Unsuspected Delirium: Differential Diagnosis and Treatment

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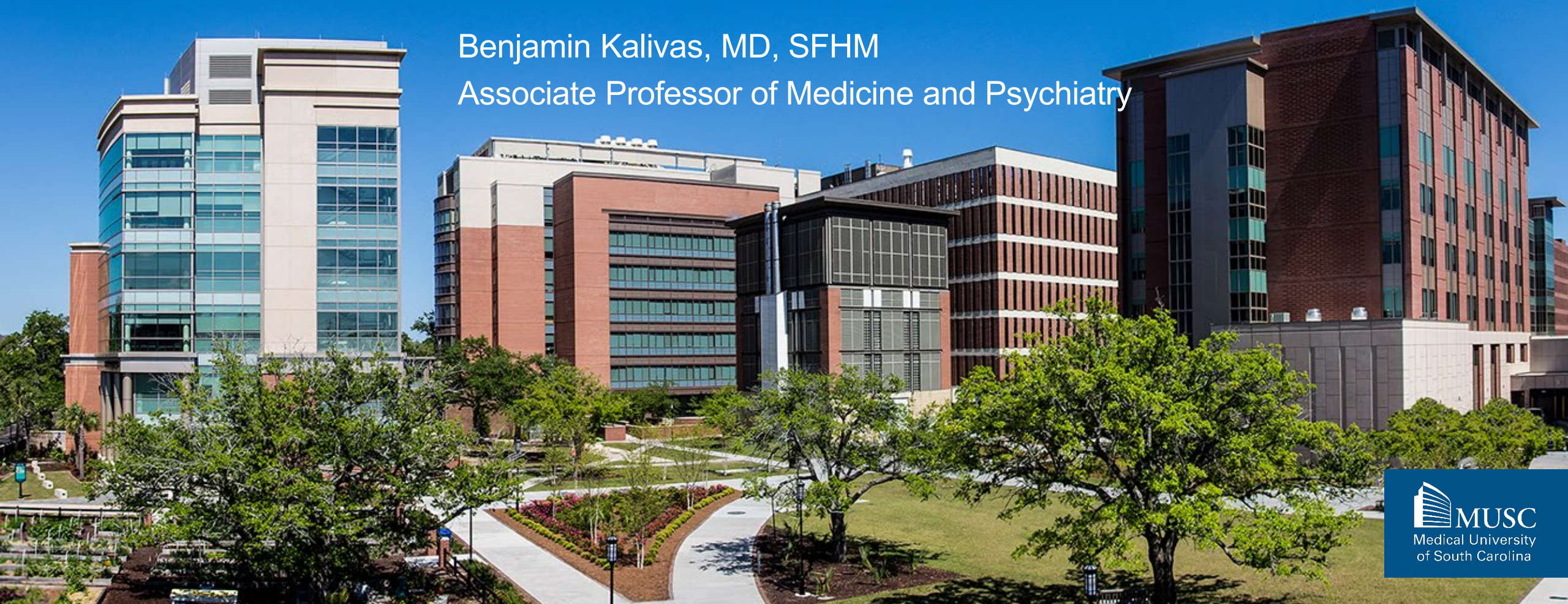

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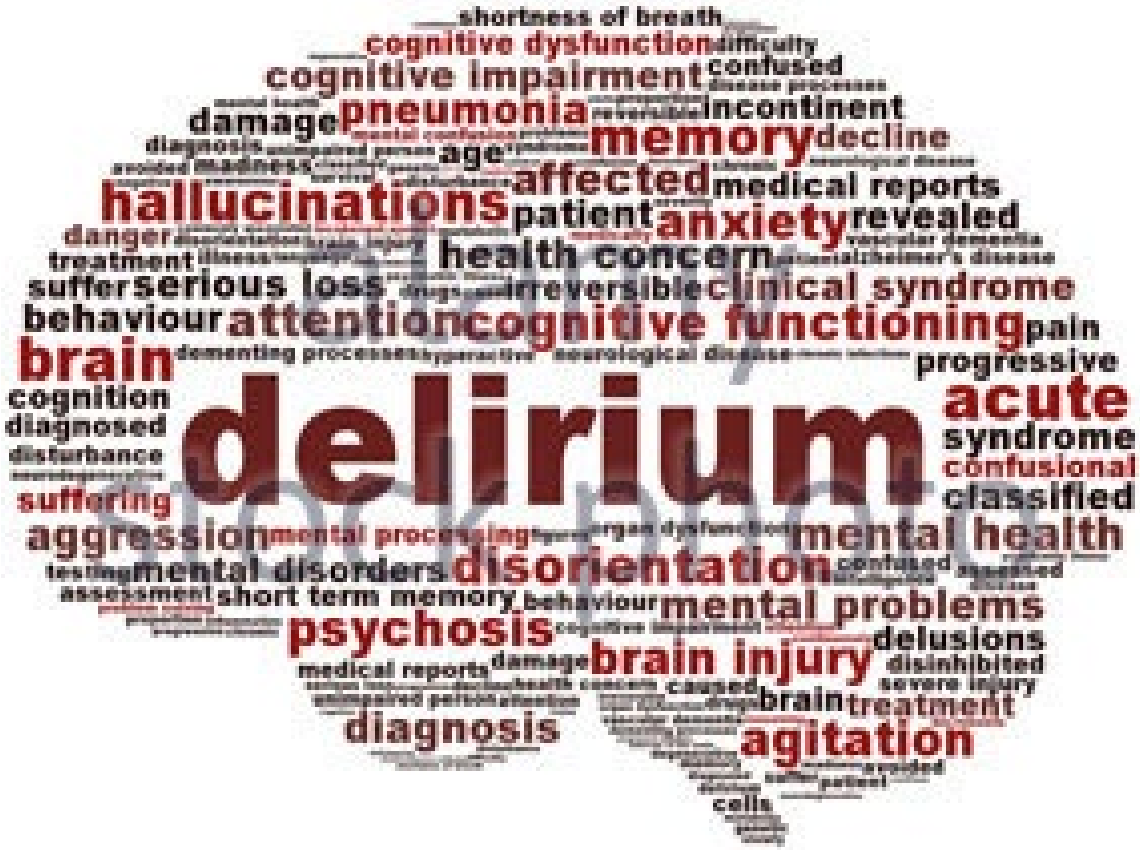
Disclosures

None

Objectives

Discuss the latest understanding of delirium—presentation, pathophysiology, precipitants and consequences

Explore latest data on management of delirium and its symptoms


shortness of breath
cognitive dysfunction
cognitive impairment
confused
damage
pneumonia
incontinent
memory
decline
diagnosis
age
madness
affected
medical reports
hallucinations
patient
anxiety
revealed
danger
health concern
treatment
suffer
serious loss
irreversible
clinical syndrome
behaviour
attention
cognitive functioning
pain
brain
progressive
cognition
diagnosed
delirium
acute
disturbance
syndrome
confusional
suffering
classified
aggression
mental processing
mental health
mental disorders
disorientation
assessment
short term memory
behaviour
mental problems
psychosis
delusions
brain injury
medical reports
damage
disinhibited
severe injury
brain
treatment
diagnosis
agitation
cells

Part 1: Diagnosing Delirium

DSM-V

Definition: Diagnostic Statistical Manual (DSM) V

A. Disturbance in ***attention*** (i.e., reduced ability to direct, focus, sustain, and shift attention) and **awareness** (reduced *orientation to the environment*).

B. The disturbance develops over a **short period of time** (usually hours to a few days), *represents an acute change from baseline attention and awareness*, and tends to **fluctuate** in severity during the course of a day.

C. An additional disturbance in cognition (e.g.memory deficit, disorientation, language, visuospatial ability, or perception).

D. *The disturbances in Criteria A and C* are not better explained by a pre-existing, established or evolving neurocognitive disorder and *do not occur in the context of a severely reduced level of arousal such as coma.*

E. There is evidence from the history, physical examination or laboratory findings that the disturbance is *a direct* physiological consequence of another medical condition, *substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies*.

Epidemiology

Delirium is common, particularly in the elderly

Systematic review of medical literature by Inouye et al. to accurately estimate the prevalence and incidence

- General Medical: prevalence of **18-35%** with an incidence of 11-14%
- ICU: prevalence of **7-50%** with an incidence of 19-82%

Likely underestimated given absence of modern screening and under-recognition of motor subtypes

12.5% of all adults admitted to MUSC

Clinical Presentation

Incident vs prevalent delirium

- Prevalent: acutely sick at presentation with AMS (delirium)
- Incident: develops during a hospitalization

Fluctuating mental status: specifically level of arousal

Motor Subtypes:

Similar impact on morbidity and mortality

HYEPERACTIVE:

- Psychomotor agitation, hyperarousal
  - Psychosis/delusions **1.6%**
- Often easier to diagnose

HYPOACTIVE:

- Psychomotor retardation, decreased arousal
- Underappreciated occurrence of psychosis/delusions **54.9%**
  - Often mistaken for depression (42% of in hospital consults for “depression” were actually delirious)
- A sleepy patient is a sick patient

MIXED:

- Combination or fluctuation between both **43.5%**

Challenging diagnosis

Many factors contribute to missed diagnosis:

- Fluctuating nature of illness
- Subtle subtypes: hypoactive
- Communication barriers between staff
- Inadequate use of delirium assessment tools
- Lack of conceptual understanding
- Similarity to and often mistaken with dementia

Challenging Diagnosis

Study of 303 elderly (median age 72yo) patients who presented to the ED, 25 (8.3%) had delirium.

- 1 in 4 were identified by the emergency room physician
- Of the 16 who were admitted to the hospital, only 1 recognized by admitting physician
- Majority of these patients had hypoactive delirium

Study of 710 elderly (mean age 83) patients admitted to medical unit. 110 (15.5%) had delirium by validated screening tool.

- 28 % of these patients were identified by clinical team in acute hospital setting

Delirium Screening Tools

Confusion Assessment Method (CAM)

- CAM-ICU
- bCAM
- pCAM
- FAM-CAM

Delirium Rating Scale (DRS)

- DRS-R98

4AT

Confusion Assessment Method (CAM)

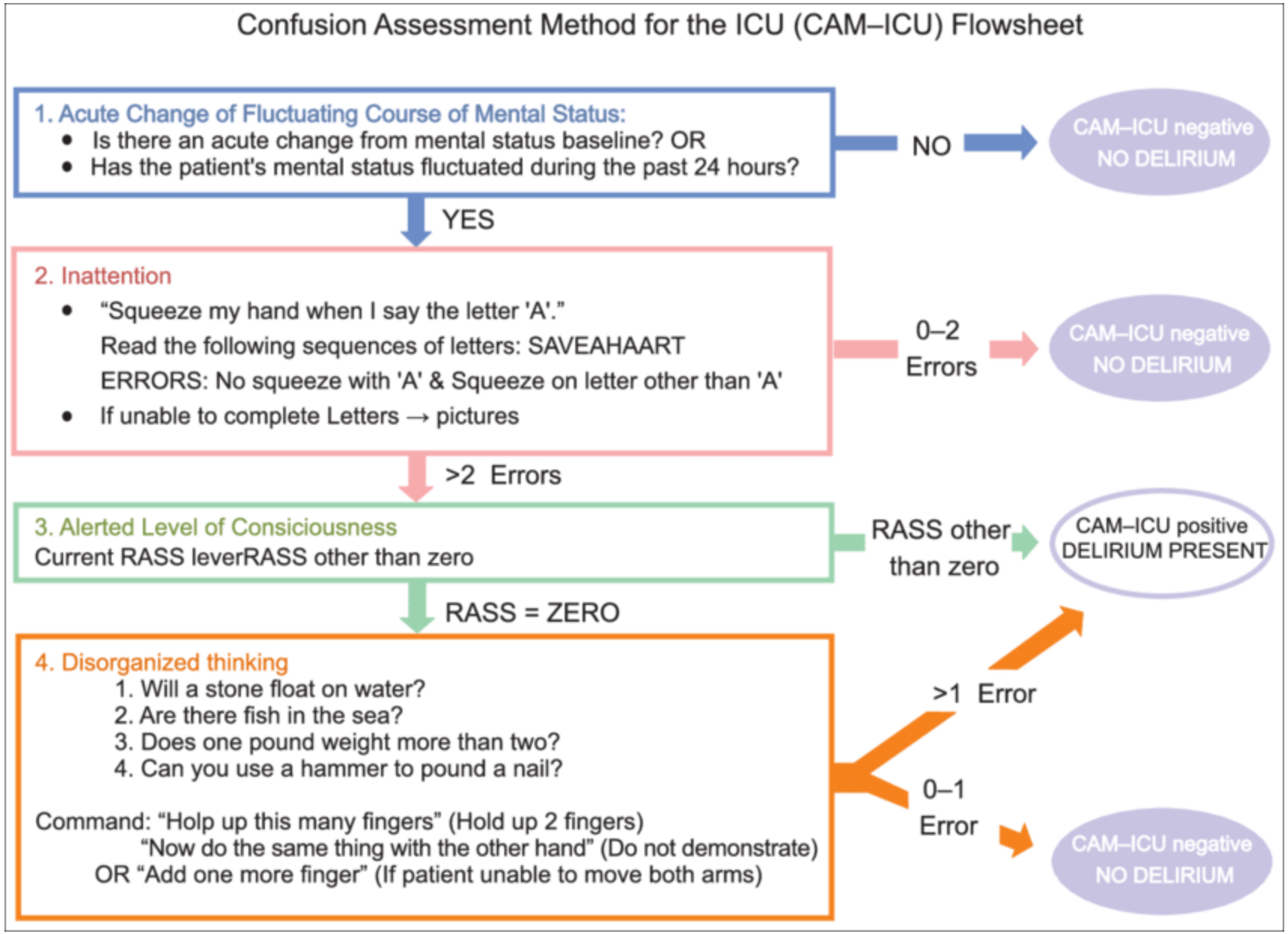
Short form

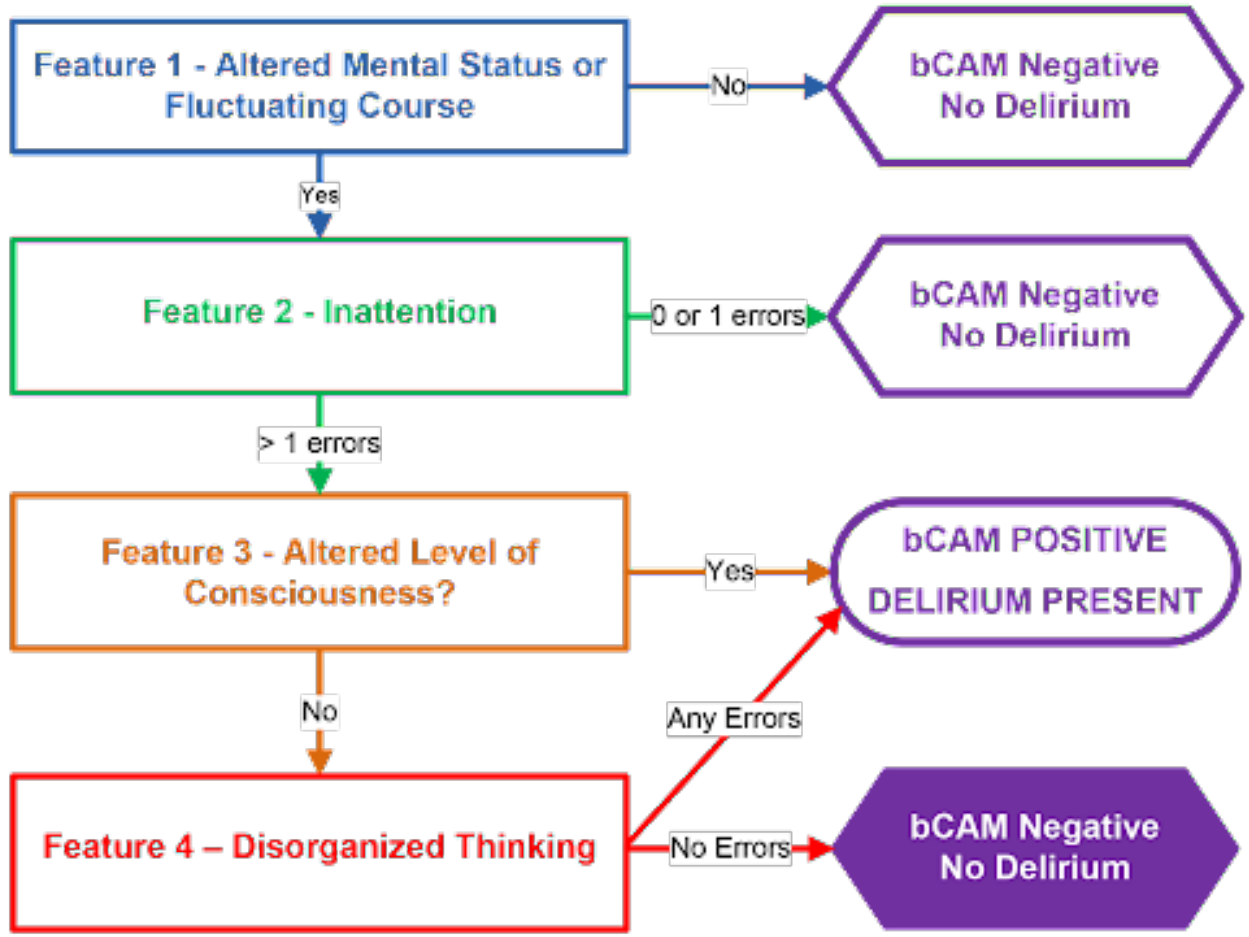
island health

The diagnosis of delirium by CAM requires the presence of BOTH features ***A*** and ***B***		
C A M **Confusion Assessment Method**	**A.** **Acute onset** and **Fluctuating course**	Is there evidence of an acute change in mental status from patient baseline? Does the abnormal behavior: ➢ come and go? ➢ fluctuate during the day? ➢ increase/decrease in severity?
	B. **Inattention**	Does the patient: ➢ have difficulty focusing attention? ➢ become easily distracted? ➢ have difficulty keeping track of what is said?
	AND the presence of EITHER feature *C or D*	
	C. **Disorganized thinking**	Is the patient's thinking ➢ disorganized ➢ incoherent For example does the patient have ➢ rambling speech/irrelevant conversation? ➢ unpredictable switching of subjects? ➢ unclear or illogical flow of ideas?
	D. **Altered level of consciousness**	Overall, what is the patient's level of consciousness: ➢ alert (normal) ➢ vigilant (hyper-alert) ➢ lethargic (drowsy but easily roused) ➢ stuporous (difficult to rouse) ➢ comatose (unrousable)

Adapted with permission from: Inouye SK, vanDyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: The Confusion Assessment Method. A new method for detection of delirium. Ann Intern Med. 1990; 113: 941-948. Confusion Assessment Method: Training Manual and Coding Guide, Copyright © 2003, Hospital Elder Life Program, LLC.

Please see the **CAM Training Manual**, available at
http://www.hospitalelderlifeprogram.org/private/cam-disclaimer.php?pageid=01.08.00


Confusion Assessment Method for the ICU (CAM–ICU) Flowsheet
1. Acute Change of Fluctuating Course of Mental Status:
• Is there an acute change from mental status baseline? OR
• Has the patient's mental status fluctuated during the past 24 hours?
NO
CAM–ICU negative
NO DELIRIUM
YES
2. Inattention
• "Squeeze my hand when I say the letter 'A'."
Read the following sequences of letters: SAVEAHAART
ERRORS: No squeeze with 'A' & Squeeze on letter other than 'A'
• If unable to complete Letters → pictures
0–2
Errors
CAM–ICU negative
NO DELIRIUM
>2 Errors
3. Alerted Level of Consiciousness
Current RASS leverRASS other than zero
RASS other
than zero
CAM–ICU positive
DELIRIUM PRESENT
RASS = ZERO
4. Disorganized thinking
1. Will a stone float on water?
2. Are there fish in the sea?
3. Does one pound weight more than two?
4. Can you use a hammer to pound a nail?
Command: "Holp up this many fingers" (Hold up 2 fingers)
"Now do the same thing with the other hand" (Do not demonstrate)
OR "Add one more finger" (If patient unable to move both arms)
>1 Error
0–1
Error
CAM–ICU negative
NO DELIRIUM


Feature 1 - Altered Mental Status or Fluctuating Course
No
bCAM Negative No Delirium
Yes
Feature 2 - Inattention
0 or 1 errors
bCAM Negative No Delirium
> 1 errors
Feature 3 - Altered Level of Consciousness?
Yes
bCAM POSITIVE DELIRIUM PRESENT
No
Any Errors
Feature 4 – Disorganized Thinking
No Errors
bCAM Negative No Delirium

DRS-R-98 SCORESHEET

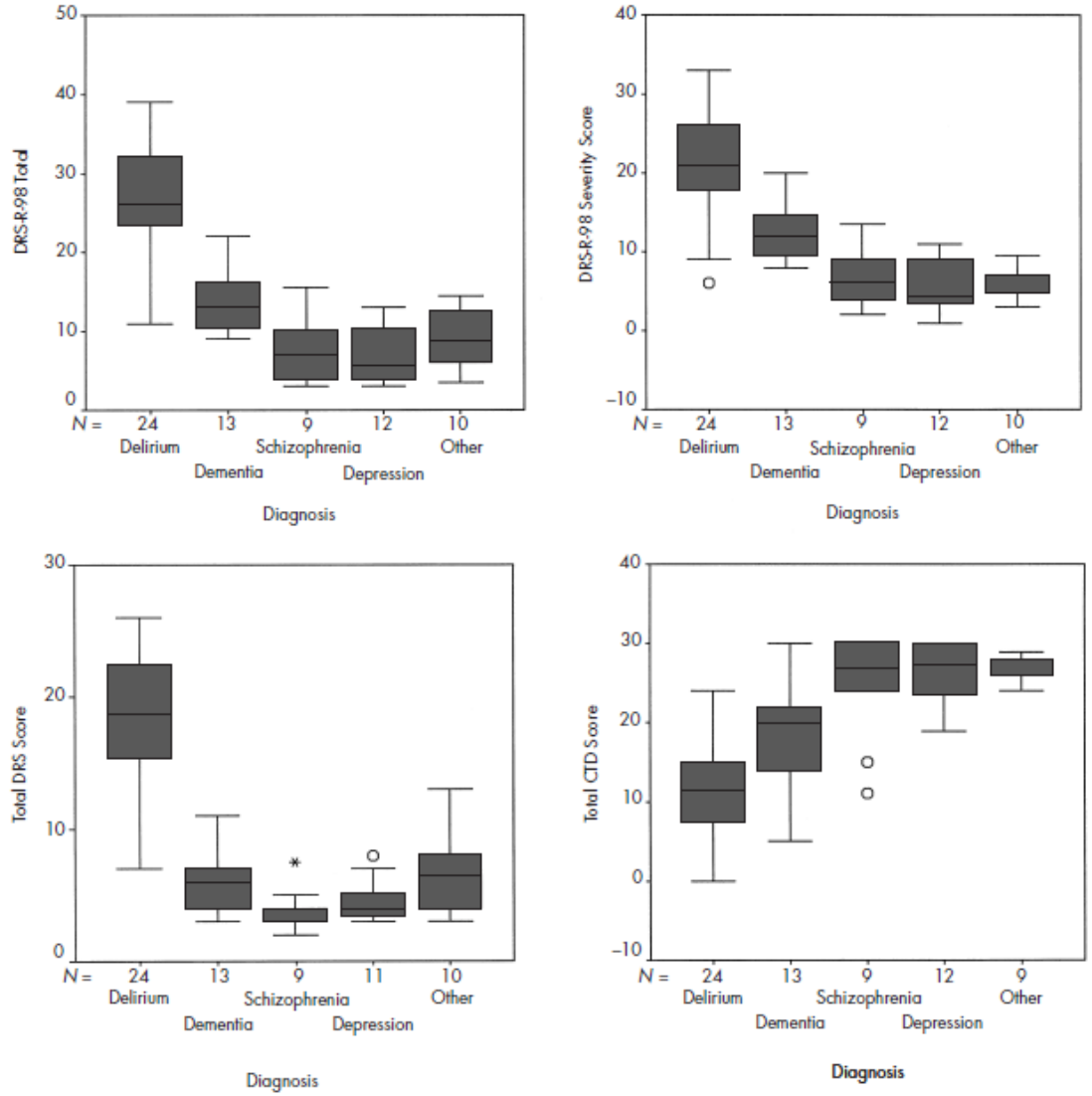
Name of patient: _____ **Date:** ___/___/___ **Time:** _____

Name of Rater: _____

SEVERITY SCORE: [ ] **TOTAL SCORE:** [ ]

Severity Item	Item Score				Optional Information
Sleep-wake cycle	0	1	2	3	Naps Nocturnal disturbance only Day-night reversal
Perceptual disturbances	0	1	2	3	Sensory type of illusion or hallucination: auditory visual olfactory tactile Format of illusion or hallucination: simple complex
Delusions	0	1	2	3	Type of delusion: persecutory Nature: poorly formed systematized
Lability of affect	0	1	2	3	Type: angry anxious dysphoric elated irritable
Language	0	1	2	3	Check here if intubated, mute, etc.
Thought process	0	1	2	3	Check here if intubated, mute, etc.
Motor agitation	0	1	2	3	Check here if restrained *Type of restraints:*
Motor retardation	0	1	2	3	Check here if restrained *Type of restraints:*
Orientation	0	1	2	3	Date: Place: Person:
Attention	0	1	2	3	
Short-term memory	0	1	2	3	Record # of trials for registration of items: Check here if category cueing helped
Long-term memory	0	1	2	3	Check here if category cueing helped
Visuospatial ability	0	1	2	3	Check here if unable to use hands
Diagnostic Item	**Item Score**				**Optional Information**
Temporal onset of symptoms	0	1	2	3	Check here if symptoms appeared on a background of other psychopathology
Fluctuation of symptom severity	0	1	2		Check here if symptoms only appear during the night

FIGURE 1. Boxplots of DRS, DRS-R-98 Total, DRS-R-98 Severity, and CTD scores for each of the five diagnostic groups. Median scores are denoted by the solid line within the boxes. The boxes represent the middle 50% of the scores. Outliers are denoted by open circles. DRS = Delirium Rating Scale; CTD = Cognitive Test for Delirium.



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?"

Assessing Attention

Complex neuroanatomical process at the core of human behavior

Management of input of information and output of behavior

- Working memory
- Sustained attention
- Switching attention
- Selective attention

Whole brain process

Assessing Attention

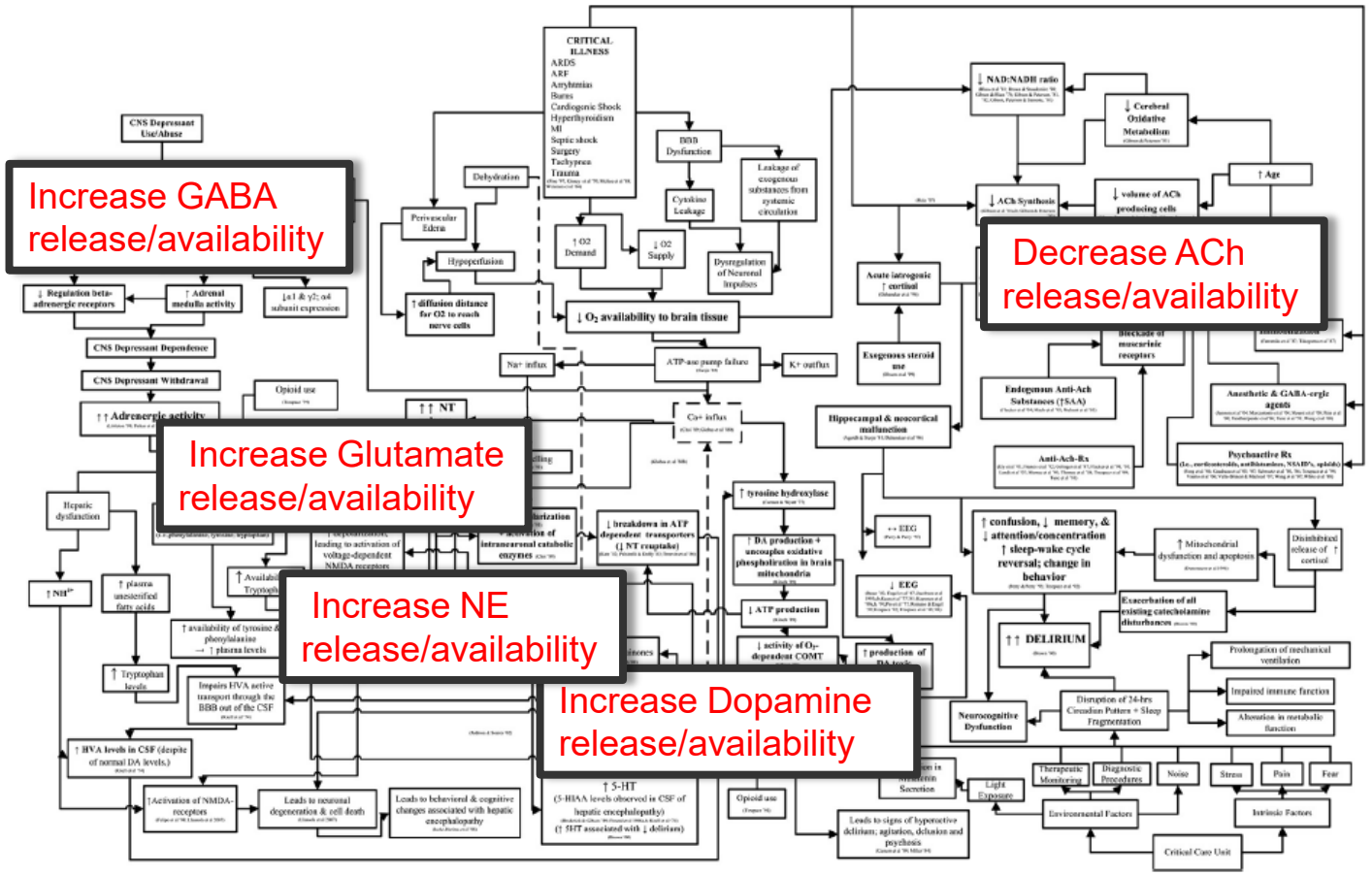
Generally preserved in early dementia (AD)

Cancellation tests (SAAVEAHEART, CASABLANCA) discriminates between delirium and dementia

Months backwards highly sensitive

Digit span, serial 7s also uses executive function/working memory, less specific to delirium

What causes delirium?



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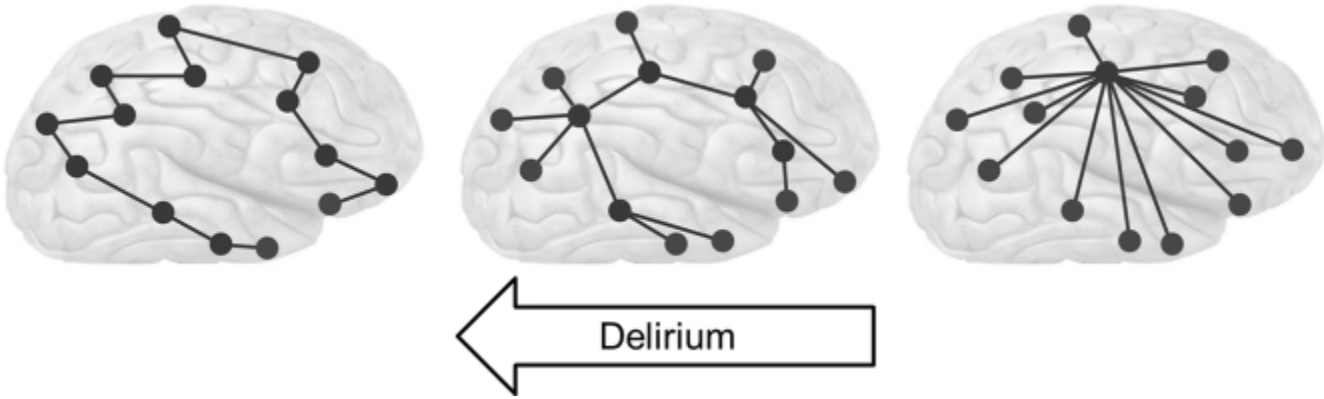
System Disintegration



Delirium vs Dementia

Delirium is an acute phenomena: **Acute Brain Failure**

Dementia is a chronic underlying process: **Chronic Brain Failure**

Dementia is a major risk factor for delirium

Important to look for change from baseline: **Acute on Chronic Brain Failure**

Specific subtypes of delirium

Hepatic Encephalopathy: Increased GABA tone shown in animal models

Delirium tremens/alcohol withdrawal: hyper-excitability of the VTA

Septic encephalopathy: dysfunction of cerebral blood flow shown by PET. Inflammatory response and endothelial/BBB break down

What causes delirium

Systemic/medical illness that leads to acute brain failure

Vulnerable brains at greater risk

Often multiple insults, some more acute than others

Drugs (pain meds, benzos, sedating, steroids).

Environmental factors (hearing aids, eye glasses, sleep/wake cycle)

Lab abnormalities (Na, K, Ca, BUN/Cr)

Infection

Respiratory status (hypoxia)

Immobility

Organ failure

Unrecognized dementia

Shock (sepsis)

Causes of Delirium (Usually more then 1!)

I WATCH DEATH

Infection/**I**atrogenic (meds)

Withdrawal
Acute metabolic
Trauma
CNS Pathology
Hypoxia

Deficiencies (B12, thiamine, folate, niacin)
Endocrine
Acute vascular
Toxins
Heavy Metals

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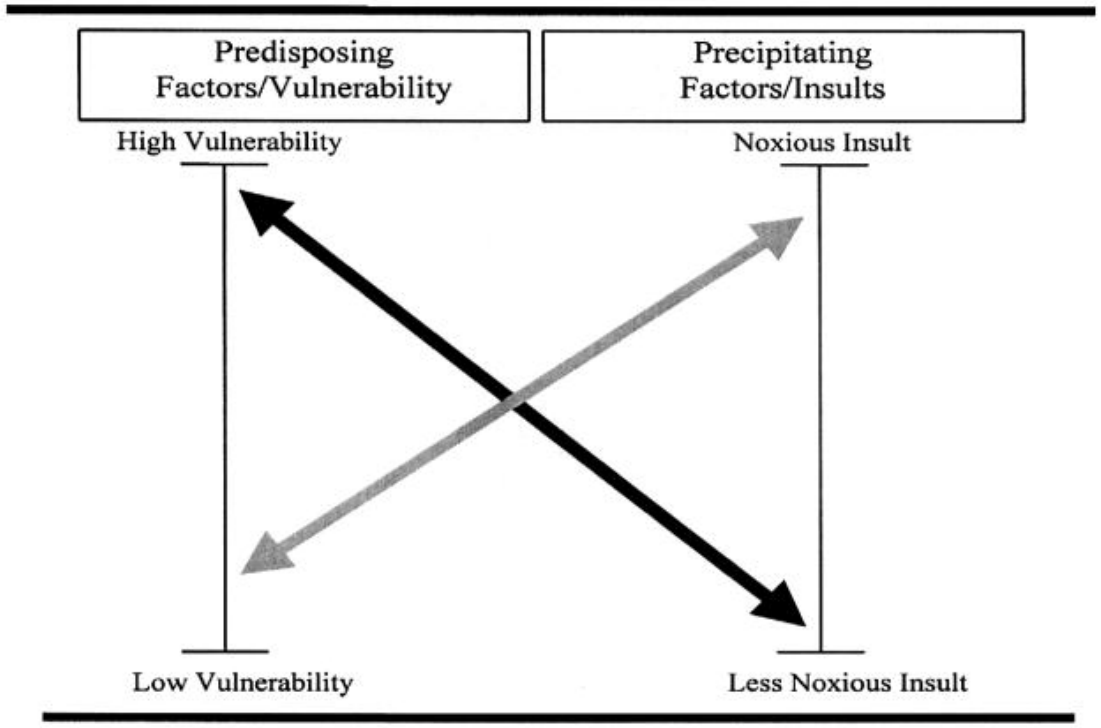
Cause of Delirium



Most often multifactorial

Predisposing Factors:

Dementia/cognitive impairment

Alcohol abuse

Advanced age

Severe comorbid illness

Sensory/functional impairment

Precipitating Factors:

Sedating or psychoactive medications

Mechanical restraints

Elevated serum urea

Surgery

Abnormal sodium

Many, many more

Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383(9920):911-922.

Potentially Modifiable Risk factors	Nonmodifiable Risk Factors
Sensory Impairment	Dementia or cognitive impairment
Immobilization (catheters or restraints)	Advancing age (>65yo)
Medications	History of delirium, stroke or falls
Acute neurological disease	Multiple comorbidities
Intercurrent illness	Male Sex
Metabolic derangement	Chronic renal or hepatic disease
Surgery	
Environment (ICU, loud, etc)	
Pain	
Emotional distress	
Sleep deprivation	

Impact of Delirium

Estimated to cost more then $164 billion per year in the US (2008)

Associated with increased mortality when controlling for severity of illness, comorbidities, etc.

- In the ICU associated with 2-4x increased 1 year mortality
- Non-ICU associated with 1.5x increased 1 year mortality

Impact of Delirium

Increased length of stay when controlling for severity of illness, age, presence of dementia, etc.

Median LOS 5 days longer in MUSC patients who screened positive for delirium

Even greater impact on LOS if delirium was not present at admission

Less likely to be discharged home, and thus more likely to be discharged to nursing or rehab facility

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Cognitive Impact of Delirium

>50% of patients will experience up to a year of cognitive impairment

Increased rate of cognitive decline in patients with dementia

Marker of cognitive reserve in vulnerable patients

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Cognitive Impairment after Critical Illness

P.P. Pandharipande, T.D. Girard, J.C. Jackson, A. Morandi, J.L. Thompson, B.T. Pun, N.E. Brummel, C.G. Hughes, E.E. Vasilevskis, A.K. Shintani, K.G. Moons, S.K. Geevarghese, A. Canonico, R.O. Hopkins, G.R. Bernard, R.S. Dittus, and E.W. Ely, for the BRAIN-ICU Study Investigators*

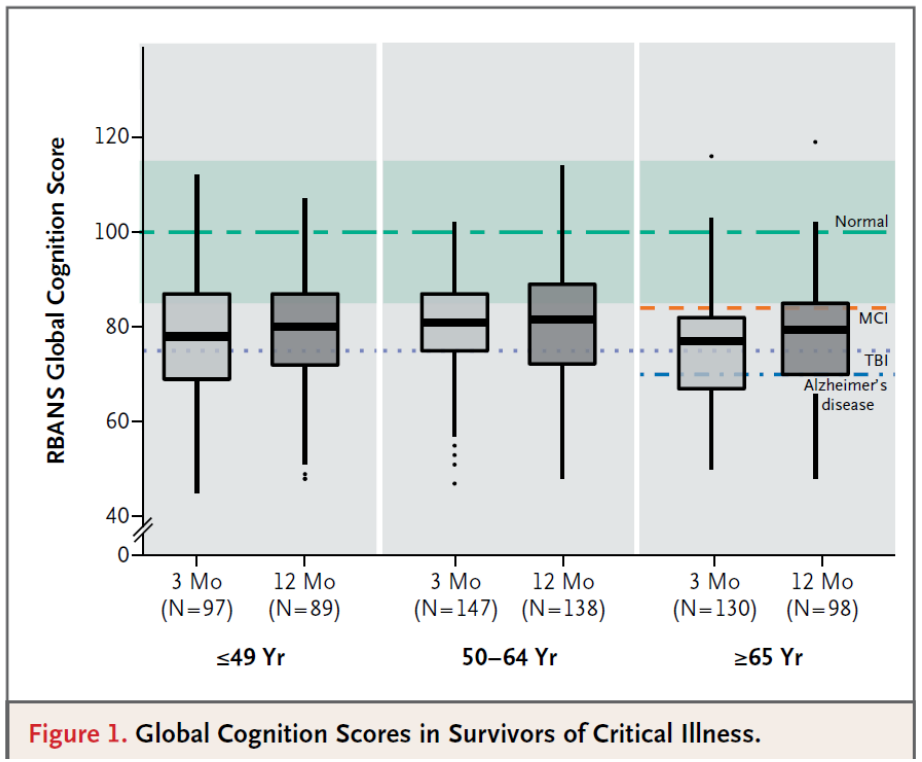

Figure 1. Global Cognition Scores in Survivors of Critical Illness.

- 861 ICU patients, 74% had delirium
- 34% of patients <49 yo had cognitive function below baseline, consistent with severe TBI at 12 months

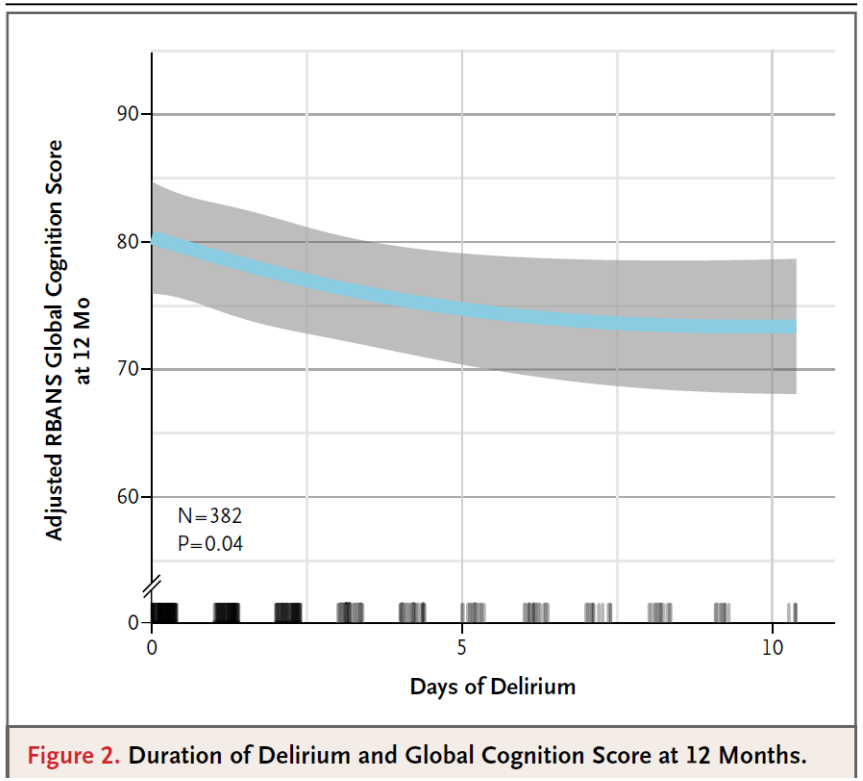

Figure 2. Duration of Delirium and Global Cognition Score at 12 Months.

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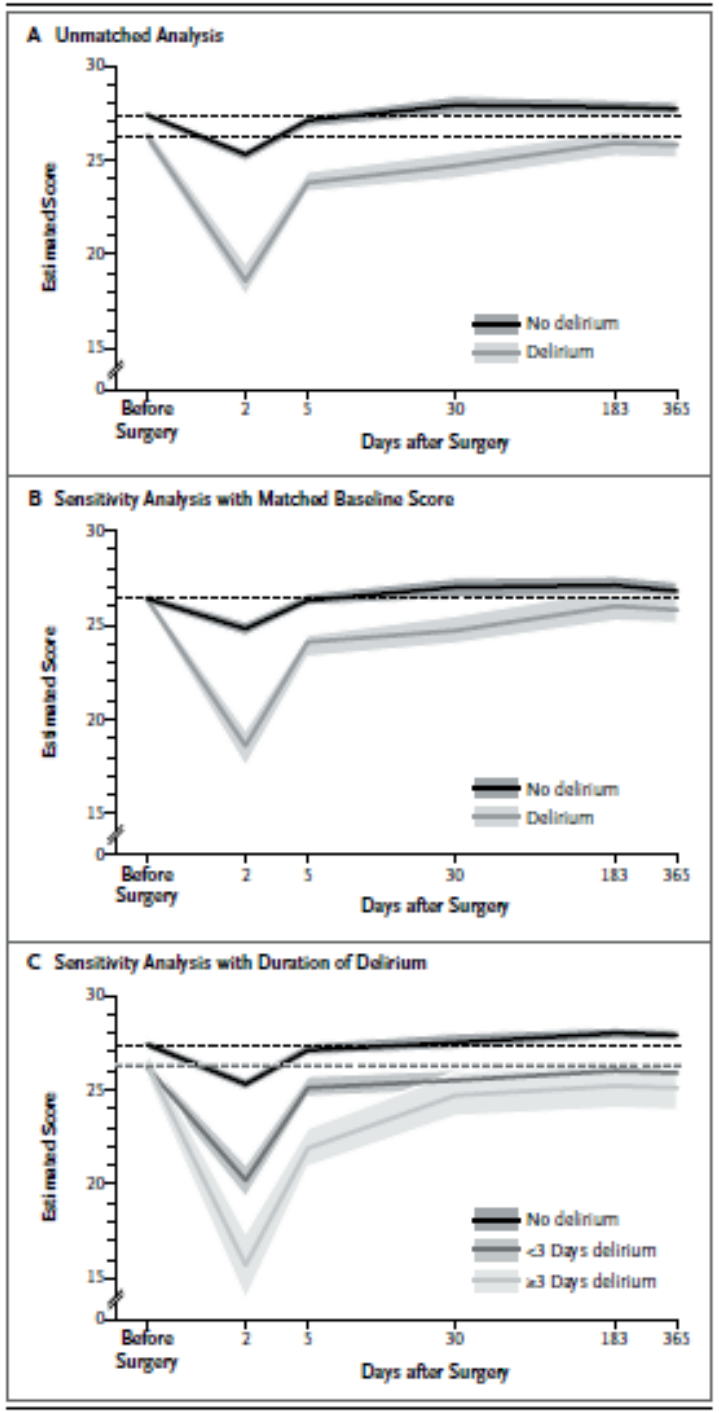

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cognitive Trajectories after Postoperative Delirium

Jane S. Saczynski, Ph.D., Edward R. Marcantonio, M.D., Lien Quach, M.P.H., M.S., Tamara G. Fong, M.D., Ph.D., Alden Gross, Ph.D., M.P.H., Sharon K. Inouye, M.D., M.P.H., and Richard N. Jones, Sc.D.

Table 3. Adjusted MMSE Scores over Time, According to Postoperative Delirium Status.*

Day of Assessment	Estimated Score		Difference in Estimated Score			Patients with Score below Baseline†		
	Delirium	No Delirium	Absolute Difference	Net Effect (95% CI)	P Value‡	Delirium	No Delirium	P Value
						percent		
Before surgery	25.8	26.9	1.1					
After surgery								
Day 2	18.1	24.8	6.7	−5.6 (−6.6 to −4.6)	<0.001	88	59	<0.001
Day 5	23.3	26.6	3.3	−2.2 (−2.8 to −1.3)	<0.001	82	51	<0.001
Day 30	24.1	27.4	3.3	−2.2 (−2.8 to −1.3)	<0.001	64	37	<0.001
Day 183	25.3	27.3	2.0	−0.9 (−1.8 to 0.0)	0.06	40	24	0.01
Day 365 and after	25.2	27.2	2.0	−0.9 (−1.8 to 0.0)	0.06	31	20	0.055

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RESEARCH PAPER

Recurrent delirium over 12 months predicts dementia: results of the Delirium and Cognitive Impact in Dementia (DECIDE) study

Sarah J. Richardson[1], Daniel H. J. Davis[2], Blossom C. M. Stephan[3], Louise Robinson[4], Carol Brayne[5], Linda E. Barnes[5], John-Paul Taylor[1], Stuart G. Parker[4], Louise M. Allan[6]

Delirium predicts development of dementia and reduction in MMSE

Table 2. Delirium as an independent predictor of new dementia diagnosis

	Analysis 1: Delirium during 2016 (yes)	Analysis 2: Total number of days with delirium during the year-long study period		Analysis 3: Total number of episodes of delirium during the year-long study period		Analysis 4: Delirium severity according to peak MDAS score during the year-long study period (per point)
		1–5 days	>5 days	1 episode	>1 episode	
Odds ratio (95% confidence interval), *P* value	8.8 (1.9–41.4), 0.006	9.3 (2.0–44.2), 0.005	8.4 (0.8–85.0), 0.072	8.6 (1.8–41.1), 0.007	13.9 (1.3–151.0), 0.031	1.3 (1.1–1.5), 0.012

Results of consecutive regression analyses exploring delirium variables which independently predict new dementia diagnosis at 1 year after hospital admission ($n = 135$). Other variables not shown but adjusted for in regression analysis were: age (at recruitment to DECIDE), sex, education, illness severity (peak total APACHE II score), baseline cognition (MMSE score at baseline), co-morbidity (total CIRS-G score recorded on recruitment to DECIDE), frailty (total Clinical Frailty Score recorded on recruitment to DECIDE, included as a continuous variable) and time between baseline and follow-up interviews.

Table 3. Delirium as an independent predictor of MMSE score at follow-up

	Analysis 1: Delirium during 2016 (yes)	Analysis 2: Total number of days with delirium during the year-long study period		Analysis 3: Total number of episodes of delirium during the year-long study period		Analysis 4: Delirium severity according to peak MDAS score during the year-long study period (per point)
		1–5 days	>5 days	1 episode	>1 episode	
Coefficient (95% confidence interval), *P* value	−1.8 (−3.5—−0.2), 0.030	−1.7 (−3.4—−0.1), 0.044	−5.1 (−8.1—−2.1), 0.001	−1.9 (−3.6—−0.2), 0.031	−1.5 (−4.7–1.7), 0.362	−0.4 (−0.6—−0.2), 0.001

Results of consecutive regression analyses exploring delirium variables which independently predict MMSE score at 1 year after hospital admission ($n = 135$). Other variables not shown but adjusted for in regression analysis were: age (at recruitment to DECIDE), sex, education, illness severity (peak total APACHE II score), baseline cognition (MMSE score at baseline), co-morbidity (total CIRS-G score recorded on recruitment to DECIDE), frailty (total Clinical Frailty Score recorded on recruitment to DECIDE, included as a continuous variable) and time between baseline and follow-up interviews.

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Part 2 Managing (maybe preventing) Delirium Objectives

Create an organized approach to how to approach delirium

Discuss the studies that have been done in pharmacologic management of delirium

Understand the limitations of delirium treatments

Step 1: What's causing the delirium

What is the baseline?

Look for all possible contributing factors

Do I need more information?

Potentially Modifiable Risk factors	Nonmodifiable Risk Factors
Sensory Impairment	Dementia or cognitive impairment
Immobilization (catheters or restraints)	Advancing age (>65yo)
Medications	History of delirium, stroke or falls
Acute neurological disease	Multiple comorbidities
Intercurrent illness	Male Sex
Metabolic derangement	Chronic renal or hepatic disease
Surgery	
Environment (ICU, loud, etc)	
Pain	
Emotional distress	
Sleep deprivation	

Causes of Delirium

I WATCH DEATH

Infection/**I**atrogenic (meds)

Withdrawal
Acute metabolic
Trauma/Uncontrolled pain
CNS Pathology
Hypoxia

Deficiencies (B12, thiamine, folate, niacin)
Endocrine
Acute vascular
Toxins
Heavy Metals

Initial basic work up

Up to date CBC, CMP and vitals

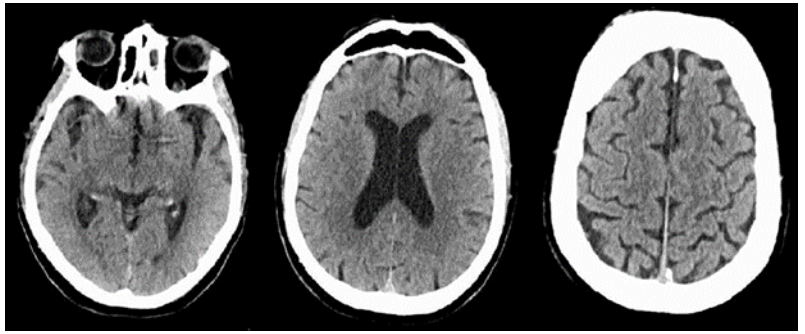
Infectious as indicated

- UA
- CXR-aspiration risk?
- Blood cultures if febrile or leukocytosis

Vitamin/hormonal-b12/folate, TSH

ABG-hypercarbia as possible cause, obese/OSA?

Do I need brain imaging?



Indications:

- Focal neurologic signs→ consider BAT
- Trauma/fall (esp if anticoagulated)

JHM 2014 retrospective study

- Only 6/220 CTs done for hospital-onset delirium were positive or equivocal
  - Excluded pts with fall, head trauma or new neuro deficit

Low yield

Consider MRI if prolonged/refractory course

Considering PRES or increased ICP (immunocompromised r/o crypto)

Do I need an EEG?

Possible Indications:

- Clinical signs of seizure
- More rapid change in level of alertness
- Non-convulsive status

Spot EEG is quick and easy to obtain

LTM only if clinically indicated.

- Could potentially make delirium worse

Do I need an EEG?

frontiers in Neurology

ORIGINAL RESEARCH
published: 19 March 2019
doi: 10.3389/fneur.2019.00263

Role of Epileptic Activity in Older Adults With Delirium, a Prospective Continuous EEG Study

*Sara Sambin[1], Nicolas Gaspard[1], Benjamin Legros[1], Chantal Depondt[1], Sandra De Breucker[2] and Gilles Naeije[1]**

[1] Neurology Department, ULB-Hôpital Erasme, Université Libre de Bruxelles (ULB), Brussels, Belgium, [2] Geriatrics Department, ULB-Hôpital Erasme, Université Libre de Bruxelles (ULB), Brussels, Belgium

	n (%)
EEG BACKGROUND	
Mild generalized slowing	40 (80%)
Moderate generalized slowing	8 (16%)
Severe generalized slowing	1 (2%)
Focal slowing	18 (36%)
Focal attenuation	10 (20%)
Sporadic discharges	10 (20%)
Focal	6 (12%)
Multifocal	3 (6%)
Bilateral independent	1 (2%)
Periodic discharges	11 (22%)
GPDs	8 (16%)
LPDs	3 (6%)
Seizures	7 (14%)
NCSE	6 (12%)

- Prospective EEGs of elderly (>65yo) delirious patients
- 12% had non-convulsive status

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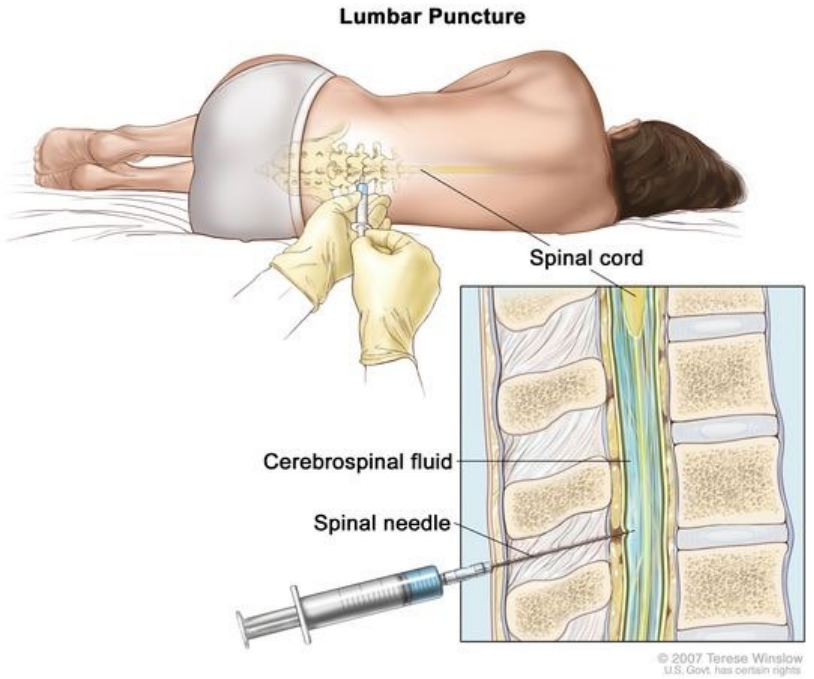
Do I need an LP?



Are they immunosuppressed?

What are you looking for?

Infection: fever, nuchal rigidity

*HSV and crypto serum PCRs

Paraneoplastic: less acute course

Possible biomarkers being studied

Catecholamines (Dopamine actually lower?!) (Henjum, et al. Brain Communications 2021)

AB42, t-tau, 5-HIAA, AChE

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Journal of Gerontology: MEDICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci. 2010 October;65A(10):1130–1136
doi:10.1093/gerona/glq090

Advance Access published on June 7, 2010

Cerebrospinal Fluid in Long-Lasting Delirium Compared With Alzheimer's Dementia

Gideon A. Caplan,[1,2] Tasha Kvelde,[1] Christina Lai,[3] Swee L. Yap,[3] Cheryl Lin,[3] and Mark A. Hill[4]

	Delirium	Dementia	
	Mean (*SD*)	Mean (*SD*)	*p* Value
CSF lactate (mmol/L)	1.87 (0.31)	1.48 (0.23)	<.001
CSF protein (g/L)	0.62 (0.33)	0.44 (0.15)	.036
CSF glucose (mmo/L)	3.90 (0.95)	3.65 (1.48)	.54
CSF S100B (pg/mL)	604.8 (163.0)	697.4 (306.9)	.33
CSF S100B (pg/mL) median (interquartile range)	640.1 (462.7–700.6)	612.5 (504.7–774.5)	
CSF neuron-specific enolase (ng/mL)	4.84 (2.02)	8.98 (2.98)	<.001
Lactate (mmol/L)	1.78 (1.62)	1.26 (0.39)	.295
Protein (g/L)	59.44 (7.50)	66.94 (3.86)	.001
Glucose (mmol/L)	6.12 (1.50)	5.87 (2.35)	.801
S100B (pg/mL)	0.34 (0.60)	0.13 (0.16)	.469
S100B (pg/mL) median (interquartile range)	0.053 (0.0–0.25)	0.024 (0.002–0.173)	

Note: CSF = cerebrospinal fluid.

Step 2: Control what you can control

Optimize your patient

- All electrolytes normalized
- BP as tight as is safe

Continue to look for additional causes/contributing factors

Environmental factors

Potentially Modifiable Risk factors	Nonmodifiable Risk Factors
Sensory Impairment	Dementia or cognitive impairment
Immobilization (catheters or restraints)	Advancing age (>65yo)
Medications	History of delirium, stroke or falls
Acute neurological disease	Multiple comorbidities
Intercurrent illness	Male Sex
Metabolic derangement	Chronic renal or hepatic disease
Surgery	
Environment (ICU, loud, etc)	
Pain	
Emotional distress	
Sleep deprivation	

Don’t forget the basics

Urinary retention

Constipation

Nutrition/hydration

Untreated pain

(Safely) Remove offending medications

- Benzodiazepines (maybe taper off)
- Anticholinergics
- Antihistamines
- H2 blockers
- Steroids
- Psychiatric medications?
- Sleep aids

Table 1. 1997 Beers List of Potentially Inappropriate Drugs for Elderly Persons[5] (With Zhan Appropriateness Classification[6])*

- Cardiovascular-renal drugs
  - Antiarrhythmic agents
    - Disopyramide SI
  - Antihypertensive agents or α-agonist/α-blockers
    - Methyldopa SI
    - Reserpine SI
  - Coronary vasodilators or cerebral/peripheral vascular disorder drugs
    - Cyclandelate NC
    - Ergot mesyloids NC
  - Urinary tract relaxants/stimulants
    - Oxybutynin SI
- Central nervous system agents
  - Sedative/hypnotic agents
    - Barbiturates† AA
    - Flurazepam AA
  - Antianxiety agents
    - Chlordiazepoxide RA
    - Diazepam RA
    - Meprobamate AA
  - Antidepressants
    - Amitriptyline‡ SI
    - Doxepin SI
- Gastrointestinal agents
  - Acid/peptic disorders
    - Belladonna alkaloids AA
    - Propantheline AA
  - Antidiarrheal agents
    - Dicyclomine AA
  - Antispasmodics/anticholinergics
    - Clidinium-chlordiazepoxide RA
    - Hyoscyamine AA
- Hematologic agents
  - Anticoagulants
    - Dipyridamole SI
    - Ticlopidine SI
- Hormones/hormonal mechanisms
  - Blood glucose regulators
    - Chlorpropamide AA
- Neurologic drugs
  - Skeletal muscle hyperactivity
    - Carisoprodol RA
    - Chlorzoxazone RA
    - Cyclobenzaprine RA
    - Metaxlone RA
    - Methocarbamol RA
- Otologics
  - Vertigo/vomiting
    - Trimethobenzamide AA
- Relief of pain
  - Analgesics
    - Meperidine AA
    - Propoxyphene RA
    - Pentazocine AA
  - Nonsteroidal anti-inflammatory and antiarthritic drugs
    - Indomethacin SI
    - Phenylbutazone NC
- Respiratory tract
  - Antihistamines
    - Chlorpheniramine SI
    - Cyproheptadine SI
    - Dexchlorpheniramine NC
    - Diphenhydramine SI
    - Hydroxyzine SI
    - Promethazine SI
    - Tripelennamine NC

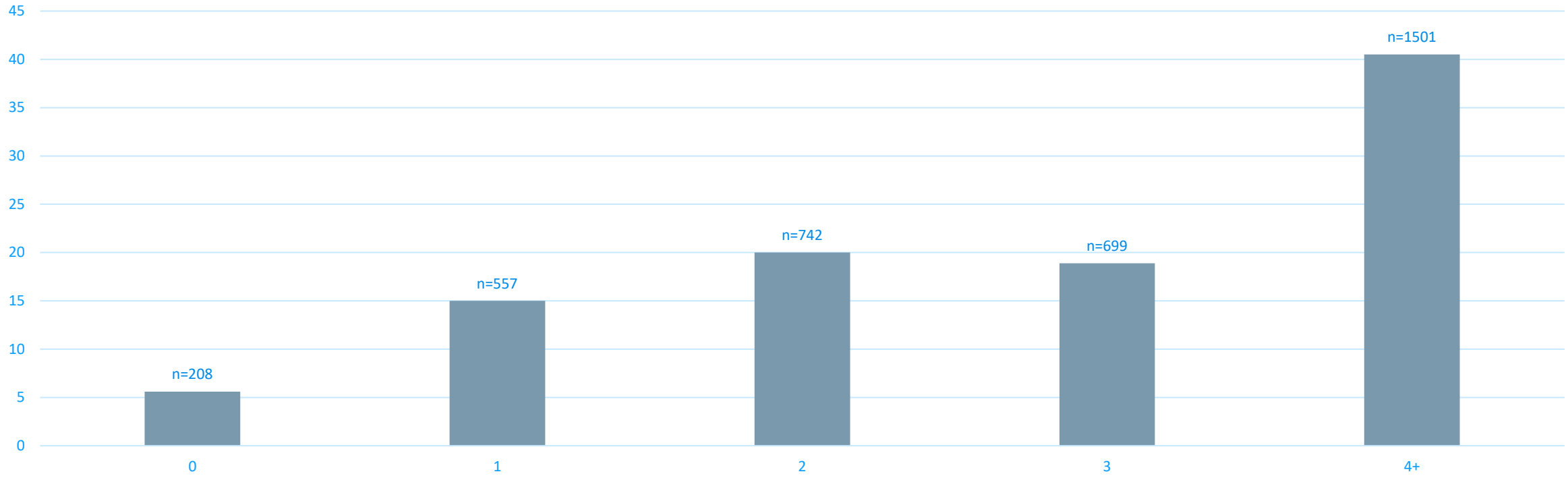
Abbreviations: AA, always avoid; NC, not classified; RA, rarely appropriate; SI, some indications.

*Organized by National Drug Code drug class, subclass, individual drugs (single or combination medications with these drugs [except clidinium alone] counted as potentially inappropriate), and Zhan appropriateness classification.

†Butabarbital, pentobarbital, and secobarbital.

‡Including amitriptyline with chlordiazepoxide and amitriptyline with perphenazine.

Figure 2: Percentage of all admissions with delirium and # of BEERS Criteria meds recieved



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Environmental interventions for delirium

Sleep:

- Lights on during day, off at night
- Move room, further from nursing station
- Sleep plan: schedule of vitals, plans
- Melatonin?

Reduce lines, tubes, restraints

Re-orientation, familiar setting (family)

Cognitive stimulation

Early mobilization

Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU

John W. Devlin, PharmD, FCCM (Chair)[1,2]; Yoanna Skrobik, MD, FRCP(c), MSc, FCCM (Vice-Chair)[3,4]; Céline Gélinas, RN, PhD[5]; Dale M. Needham, MD, PhD[6]; Arjen J. C. Slooter, MD, PhD[7]; Pratik P. Pandharipande, MD, MSCI, FCCM[8]; Paula L. Watson, MD[9]; Gerald L. Weinhouse, MD[10]; Mark E. Nunnally, MD, FCCM[11,12,13,14]; Bram Rochwerg, MD, MSc[15,16]; Michele C. Balas, RN, PhD, FCCM, FAAN[17,18]; Mark van den Boogaard, RN, PhD[19]; Karen J. Bosma, MD[20,21]; Nathaniel E. Brummel, MD, MSCI[22,23]; Gerald Chanques, MD, PhD[24,25]; Linda Denehy, PT, PhD[26]; Xavier Drouot, MD, PhD[27,28]; Gilles L. Fraser, PharmD, MCCM[29]; Jocelyn E. Harris, OT, PhD[30]; Aaron M. Joffe, DO, FCCM[31]; Michelle E. Kho, PT, PhD[30]; John P. Kress, MD[32]; Julie A. Lanphere, DO[33]; Sharon McKinley, RN, PhD[34]; Karin J. Neufeld, MD, MPH[35]; Margaret A. Pisani, MD, MPH[36]; Jean-Francois Payen, MD, PhD[37]; Brenda T. Pun, RN, DNP[23]; Kathleen A. Puntillo, RN, PhD, FCCM[38];

Daily sedation interruption

Light sedation (RASS goal of 0 to -2)

Avoid benzodiazepines

Analgesia only sedation if possible

Early mobility

**No specific recommendation on pharmacologic interventions (treatment or prevention)

(Devlin 2018)

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Early Mobility

Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial

William D Schweickert, Mark C Pohlman, Anne S Pohlman, Celerina Nigos, Amy J Pawlik, Cheryl L Esbrook, Linda Spears, Megan Miller, Mietka Franczyk, Deanna Deprizio, Gregory A Schmidt, Amy Bowman, Rhonda Barr, Kathryn E McCallister, Jesse B Hall, John P Kress

(Schweickert 2009)

	Intervention (n=49)	Control (n=55)	p value
Return to independent functional status at hospital discharge	29 (59%)	19 (35%)	0·02
ICU delirium (days)	2·0 (0·0–6·0)	4·0 (2·0–7·0)	0·03
Time in ICU with delirium (%)	33% (0–58)	57% (33–69)	0·02
Hospital delirium (days)	2·0 (0·0–6·0)	4·0 (2·0–8·0)	0·02
Hospital days with delirium (%)	28% (26)	41% (27)	0·01
Barthel Index score at hospital discharge	75 (7·5–95)	55 (0–85)	0·05
ICU-acquired paresis at hospital discharge	15 (31%)	27 (49%)	0·09
Ventilator-free days*	23·5 (7·4–25·6)	21·1 (0·0–23·8)	0·05
Duration of mechanical ventilation (days)	3·4 (2·3–7·3)	6·1 (4·0–9·6)	0·02
Duration of mechanical ventilation, survivors (days)	3·7 (2·3–7·7)	5·6 (3·4–8·4)	0·19
Duration of mechanical ventilation, non-survivors (days)	2·5 (2·4–5·5)	9·5 (5·9–14·1)	0·04
Length of stay in ICU (days)	5·9 (4·5–13·2)	7·9 (6·1–12·9)	0·08
Length of stay in hospital (days)	13·5 (8·0–23·1)	12·9 (8·9–19·8)	0·93
Hospital mortality	9 (18%)	14 (25%)	0·53

Data are n (%), median (IQR), or mean (SD). ICU=intensive care unit. *Ventilator-free days from study day 1 to day 28. Barthel Index scale 0–100, APACHE II scale 0–71.

***Table 3:* Main outcomes according to study group**

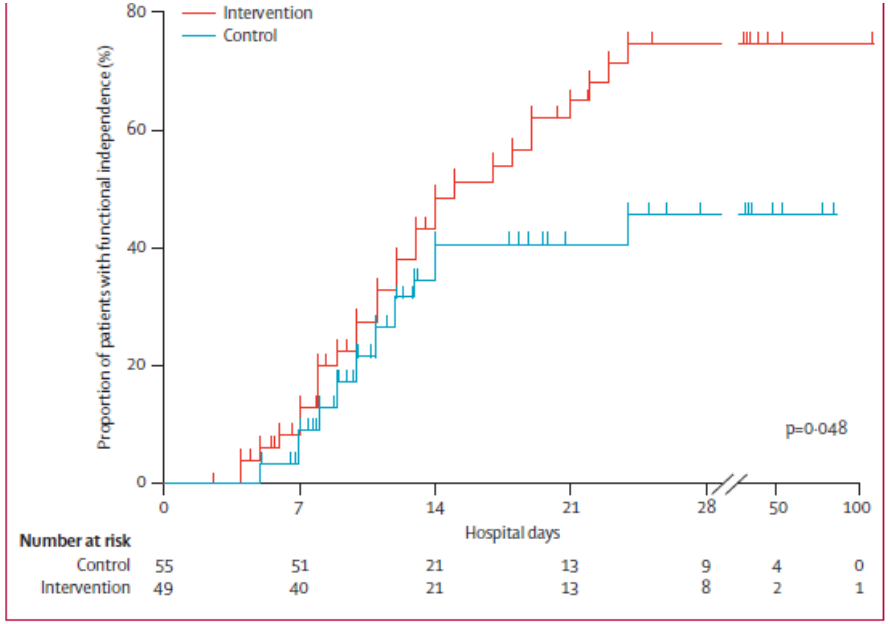

***Figure 2:* Probability of return to independent functional status in intervention and control groups**

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Pharmacologic Prevention?

JOURNAL OF THE AMERICAN GERIATRICS SOCIETY

AGS Geriatrics Healthcare Professionals
Leading Change. Improving Care for Older Adults.

CLINICAL INVESTIGATIONS

Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis

Karin J. Neufeld, MD, MPH,[*a] *Jirong Yue, MD,*[§a] *Thomas N. Robinson, MD, MPH,*[‖] *Sharon K. Inouye, MD, MPH,*[**††b] *and Dale M. Needham, MD, PhD*[††b]

Meta-analysis: 19 studies of medical and surgical patients

Current evidence does not support the use of antipsychotics for the prevention (or treatment) of delirium.

Pharmacologic Prevention?

Dexmedetomidine: Alpha-2 agonist

- Reduction in delirium incidence (when compared to lorazepam and midazolam)
- 'Safer sedative'?
- Value as an additive to ICU sedation. Possible reduction of use of more offensive medications
- Not well studied in non-ICU.

Melatonin: Hormone created in pineal gland used in circadian rhythm

- Emerging but mixed evidence
- Meta-analysis of 4 RCTs trends towards benefit (Chen, et al, 2016)
- Lower side effects than other options
- Schedule, low dose

Suvorexant: (Belsomra) Orexin antagonist. Sleep-aid by design

- Meta-analysis (Xu, et al, 2020) of 7 studies with significant reduction in delirium incidence, time to delirium
- Did not effect other outcomes (LOS, mortality, etc)

Step 3: Does my patient need medication for behavioral control

Non-pharmacologic interventions have failed

Patient is at risk of harm to self, staff or others

Patient behavioral symptoms are interfering with treatment

Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU

John W. Devlin, PharmD, FCCM (Chair)[1,2]; Yoanna Skrobik, MD, FRCP(c), MSc, FCCM (Vice-Chair)[3,4]; Céline Gélinas, RN, PhD[5]; Dale M. Needham, MD, PhD[6]; Arjen J. C. Slooter, MD, PhD[7]; Pratik P. Pandharipande, MD, MSCI, FCCM[8]; Paula L. Watson, MD[9]; Gerald L. Weinhouse, MD[10]; Mark E. Nunnally, MD, FCCM[11,12,13,14]; Bram Rochwerg, MD, MSc[15,16]; Michele C. Balas, RN, PhD, FCCM, FAAN[17,18]; Mark van den Boogaard, RN, PhD[19]; Karen J. Bosma, MD[20,21]; Nathaniel E. Brummel, MD, MSCI[22,23]; Gerald Chanques, MD, PhD[24,25]; Linda Denehy, PT, PhD[26]; Xavier Drouot, MD, PhD[27,28]; Gilles L. Fraser, PharmD, MCCM[29]; Jocelyn E. Harris, OT, PhD[30]; Aaron M. Joffe, DO, FCCM[31]; Michelle E. Kho, PT, PhD[30]; John P. Kress, MD[32]; Julie A. Lanphere, DO[33]; Sharon McKinley, RN, PhD[34]; Karin J. Neufeld, MD, MPH[35]; Margaret A. Pisani, MD, MPH[36]; Jean-Francois Payen, MD, PhD[37]; Brenda T. Pun, RN, DNP[23]; Kathleen A. Puntillo, RN, PhD, FCCM[38];

Guidelines do not recommend use of antipsychotics due to insufficient high quality studies

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

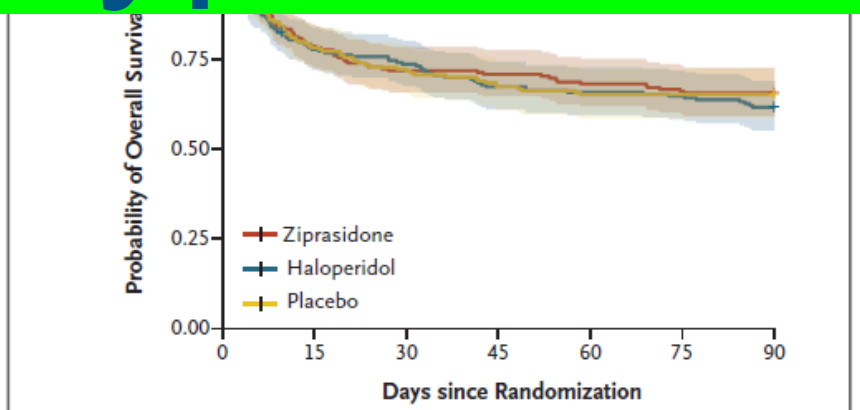
Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness

588 patien

Ziprasidon

No differe

Do not use antipsychotics for hypoactive delirium!



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.

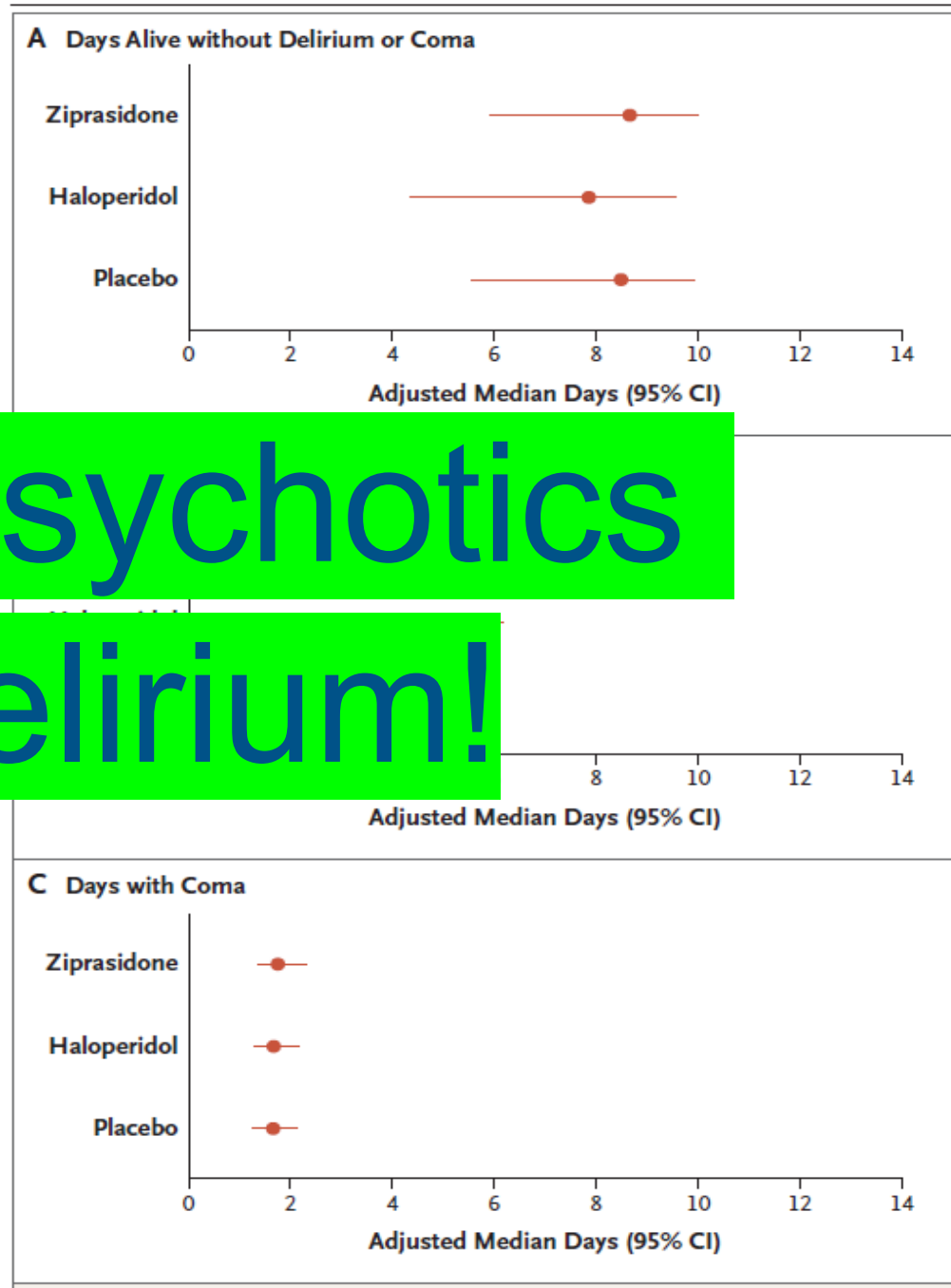


Figure 2. Effects of Haloperidol, Ziprasidone, and Placebo on Days Alive without Delirium or Coma, Days with Delirium, and Days with Coma.

Behavioral symptoms and agitation from delirium

A few things to keep in mind when recommending antipsychotics:

- Black box warning for all cause mortality in patients with dementia
- Multiple studies that show no benefit
- Critical Care Medicine guidelines say not to use
- Meds not without side effects (EPS, QT prolongation)
- Not all antipsychotics are the same

Behavioral symptoms and agitation from delirium

You're choosing the best sedative for your patient

Efficacy and safety of quetiapine in critically ill patients with delirium: A prospective, multicenter, randomized, double-blind, placebo-controlled pilot study*

John W. Devlin, PharmD; Russel J. Roberts, PharmD; Jeffrey J. Fong, PharmD; Yoanna Skrobik, MD; Richard R. Riker, MD; Nicholas S. Hill, MD; Tracey Robbins, RN; Erik Garpestad, MD

Pilot study, 18 in each arm. Quetiapine (+PRN Haloperidol) vs placebo

Shorter duration of delirium in quetiapine arm

Reduction in use of other sedatives

Behavioral symptoms and agitation for delirium

Your pharmacologic tools:

- Antipsychotics
- Dexmedetomidine (alpha-2 agonist)
- Benzodiazepines
- Melatonin

Pharmacologic Treatment

No FDA approved medications for treatment of delirium

Antipsychotics: Diverse drug class, widely used

- Many studies, mixed evidence
- Recent m … lence, duration,
- Very patie
- Treating s
  - Psych
  - Agitat
  - Patier
  - Risk reduction

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. RISPERDAL® (risperidone) is not approved for the treatment of patients with dementia-related psychosis.
[See Warnings and Precautions (5.1)]

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Antipsychotics and QTc

- Concern for QTc prolongation, development of Torsades de Pointes and/or ventricular fibrillation and sudden cardiac death
- Antipsychotics bind to Potassium channel (as do all QT prolonging drugs)
- Do not need to wait to give antipsychotic in an agitated/dangerous patient to get a baseline EKG

	Women (msec)	Men (msec)
Normal	<450	<430
Borderline	451-470	431-450
Prolonged	>470	>450

a These values assume the absence of any drug or disease.

- Risk factors: Older (>65yo), known cardiac disease, electrolyte disturbance, female sex
- Risk increases with higher dose of medication

Ray, W, et al. Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death. NEJM. 2009. **360.**

Antipsychotics and QTc

QT corrected for rate

- Bazett= $QT/(RR^{1/2})$
- Fridericia= $QT/(RR^{1/3})$

Most (if not all cases) of sudden cardiac death occur at very large doses (>50mg of haldol/day)

Drug	QTc (Bazett) [msec]	QTc (Fridericia) [msec]	Heart rate (beats per min)
Thioridazine	+35.8	+29.6	+5.7
Ziprasidone	+20.6	+15.6	+4.6
Quetiapine	+14.5	+4.8	+11.2
Risperidone	+10.0	+3.0	+6.4
Olanzapine	+6.4	+1.1	+6.5
Haloperidol	+4.7	+7.3	−2.9

How to approach QTc and Antipsychotics

1. Obtain EKG for baseline and monitoring, when safely able to do so, proceed with great caution if >500
2. Limit additional QT prolonging drugs if possible
3. Do not exceed upper limit of recommended dose
    a) Haldol 20mg/day, Seroquel 300-600mg/day, Zyprexa 20mg/day
4. Restrict dose in those with pre-existing heart disease
5. Ensure electrolytes are stable and replaced as indicated
6. Stop antipsychotics if QT increases or exceeds 500
7. Stop/reduce antipsychotic when no longer needed

Practical selection of antipsychotic for hyperactive delirium

- Single agent preferred
- Start low dose
- Recognize diminishing returns of increased dose
- Always have a discontinuation plan

Typical or atypical

Haloperidol (Haldol)

- Multiple formulations (IV/PO/IM)
- Risk of dystonia/EPS, NMS, TD and QT prolongation
- IV for severe agitation
- Risk of high doses with schedule + PRN
- Staff more comfortable

Quetiapine (Seroquel)

- Only PO
- Risk of orthostasis (falls), NMS (less so?), QT prolongation
- Hard to give pill when severely agitated
- Low risk of achieving high daily dose
- Good for ‘sundowning’

Olanzapine (Zyprexa)

- PO (pill and ODT) and IM
- Orthostasis, high dose is anticholinergic
- Risk of NMS, QT prolongation
- Can’t give with IV lorazepam
- Higher potency=less dosing intervals

How much do I give?

Haloperidol (Haldol)

Daily Max 20mg/day

Acute agitation (once)

- 2mg IV or 5mg PO.
- Frail/elderly 0.5-1mg IV or 2.5mg PO

Scheduled (chronic)

- 5mg PO Q8H (or more frequent)
- Include PRN doses (2mg IV).

Quetiapine (Seroquel)

Daily Max 1200mg/day (300-600mg/day)

Acute agitation

- 25-50mg PO
- Frail/elderly 12.5-25mg

Scheduled

- 25mg Q8H (consider 50mg QHS)
- 25mg Q8H PRN agitation

Olanzapine (Zyprexa)

Daily Max 20mg/day

Acute agitation (once)

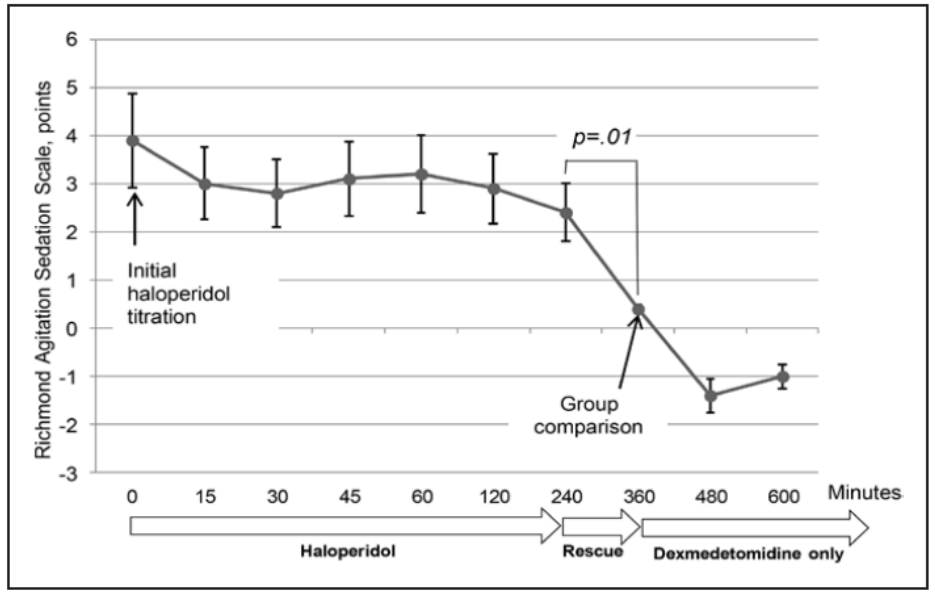
- 2.5-5mg IM/PO
- Frail/elderly 2.5mg IM/PO

Scheduled

- 2.5-5mg PO daily
- Consider PRN dosing (2.5mg Q8H PRN)

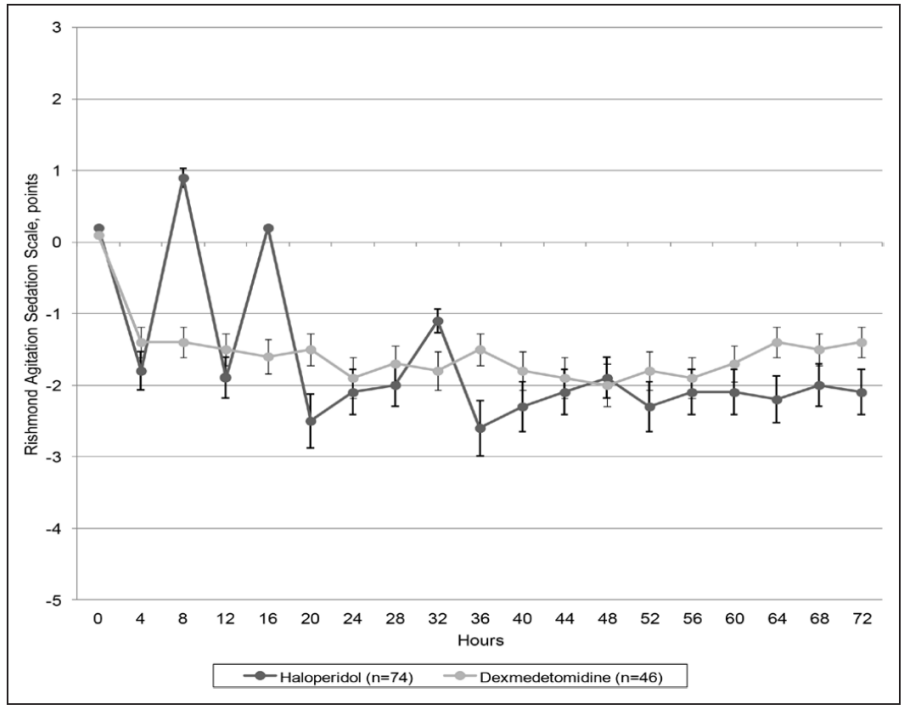
Dexmedetomidine for the Treatment of Hyperactive Delirium Refractory to Haloperidol in Nonintubated ICU Patients: A Nonrandomized Controlled Trial*

Genís Carrasco, PhD, MD; Nacho Baeza, MD; Lluís Cabré, PhD, MD; Eugenia Portillo, RN; Gemma Gimeno, RN; David Manzanedo, RN; Milagros Calizaya, MD



Not randomized
Used for rescue with haloperidol failure in non-intubated patients

Conclusion: safe alternative in patients not responding to antipsychotic



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When to use a benzodiazepine in treating agitation from delirium

- Concurrent catatonia (hyperactive catatonia)—more next week
- Withdrawal syndromes
- Refractory symptoms
- Immediate procedural need and antipsychotics not working (LP, MRI)
    - How bad do you need it?
- End of life

JAMA | Preliminary Communication

Effect of Lorazepam With Haloperidol vs Haloperidol Alone on Agitated Delirium in Patients With Advanced Cancer Receiving Palliative Care
A Randomized Clinical Trial

David Hui, MD, MSc; Susan Frisbee-Hume, MS; Annie Wilson, MSN; Seyedeh S. Dibaj, PhD; Thuc Nguyen, RN; Maxine De La Cruz, MD; Paul Walker, MD; Donna S. Zhukovsky, MD; Marvin Delgado-Guay, MD; Marieberta Vidal, MD; Daniel Epner, MD; Akhila Reddy, MD; Kimerson Tanco, MD; Janet Williams, MPH; Stacy Hall, MSN; Diane Liu, MSc; Kenneth Hess, PhD; Sapna Amin, PharmD; William Breitbart, MD; Eduardo Bruera, MD

90 patients randomized to haloperidol + lorazepam or haloperidol + placebo

Adding lorazepam resulted in less need for PRN antipsychotics and increased in perceived comfort by blinded caregivers and nurses

JAMA | Preliminary Communication

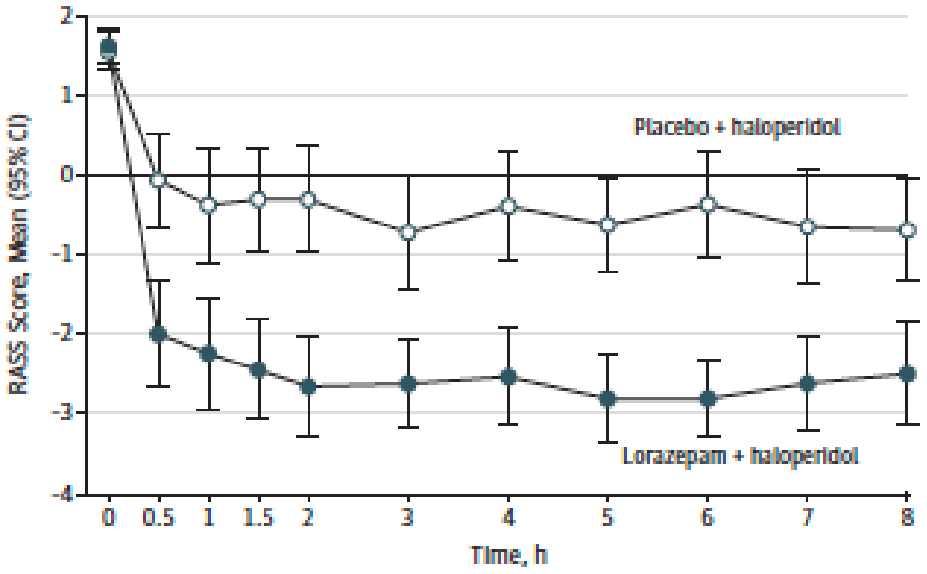
Effect of Lorazepam With Haloperidol vs Haloperidol Alone on Agitated Delirium in Patients With Advanced Cancer Receiving Palliative Care
A Randomized Clinical Trial

David Hui, MD, MSc; Susan Frisbee-Hume, MS; Annie Wilson, MSN; Sayedeh S. Dibaj, PhD; Thuc Nguyen, RN; Maxine De La Cruz, MD; Paul Walker, MD; Donna S. Zhukovsky, MD; Marvin Delgado-Guay, MD; Marieberta Vidal, MD; Daniel Epner, MD; Akhila Reddy, MD; Kimerson Tanco, MD; Janet Williams, MPH; Stacy Hall, MSN; Diana Liu, MSc; Kenneth Hess, PhD; Sapna Amin, PharmD; William Breitbart, MD; Eduardo Bruera, MD

Haloperidc ed to haloperido

Perception p

A RASS scores from baseline to 8 h



No. of patients											
Lorazepam + haloperidol	29	29	29	29	29	29	28	26	26	26	26
Placebo + haloperidol	29	29	29	29	29	29	28	27	27	26	26

Is there a role for benzodiazepines?

Persistent agitated delirium, alcohol withdrawal delirium

Most trials found lorazepam/midazolam made symptoms worse, or less effective then antipsychotics

- Breitbart et al. haloperidol vs chlopromazine vs lorazepam stopped early bc of sedation in lorazepam group

May be helpful when antipsychotics contraindicated; Lewy body and Parkinsons

JAMA Psychiatry | Original Investigation

Association of Delirium Response and Safety of Pharmacological Interventions for the Management and Prevention of Delirium

A Network Meta-analysis

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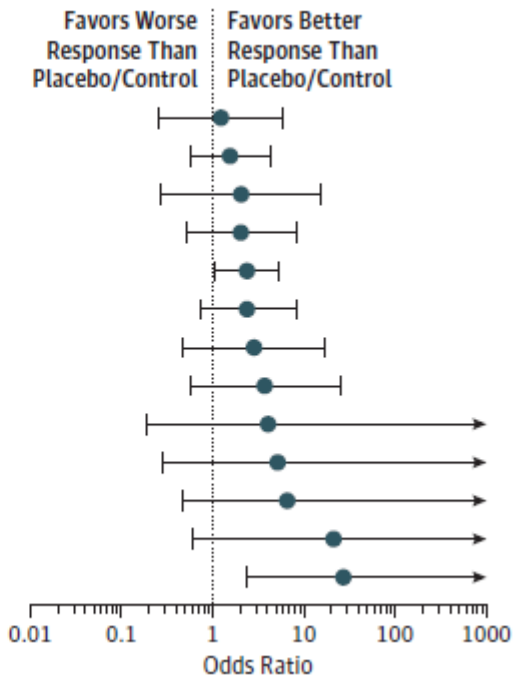
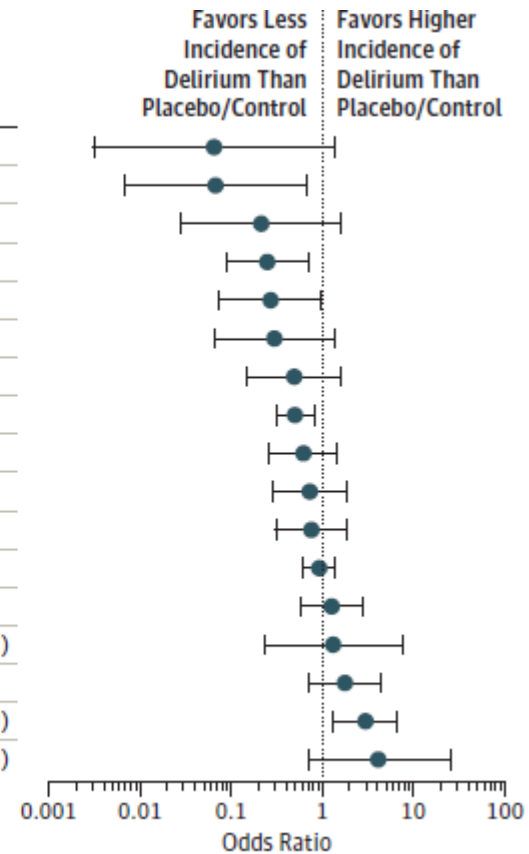
C Treatment response

Source	Odds Ratio With 95% CI and 95% Prediction Interval	
Ondansetron hydrochloride	1.23 (0.24-6.22)	(0.03-53.71)
Risperidone	1.57 (0.56-4.38)	(0.07-37.78)
Haloperidol plus rivastigmine tartrate	2.06 (0.27-15.71)	(0.03-147.19)
Dexmedetomidine hydrochloride	2.06 (0.51-8.34)	(0.06-70.60)
Haloperidol	2.37 (1.04-5.43)	(0.12-48.80)
Olanzapine	2.46 (0.71-8.57)	(0.08-72.49)
Ziprasidone hydrochloride	2.89 (0.48-17.29)	(0.05-153.40)
Quetiapine fumarate	3.78 (0.55-25.84)	(0.06-235.65)
Amisulpride	4.10 (0.18-91.61)	(0.01-1256.98)
Lorazepam	5.34 (0.28-101.95)	(0.02-1308.79)
Chlorpromazine hydrochloride	6.68 (0.47-95.24)	(0.04-1089.82)
Rivastigmine tartrate	21.87 (0.61-790.15)	(0.04-13477.64)
Haloperidol plus lorazepam	28.13 (2.38-333.08)	(0.22-3563.80)



D Occurence rate of delirium

Source	Odds Ratio With 95% CI and 95% Prediction Interval	
Suvorexant	0.06 (0.00-1.36)	(0.00-1.91)
Ramelteon	0.07 (0.01-0.66)	(0.00-0.92)
Donepezil hydrochloride	0.21 (0.03-1.62)	(0.02-2.27)
Olanzapine	0.25 (0.09-0.69)	(0.06-1.05)
Risperidone	0.27 (0.07-0.99)	(0.05-1.45)
Propofol plus midazolam hydrochloride	0.30 (0.07-1.33)	(0.05-1.92)
Ondansetron hydrochloride	0.49 (0.15-1.60)	(0.10-2.38)
Dexmedetomidine hydrochloride	0.50 (0.31-0.80)	(0.17-1.47)
Rivastigmine tartrate	0.62 (0.26-1.46)	(0.17-2.32)
Lorazepam	0.73 (0.28-1.89)	(0.18-2.94)
Melatonin	0.76 (0.30-1.87)	(0.19-2.94)
Haloperidol	0.91 (0.60-1.38)	(0.32-2.61)
Gabapentin	1.26 (0.58-2.77)	(0.36-4.49)
Clonidine hydrochloride	1.33 (0.23-7.57)	(0.17-10.72)
Propofol	1.78 (0.70-4.51)	(0.45-7.05)
Midazolam hydrochloride	2.98 (1.30-6.80)	(0.81-10.90)
Midazolam hydrochloride plus clonidine hydrochloride	4.16 (0.69-25.25)	(0.49-35.66)



Delirium prevention with melatonin/ramelteon?

Diverse studies, with limited high quality RCTs and mixed results

Generally low risk

- Low dose (1-3mg)
- Scheduled

CCM: 2025 UPDATE- recommend using melatonin for sleep over not-melatonin

Step 4: Educate team, nursing and family

Document clearly

Convey severity to team

Discuss with family, empower them to help

Questions?

MUSC
Medical University
of South Carolina