Recognizing and Managing Delirium

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Disclosures

- No conflicts of interest for this talk
- No financial relationships in past 3 years
- **Use of non-FDA approved pharmacologic agents** will be referenced
- Chair: **Johns Hopkins Delirium Consortium**
- Past President: **American Delirium Society (ADS)**
- Chair: **Advisory Board to ADS**

Overview & Objectives “Getting our Ducks in a Row”

After this lecture, attendees will be able to:

- Define delirium and related conditions
- Describe common short- and long-term outcomes
- List major predisposing & precipitating factors of delirium
- Discuss prevention/management
  - Pharmacologic
  - Non-pharmacologic strategies

Look for the baby duck slides!

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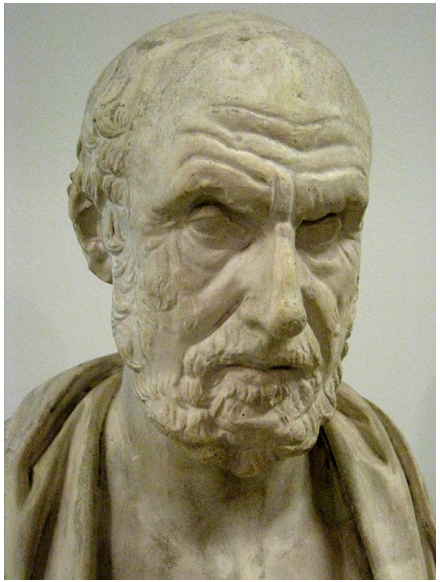
History of the Syndrome of Delirium
"The Top-Down View"



Hippocrates 460 - 370 BC

- ~ 2500 years ago
- Described: phrenitis (& lethargus)
- An acute disorder
- Associated with fever
- Problems with cognition, behavior
- Disrupted sleep & unstable moods

Remarkably consistent clinical description of the syndrome

Definition of Delirium: DSM-5

- Key feature is disturbance in attention/awareness
- Of relatively abrupt onset and symptoms that fluctuate
- New cognitive deficits eg., poor memory, disorientation, perceptual disturbances
- Not due to other neuropsychiatric disturbance (i.e. dementia)
- Due to underlying physiological disturbance
  - Other features often include but are not necessary for the diagnosis:
    - Sleep-wake cycle disturbance or reversal in majority of cases
    - Emotional lability or irritability
    - Hallucinations (oneroid = dream-like), illusions and delusions
    - Motor changes: agitation/or lethargy

Reference: APA, Diagnostic and Statistical Manual 5th Edition 2013

Encephalopathy vs. Delirium

“Delirium”

- Top-down approach
- Describes a particular clinical syndrome which can be due to a multitude of causes

“Encephalopathy”

- Bottom-up approach – focused on the lesion/cause
- Includes a wide variety of states: coma, delirium

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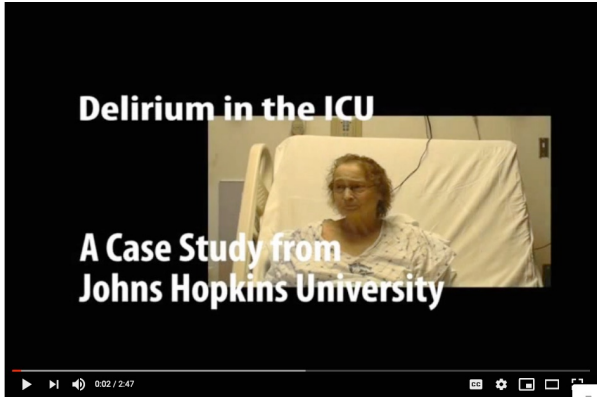
Why do we Care?

- Its common and commonly missed
- Delirium is associated with BAD outcomes
- Very distressing for patients and their loved ones
- You can watch the following interview with a patient at the following website:

https://www.youtube.com/watch?v=Xs1MNBcTL9I



You can see other videos

At the OACIS website:

https://www.hopkinsmedicine.org/pulmonary/research/outcomes-after-critical-illness/oacis-videos-news.html#videos

Why do we Care?
Delirium: Short Term Outcomes

- Associated with increased healthcare utilization
  - Increased mechanical ventilation duration (9 vs. 4 days)
  - Increased ICU length of stay (8 vs.5 days)
  - Increased hospital length of stay (21 vs. 11 days)
- Higher ICU costs ($22,000 vs. $13, 000)
- Estimated national annual costs $4 to $16 Billion
- Patient and caregiver suffering

Ely. ICM 2001; 27, 1892-1900. Ely, JAMA 2004; 291: 1753-1762. Lin, SM CCM 2004; 32: 2254-2259. Milbrandt E.,CCM 2004; 32:955-962. Jackson. Neuropsychology Review 2004; 14: 87-98.
Oimet ICM 2007; 33:1007-1013.

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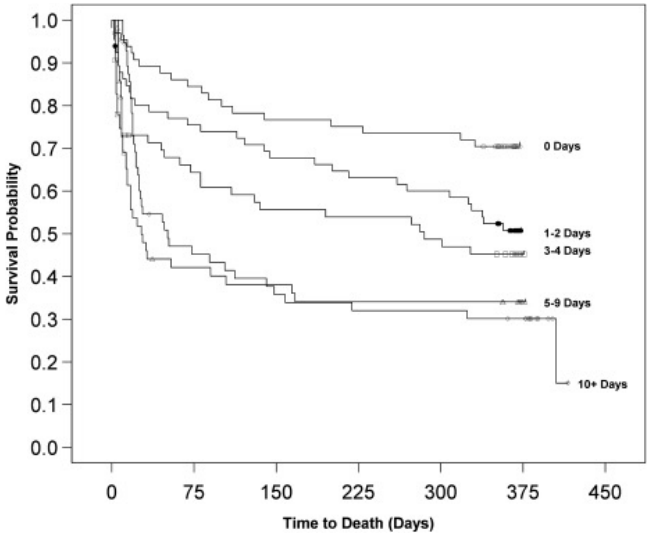
Outcome of delirium in critically ill patients: systematic review and meta-analysis

BMJ 2015;350:h2538

Jorge I F Salluh,[1] Han Wang,[2] Eric B Schneider,[2] Neeraja Nagaraja,[2] Gayane Yenokyan,[3] Abdulla Damluji,[4] Rodrigo B Serafim,[1,5] Robert D Stevens[6]

Delirious patients have a *higher risk* of death in the ICU…

	Relative Risk (95% CI)
ICU Mortality (95% CI)	2.19 (1.78 – 2.70)
adjusted for age, sex and APACHE	2.72 (1.75 – 3.69)



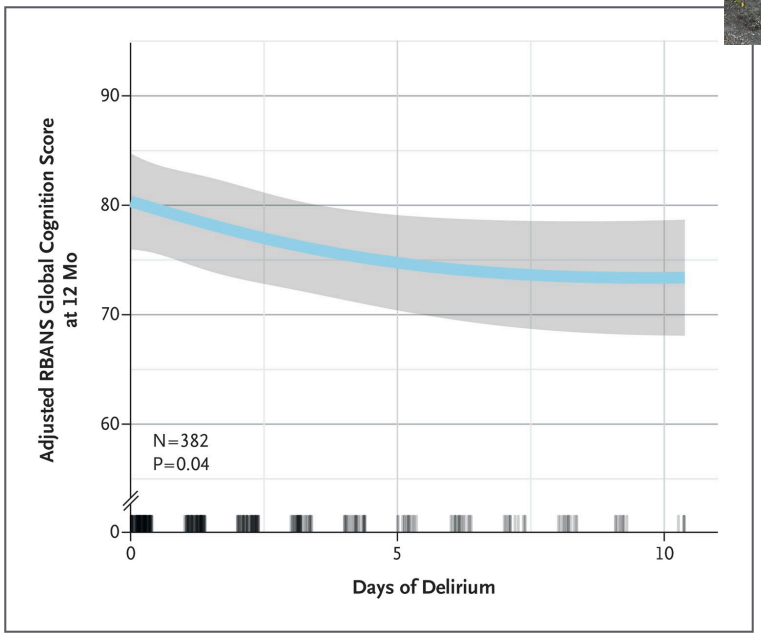
…and in the year after discharge.

Pisani MA, et al. Am J Respir Crit Care Med. 2009;180:1092-7.

This adapted slide from Dale Needham MD PhD

Why do we Care?
Delirium: Long Term Outcomes

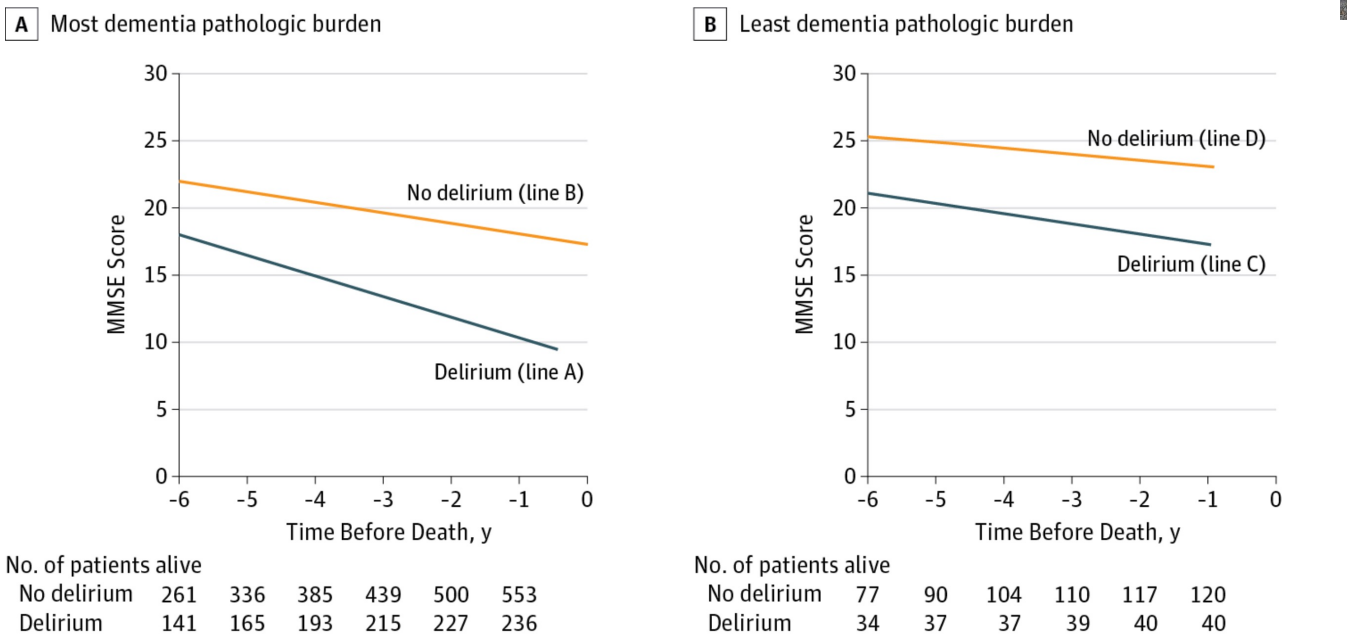
- Functional decline
- New nursing home placement
- Persistent cognitive decline:
  - Those developing delirium have cognitive dysfunction up to 6-12 months after discharge and longer



Pandharipande PP, et al N Engl J Med 2013; 369:1306-1316.
Saczynski JS, et al N Engl J Med. 2012 Jul 5;367(1):30-9.

Association of Delirium With Cognitive Decline in Late Life: A Neuropathologic Study of 3 Population-Based Cohort Studies

JAMA Psychiatry. 2017;74(3):244-251. doi:10.1001/jamapsychiatry.2016.3423



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Epidemiology: Where Do We Find Delirium?

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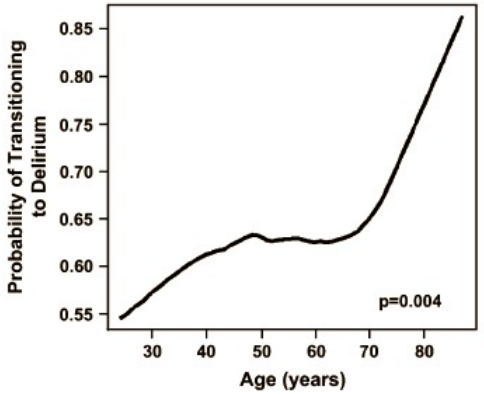
Prevalence

- Critically Ill Mechanically Ventilated Population
  - 60 – 85%
- General Medical Inpatient Units
  - 10 - 40%
- Medical Oncology Units
  - 20 – 70%
- Orthopedic Surgery: Hip fracture repair
  - 20 – 40%
- Why the variability?

As a Rule… More Delirium with:

- Increased Severity of Illness
- Older Age
- Cognitive Impairment

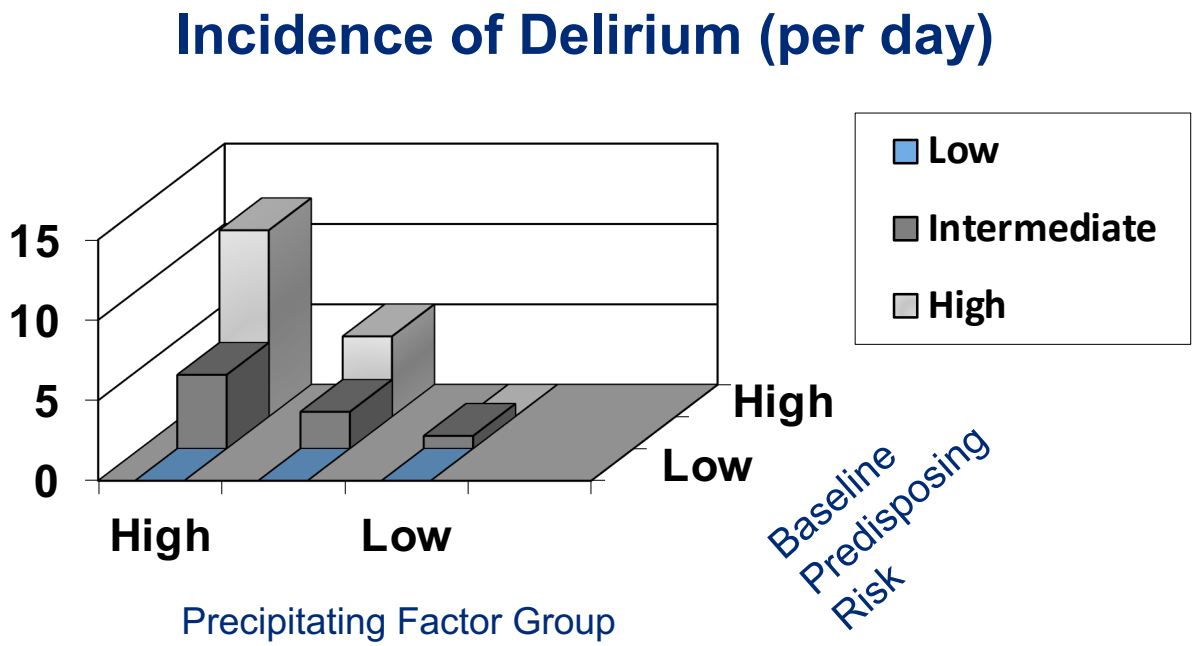


Probability of transitioning to delirium ↑ dramatically (by 2%) for each year of life after age 65.

The more ill the patient, the greater the likelihood of delirium.

Pandharipande et al. Anesthesiology 2006;104(1):23

Delirium Risk Model



Inouye & Charpentier; JAMA. 1996 20;275:852-7

Predisposing Factors - Vulnerability

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- Baseline cognitive impairment
  - 2.5 X↑ risk if Demented
  - 25-31% of delirious patients have underlying dementia
- Chronic medical conditions:
  - Any medical illness
- Visual impairment
- Hearing impairment
- Functional impairment
- History of ETOH or other drug abuse

The more predisposing risk factors …
The more likely delirium will develop.
Therefore - target high-risk patients for prevention.

Inouye et al Ann Intern Med 1993;119:474-481

Precipitating Risk Factors - Insults

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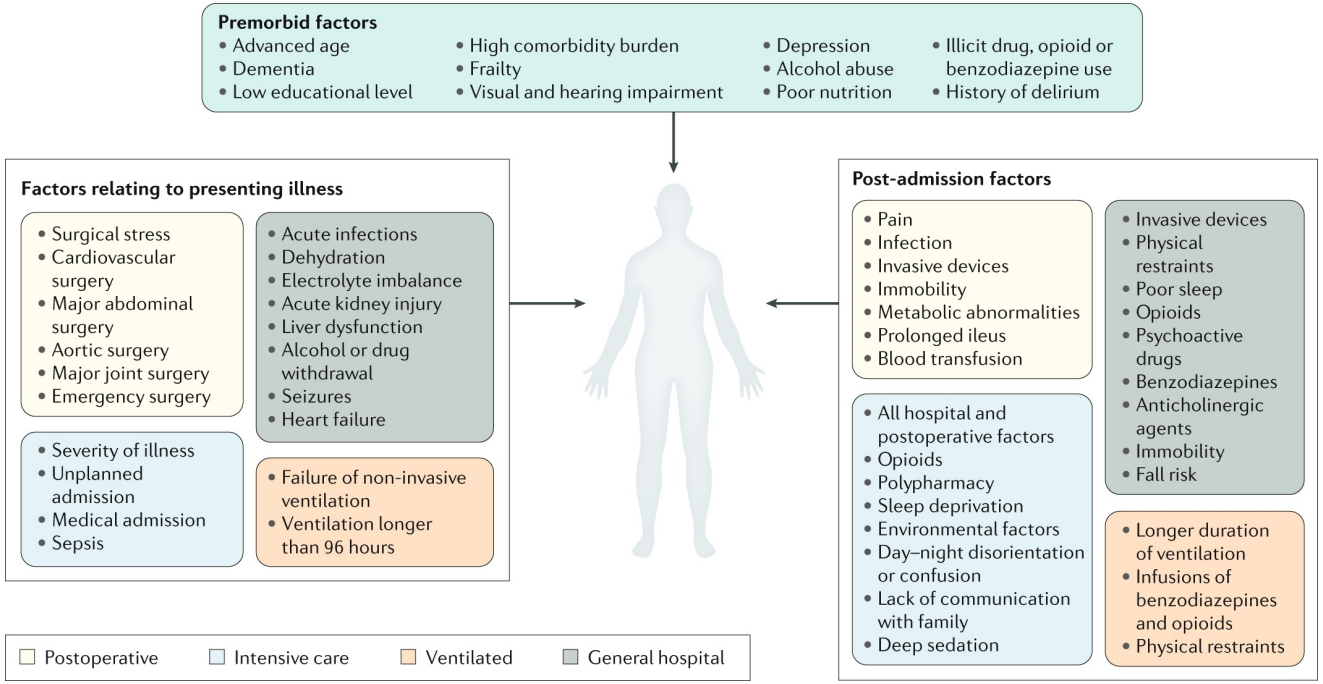
- Medications
- New medical illnesses
- Infections
- ETOH/drug withdrawal
- Fluid/electrolyte abnormalities
- Urinary retention
- Fecal impaction
- Immobility
- Environmental influences
- Physical restraints
- Indwelling catheters
- Uncontrolled pain
- Sleep deprivation

Inouye et al Ann Intern Med 1993;119:474-481

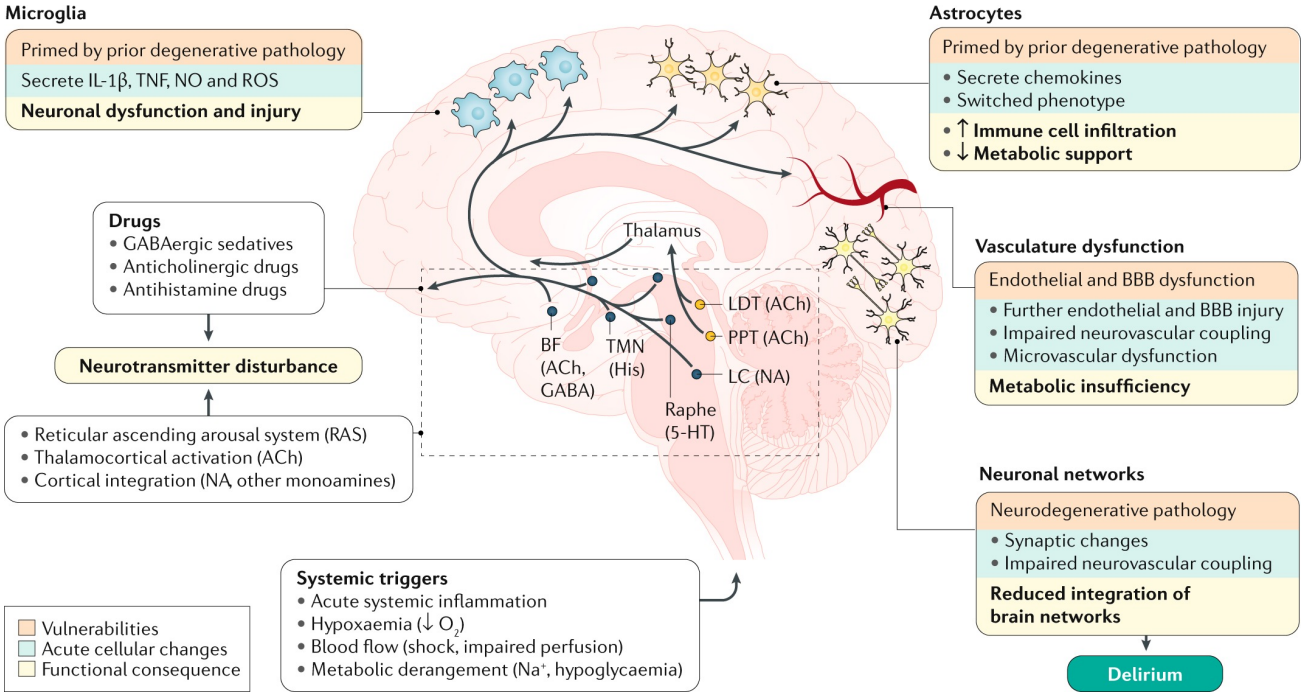
Risk Factors for Delirium



Reference: Wilson, J.E., Mart, M.F., Cunningham, C. *et al.* Delirium. *Nat Rev Dis Primers* 6, 90 (2020). https://doi.org/10.1038/s41572-020-00223-4

What is the underlying pathophysiology?

Major Mechanisms in Delirium



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Identification

33-95% of in hospital cases of delirium

- Missed - especially the hypoactive presentation
- Misdiagnosed as depression, psychosis or dementia
- Delirium trumps all other psychiatric dx
  - Can't make a diagnosis about depression or psychosis until delirium clears
- Often missed because cognition not tested actively
  - " How are your feeling today Mrs. Smith?"
- May co-occur with dementia

Inouye, J Ger Psy and Neurol., 11(3) 1998; Bair, Psy Clin N Amer 21(4)1998

Identification of Delirium

- History
  - Acute change from a previous baseline (collateral information)
- Mental State Exam
  - Changes in level of arousal (fluctuating level of consciousness)
  - Cognitive disturbances: Disorientation, ability to recall
  - Difficulty sustaining attention (days of the week backwards, serial 7's or "world" backwards)
  - Difficulty learning new information (decreased short term recall)
- Laboratory Investigations
  - EEG - Slowing of background rhythm "generalized dysfunction" but not 100% sensitive or specific
- Further history, physical exam and investigation
  - To identify etiology of the delirium

Sands, M. B.,et al. Palliat Med 2010; 24(6): 561-565.

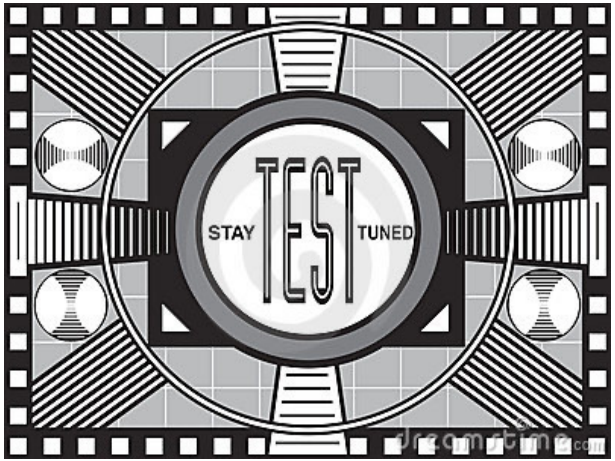
Identification of Delirium

- Tips for eliciting history from family:
  - “This isn’t my granny!”
  - When did this change occur? In relation to what?
    - May help aide differential diagnosis
    - Medicine changes including new over-the-counter preps.
    - Other symptoms such as cough and fever

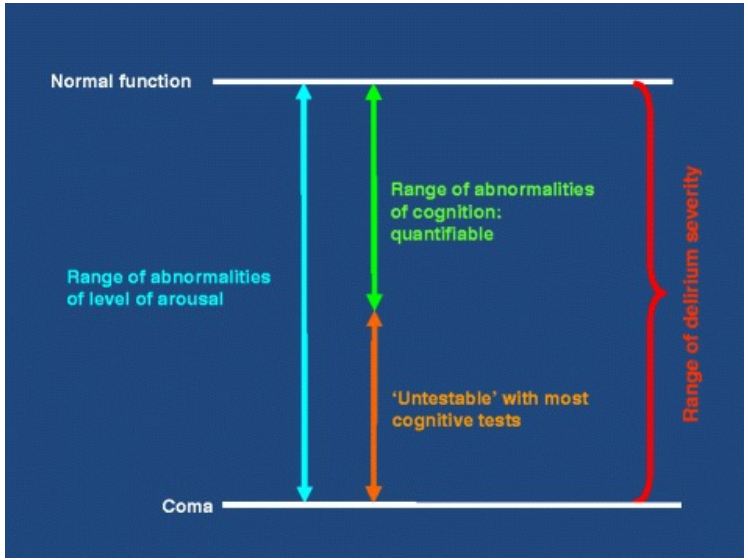
Sands, M. B.,et al. Palliat Med 2010; 24(6): 561-565.

Actively Test Cognition

- Attention
  - Months of the year backwards
  - Days of the week backwards
  - Spell “world” backwards; serial 7’s
- Orientation
  - Time: Day, date, month, season, year
  - Place: Hospital, floor, building, street, city, state
- Recall – immediate and short term
- Use standardized screening tool:
  - 4AT http:\\ 4AT.com or CAM-ICU in nonverbal patients
  - MMSE: Mini-mental State Exam
  - MOCA: Montreal Cognitive Assessment



Attention and Arousal: Beware of the “Sleepy” Patient



Overlap between hypoactive delirium and reduced arousal states (hyperactive delirium not included).
European Delirium Association and American Delirium Society BMC Medicine 2014 ***12****:141 doi:10.1186/s12916-014-0141-2*

This test is used in the Johns Hopkins Medical system in patients who can speak.

Unique screening tool as it rates the sleepy patient as “Positive”

4AT

(label)

Patient name:

Date of birth:

Patient number:

Assessment test for delirium & cognitive impairment

Date: **Time:**

Tester:

CIRCLE

[1] ALERTNESS

This includes patients who may be markedly drowsy (eg. difficult to rouse and/or obviously sleepy during assessment) or agitated/hyperactive. Observe the patient. If asleep, attempt to wake with speech or gentle touch on shoulder. Ask the patient to state their name and address to assist rating.

Normal (fully alert, but not agitated, throughout assessment)	**0**
Mild sleepiness for <10 seconds after waking, then normal	**0**
Clearly abnormal	**4**

[2] AMT4

Age, date of birth, place (name of the hospital or building), current year.

No mistakes	**0**
1 mistake	**1**
2 or more mistakes/untestable	**2**

[3] ATTENTION

Ask the patient: “Please tell me the months of the year in backwards order, starting at December.” To assist initial understanding one prompt of “what is the month before December?” is permitted.

Months of the year backwards

Achieves 7 months or more correctly	**0**
Starts but scores <7 months / refuses to start	**1**
Untestable (cannot start because unwell, drowsy, inattentive)	**2**

[4] ACUTE CHANGE OR FLUCTUATING COURSE

Evidence of significant change or fluctuation in: alertness, cognition, other mental function (eg. paranoia, hallucinations) arising over the last 2 weeks and still evident in last 24hrs

No	**0**
Yes	**4**

4 or above: possible delirium +/- cognitive impairment
1-3: possible cognitive impairment
0: delirium or severe cognitive impairment unlikely (but delirium still possible if [4] information incomplete)

4AT SCORE ☐

GUIDANCE NOTES Version 1.2. Information and download: **www.the4AT.com**

The 4AT is a screening instrument designed for rapid initial assessment of delirium and cognitive impairment. A score of 4 or more *suggests* delirium but is not diagnostic: more detailed assessment of mental status may be required to reach a diagnosis. A score of 1-3 suggests cognitive impairment and more detailed cognitive testing and informant history-taking are required. A score of 0 does not definitively exclude delirium or cognitive impairment: more detailed testing may be required depending on the clinical context. Items 1-3 are rated *solely on observation of the patient at the time of assessment.* Item 4 requires information from one or more source(s), eg. your own knowledge of the patient, other staff who know the patient (eg. ward nurses), GP letter, case notes, carers. The tester should take account of communication difficulties (hearing impairment, dysphasia, lack of common language) when carrying out the test and interpreting the score.

Alertness: Altered level of alertness is very likely to be delirium in general hospital settings. If the patient shows significant altered alertness during the bedside assessment, score 4 for this item. **AMT4 (Abbreviated Mental Test - 4):** This score can be extracted from items in the AMT10 if the latter is done immediately before. **Acute Change or Fluctuating Course:** Fluctuation can occur without delirium in some cases of dementia, but marked fluctuation usually indicates delirium. To help elicit any hallucinations and/or paranoid thoughts ask the patient questions such as, “Are you concerned about anything going on here?”; “Do you feel frightened by anything or anyone?”; “Have you been seeing or hearing anything unusual?”

www.4AT.com

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Treatment

- Delirium
- A psychiatric presentation
- Underlying medical problem
- Find and correct the cause
- Often more than one cause
- Use the following: “THINK” delirium

What to THINK about when delirium is present

T

Too Many Medications – polypharmacy (anticholinergics)
Too Little Water – dehydration
Toxicity from Organ Failure - heart, liver, kidney
Tremens - alcohol and benzodiazepine withdrawal
Thiamine or other nutritional deficiency

H

Hypoxemia – pulmonary embolus, pneumonia

I

Infection/sepsis
Immobilization

N

Nonpharmacological interventions – hearing aids, glasses, reorientation, music, noise control, ambulation – up and out of bed throughout the day, sleep protocols for night, family rooming-in

K

K+ or Electrolyte problems including hypo-Mg^{+2}

**** Adapted with permission from: Marta Render, MD – Veteran Affairs In-patient Evaluation Center (IPEC)***

Pharmacologic Strategies

First principle:

- Do No Harm
- Minimize drugs associated with delirium
- Can we prevent or treat delirium with medicine?

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Pharmacologic prevention and treatment of delirium in intensive care patients: A systematic review ☆

Journal of Critical Care 30 (2015) 799–807

Rodrigo B. Serafim, MD, MSc [a,b,c], Fernando A. Bozza, MD, PhD [a,d], Marcio Soares, MD, PhD [a,e], Pedro Emanuel A.A. do Brasil, MD, PhD [a], Bernardo R. Tura, MD, PhD [a], E. Wesley Ely, MD [f,g], Jorge I.F. Salluh, MD, PhD [a,e,*]

- 15 studies on delirium prevention
- 7 studies on delirium treatment (time to delirium resolution)
- Therapies evaluated included:
  - Dexmedetomidine
  - Rivastigmine
  - Haloperidol and atypical antipsychotics
  - Statins
  - Dexamethasone
- **No agent could *consistently* prevent or treat delirium**

Adapted slide developed by Dale Needham MD PhD

Prevention of Delirium Using Antipsychotics?

Author, year	Intervention	Control	Route of administration	Tool	Incidence, n/N: Intervention	Incidence, n/N: Control	RR (95% CI)
First-generation antipsychotic vs. placebo							
Wang 2012	Haloperidol	Placebo	IV	CAM-ICU	35/229	53/228	0.66 (0.45, 0.97)
Kalisvaart, 2005	Haloperidol	Placebo	Oral	DSM-IV and CAM-ICU	32/212	36/218	0.91 (0.59, 1.42)
Abdelgalel, 2016	Haloperidol	Placebo	IV	CAM-ICU	10/30	13/30	0.77 (0.40, 1.47)
Kaneko, 1999	Haloperidol	Placebo	IV	DSM	4/38	13/40	0.32 (0.12, 0.91)
van den Boogaard, 2018	Haloperidol	Placebo	IV	CAM-ICU or ICDSC	383/1082	233/707	1.07 (0.94, 1.23)
Schrijver, 2018	Haloperidol	Placebo	Oral	DOSS≥3, DSM-IV	23/118	18/124	1.34 (0.76, 2.36)
Al-Qadheeb, 2016	Haloperidol	Placebo	IV	ICDSC≥4, DSM-IV	12/34	9/34	1.33 (0.65, 2.74)
Fukata, 2014	Haloperidol	Placebo	IV	NEECHAM<20	25/59	20/60	1.27 (0.80, 2.02)
Khan, 2018	Haloperidol	Placebo	IV	CAM-ICU	15/68	19/67	0.78 (0.43, 1.40)
Subtotal (I-squared = 44.5%, p = 0.072)							0.94 (0.77, 1.16)
Second-generation antipsychotic vs. placebo							
Hakim, 2012	Risperidone	Placebo	Oral	DSM	7/51	17/50	0.40 (0.18, 0.89)
Larsen, 2010	Olanzapine	Placebo	Oral	DSM-IIIR	28/196	82/204	0.36 (0.24, 0.52)
Prakanrattana, 2007	Risperidone	Placebo	ODT	CAM-ICU	7/63	20/63	0.35 (0.16, 0.77)
Subtotal (I-squared = 0.0%, p = 0.956)							0.36 (0.26, 0.50)

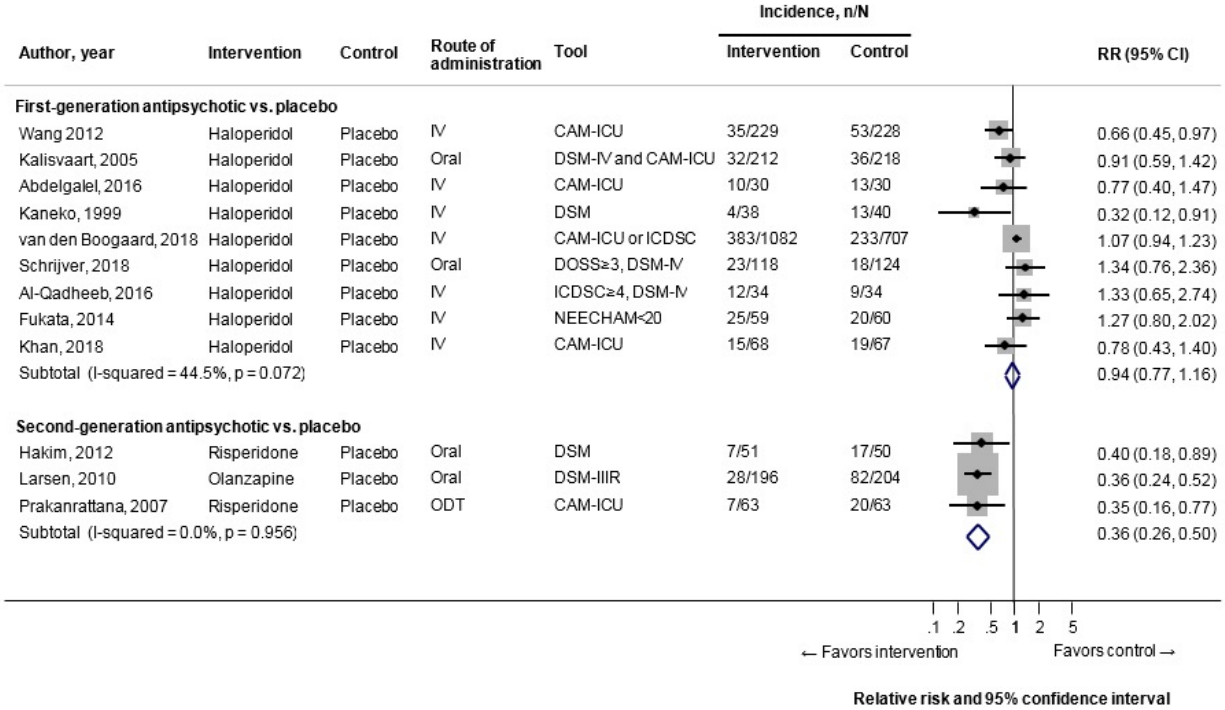
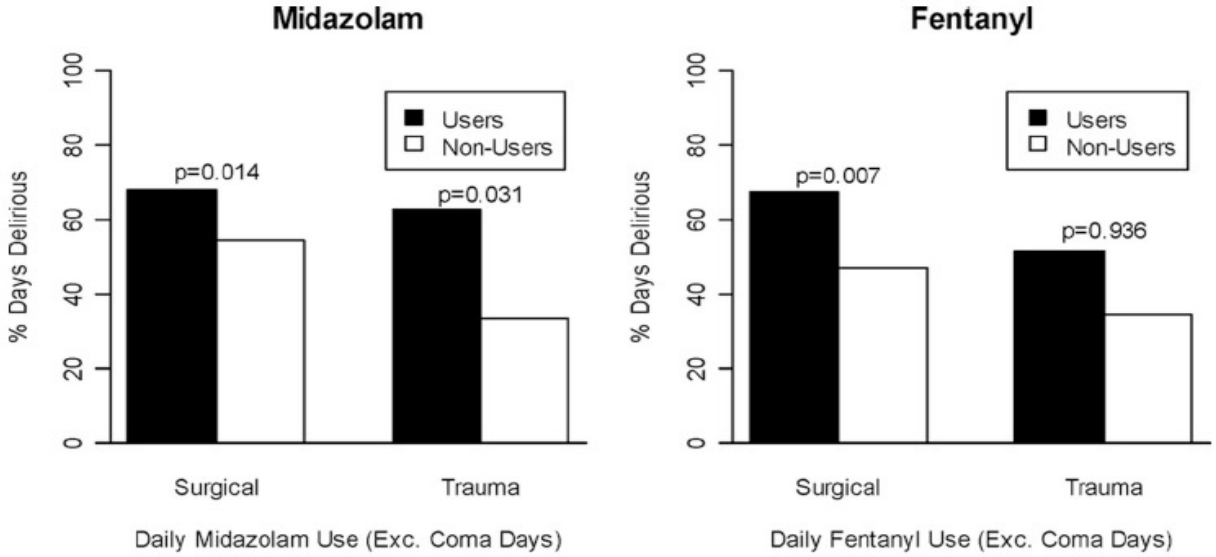


Figure 4. Meta-analysis of delirium incidence in trials comparing either haloperidol or second-generation antipsychotics with placebo among patients at risk for delirium

Neufeld KJ, et al DOI: https://doi.org/10.23970/AHRQEPCCER219

Prevalence and Risk Factors for Development of Delirium in Surgical and Trauma Intensive Care Unit Patients

Pratik Pandharipande, MD, MSCI, Bryan A. Cotton, MD, FACS, Ayumi Shintani, PhD, MPH, Jennifer Thompson, MPH, Brenda Truman Pun, MSN, ACNP, John A. Morris, Jr., MD, FACS, Robert Dittus, MD, MPH, and E. Wesley Ely, MD, MPH

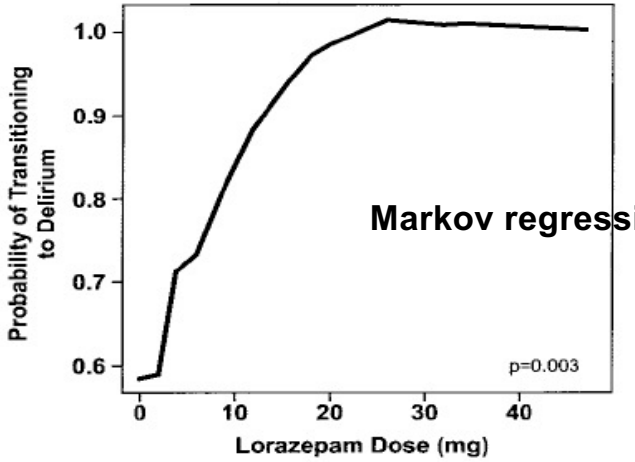


Pandharipande P et al., J Trauma 2008;65:34-41.

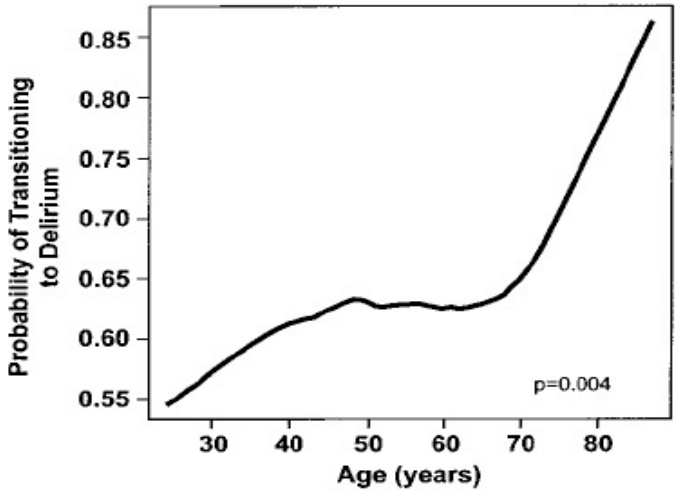
Adapted slide developed by Dale Needham MD PhD

Lorazepam Is an Independent Risk Factor for Transitioning to Delirium in Intensive Care Unit Patients

Pratik Pandharipande, M.D., M.S.C.I., Ayumi Shintani, Ph.D., M.P.H.,† Josh Peterson, M.D., M.P.H.,‡ Brenda Truman Pun, R.N., M.S.N., A.C.N.P.,§ Grant R. Wilkinson, Ph.D., D.Sc.,‖ Robert S. Dittus, M.D., M.P.H.,# Gordon R. Bernard, M.D.,** E. Wesley Ely, M.D., M.P.H.††*



Markov regression model



Probability of transition to delirium increased with lorazepam dose given in prior 24 hrs

Risk of delirium increased dramatically for each year of life after 65 year of age

Pandharipande P et al., Anesthesiology 2006;104:21-26.

Adapted slide developed by Dale Needham MD PhD

Sedation Protocols

Goal patient below…

- RASS goal: 0 = ALERT and AWAKE
- Fentanyl & midazolam (A-1)
- Avoid infusions, use prn
  - Initially q 5 min (if needed)
  - Then q 1-2hr
- Daily stop of prn & infusion
- Anticipate agitation
  - Do not use benzo
  - Use IV haloperidol (check QTc)

Hager et al, 2013; Crit Care Med; 41: 1435 - 1442

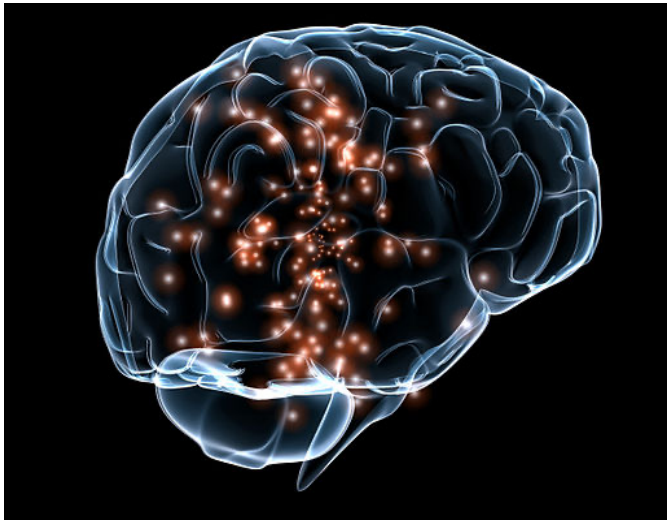
Pharmacologic Interventions – Take-away

- Do no harm: minimize psychoactive meds and sedation
- Antipsychotics do not appear to decrease delirium incidence or LOS
- If needed for symptomatically (distress and anxiety) – stop them with resolution of symptoms ASAP
- Melatonin agonists – not much signal in post-op populations

Management & Prevention of Delirium

Non-pharmacologic strategies:

- Early physical and cognitive rehabilitation
- Improved sleep
- Multi-faceted non-pharm protocols



Adapted slide developed by Dale Needham MD PhD

Summary of ICU Mobility Outcomes

www.hopkinsmedicine.org/OACIS

- Improves delirium
- Improves physical function
- Decreases LOS
- Improves Physical Function QOL
- Timing of mobility matters – early
- Sedation practices matter
- Mobility matters, not who delivers it

This adapted slide originally from Carrie Goodson MD

JHH MICU Sleep QI

Crit Care Med 2013

The Effect of a Quality Improvement Intervention on Perceived Sleep Quality and Cognition in a Medical ICU*

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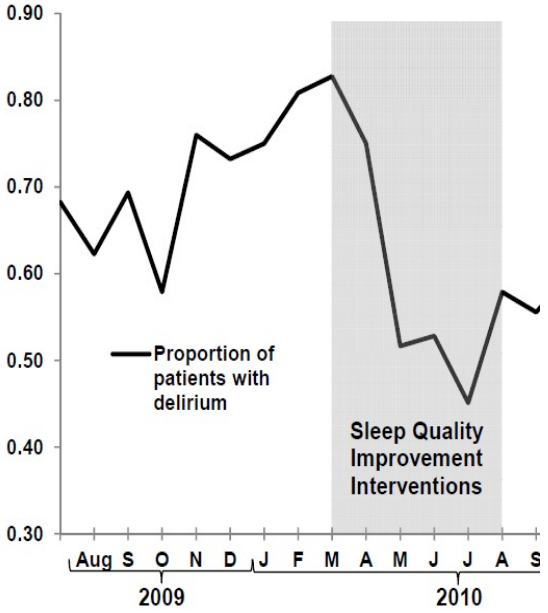
Table 4. ICU cognitive and secondary outcomes

ICU outcome	Baseline *N* = 110 patients, 634 patient-days	Sleep QI *N* = 175 patients, 826 patient-days	QI vs. Baseline Adjusted Odds Ratio or Difference (95% CI)	*P* Value
Delirium outcomes				
Delirium/coma-free days in MICU, no. (%)	272 (43)	399 (48)	1.64 (1.04-2.58)	0.03[a]
Patients without delirium/coma during ICU stay, no. (%)	34 (31)	89 (51)	2.20 (1.13-4.27)	0.02[a]



Adapted slide developed by Dale Needham MD PhD

JOHNS HOPKINS MEDICINE

Efficacy of Non-Pharmacological Interventions to Prevent and Treat Delirium in Older Patients: A Systematic Overview. The SENATOR project ONTOP Series

Iosief Abraha[1]*, Fabiana Trotta[1], Joseph M. Rimland[2], Alfonso Cruz-Jentoft[3], Isabel Lozano-Montoya[3], Roy L. Soiza[4], Valentina Pierini[5], Paolo Dessì Fulgheri[5], Fabrizia Lattanzio[2], Denis O'Mahony[6], Antonio Cherubini[1]

PLOS ONE

2015 Jun 10;10(6):e0123090.
doi: 10.1371/journal.pone.0123090.
eCollection 2015

31 primary studies in last 20 years from 26 systematic reviews

- Age ≥ 60
- Surgical and Medical acute care setting
- Single and multi-component interventions

  - Staff Education
  - Multi–disciplinary team
  - Avoidance of Sensory Deprivation
  - Orientation Protocol
  - Sleep protocol
  - Early mobilization
  - Hydration
  - Nutrition
  - Oxygen delivery
  - Pain control
  - Drug list review – stop unneeded meds

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Pooled Delirium Incidence Reduced by:

- 29% in surgical setting
- RR 0.71 (95% CI: 0.59 to 0.86)

- 35% in medical setting
- RR 0.65 (95% CI: 0.49 to 0.86)

Adapted slide developed by Dale Needham MD PhD

What do these non-pharmacologic interventions look like in the ICU?

Reading the Newspaper

Provided by: Satoru Hashimoto MD; Director of Intensive Care, Kyoto Prefectural University of Medicine, Japan

Enjoying Difficult Sudoku

Provided by: Satoru Hashimoto MD; Director of Intensive Care, Kyoto Prefectural University of Medicine, Japan

Walking outside of the ICU

Walking outside for Sunshine Therapy

Early Mobility

Wii-hab

Kho J Crit Care 2012;27:219e1-e6

Hydrotherapy

Felten-Barentsz AJRCCM 2015;191(4):476-77
Wegner Austral Crit Care 2017 in press

Prevention and Treatment Summary

- Need to detect delirium
  - Test cognition (4AT or CAM-ICU)
- Correct the underlying causes
- Do no harm
  - Reduce deliriogenic meds
  - Reduce sedation
- Use non-pharmacologic bundled care for prevention & treatment
  - Increased mobility
  - Cognitive rehabilitation
  - Improved sleep

Thank you for Your Time