

## Approaching Intensive Care Unit Delirium

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### Disclosure

- I do not have any relevant financial or non-financial disclosures
- Some medications will be discussed for non-FDA labeled indications

#### Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

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- Red font and quotations will be used to reference the guidelines.
- Grades for recommendations will appear in parentheses
  - Letters A, B, C, D, and E denote quality of evidence, with A being the strongest
  - Strength of the recommendation from the as "1" strong or "2" weak
  - The direction of the recommendation is denoted as "+" for and "-" against

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

### Objectives

- Discuss the impact of intensive care unit (ICU) delirium on patient outcomes
- Outline strategies for prevention and management of ICU delirium

### Defining delirium

Delirium is defined as a disturbance of consciousness that is accompanied by a change in cognition that cannot be better accounted for by a preexisting or evolving dementia" - American Psychiatric Association

Morandi A, et al. Intensive Care Med. 2008; 34:1907-1915. Diagnostic and Statistical Manual of Mental Disorders - 4th Ed. 2000

### Delirium across continuum of care

**Prevalence of delirium**

- Emergency room (8% to 19%)
- Acute care setting (30%)
- ICU (20% to 60%)
  - 19% in the first 24 hours
  - 32% each ICU day
  - 63% to 88% of those who are mechanically ventilated

Time Point	Without Dementia (%)	With Dementia (%)
On Admission	26.4	41.7
By End of ICU Period	59.8	66.7
By End of Post-ICU Period	63.4	86.1

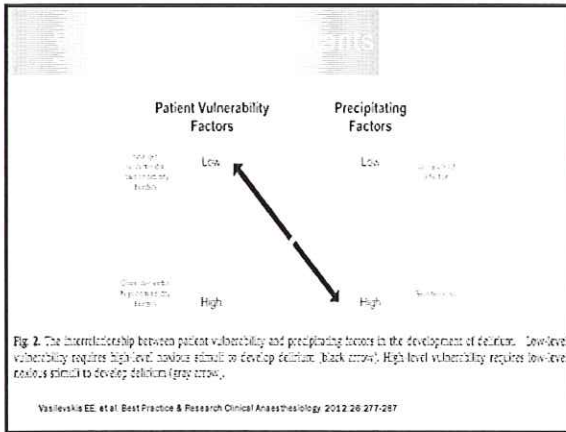
Mitchell L, et al. JGIM. 2003; 18:597-608 (figure); Han J, et al. Acad Emerg Med. 2009; 16:129-130; Neugott SL, et al. Ann Emerg Med. 1995; 25: 755-758; Han JH, et al. Ann Emerg Med. 2003; 41:622-647; Parsons J, et al. JAMA. 2005; 293(10): 1297-1305; By DM, et al. JAMA. 2005; 293(10): 1297-1305; By DM, et al. Intensive Care Med. 2002; 27:1892-1899; By DM, et al. JAMA. 2004; 291:1733-1742; Lari J, et al. Crit Care Med. 2009; 37:1888-1905; Pun BT, et al. Crit Care Med. 2009; 37:1379-1389; Thacker R, et al. General Hospital Psychiatry. 2003; 32:407-411; Bellu J, et al. Critical Care. 2003; 7:R152; van den Broek P, et al. Crit Care. 2003; 7:R154

### Risk factors

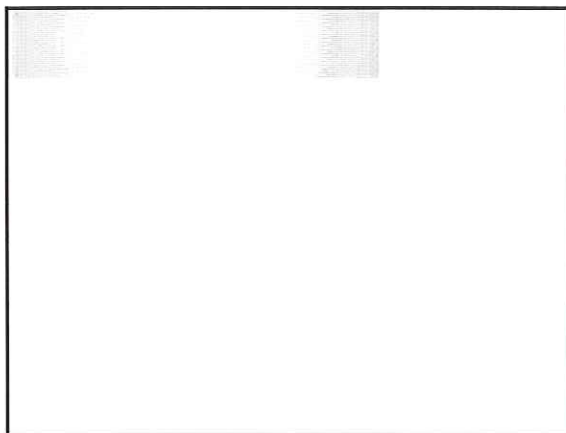
- Baseline vulnerability
- Precipitating events

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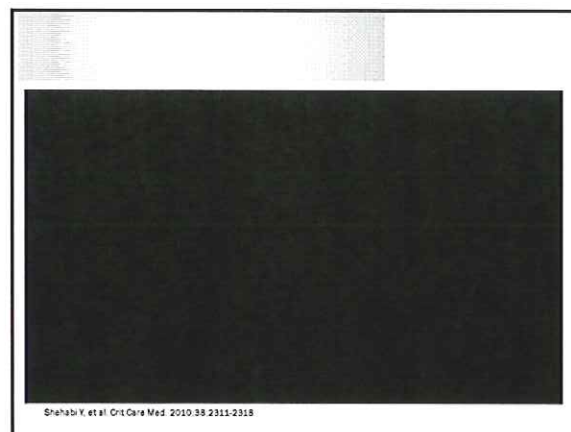
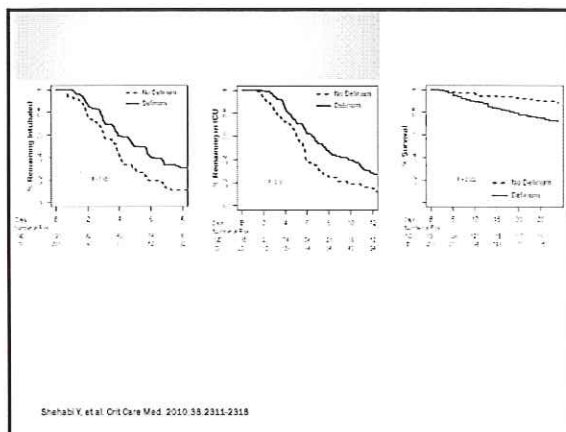
    graph LR
      A[Risk factors] --> B[Patient outcomes]
      B --> C[Prevention]
      C --> D[Treatment]
  
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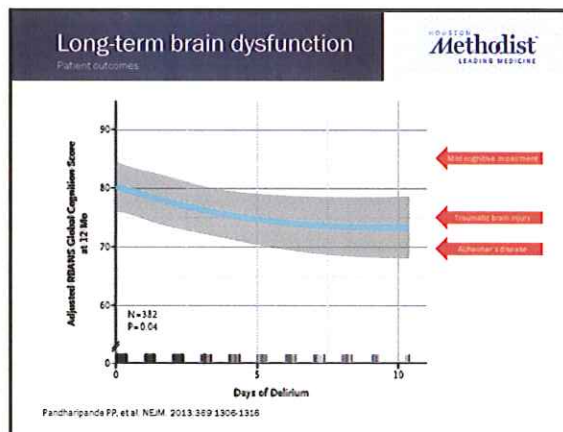
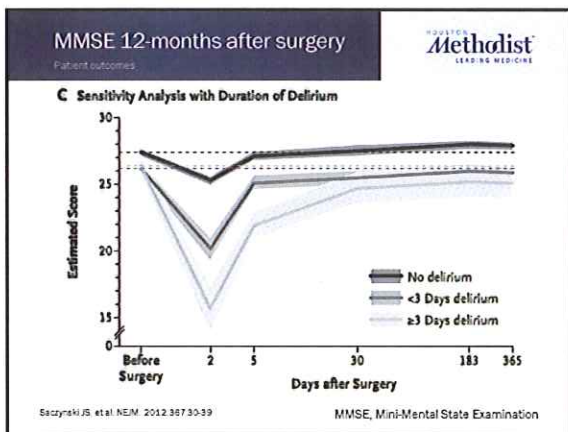


- Genetics
  - Demographics
    - Advanced age
    - Visual impairment
  - Chronic conditions
    - Pre-existing Dementia
    - Alcoholism
    - History of hypertension
    - Depression
    - Malnutrition
    - Home use of opioids, benzodiazepines, or anticholinergics
  - Acute conditions
    - High severity of illness at admission
    - Coma
    - Acute kidney injury or liver failure
    - Dehydration
    - Electrolyte or pH abnormalities
    - Infection
    - Central nervous system insults or seizures
  - Medications
    - Benzodiazepines
    - Conflicting data on risk of opioid therapy and propofol
    - Benzodiazepine or ethanol withdrawal
    - Diphenhydramine and anticholinergics
  - Environmental
    - Immobility
    - Procedures such as catheter insertion
    - Lack of sleep
    - Overstimulation
    - Lack of environmental orientation
- Ely EW, et al. JAMA. 2004;291:1753-1762; Piani MA, et al. Am J Respir Crit Care Med. 2009;180:1092-1097; Vasilevska EE, et al. Crit Care Med. 2012;38:5683-5691; Van den Broek P, et al. BMJ. 2012;344:e100; Barr J, et al. Crit Care Med. 2013; 41:293-300; Vasilevska EE, et al. Best Practice & Research Clinical Anaesthesiology. 2012;26:277-287



- Prolonged ICU stay
  - Prolonged mechanical ventilation
  - Increased hospital stay
  - Increased mortality
  - Post-ICU cognitive impairment
  - Increased catheter removal and self-extubation
- Ely EW, et al. JAMA. 2004;291:1732-1742; Shehabi Y, et al. Crit Care Med. 2010;38:2311-2318  
 Gined TD, et al. Crit Care Med. 2010;38:1513-1520; Barr J, et al. Crit Care Med. 2013; 41:263-306



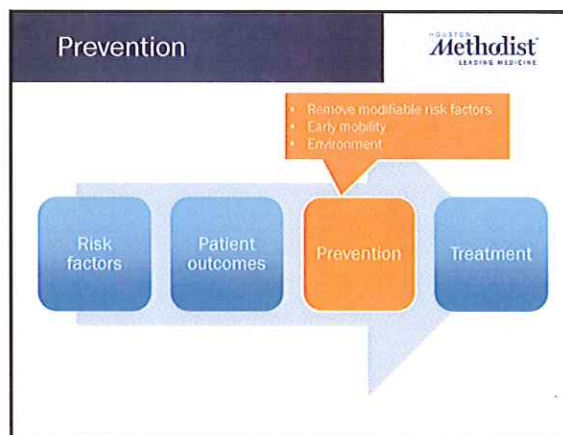


### Question for audience

Methodist LEADING MEDICINE

Which of the following is associated with ICU delirium?

- A. Decreased ICU length of stay
- B. Decreased hospital length of stay
- C. Decreased mortality
- D. Longer duration of mechanical ventilation**



### ABCDE

Delirium prevention

Methodist LEADING MEDICINE

- **A**wakening & **B**reathing **C**oordination
  - Conduct spontaneous awakening trials (SATs) and spontaneous breathing trials (SBTs) daily (+1B)
- **C**hoice of sedative
  - Avoid benzodiazepines if possible (+2B)
  - Use the lowest dose of sedations possible (+1B)
- **D**elirium monitoring
  - Screen for delirium using the CAM-ICU q12 h (A)
  - THINK! about common causes of delirium
- **E**xercise/**E**arly mobility

Vasilevskia EE, et al. Crit Care Med. 2010;38:5683-5691. Barr J, et al. Crit Care Med. 2013;41:263-308

### “THINK” delirium!

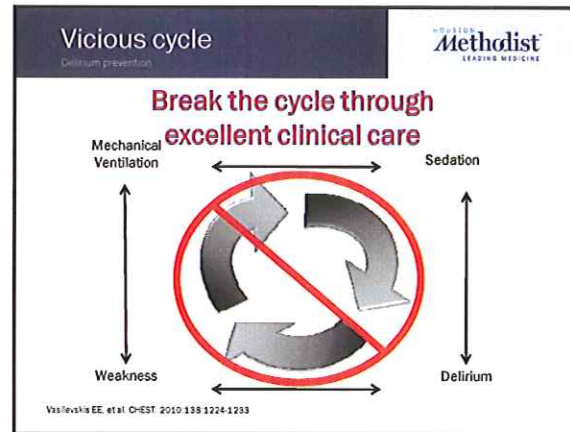
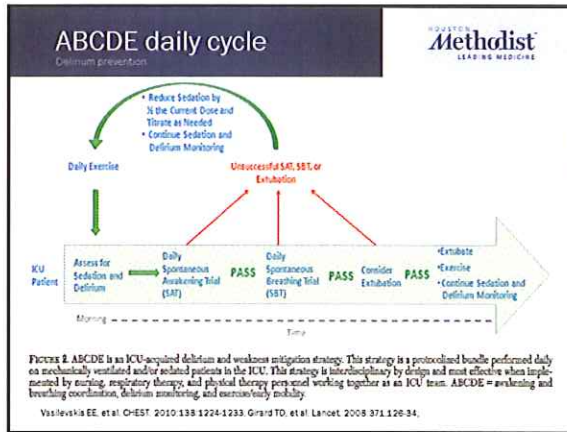
Delirium prevention

Methodist LEADING MEDICINE

- Toxic situations and medications
- Hypoxemia/Hypoglycemia
- Infection/sepsis/inflammation/immobility
- Nonpharmacological interventions
- K<sup>+</sup> (potassium) and other electrolytes

*Acronym to help you remember common modifiable risk factors that can be addressed in a newly delirious patient*

Bilas MD, et al. Critical Care Nurse. 2012;32:40-48



- ### Optimize sedation
- Delirium prevention
- Consider non-benzodiazepine-based sedation (dexmedetomidine or propofol) instead of benzodiazepines (+2B)
  - Target light sedation (RASS 0 or -1) (+1B)
  - Conduct SATs and SBTs daily (+1B)
  - Consider analgesia-first sedation to decrease sedative exposure (+2B)
- Barr J, et al. Crit Care Med. 2013; 41:263-306

- ### Minimize potentially harmful medications
- Delirium prevention
- \*Caution: There is controversy concerning which medications actually cause ICU delirium\*
- \*Acute care data may not accurately reflect the ICU\*
- Benzodiazepines (diazepam, lorazepam, and midazolam)
  - Opioids (morphine, hydromorphone, and fentanyl)
  - Anticholinergics (diphenhydramine and famotidine)
  - Muscle relaxants (carisoprodol and cyclobenzaprine)
  - Corticosteroids (can impair the sleep-wake cycle)
  - Metoclopramide

### Haloperidol data conflicts

Delirium prevention

Randomized trials of haloperidol for delirium prevention

Study	Intervention	Control	Population	Median APACHE II	Incidence of Delirium	ICU hours
Al-Qadheeb, 2013	Haloperidol 1mg IV q8 hours (n=24)	Placebo (n=34)	Subsyndromal delirium, 71% medical	20	≈ (35% vs. 23%)	n/a
Wang, 2012	Haloperidol 0.1 mg/h infusion x 12 hours (n = 229)	Placebo (n = 228)	>65y/o after noncardiac surgery	9	↓ (15% vs. 23%)	↓ (21 vs. 13)

Low severity of illness      Average of 1 ICU day

Not enough evidence to support haloperidol prophylaxis

Wang W, et al. Crit Care Med. 2012;40:1-9. Al-Qadheeb N, et al. Critical Care Medicine. 2013;41(12):abstract482

- ### Improve sleep quality
- Delirium prevention
- Sleep deprivation is common in the ICU
    - Impaired wound healing and cellular immune function
    - Potential cause of delirium and physiologic stress
  - Promote sleep in adult ICU patients (+1C)
    - Control light and noise
    - Cluster nursing activities to provide uninterrupted time at night
    - Decrease stimuli at night (eye masks & ear plugs)
- Barr J, et al. Crit Care Med. 2013; 41:263-306




### Sleep hygiene

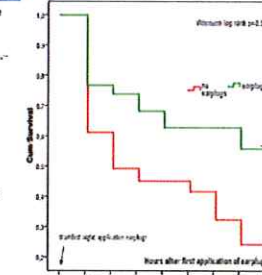
Delirium prevention

**RESEARCH** *Open Access*

The effect of earplugs during the night on the onset of delirium and sleep perceptions: a randomized controlled trial in intensive care patients



- RCT of 136 non-delirious patients with an expected ICU LOS > 24 hours
- Intervention was earplugs at night from 22:00 to 6:00
- Primary outcome was a decreased incidence of delirium or confusion

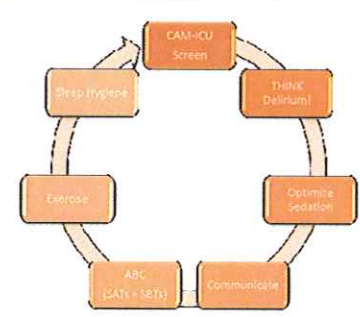


with earplugs	48	31	21	14	8	4	2
without earplugs	47	30	20	13	7	4	2

Van Rompaey Critical Care 2012, 18:R73  
Eye mask photo: [http://www.matsys.co.uk/media/catalog/product/cache/1/image/700x/907/849/3302567056495827336495/4\\_5/450\\_e.jpg](http://www.matsys.co.uk/media/catalog/product/cache/1/image/700x/907/849/3302567056495827336495/4_5/450_e.jpg)

### Cycle should occur every shift


Delirium prevention



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### Treatment

Delirium prevention



- Non-BZD sedation
- Antipsychotics are controversial

### Recommendations

Pharmacologic treatment

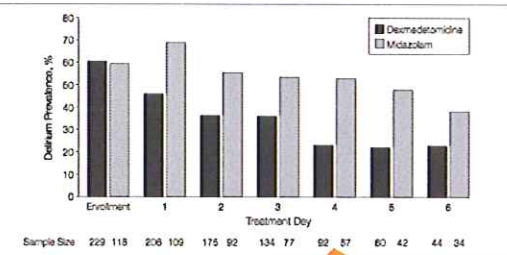
- Non-benzodiazepine based sedation
- "Atypical antipsychotics may reduce the duration of delirium in adult ICU patients (C)"
  - Not recommended in patients at significant risk for torsades de pointes (-2C)
  - Only a few small trials have been conducted (e.g. Devlin 2010)
  - Only consider after all other interventions have been attempted
- Do not use rivastigmine (-1B) (may increase mortality)

Bar-J, et al. Crit Care Med 2013; 41:263-306  
van Eijl, et al. Lancet 2010; 376:1829-1837

### Dexmedetomidine

Pharmacologic treatment

**Figure 2. Daily Prevalence of Delirium Among Intubated Intensive Care Unit Patients Treated With Dexmedetomidine vs Midazolam**



Treatment Day	Dexmedetomidine (%)	Midazolam (%)
Enrollment	~60	~60
1	~55	~70
2	~45	~55
3	~40	~55
4	~25	~55
5	~25	~55
6	~25	~45

Sample Size: Enrollment (229/118), Day 1 (208/109), Day 2 (175/92), Day 3 (134/77), Day 4 (92/57), Day 5 (60/42), Day 6 (44/34)

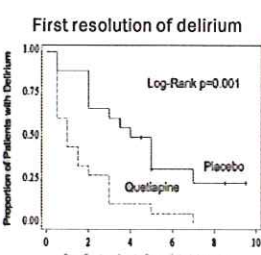
Riker FR, SEDCOM trial. JAMA. 2009;301:489-499

Was treatment effect from (1) giving DEX or (2) removing midazolam?

### Quetiapine in 36 patients

Pharmacologic treatment

**First resolution of delirium**




Log-Rank p=0.001

Outcome	Quetiapine (n=18)	Placebo (n=18)	P value
Hours of delirium, median	36	120	0.006
Recurrence of delirium after initial resolution	22%	44%	0.29
Hours of agitation, median	6	36	0.02

Devlin JW, et al. Critical Care Medicine. 2010;38:419-427

### No HOPE for haloperidol

Pharmacologic treatment




- January 2013: "There is no published evidence that treatment with haloperidol reduces the duration of delirium in adult ICU patients (No evidence)"
- September 2013: HOPE-ICU study found no benefit from haloperidol for the prevention/treatment of delirium
  - No benefit for prevention/treatment of delirium
  - May prevent/treat acute episodes of agitation

	Haloperidol (n=71)	Placebo (n=70)	p value
Alive, delirium-free, coma-free days in first 14 days*	5 (0 - 10)	6 (0 - 11)	0.53
Days in delirium	5 (2 - 8)	5 (1 - 8)	0.99
28-day mortality	28%	27%	n/a


\* Primary outcome. Study planned to enroll 128 patients to detect a 2 day reduction in delirium days  
 Bart J, et al. Crit Care Med. 2013. 41: 263-306. Page VI, et al. Lancet Respiratory Medicine. 2013. 1: 515-523

### Ongoing trials



- Wes Ely - MIND-USA (NCT01211522): RCT (n~800) from 2011 to 2016 comparing haloperidol, ziprasidone, and placebo for 14-day delirium/coma free days
- Pratik Panharipande - MENDS II (NCT01739933): RCT (n~500) from 2012 to 2018 comparing dexmedetomidine to propofol for 14-day delirium/coma free days
- Yoanna Skrobik - SKY-DEX (NCT01791296): RCT (n~100) from 2011 to 2014 comparing nighttime infusion of dexmedetomidine to placebo for incidence of delirium

### Acknowledgments



- Publicly available educational material from [www.icudelirium.org](http://www.icudelirium.org) was used to develop this presentation.

