A New Frontier In Critical Care: Saving the Injured Brain

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Disclosures

- Physician-scientist, Vanderbilt University, Nashville TN, USA
- Honoraria from Pfizer, Orion for CME Activities
- Consulting with Philips and Masimo
- PI for MIND-USA and SCCM’s ICU Liberation
- NIH and VA U.S. Federal Funding
Over 20 Years of Research at Vanderbilt and VA

1998-2019...
Strange to say, he seemed immediately to have become perfectly calm; not a trace of his recent delirium nor of the panic fear that had haunted him of late. It was the first moment of a strange sudden calm.

In *Crime and Punishment*, Dostoyevsky used "delirium" 31 times.
Long-Term Cognitive Impairment after Critical Illness


ABSTRACT

BACKGROUND
Survivors of critical illness often have a prolonged and disabling form of cognitive impairment that remains inadequately characterized.
The Picture of Dementia Following ICU Care

![Box plot chart showing RBANS Global Cognitive Score for different groups and time points.](chart.png)
Who gets this dementia?

NIH parlance: ADRD

Alz Dz, Vascular, Lewy Body, Mixed, Frontotemporal, Creutzfeldt-Jakob, NPH, Parkinson’s, Huntington’s, Wernicke-Korsakoff, and Post-Critical Illness ADRD (?)
Hospitalization

Figure 2: Rate of decline in global cognition in those who had hospitalization (before and after) or no hospitalization.

Blue line indicates mean slope before hospitalization and red line indicates mean slope after hospitalization in a person who was hospitalized, compared to the average slope in a person who was not hospitalized (black line). Dotted line indicates mean time of hospitalization. Break in line after average time of hospitalization indicates lack of observation immediately after hospitalization (mean 213 days between hospitalization and subsequent cognitive assessment).
Elective vs Emergent Hospitalization

**Figure 2** Rate of decline in global cognition in those who had hospitalization (before and after) or no hospitalization

**Figure 3** Rate of decline in global cognition in those who had elective hospitalization, nonelective hospitalizations, or no hospitalization

Blue line indicates mean slope before hospitalization and red line indicates mean slope after hospitalization in a person who was hospitalized, compared to the average slope in a person who was not hospitalized (black line). Dotted line indicates mean time of hospitalization. Break in line after average time of hospitalization indicates lack of observation immediately after hospitalization (mean 213 days between hospitalization and subsequent cognitive assessment).

Green lines indicate mean slopes before (dashed) and after (solid) the mean time of hospitalization in a person experiencing an elective hospitalization, and red lines indicate mean slopes before and after hospitalization for a person experiencing a nonelective hospitalization, compared to average slope in a person who was not hospitalized (black). Break in the after average time of hospitalization indicates lack of observation immediately after hospitalization (mean 213 days between hospitalization and subsequent cognitive assessment).

James et al, Neurology 2019;92:1-10
mindUSA
modifying the impact of ICU-associated neurological dysfunction
Haloperidol Use for Delirium in the ICU became usual care

Fall 2018, Mastering Intensive Care podcast producer Dr. Andrew Davies, Melbourne Australia
1st Report of Haldol for ICU Delirium
40 years ago...1978

No. 395
INTRAVENOUS USE OF HALOPERIDOL FOR ACUTE DELIRIUM IN INTENSIVE CARE SETTINGS

Ned. H. Cassem, M.D. (M), Chief, Psychiatric Consultation-Liaison Service, Massachusetts General Hospital, Boston

SUMMARY:
Patients recovering from cardiac surgery occasionally become so delirious and agitated that immediate tranquilization is necessary. In a series of 15 patients the use of intravenous haloperidol was studied. All patients had indwelling arterial, left atrial, Swann-Ganz, and central venous pressure lines, two pacing wires each in right atrium and left ventricular, foley catheter, one or more peripheral venous lines, and often the
Haloperidol Use for Delirium in the ICU became usual care

Recommendations: Haloperidol is the preferred agent for the treatment of delirium in critically ill patients. (Grade of recommendation = C)
Global use of Haloperidol for ICU Delirium

- Africa
- Asia
- Europe
- North America
- Oceania
- South America

Morandi A. Crit Care Med 2017;45:e1111-22
Risk of Death in Elderly Users of Conventional vs. Atypical Antipsychotic Medications

Philip S. Wang, M.D., Dr.P.H., Sebastian Schneeweiss, M.D., Jerry Avorn, M.D., Michael A. Fischer, M.D., Helen Mogun, M.D., and M. Alan Bloch, M.D.

Schneider LS, JAMA 2005;294:1934-43

Risk of Death With Atypical Antipsychotic Drug Treatment for Dementia
Meta-analysis of Randomized Placebo-Controlled Trials

Lou S. Schneider, MD, MS
Karen S. Dagerman, MS
Philip Insel, MS

Wang PS, NEJM 2005;353:2335-41
Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness


Girard TD, et al. NEJM 2018;379:2506-16
Haloperidol
mainly blocks DA

D2 antagonism

Traditional Teaching: “Dopamine blockade in the cerebral cortex improves cognition and reduces delirium.”

Ziprasidone
blocks 6 receptors, agonist at 1

5-HT2A
5-HT1A agonist
5-HT2C
5-HT1D
D2
α1
H1
α2
# MIND-USA: Baseline Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo N=184</th>
<th>Haloperidol N=192</th>
<th>Ziprasidone N=190</th>
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<tbody>
<tr>
<td>APACHE II</td>
<td>30</td>
<td>28.5</td>
<td>28</td>
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<tr>
<td>SOFA</td>
<td>11</td>
<td>11</td>
<td>10</td>
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<tr>
<td>Mechanical Ventilation</td>
<td>175 (95%)</td>
<td>185 (96%)</td>
<td>185 (97%)</td>
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<tr>
<td>Shock on Pressors</td>
<td>65 (35%)</td>
<td>58 (30%)</td>
<td>64 (34%)</td>
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<tr>
<td>Medical / Surgical ICU</td>
<td>72% / 28%</td>
<td>73% / 27%</td>
<td>71% / 29%</td>
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<td>Admission Diagnoses</td>
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<tr>
<td>ARDS or Sepsis</td>
<td>74 (40%)</td>
<td>87 (45%)</td>
<td>68 (36%)</td>
</tr>
<tr>
<td>COPD, CHF, Cirrhosis</td>
<td>35 (19%)</td>
<td>29 (15%)</td>
<td>37 (19%)</td>
</tr>
<tr>
<td>Other Diagnoses</td>
<td>75 (41%)</td>
<td>76 (40%)</td>
<td>85 (45%)</td>
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</table>
MIND-USA: primary outcome

A: Delirium/Coma-Free Days
- Ziprasidone
- Haloperidol
- Placebo

B: Delirium Days
- Ziprasidone
- Haloperidol
- Placebo

C: Coma Days
- Ziprasidone
- Haloperidol
- Placebo

Adjusted Median Days (95% Confidence Interval)
MIND-USA: 90-Day Survival

Kaplan-Meier Curve, 90-Day All-Cause Death

Probability of Overall Survival (%)

Number at risk (cumulative number of deaths)

- Ziprasidone: 190 (9), 150 (49), 137 (53), 136 (55), 130 (66), 126 (64), 125 (65)
- Haloperidol: 192 (9), 169 (42), 141 (50), 129 (62), 126 (59), 126 (57), 118 (73)
- Placebo: 184 (9), 143 (39), 132 (39), 120 (53), 119 (63), 119 (63), 119 (63)

Days after Randomization
MIND-USA: Key 2° Outcomes

A: Liberation from MV

B: ICU Discharge

C: ICU Readmission

D: Hospital Discharge

Days after Randomization
MIND-USA: Hypoactive Delirium

Duration of Hypoactive Delirium by Treatment

Kruskal-Wallis test: $X^2 = 0.16; df = 2; P = 0.92$

Treatment vs Duration of Hypoactive Delirium

Adj P = 0.62
MIND-USA: Hyperactive Delirium

Duration of Hyperactive Delirium by Treatment

Kruskal-Wallis test: $X^2 = 0.89$, df = 2; $P = 0.64$

Treatment vs Duration of Hyperactive Delirium

Adjusted analysis using proportional odds logistic regression.

Adj $P = 0.58$
A long habit of not thinking a thing wrong, gives it a superficial appearance of being right…”

Common Sense, Thomas Paine, c. 1776
ABCDEF Bundle: Science & Philosophy
(based on 40 Lancet, JAMA, NEJM papers + ~350 others)

• Analgesia: Assess, Prevent, Manage Pain
• Both SATs and SBTs: Stop Drugs, Stop Vent
• Choice of Analgesia and Sedation
• Delirium: Assess, Prevent, Manage
• Early Mobility and Exercise, Environment
• Family Engagement and Empowerment
A-E and A-F Bundle References

ABCDEF Bundle

2. Vasilevskis EE, Chest, 2010;138:1224-33
10. Barnes-Daly MA, Crit Care Med, 2017;45:171-78
14. Barnes-Daly MA, World Evid Based Nurs, 2018;15:206-16
15. Pun BT, Crit Care Med 2019;47:3-14
17. Balas MC, Crit Care Nurse 2019;39:46-60
Liberated...?
Liberated...
Early Mobility and Family in Poland:

Ventilated Patient and Her Husband with Shopping Cart

Ely EW CCM 2017;45:321-30
Courtesy of Dr. Kasia Kotfis in Szczecin, Poland
Mr. D and Wanda
Survival and Delirium-Coma Freedom
Implementing ABCDEF Bundle in >6,000 patients

Mortality Improvement

N = 6,064 subjects
OR = 1.15, p-value < 0.001

Delirium and Coma Freedom

N = 5,581 subjects
IRR = 1.15, p-value < 0.001

NOTE: Adjusted for age, APACHE III, and mechanical ventilation
7 California Hospitals, Interprofessional QI Implementation project

Barnes-Daly MA, CCM 2017;45:171-8
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, FCCM1; Michele C. Balas, PhD, RN, CCRN-K, FCCM, FAAN2-3; Mary Ann Barnes-Daly, MS, RN, CCRN-K, DC4; Jennifer L. Thompson, MPH5; J. Matthew Aldrich, MD6; Juliana Barr, MD, FCCM7,8; Diane Byrum MSN, RN, CCRN-K, CCNS, FCCM9; Shannon S. Carson, MD10; John W. Devlin, PharmD, FCCM11; Heidi J. Engel, PT, DPT12; Cheryl L. Esbrook, OTR/L, BCPR13; Ken D. Hargett, MHA, FAARC, FCCM14; Lori Harmon, RRT, MBA15; Christina Hielsberg, MA15; James C. Jackson, PsyD1; Tamra L. Kelly, BS, RRT, MHA4; Vishakha Kumar, MD, MBA15; Lawson Millner, RRT16; Alexandra Morse, PharmD4; Christiane S. Perme, PT, CCS, FCCM14; Patricia J. Posa, BSN, MSA, CCRN-K17; Kathleen A. Puntillo, PhD, RN, FAAN, FCCM18; William D. Schweickert, MD19; Joanna L. Stollings, PharmD, FCCM20; Alai Tan, PhD2; Lucy D’Agostino McGowan, PhD21; E. Wesley Ely, MD, MPH, FCCM1,22
ICU Liberation Hospitals and Regions
ICU Liberation Collaborative

- Gordon Moore Foundation (Intel Billionaire)
- SCCM (Sepsis, ICU Liberation, Thrive)
- Aug 2015 to April 2017
- 68 Adult American ICUs, 10 Pediatric
- Medical, Surgical, Cardiac, Neuro ICUs
- ABCDEF Bundle implementation
- 15,226 patients
- All regression models adjusted for 18 confounders chosen *a priori*
ABCDEF bundle performance... improves ICU discharge
ABCDEF bundle performance... improves hospital discharge
Performance...reduces death
Performance improves... coma, delirium, restraints

[Graph showing the adjusted probability of outcomes for coma, delirium, and physical restraints as a function of the percent of eligible ABCDEF bundle elements performed.]
Performance reduces... ICU readmission and NH transfers
Future Directions
Mobilizing the Brain with Sudoku & Scrabble
Providing Lux to Restore Circadian Rhythm

VitalSky Basic

VitalSky Advanced
Clarifying the Relationship between Delirium and ADRD (NIA PAR-18-029)

Study Overview

<table>
<thead>
<tr>
<th>Patient Timeline</th>
<th>ICU</th>
<th>Year 1</th>
<th>Year 10</th>
<th>Year 15</th>
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<td>Risk Factors, Diagnostic Tools, Mechanistic Paths, Phenotypes, Histopathology</td>
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**Aim 1:** 10+ Year Clinical Dementia Assessments
- **Original Cohort**
  - BRAIN-ICU-1 (2013 NEJM)
- **Extended Cohort**
  - Vanderbilt Funded
- **Extended Cohort**
  - BRAIN-ICU-1

**ICU patients**

With and Without Delirium

**Aim 2:** ADRD Mechanism with Biomarkers: MRI, Plasma, CSF
- **New Cohort**
  - Vanderbilt & Rush Univ.

**Aim 3:** Acute and Chronic Neuropathology Profiles
- **New Cohort**
  - Vanderbilt & Rush Univ.

Extended Cohort
- **BRAIN-ICU-2**
  - 2023 Grant Renewal

Legend: *This RO1 Proposal (2019-2023)
### CIBS Collaborators

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<tr>
<th>Surgery</th>
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<th>Biomedical Informatics</th>
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