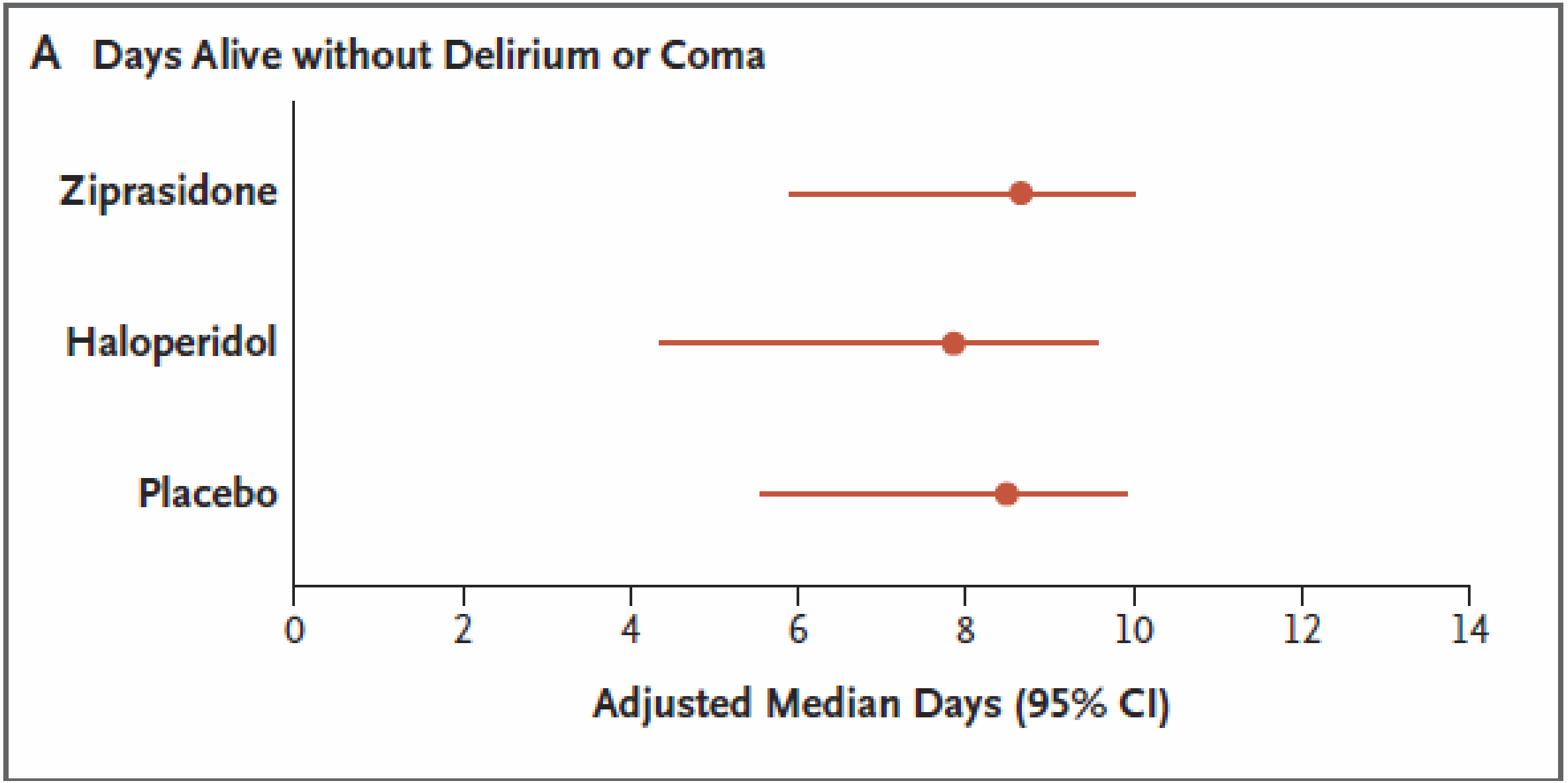
Recommendation:
We ***suggest NOT*** routinely using haloperidol and atypical antipsychotic to treat delirium (conditional recommendation, low quality of evidence).

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

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

Long-term outcomes after treatment of delirium during critical illness with antipsychotics (MIND-USA): a randomised, placebo-controlled, phase 3 trial

Matthew F Mart, Leanne M Boehm, Amy L Kiehl, Michelle N Gong, Atul Malhotra, Robert L Owens, Babar A Khan, Margaret A Pisani, Gregory A Schmidt, R Duncan Hite, Matthew C Exline, Shannon S Carson, Catherine L Hough, Peter Rock, Ivor S Douglas, Daniel J Feinstein, Robert C Hyzy, William D Schweickert, David L Bowton, Andrew Masica, Onur M Orun, Rameela Raman, Brenda T Pun, Cayce Strength, Mark L Rolfsen, Pratik P Pandharipande, Nathan E Brummel, Christopher G Hughes, Mayur B Patel, Joanna L Stollings, E Wesley Ely, James C Jackson, Timothy D Girard

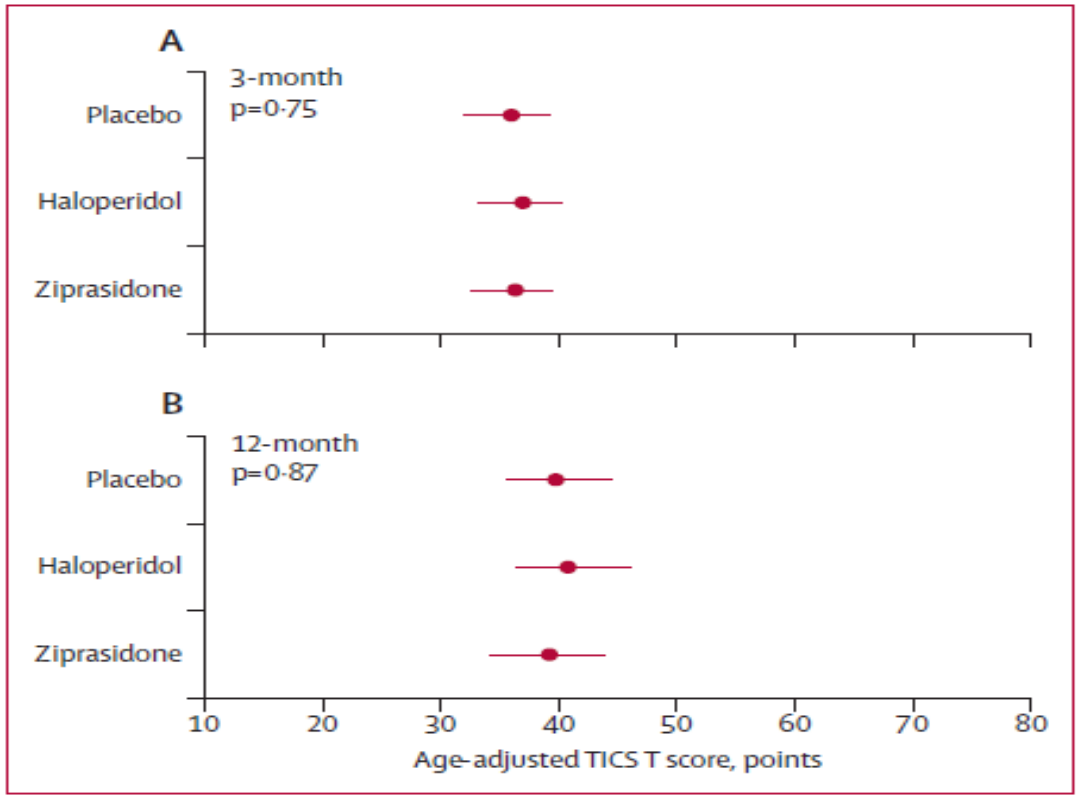


Figure 2: **Long-term cognition by treatment group**
Global cognition, as measured by TICS T score, at 3-month (A) and 12-month (B) follow-up after critically ill patients with delirium were treated with placebo, haloperidol, or ziprasidone. Data are adjusted median (95% CI). Treatment effects were estimated after adjusting for pre-randomisation predictors of cognition, including age, sex, race, baseline frailty, level of education, and baseline score on the short IQCODE. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. TICS=Telephone Interview for Cognitive Status.

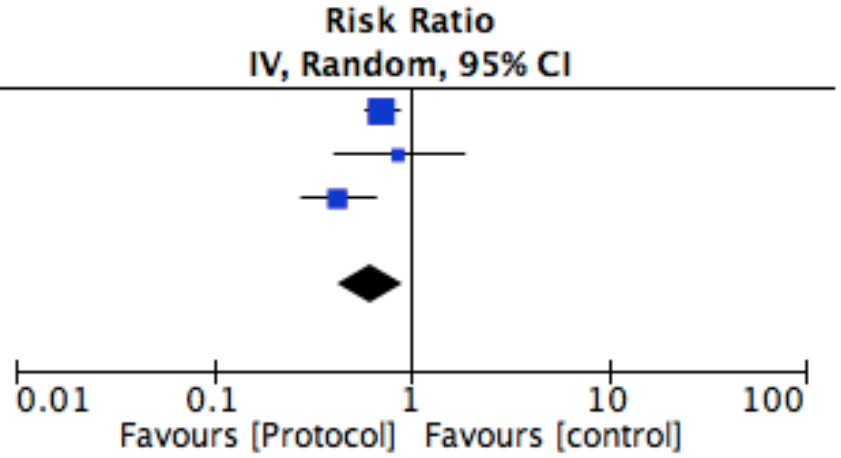
Lancet Respir Med 2014;12:599-607

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)



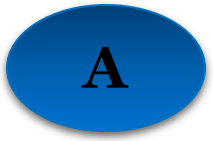
Delirium prevalence: RR: 0.62; 95% CI, 0.42 to 0.91 (for n=3 before-after studies)

<u>Recommendation:</u>

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

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

ABCDEF Bundle Elements



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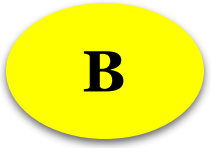

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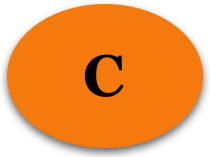

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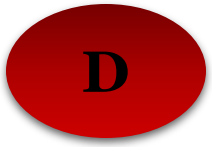

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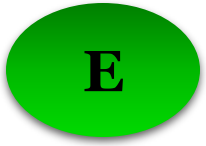

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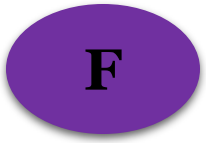

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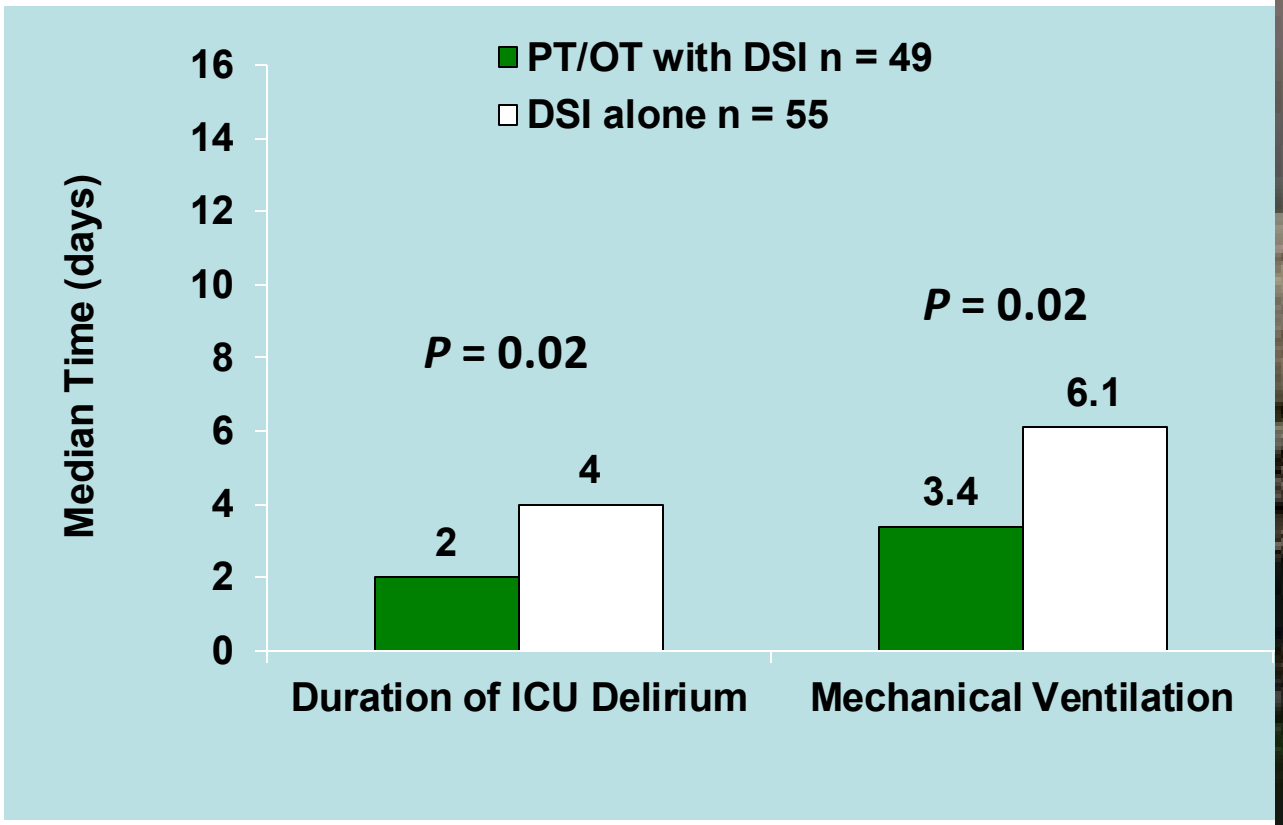
Early Exercise and Mobility



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

Early Rehabilitation and Mobilization

We **suggest** performing rehabilitation or mobilization in critically ill adults (conditional recommendation, low quality evidence).

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

Effect of early mobilisation on long-term cognitive impairment in critical illness in the USA: a randomised controlled trial

Bhakti K Patel, Krysta S Wolfe, Shruti B Patel, Karen C Dugan, Cheryl L Esbrook, Amy J Pawlik, Megan Stulberg, Crystal Kemple, Megan Teele, Erin Zeleny, Donald Hedeker, Anne S Pohlman, Vineet M Arora, Jesse B Hall, John P Kress

	Usual care group (n=99)	Intervention group (n=99)	p value
Time from intubation to first PT or OT session (days)	4·7 (3·3–6·8)	1·1 (0·8–2·0)	<0·0001
Number of daily therapy sessions			
Mechanical ventilation	0 (0–0)	2 (1–3)	<0·0001
ICU admission	0 (0–1)	4 (2–6)	<0·001
During hospitalisation	2 (1–4)	5 (3–9)	<0·0001
Delirium duration in ICU (days)	1 (0–3)	0 (0–2)	0·0050
Proportion of ICU days in delirium	25% (0–55·6)	0% (0–28·6)	0·0011

	Usual care group (n=99)	Intervention group (n=99)	Absolute difference	p value
Primary outcome				
Cognitive impairment at 1 year	43 (43%)	24 (24%)	−19·2%(−32·1 to −6.3)	0·0043
MoCA* score at 1 year	23 (21–26)	26 (24–28)	3 (1 to 4)	0·0001

Lancet Respir Med 2023;11:563-72

Conclusions

- ICU delirium (and its duration) is strongly associated with long-term cognitive impairment/dementia:
  - Causal relationship not established
  - Patients with baseline dementia excluded from most studies
  - Mechanisms not well-investigated
- While the ABCDEF bundle reduces ICU delirium, unclear if it improves long-term cognition
- Only one ICU intervention (mobility) shown to reduce ICU delirium has been rigorously shown to improve long-term cognition