Delirium Prevention and Treatment in Critically Ill Adults

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Disclosures

Research Funding:

- NIA
- NHLBI

QUALITY OF LIFE

Delirium

ICU Survival

ICU Survivorship

Return to Independence

Persistent Cognitive Defects

Depression

Executive Function

ICU memories

Reduced Functionality

Family stress

COVID – 19

- Viral Encephalitis
- Stroke
- Hypoxia ➡ Seizures

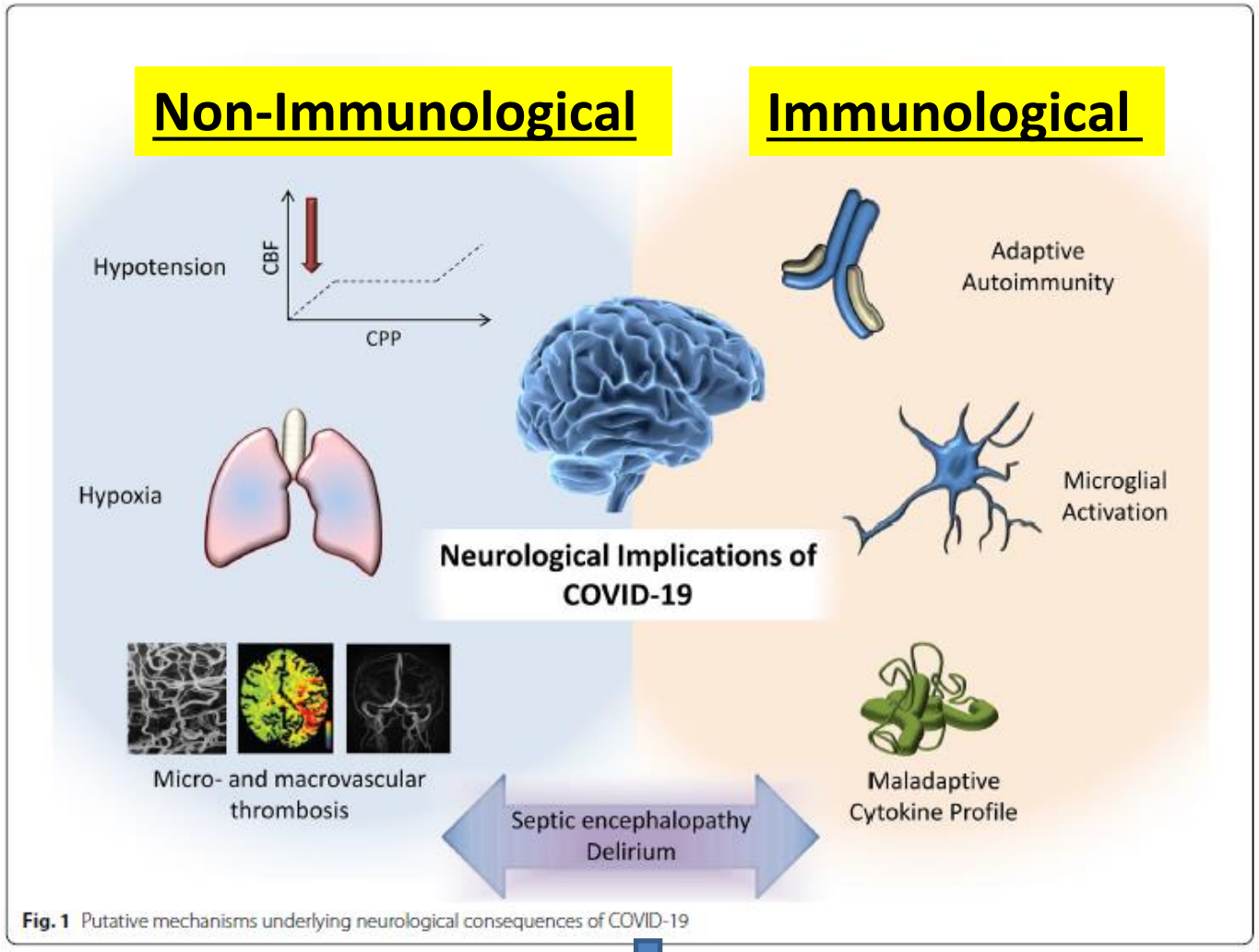


Fig. 1 Putative mechanisms underlying neurological consequences of COVID-19

- Cytokine Storm
- Maladaptive CNS response

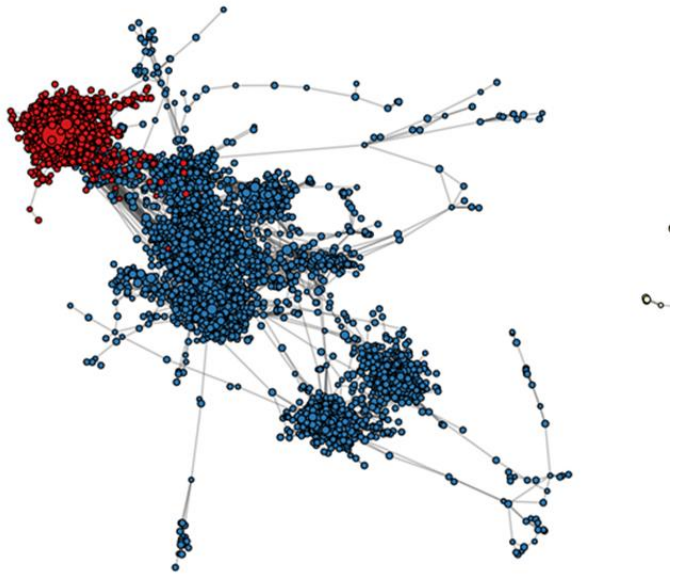
Encephalopathy: Delirium or Coma

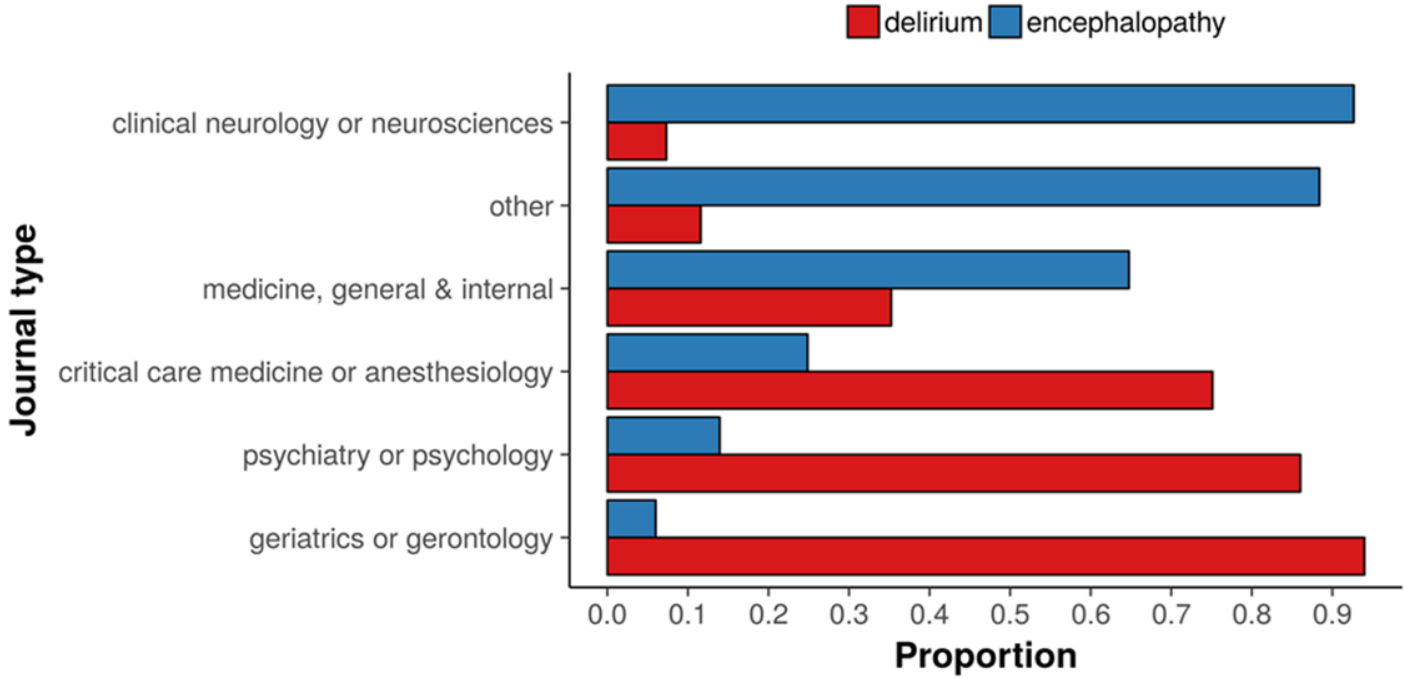
Needham EJ, et al. Neurocrit Care 2020

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:

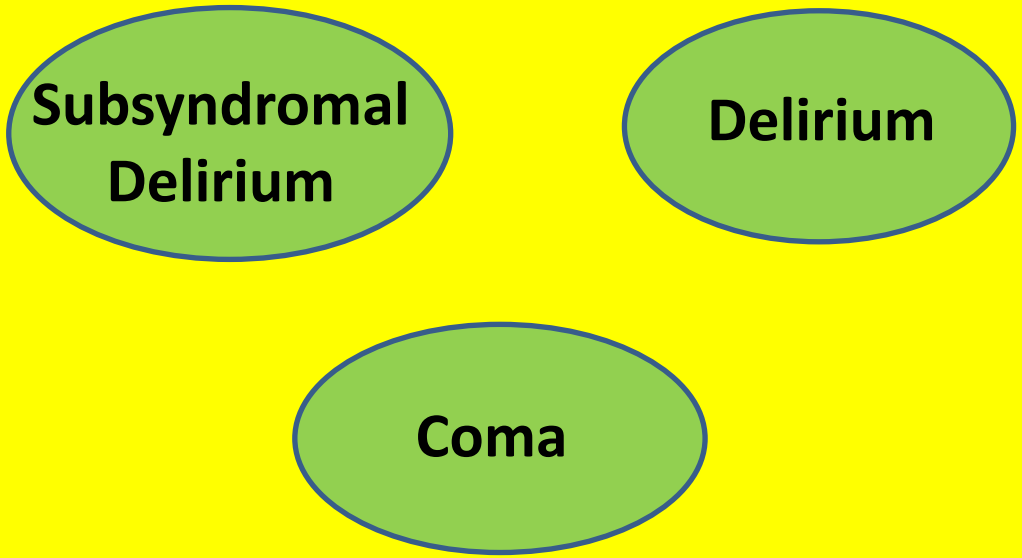
n=5,709 delirium–titled n=13,156 encephalopathy-titled

Only n=13 had both in title

N=7 Delphi Rounds

Preferred Terms

Acute Encephalopathy
[rapidly developing (< 4 wks) pathiobiologic process in the brain]



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

The 3 Most Important Strategies to Reduce Delirium

1. Recognize and reduce modifiable risk factors for delirium every day.
2. Use a multimodal protocol (e.g. ABCDEF bundle) focused on non-pharmacologic interventions in all patients to reduce delirium.
3. Generally avoid pharmacologic interventions to reduce delirium:
   – Medications should generally be reserved for the short-term treatment of clinically important delirium symptoms

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: benzodiazepine use, blood transfusions
Non-modifiable: greater age, dementia, prior coma, pre-ICU emergency surgery or trauma, and increasing APACHE & ASA scores

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

Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicen[illegible] study

Brenda T Pun, Rafael Badenes*, Gabriel Heras La Calle, Onur M Orun, Wencong Chen, Rameela Raman, Beata-[illegible]
Stephanie Wilson-Linville, Borja Hinojal Olmedillo, Ana Vallejo de la Cueva, Mathieu van der Jagt, Rosalía Navar[illegible]
Günseli Orhun, Carolina Ferrer Gómez, Karla Núñez Vázquez, Patricia Piñeiro Otero, Fabio Silvio Taccone, Elena [illegible]
Hilde Woien, Guillaume Lacave, Hollis R O'Neal Jr, Sarah J Peterson, Nathan E Brummel, Timothy D Girard, E Wes[illegible]
for the COVID-19 Intensive Care International Study Group†*

Lancet Respir Med 2021 (ahead of press January 8 2021)

- 69 Adult ICUs; 14 countries up to April 28, 2020
- Daily delirium/coma (up to 21 ICU days)
- Baseline and daily risk factors for delirium
- Delirium-related management strategies
- Ventilator use, ICU admission, mortality up to 28 days

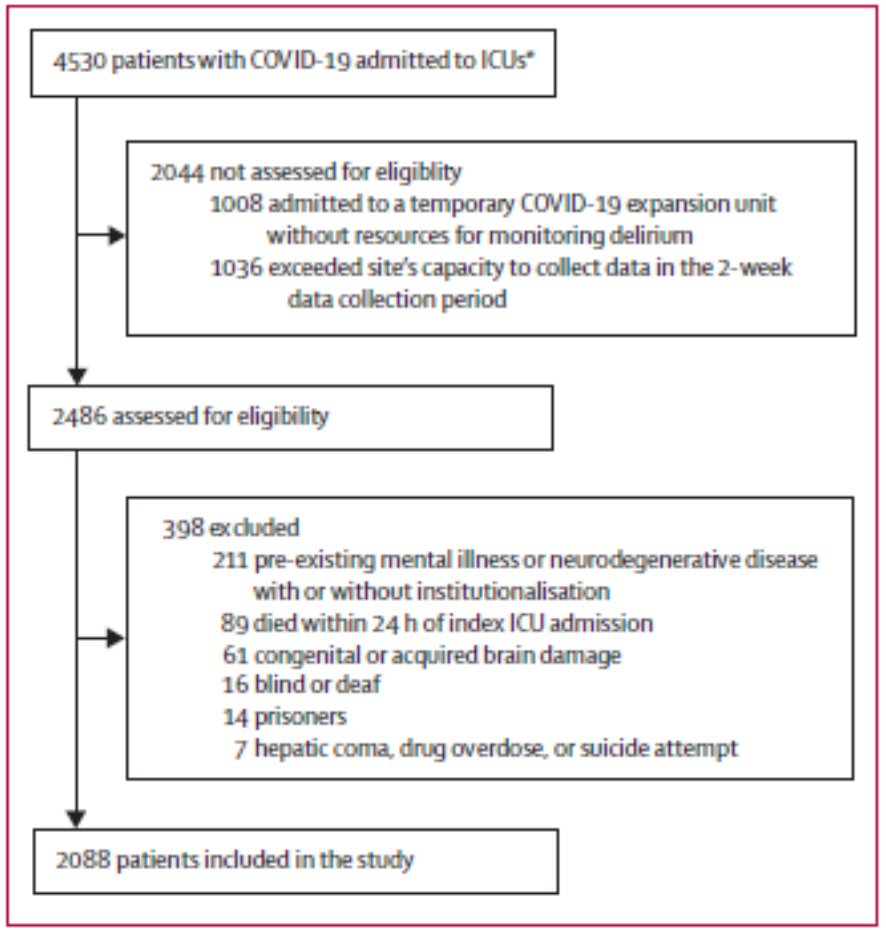


Figure 1: **Study flow diagram**
ICU=intensive care unit. *All patients who were COVID-19 positive and admitted to an ICU from the first reported case in each ICU until April 28th, 2020, were considered for inclusion.

	Patients (n=2088)
Age, years*	64·0 (54·0–71·0)
Sex	
Men	1497 (71·7%)
Women	591 (28·3%)
Use of prone positioning	1317 (63·1%)
Duration of proning, days	4·0 (2·0–6·0)
Use of continuous opioid infusion while on invasive mechanical ventilation‡‡	
Ever used	1659 (79·5%)
Duration of use, days	11 (7–17)
Use of continuous sedative infusion while on invasive mechanical ventilation	
Benzodiazepine	
Ever used	1337 (64·0%)
Duration of use, days	7·0 (4·0–12·0)
Propofol	
Ever used	1481 (70·9%)
Duration of use, days	7·0 (4·0–11·0)
Dexmedetomidine	
Ever used	920 (44·1%)
Duration of use, days	4·0 (2·0–7·0)
Clonidine	
Ever used	191 (9·1%)
Duration of use, days	5·0 (2·0–8·0)
Ketamine	
Ever used	140 (6·7%)
Duration of use, days	4·0 (2·0–6·0)
Sevoflurane	
Ever used	47 (2·3%)
Duration of use, days	3·0 (1·0–4·0)

	Patients (n=2088)
Coma	
Prevalence (ever comatose in 21 days)	1704 (81·6%)
Coma duration, days*	10·0 (6·0–15·0)
Persistently comatose until death or day 21	313 (15·0%)
Delirium†	
Prevalence (ever delirious in 21 days)	1147 (54·9%)
Delirium duration, days*	3·0 (2·0–6·0)
Delirium subtype‡§	
Ever hypoactive	388/925 (41·9%)
Hypoactive only delirium duration, days	2·0 (1·0–4·0)
Ever hyperactive	479/925 (51·8%)
Hyperactive only delirium duration, days	2·0 (1·0–4·0)
Acute brain dysfunction (coma or delirium)	
Coma or delirium duration, days	12·0 (7·0–18·0)
Days alive without delirium or coma in 21 days¶	5·0 (0·0–14·0)
Index length of stay in ICU in 28 day period	14·0 (8·0–25·0)
Ventilator-free days in 28 day period‖	7·0 (0·0–20·0)
Vital status on day 28	
Dead	601 (28·8%)
Alive	1416 (67·8%)
Unknown	71 (3·4%)

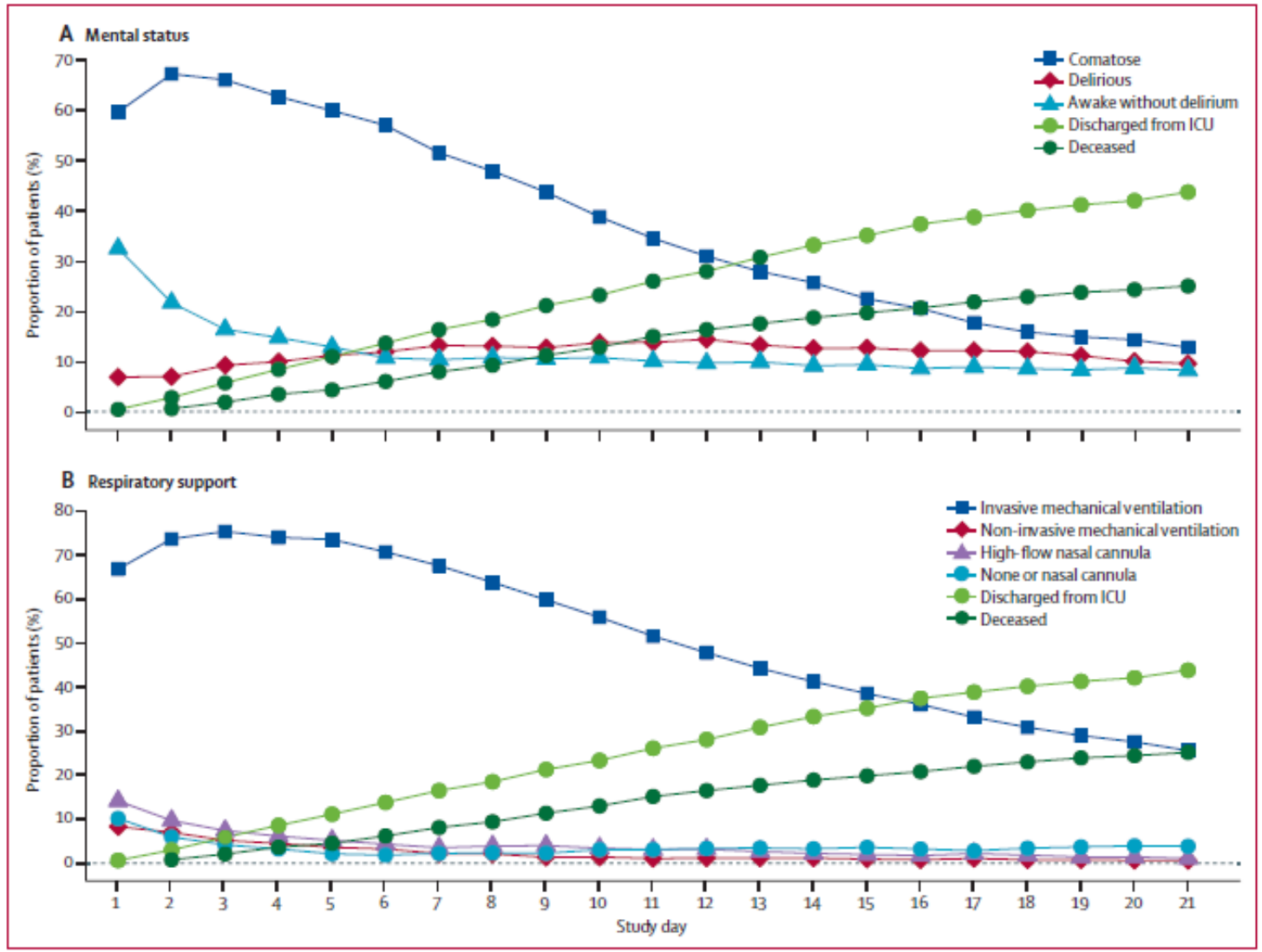


Figure 2: **Mental status and respiratory support status in the 21-day study period (n=2088)**
(A) Mental status over time. Coma was defined as a day when the patients were unresponsive to verbal stimulation (Richmond Agitation-Sedation Scale score of −4 or −5 or Glasgow Coma Scale score of <8). Patients were considered delirious if they had a positive delirium assessment scale assessment (Confusion Assessment Method for the Intensive Care Unit or the Intensive Care Delirium Screening Checklist) documented. All other patients were considered awake without delirium. Discharge represents discharge from the intensive care unit. (B) Respiratory status over time. ICU=intensive care unit.

	Performance of ABCDEF bundle on days eligible for assessment (n/N [%])*	Performance of ABCDEF bundle on all study days (n=27 022)
Element A (assess, prevent, and manage pain)	19 827/27 022 (73·4%)	19 827 (73·4%)
Element B		
Spontaneous awakening trial	5165/21 699 (23·8%)	5165 (19·1%)
Spontaneous breathing trial	5174/22 687 (22·8%)	5174 (19·1%)
Element C		
Assessment of sedation-agitation	26 501/27 022 (98·1%)	26 501 (98·1%)
Avoidance of benzodiazepine†	11 892/22 687 (52·4%)	11 892 (44·0%)
Element D (assess, prevent, and manage delirium)	11 044/13 330 (82·9%)	11 044 (40·9%)
Element E (early mobility and exercise)	4519/13 330 (33·9%)	4519 (16·7%)
Element F (family engagement and empowerment)	4599/27 022 (17·0%)	4599 (17·0%)
In-person visitation with family or friends	2192/27 022 (8·1%)	2192 (8·1%)
Virtual visitation only with family or friends	2407/27 022 (8·9%)	2407 (8·9%)

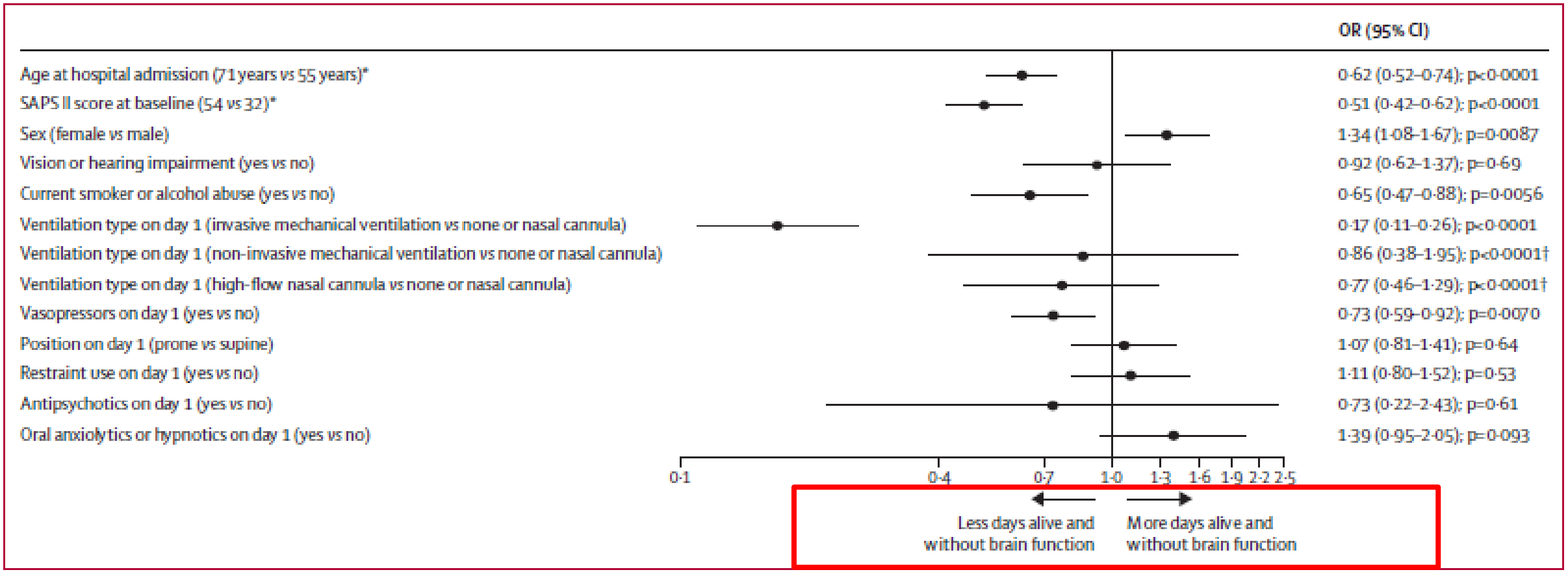


***Figure 4*: Forest plot of days alive and free of coma or delirium**

All patients who had at least 90% delirium or coma assessments during their index intensive care unit stay were included in this analysis (n=2062). Risk factors with an OR of less than 1 indicate a negative patient outcome (fewer days alive and free of brain dysfunction coma or delirium). OR=odds ratio. SAPS II=Simplified Acute Physiology Score II. *For all continuous variables (age, SAPS II, proportion of ABCDE elements performed), comparisons shown in parentheses correspond to the 75th vs 25th percentile values for that variable. †p values shown represent the overall p values for the variable and are not associated with the level to level comparisons within these variables, which are represented by the 95% CIs.

Intensive Care Med (2020) 46:2342–2356
https://doi.org/10.1007/s00134-020-06307-9

REVIEW

Analgesia and sedation in patients with ARDS

Gerald Chanques[1,2*], Jean-Michel Constantin[3], John W. Devlin[4,5], E. Wesley Ely[6,7,8], Gilles L. Fraser[9], Céline Gélinas[10], Timothy D. Girard[11], Claude Guérin[12,13], Matthieu Jabaudon[14,15], Samir Jaber[1,2], Sangeeta Mehta[16], Thomas Langer[17,18], Michael J. Murray[19], Pratik Pandharipande[20], Bhakti Patel[21], Jean-François Payen[22], Kathleen Puntillo[23], Bram Rochwerg[24], Yahya Shehabi[25,26], Thomas Strøm[27,28], Hanne Tanghus Olsen[27] and John P. Kress[21]

ICU liberation strategy for ARDS

home

A ssess, prevent and manage pain
B oth awakening & spontaneous breathing trial
C hoice of drugs
D elirium monitoring & management
E arly mobility & exercice
F amily engagement & empowerment
- R espiratory Drive Control

①TOP PRIORITY
Assess, prevent and manage
increased respiratory drive related factors
- ☑ stress related symptoms (e.g. pain, discomfort, anxiety, dyspnea)
- ☑ physiological factors (e.g. hyperthermia, acidosis, hypercabnia)

Patient's factors

Ventilator's factors

① TOP PRIORITY
Control Respiratory Drive
- ☑ Assess, prevent and manage Patient related factors

Set the ventilator first in case of patient/ventilator asynchrony
- ☑ adapt the ventilator to the patient and not the patient to the ventilator
- ☑ Spontaneous breathing mode as soon as possible

1. First, favor non pharmacological interventions (e.g. relaxation, ventilator setting), multimodal analgesia with non opioids
2. In last step only: Use or increase opioids ± sedatives/ psycho-active agents ± NMBA
3. Consider intermittent ordering before continuous infusion

②

②

Chanques G, et al. Intensive Care Med 2020 (in press)

Non-Pharmacological Treatment: Multi-component

(excluding AF Bundle)

PICO Question		
P	Critically ill adults	
I	Multicomponent strategy including (but not limited to):	
	• Strategies to reduce or shorten delirium (reorientation, cognitive stimulation)	
	• Sleep improvement (minimize light/noise)	
	• Improve wakefulness (reduce sedation)	
	• Reduce immobility	
	• Reduce visual or hearing impairment (eye glasses and hearing aids)	
C	No use of this strategy	
O	Delirium duration	Duration of mechanical ventilation
	ICU LOS	Mortality

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

Non-Pharmacological Treatment: Multi-component (excluding AF bundle)

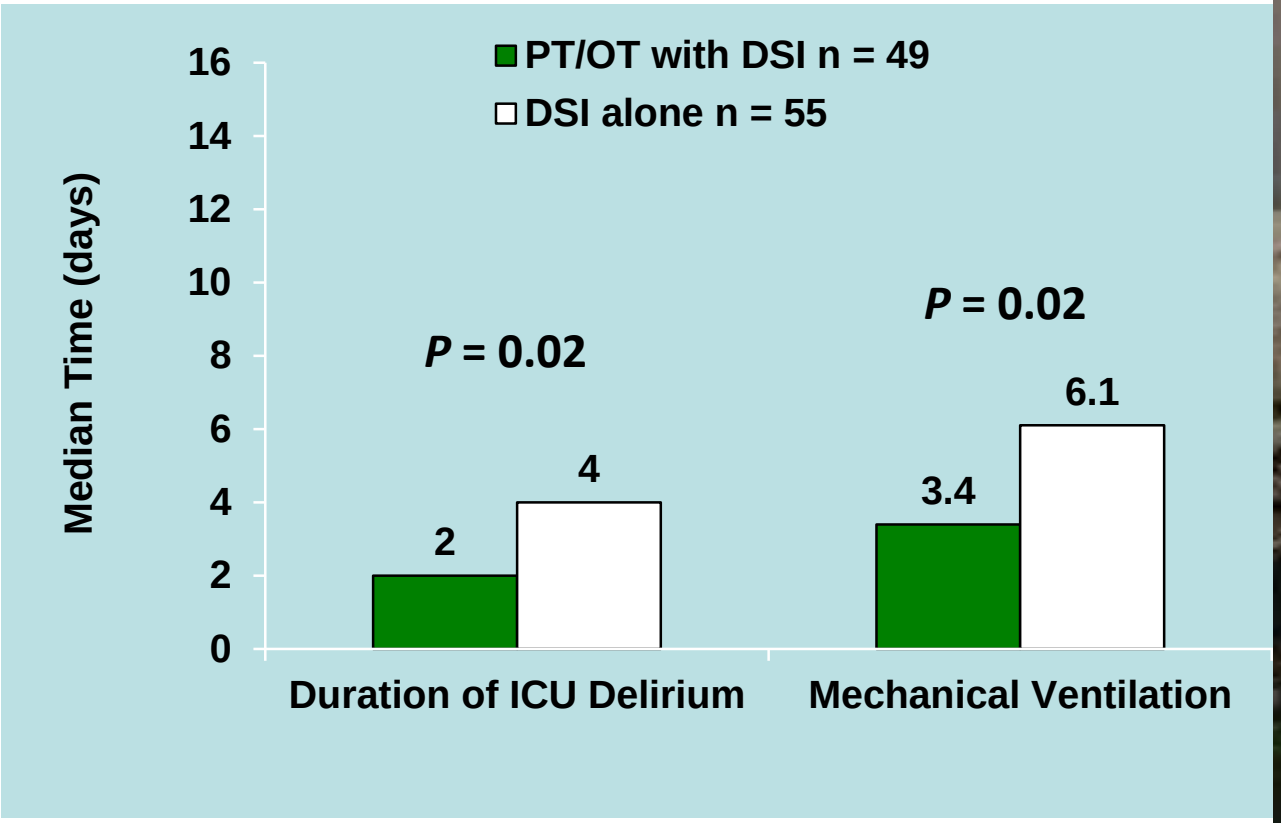
Rationale: 5 studies (1 RCT*, 4 Before-after), 1318 pts

- Use of these strategies was associated with:
  - Reduced delirium significantly, OR=0.59 (95% CI, 0.39 to 0.88)
  - Decreased ICU duration of delirium, ICU LOS & hospital mortality

Author (year)	*Design/ Population*	*Intervention vs control*
Colombo (2012)	Before-after Mixed ICU	N=144 vs N=170 (Usual care) Reorientation strategy, and environmental, acoustic and visual stimulation
Foster (2013)	Before-after Mixed ICU	N=84 vs N=164 (Usual care) MCI protocol (sedation, sleep-wake, sensory stimulation, mobility and music)
Moon (2015)	RCT* Mixed ICU	N=60 vs N=63 (Usual care, no prevention program) MCI prevention program: delirium risk monitoring, cognition and orientation, environment, early therapeutic intervention
Hanison (2015)	Before-after Mixed ICU	N=127 vs N=23 (Usual care) 2 cycle MCI program: 1st cycle: reducing delirogenic drugs, daily sedation breaks, environment changes, more light exposure, use of communication aid, 2nd cycle: natural light, use of clocks
Rivosecchi (2016)	Before-after Mixed ICU	N=253 vs N=230 (Usual care) MCI program: music, opening blinds, reorientation and cognitive stimulation, eye/ear protocol

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

Early Mobilization



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

Recommendation

- Given a small benefit and the low overall quality of evidence, panel members agreed:
  - desirable consequences ***probably*** outweigh undesirable consequences

Formal Recommendation:

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

- Supports performing rehab/mobility over usual care or similar interventions with a reduced duration, frequency, or later onset
- **Implementation influenced by feasibility, staffing & resources across ICUs**

Non-Pharmacologic Interventions to Improve Sleep

PICO Question		
P	Critically ill adult patients in an ICU	
I	• Assist control mode at night	• Acupressure
	• Adaptive ventilation at night	• Music
	• NIV-specific ventilator	• Noise Reduction
	• Aromatherapy	• Light Reduction
C	No use of the intervention	
O	• Time spent at each sleep stage • Sleep duration • Sleep fragmentation • Circadian rhythm	• Delirium occurrence • Duration of mechanical-ventilation • ICU mortality • Patient experience

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

Use of Noise and Light Reduction Strategies to Improve Sleep

Rationale:

- Two RCTs and two observational studies evaluated the night time use of earplugs (with/without eye shades) in non-sedated ICU pts
  - Improved patient-reported sleep quality
  - Reduced delirium
  - Pooled analysis from 2 observational studies associated earplug use with a 20% increased chance of achieving 4 hrs sleep
- Studies not blinded, some patients refused earplugs and sicker patients not evaluated.
- Earplugs/eyeshades little risk and low cost

Recommendation:

We suggest using noise and light reduction strategies to improve sleep in critically ill adults (conditional recommendation, low quality of evidence).

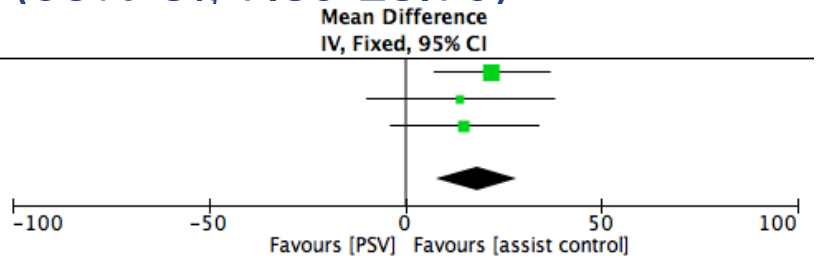
Devlin JW, et al. Crit Care Med 2018; 46 (9); e825-873

Assist Control (vs. PS) ventilator mode at night

- **Sleep Efficiency** (3 RCTs, 61 pts)
  - Increased by mean difference of 18.33% (95% CI, 7.89-28.76)

Study or Subgroup	Control Ventilation Mean	SD	Total	PSV Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Andrejak 2013	61	25	26	39	29	26	50.3%	22.00 [7.28, 36.72]
Cabello 2008	58	28.2	15	44	37.8	15	19.1%	14.00 [-9.87, 37.87]
Toublanc 2007	65	25	20	50	35	20	30.6%	15.00 [-3.85, 33.85]
Total (95% CI)			**61**			**61**	**100.0%**	**18.33 [7.89, 28.76]**

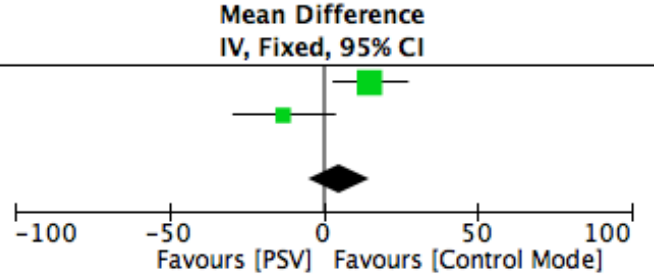
Heterogeneity: $Chi^2 = 0.49$, df = 2 (P = 0.78); $I^2 = 0\%$
Test for overall effect: Z = 3.44 (P = 0.0006)



- **% of sleep time spent in REM sleep** (2 RCTs, 42 pts)
  - Increased by mean difference of 2.79% (95% CI, 0.53-5.05)

Study or Subgroup	Control Mode Mean	SD	Total	PSV Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Andrejak 2013	35	23	26	20	21	26	65.3%	15.00 [3.03, 26.97]
Cabello 2008	54	23.7	15	67	22.2	15	34.7%	-13.00 [-29.43, 3.43]
Total (95% CI)			**41**			**41**	**100.0%**	**5.29 [-4.38, 14.97]**

Heterogeneity: $Chi^2 = 7.29$, df = 1 (P = 0.007); $I^2 = 86\%$
Test for overall effect: Z = 1.07 (P = 0.28)



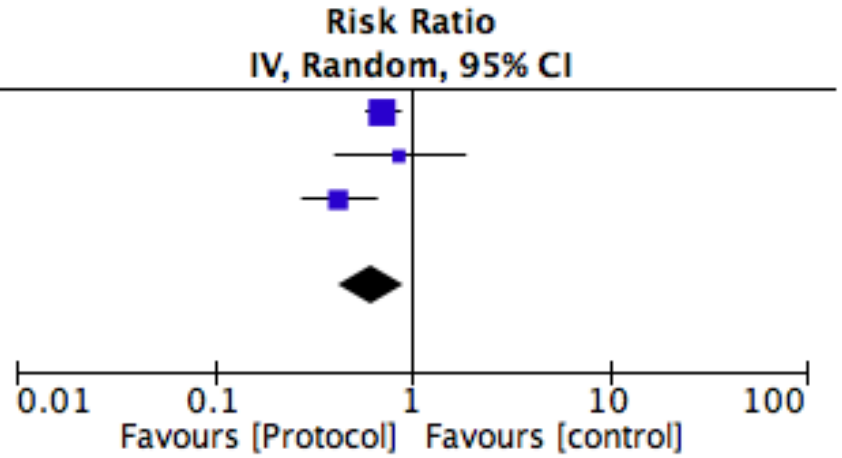
Recommendation:
We suggest using assist control ventilation at night (vs. pressure support ventilation) to improve sleep in critically ill adults (conditional recommendation, low quality of evidence)

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)

Recommendation:

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

Dr. DRE:

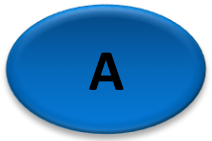
***Important to use a standardized approach to mitigate delirium risk factors on a daily basis during ICU IPT rounds**

Diseases	New onset sepsis/infection Worsening organ dysfunction Worsening hypoxemia Dehydration
DRug Removal	Sedative down-titration e.g. SATs Stop/reduce psychoactive meds
Environment	Immobilization Sleep disruption Noise/light Hearing aids/glasses

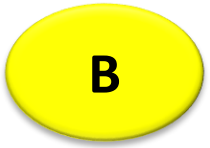
The 3 Most Important Strategies to Reduce Delirium

1. Recognize and reduce modifiable risk factors for delirium every day.
2. Use a multimodal protocol (e.g. ABCDEF bundle) focused on non-pharmacologic interventions in all patients to reduce delirium.
3. Generally avoid pharmacologic interventions to reduce delirium:
   – Medications should generally be reserved for the short-term treatment of clinically important delirium symptoms

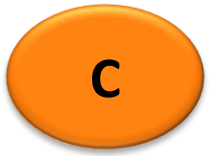
ABCDEF Bundle Elements



Assess, Prevent and manage Pain

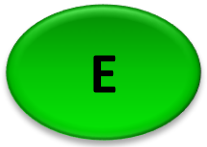


Both SAT and SBT



Choice of Analgesia and Sedation

Delirium: Assess, Prevent and Manage

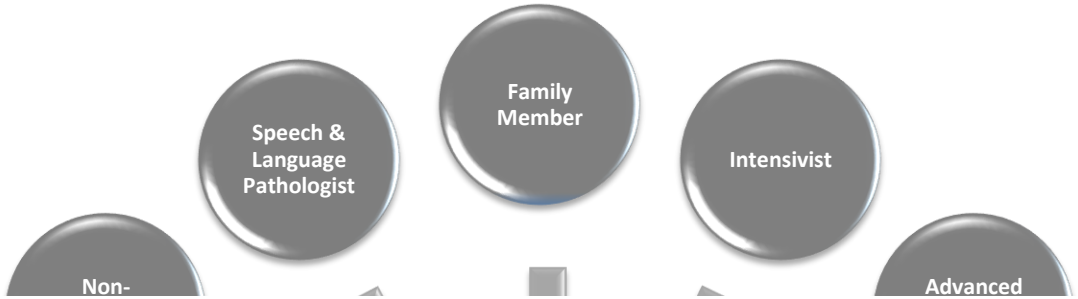


Early Mobility and Exercise

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.


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



Best Practices for Conducting Interprofessional Team Rounds to Facilitate Performance of the ICU Liberation (ABCDEF) Bundle

Joanna L. Stollings, PharmD, FCCM, FCCP[1,2]; John W. Devlin, PharmD, FCCM, FCCP[3,4]; John C. Lin, MD[5]; Brenda T. Pun, DNP, RN, FCCM[2,6]; Diane Byrum, MSN, RN, CCRN-K, CCNS, FCCM[7]; Juliana Barr, MD, FCCM[8,9]

Non-Pharmacological Treatment: Multi-component – AF Bundle

ABCDE bundle multi-intervention approach (1 Before-after), 296 pts

- Significantly associated with:
  - Less delirium, 49% vs. 62%, OR=0.55 (95% CI, 0.33 to 0.93)

ABCDEF bundle approach (1 Cohort study), 6064 pts

- Included a focus on "F", Family engagement
- Improvement in bundle compliance significantly associated with:
  - Reduced mortality & more coma/delirium free ICU days

Recommendation:
We ***suggest*** using a multicomponent, non-pharmacologic intervention that is focused on (but not limited to) **reducing modifiable risk factors** for delirium, improving cognition, and optimizing sleep, mobility, hearing, and vision in critically ill adults (conditional recommendation, low quality of evidence)

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

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

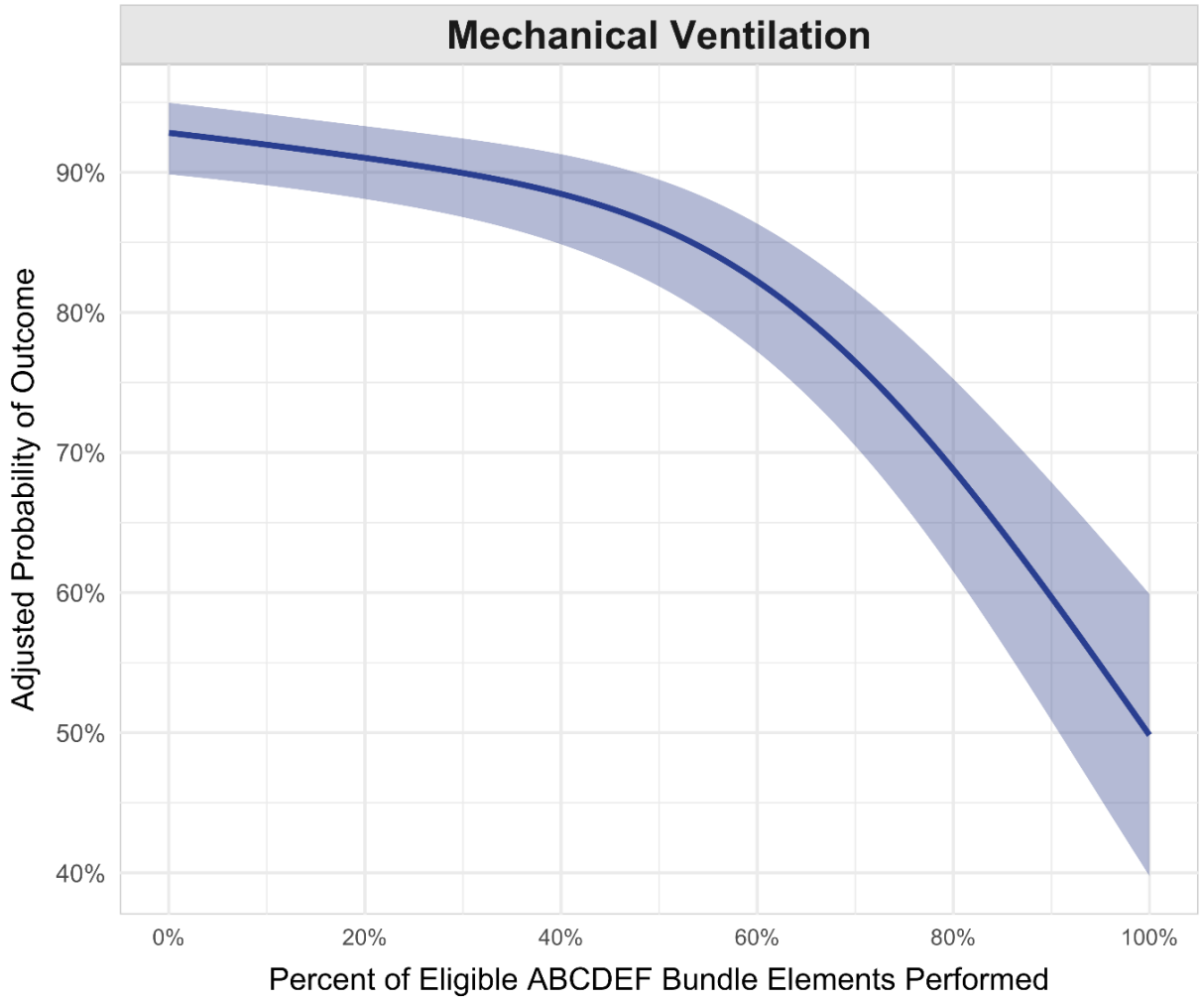
Pun B, et al. *Crit Care Med.* 2019; 47:3-14

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

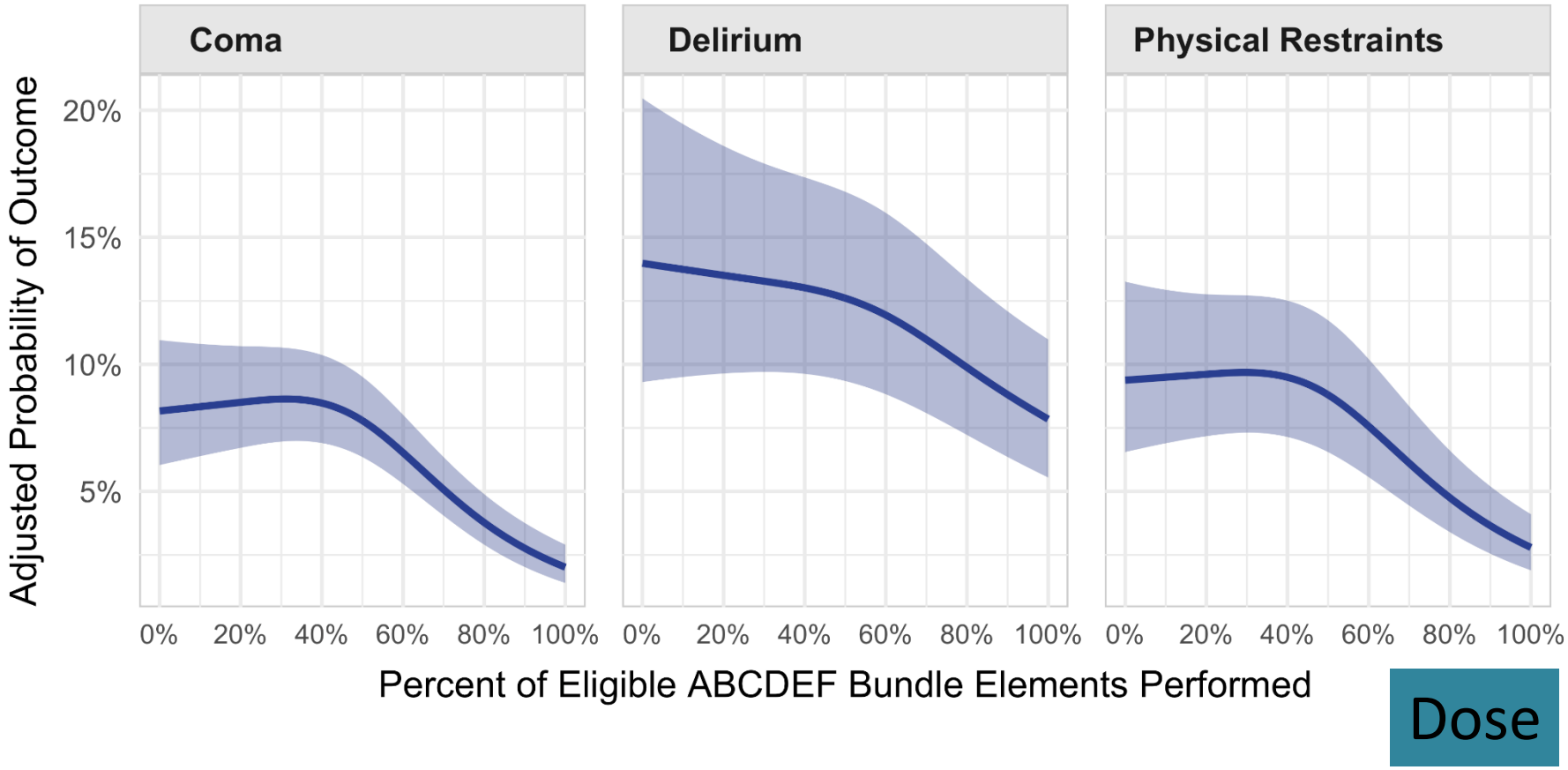
Results: Symptom-Related Outcomes



Dose

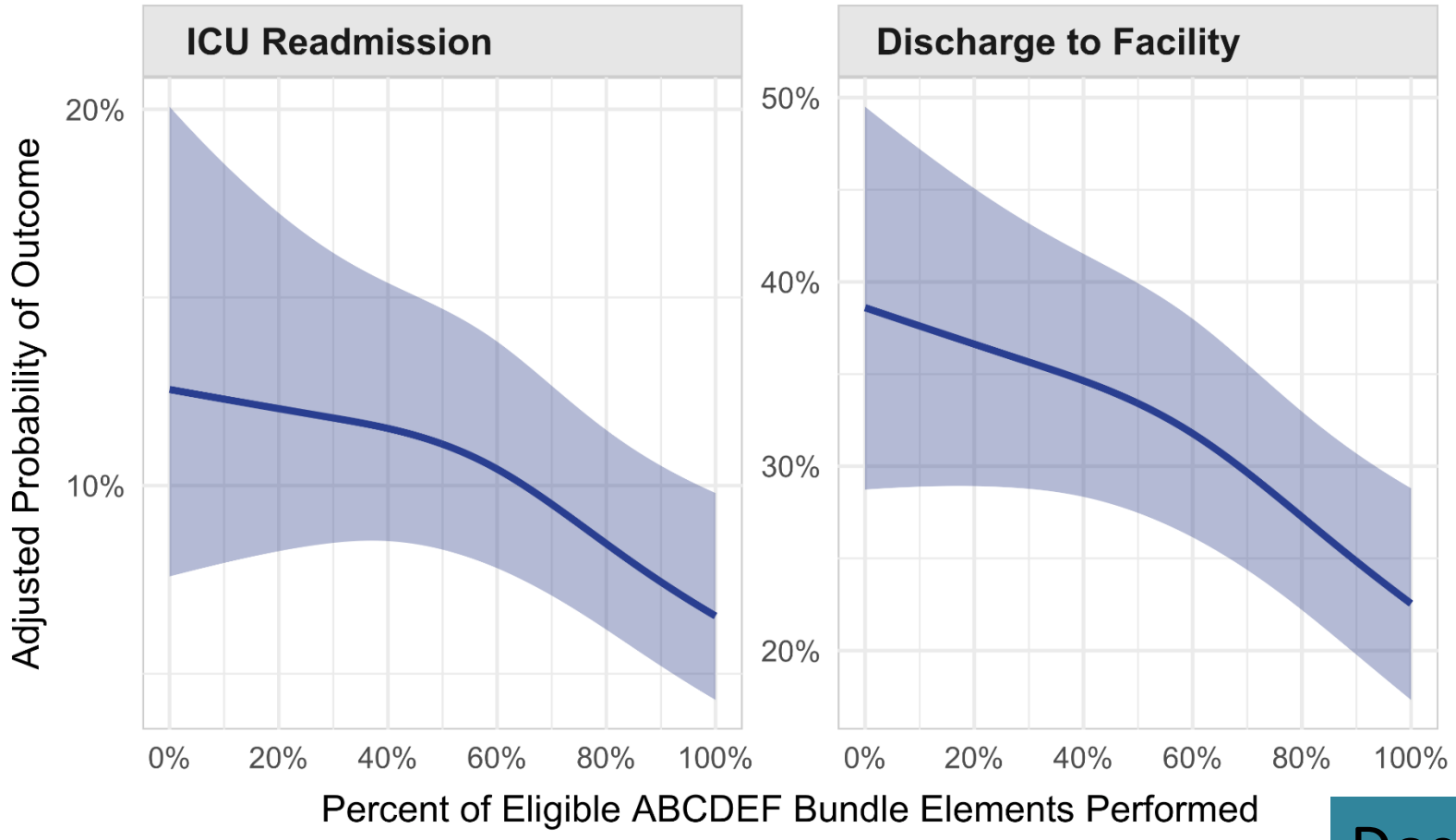
Pun B, et al. *Crit Care Med.* 2019; 47:3-14

Results: Symptom-Related Outcomes



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

Results: System-Related Outcomes



Dose

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]

Barriers and Solutions to ABCDEF Bundle Use in Critically Ill Adults with COVID-19

Covid-19 Barrier/Concern	Potential Solution
A: Assess Prevent and Manage Pain • Pain is prevalent and associated with agitation and/or increased delirium • Ability to recognize pain is reduced in deeply sedated patients • Painful neuropathies prevalent: prolonged immobility/viral invasion of peripheral nerves	• Pain/discomfort is common in medical ICU patients • Use behavioral assessment tools (e.g. Critical Care Pain Observation Tool) to evaluate pain • Consider gabapentin or pregabalin use
A: Both Spontaneous Awakening Trial and Spontaneous Breathing Trials • Deep sedation is common with MV COVID-19 patients despite coma being an important risk factor for delirium occurrence • Perception: no benefit in conducting an SAT if patient is not likely to pass SBT screen	• Conduct regular RASS assessments; RT or MD can conduct in absence of the RN • Use Bispectral (BIS) monitoring during continuous NMB therapy • Strong data to support management of ARDS patients at lighter sedation goals; routine NMB in ARDS does not improve outcome • Evaluate a new sedative goal each day • Daily sedative de-escalation should be considered regardless of SBT/extubation likelihood • A sedated patient should be assumed to have disrupted sleep.

Devlin JW, et al. Crit Care Explorations 2020 (ahead of press June 12)

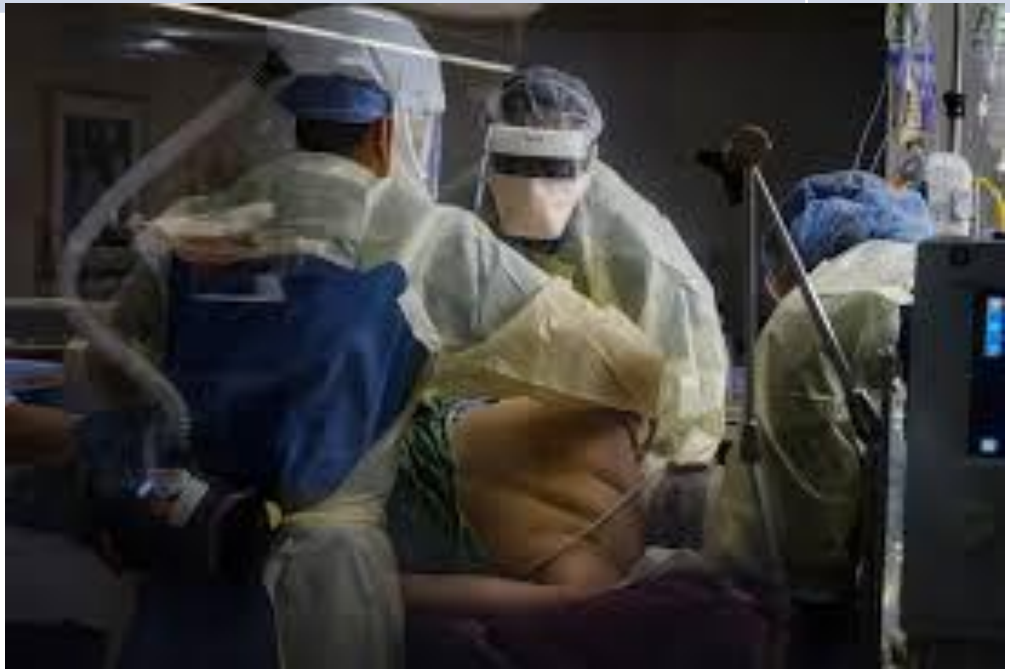
Barriers and Solutions to ABCDEF Bundle Use in Critically Ill Adults with COVID-19

Covid-19 Barrier/Concern	Potential Solution
C: Choice of Analgesia and Sedation • Use of benzodiazepines (strongly associated with delirium) is greater in the face of propofol safety concerns, drug shortages and desire for deep sedation • Symptoms from opioid/sedative withdrawal may mimic delirium	• Propofol-associated hypertriglyceridemia is common in COVID-19; may be related to cytokine storm-related hemophagocytic lymphohistiocytosis (HLH); ignore TG < 800 mcg/dL • Many 3rd-line sedatives associated with reduced delirium vs benzodiazepines (e.g., phenobarbital) • Administer opioids/sedatives via feeding tube to wean IV opioids and sedatives and prevent withdrawal reactions.
D: Delirium: Assess, Prevent and Manage • Delirium screening efforts may be compromised by reduced time at bedside and deeper sedation. • Challenging to recognize and reduce potential modifiable risk factors for delirium • Non-pharmacologic delirium reducing interventions challenging to apply	• Evaluate delirium when patient maximally awake (e.g., post SAT) • Assume delirium is present if delirium cannot be evaluated. • Non-RN bedside clinicians can be trained to screen for delirium • Systematically evaluate for new delirium risk factors on a daily basis • Antipsychotic therapy generally not needed unless agitation or delirium-associated fear/hallucinations are detected. • Drug-associated delirium (e.g. benzodiazepines; steroids) is dose-related • Apply eye glasses/hearing aids/reorientation efforts/music/electronic contact with family when feasible • Simplify nocturnal interventions and reduce room light/hallway noise to promote sleep.

Devlin JW, et al. Crit Care Explorations 2020 (ahead of press June 12)

Barriers and Solutions to ABCDEF Bundle Use in Critically Ill Adults with COVID-19

Covid-19 Barrier/Concern	Potential Solution
E: Early Mobility and Exercise • Although early mobility is associated with reduced delirium; many barriers preclude its use: - Deep sedation prevalent - PT/OTs may not be in ICU - Less time for RN/RT at bedside • Contact precautions may preclude out of room mobility efforts	• In-bed, range of motion exercises should be administered at least daily • ICU MD/RN can obtain daily rehab/mobility goals from PT/OT non in ICU via facetime/phone • Mobility (e.g. standing/walking place in room) is beneficial • Patients can be masked for hallway walking.



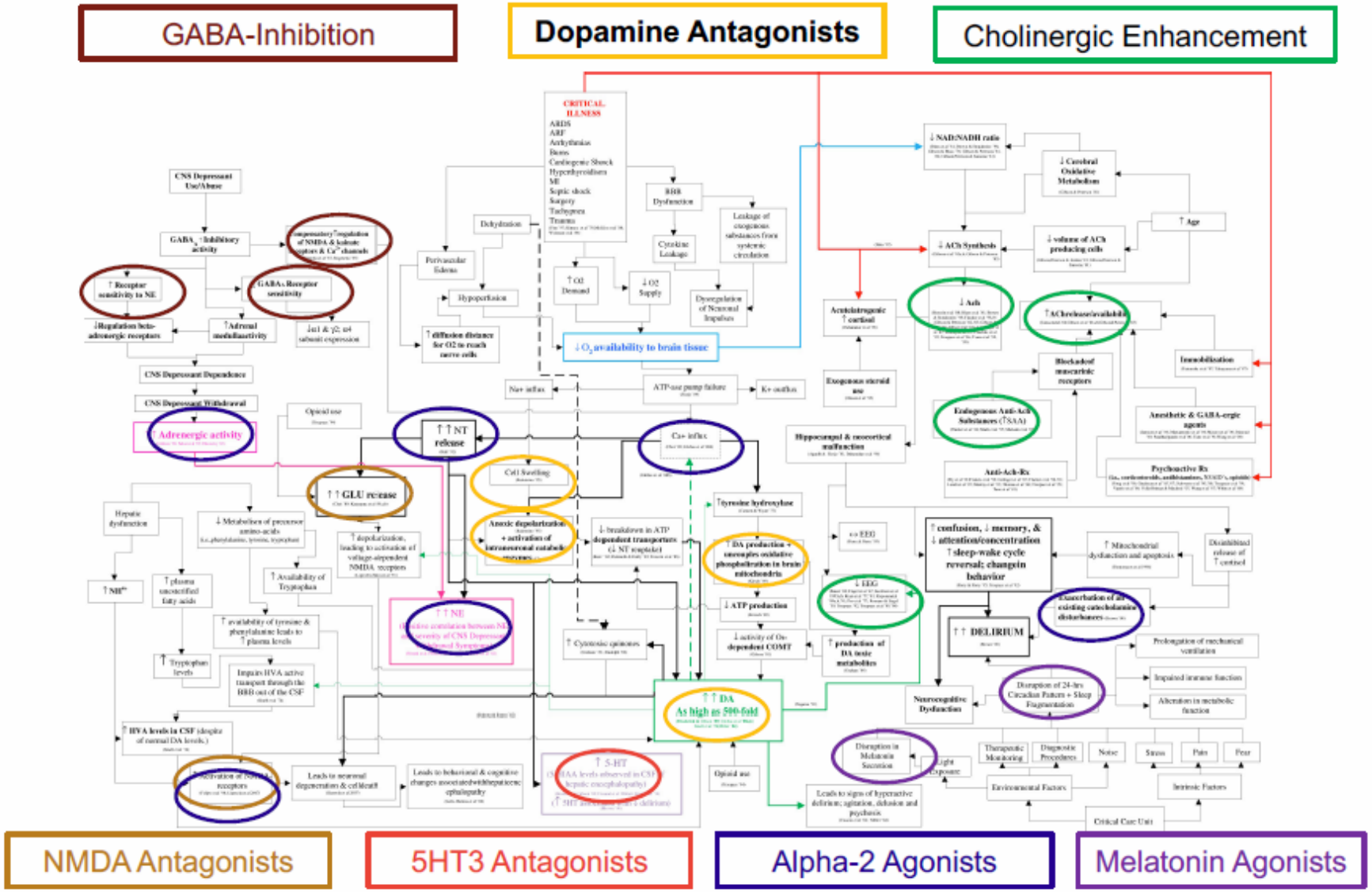
Devlin JW, et al. Crit Care Explorations 2020 (ahead of press June 12)

The 3 Most Important Strategies to Reduce Delirium

1. Recognize and reduce modifiable risk factors for delirium every day.
2. Use a multimodal protocol (e.g. ABCDEF bundle) focused on non-pharmacologic interventions in all patients to reduce delirium.
3. Generally avoid pharmacologic interventions to reduce delirium:
   - Medications should generally be reserved for the short-term treatment of clinically important delirium symptoms

Pharmacologic Intervention

Maldonado, *Crit Care Clin* 2008



Delirium Pharmacological Prevention: Critically Ill Adults

Question:
Should a pharmacologic agent (versus no use of this agent) be used to ***prevent*** delirium in ***all*** critically ill adults?

Rationale: 3 RCTs, 1283 pts

Significant reduction in delirium incidence favoring the pharmacologic agent:

- **Haloperidol*** (457 pts), RR 0.66; 95% CI, 0.45 to 0.97; low quality
- **Risperidone** (126 pts), RR 0.35; 95% CI, 0.16 to 0.77; low quality
- **Dexmedetomidine**** (700 pts), OR 0.35; 95% CI, 0.22 to 0.54; low quality

****Su et al Dexmed for prevention of delirium in elderly patients after non-cardiac surgery. *Lancet* 2016 low severity of illness; only surgical pts, assessing short-term outcomes; cost & side effects**

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

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, Cliona 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

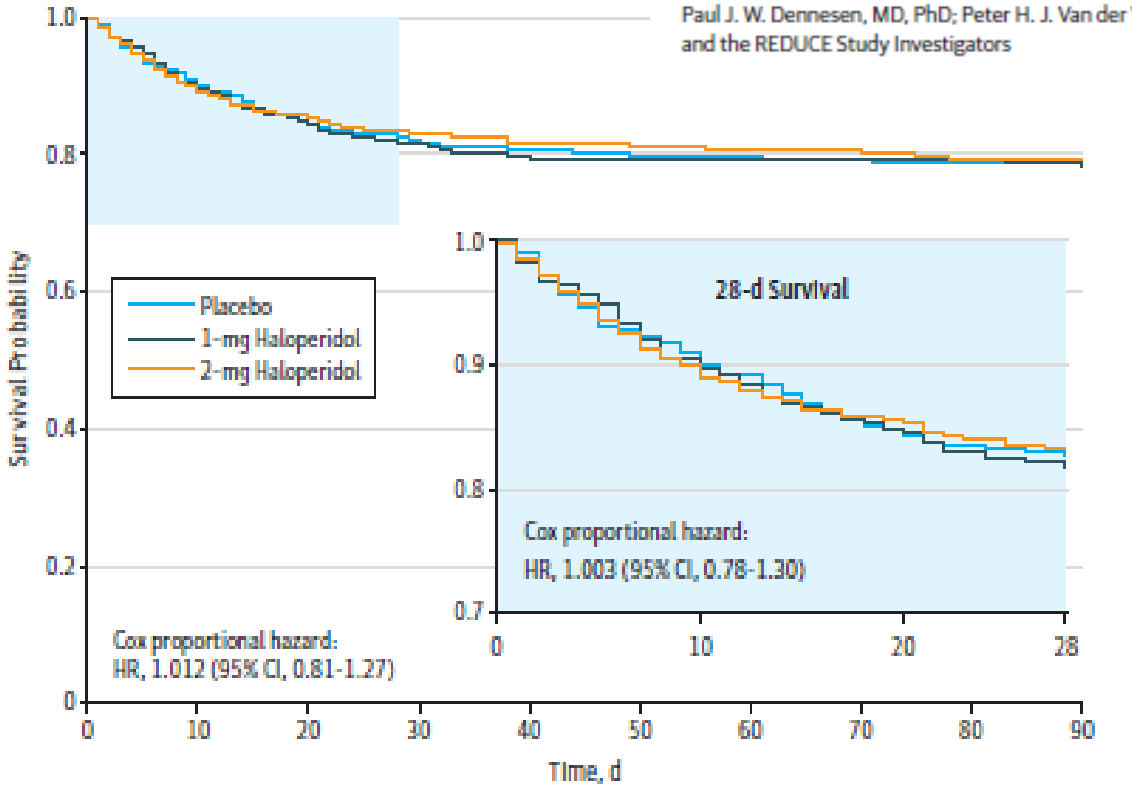
No difference in delirium incidence between haloperidol (1 mg IV q6h or 2mg IV q6h) and placebo

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



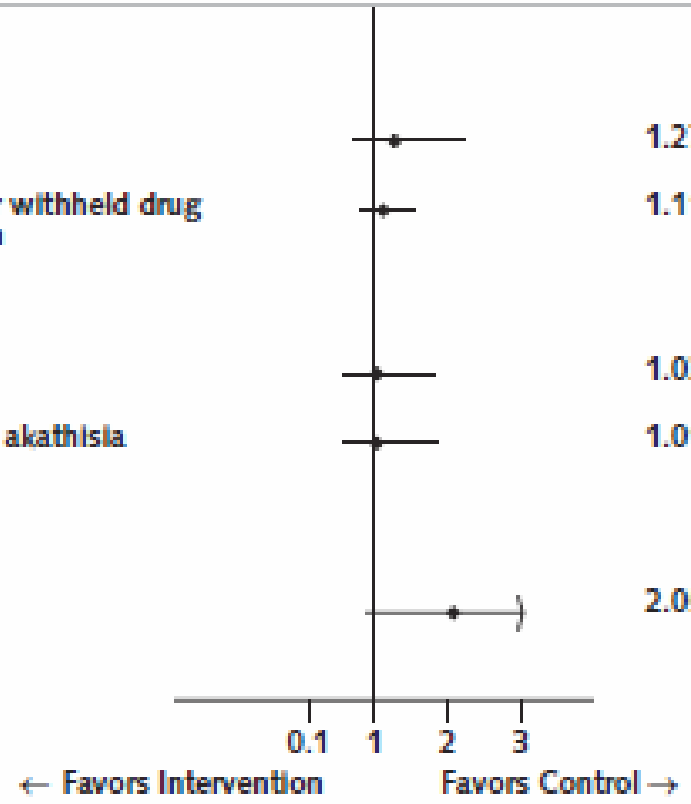
No. at risk										
Placebo	707	644	600	580	571	565	563	559	557	556
1-mg Haloperidol	350	317	297	285	279	278	278	278	277	276
2-mg Haloperidol	732	658	627	609	599	595	591	589	582	579

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 Meta-analysis	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

Dexmedetomidine to Improve Sleep

Rationale:

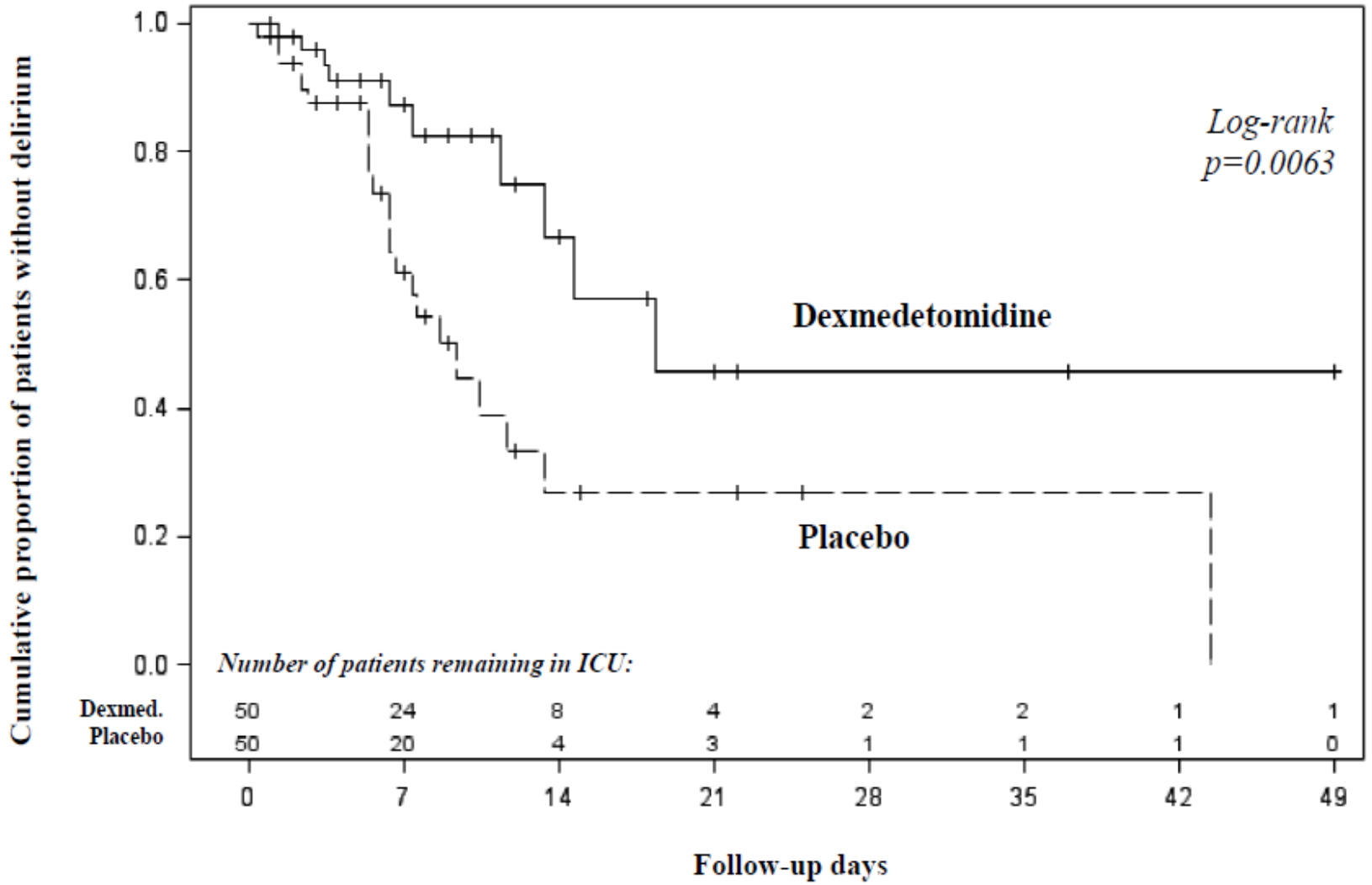
- 2 RCTs (n=74)
  - 1 RCT evaluated MV adults requiring sedation
  - 1 RCT in non-MV adults
- Significant increase in Stage 2 sleep
  - Mean difference = + 47.85% min (95% CI, 24.05-71.64)
- Significant decrease in Stage 1 sleep
  - Mean difference = - 30.37% min (95% CI, -50.01 to -10.73)
- No effect on sleep fragmentation or % time spent in REM sleep
- *Neither delirium, duration of MV, ICU LOS or patient preference evaluated in either RCT
- Concerns about generalizability to all ICU adults, hemodynamic effects, and cost in terms of using dexmedetomidine to ONLY improve sleep (vs. when an IV sedative is needed)

Recommendation:

We make no recommendation regarding the use of dexmedetomidine 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

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



No difference in LEEDS Sleep Score between groups

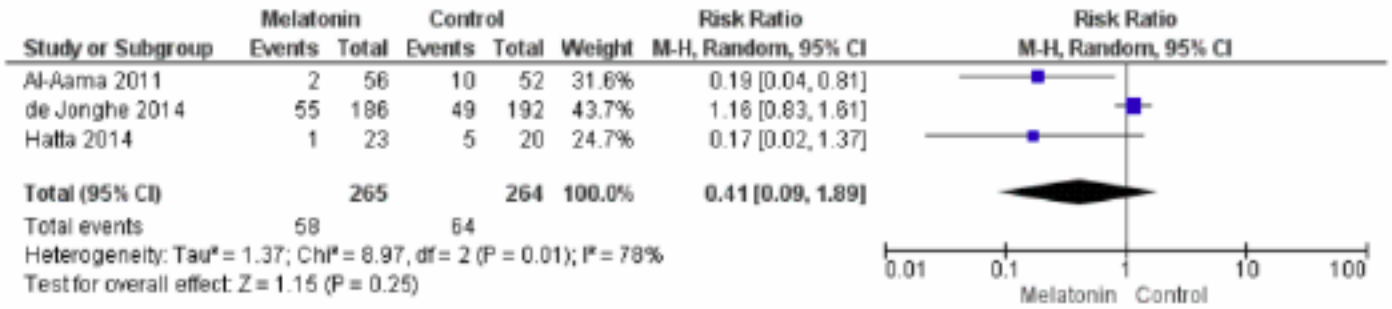
Skrobik Y, Duprey M, Hill NS, Devlin JW. AJRCCM 2018

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

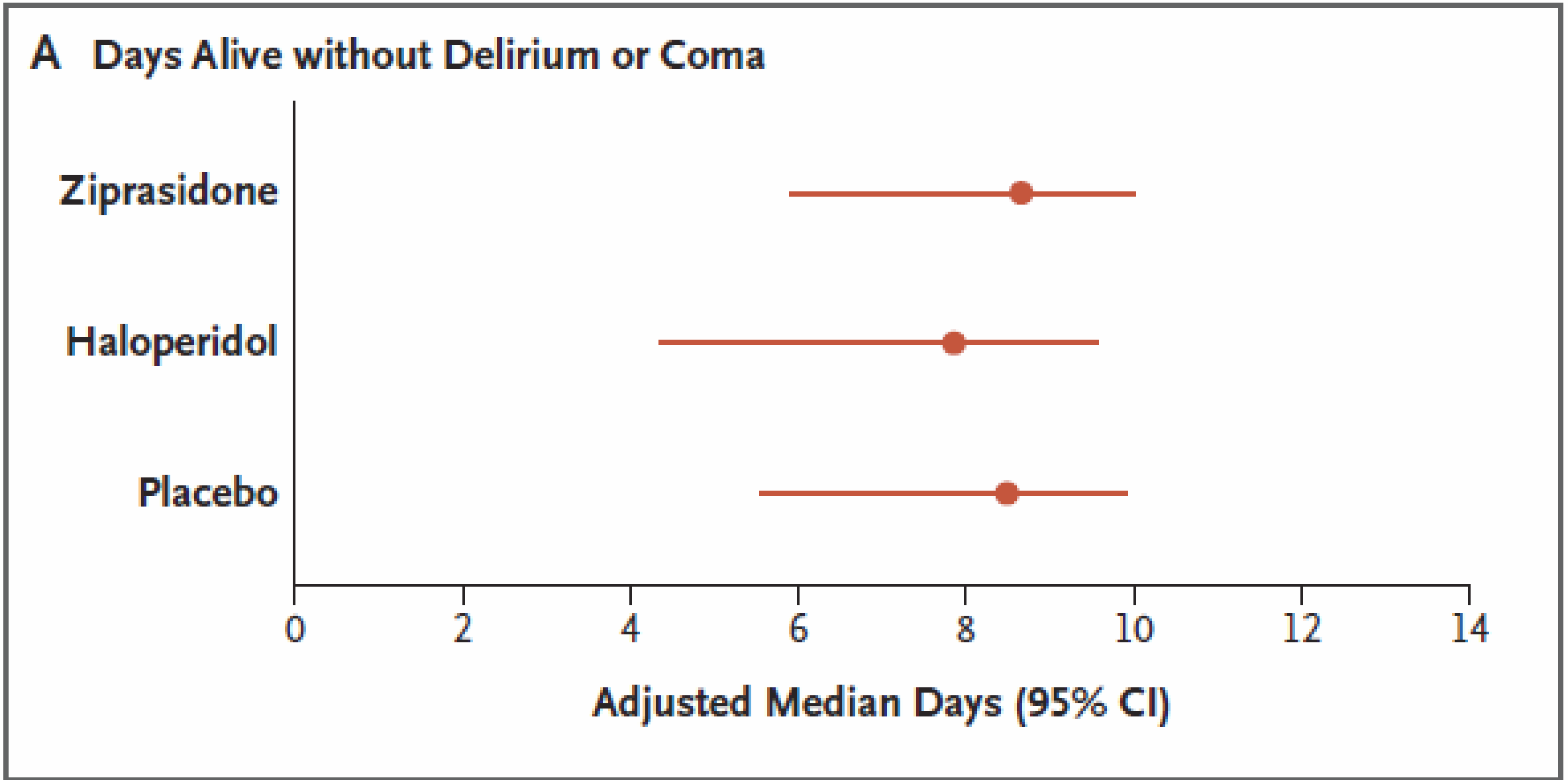
Delirium Pharmacological Treatment

PICO Question		
P	Critically ill adult patients in an ICU	
I	• Haloperidol	• Atypical antipsychotic
	• Statin	• Dexmedetomidine
C	No use of the medication	
O	• Delirium duration	• Duration of mechanical-ventilation
	• ICU LOS	• Mortality

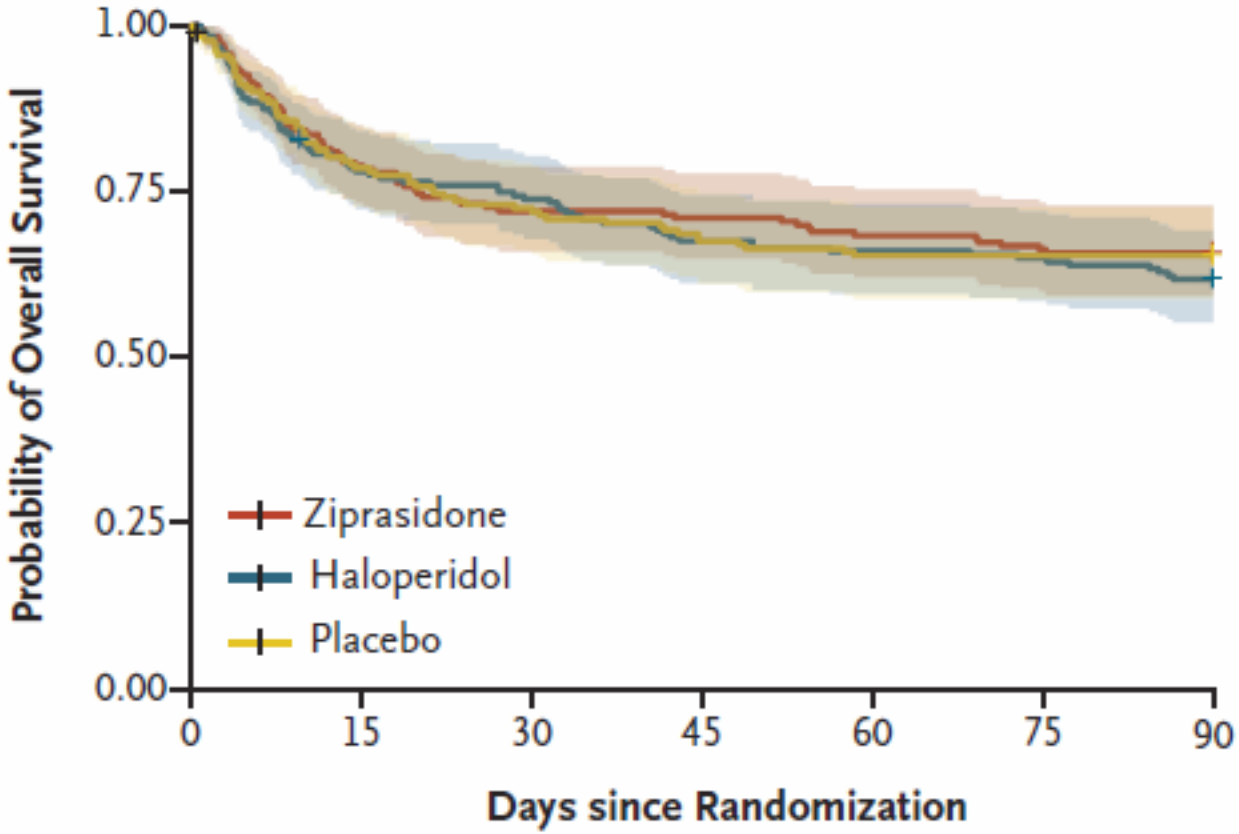
Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness

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 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%)**

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).

Medication Overload: America's Other Drug Problem

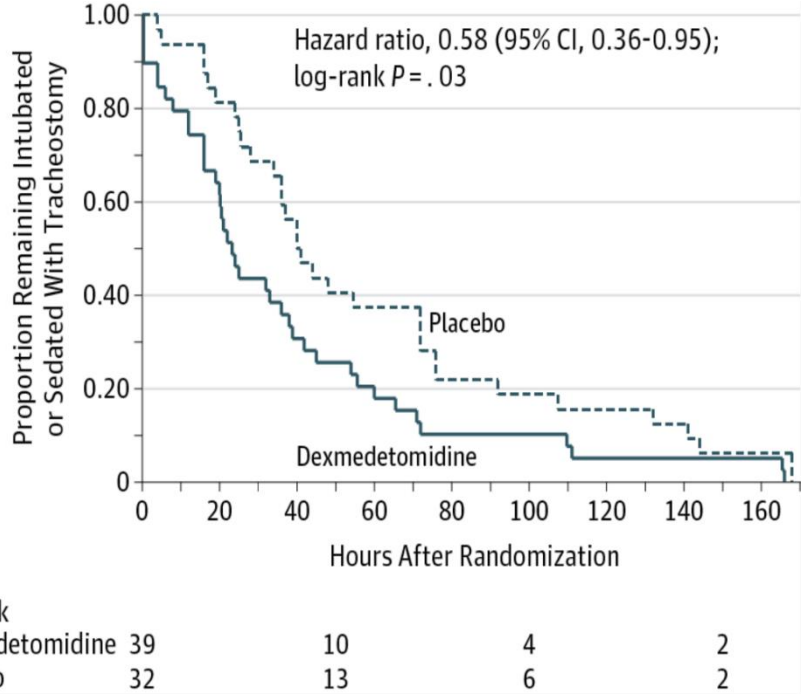
How the drive to prescribe is harming older adults

LOWN INSTITUTE

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).

The 3 Most Important Strategies to Reduce Delirium in the ICU

1. **Recognize and reduce modifiable risk factors for delirium every ICU day.**
2. **Use a multimodal protocol (e.g. ABCDEF bundle) focused on non-pharmacologic interventions in all ICU patients to reduce delirium.**
3. **Generally <u>avoid</u> pharmacologic interventions to reduce delirium in the ICU:**
   - **Medications should generally be reserved for the short-term treatment of clinically important delirium symptoms**

ICU memories

QUALITY OF LIFE

ICU Survival

ABCDEF Bundle

Depression

ICU Survivorship

Return to Independence

Persistent Cognitive Defects

Executive Function

Family stress

Reduced Functionality

PTSD