Delirium:

Why "Pleasantly Confused" Isn't So Pleasant!

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Disclosures

- I have no financial relationships or affiliations to disclose.
- I will not discuss off-label use and/or investigational use in my presentation.
- My views do not reflect those of the Veterans Administration or UAB School of Medicine.

Objectives

- Understand the epidemiology of delirium
- Identify the clinical features of delirium and the significance especially in older adults
- Enhance the ability to distinguish delirium from dementia and depression
- Identify risk factors for delirium
- Describe the roles of interprofessional team members in delirium prevention and management, and *limited role for medication*

Case: Mr. M

- 71 yo male Vietnam Veteran admitted to inpatient medicine wards with “acute confusion & A/V hallucinations”
- HPI: weakness, inability to get out of chair, worsening confusion x 3 days PTA
- PMH: T2DM with PPN, OSA, PTSD, prostate cancer, MDD/generalized anxiety, CKD, chronic LBP/DJD
- Social: HS/Vocational school – carpenter; no substances, disabled x “years” due to multiple spine surgeries/back pain, wife x 48 yrs, 3 kids
- FH: both parents and many sibs with dementia
- Prescribed Home Meds: gabapentin 1800mg, hydroxyzine 50 mg, sertraline 100 mg, melatonin 10 mg, oxycodone 15 mg , ranitidine 300 mg, simvastatin 80 mg

Case: Mr. M

- Findings: Weak trunk/quads, mild AKI; B12 287; CTH neg.; UR/FI ruled out; most meds held or decr.; SLUMS 10/30 day #2…
- Geri Med asked to see: "*rule out Lewy Body Dementia"*
- Entire history per chart/wife given global state of disorientation, rambling nonsensically
- Function: Endorses dizziness, falls, UI/FI since prostate ca Tx, trouble walking (Rollator), memory/driving probs (per family), chronic LBP, hearing imp., refusal to tolerate CPAP so doesn't wear/never sleeps well; has spent last 40 yrs in same chair day & night, seeing/hearing son's dog in hospital room since admission – thinks he's home
- But why did he get confused NOW???
- Upon extensive questioning, wife admits he was using something at home to help with "*head congestion caused by attempts to wear CPAP…*"

Defining Delirium

Delirium

- Acute disorder of attention and global cognition (memory and perception)
- From Latin “lira” – the ridge left by plowing
- Verb *delirare* = make an irregular ridge; off the track
- MANY synonyms which add to the confusion
  - Acute confusional state
  - Acute mental status change
  - Organic brain syndrome
  - Crazy NOS
  - Subacute befuddlement
  - Toxic or metabolic encephalopathy

DSM V Criteria

- Disturbance in attention (ie, reduced ability to direct, focus, sustain and shift attention and awareness)
- Change in cognition (eg, memory deficit, disorientation, language disturbance) or a perceptual disturbance not better accounted for by existing condition such as dementia
- Acute and fluctuating
- Evidence that it is a consequence of a medical condition, drug, medication, or multiple sources

Epidemiology

- Common in hospitalized elderly
  - Medical service:
  - Surgical service:
  - ICU:
  - Post-acute care (skilled rehab):

Epidemiology

- Common in hospitalized elderly
  - Medical service: 30%
  - Surgical service: 10-50%
  - ICU: Up to 70%
  - Post-acute care (skilled rehab): 20-60%
  - Hospice/Palliative: 90%
- Often unrecognized or diagnosed late
- 2.6 million older adults annually
- 5 older patients in US hospitals become delirious every minute, every day

Inouye SK, NEJM 206;354:1157-65; Lancet 2014;383:911-922; U.S. Dept. HHS, AoA Report, Profile of Older Americans 2011

Consequences of Delirium: So What?

- Longer hospital stay
- Functional decline – falls, incontinence, restraint use/loss of mobility, pressure ulcers
- Poor oral intake, risk of aspiration pneumonia
- Unable to make decisions about their care
- Higher risk for permanent institutionalization
- Cognitive decline with persistent symptoms up to 12 months "and beyond…" *with associated trauma*
- **Mortality:**
  - Hospital mortality: 22-76%
  - One-year mortality: 35-40% (*longer the delirium, the worse the outcome*)
  - **TEN TIMES the mortality of sepsis**

Inouye SK. NEJM 2006;
McCusker J. Arch Int Med 2002

Delirium Predicts 1-Year Mortality

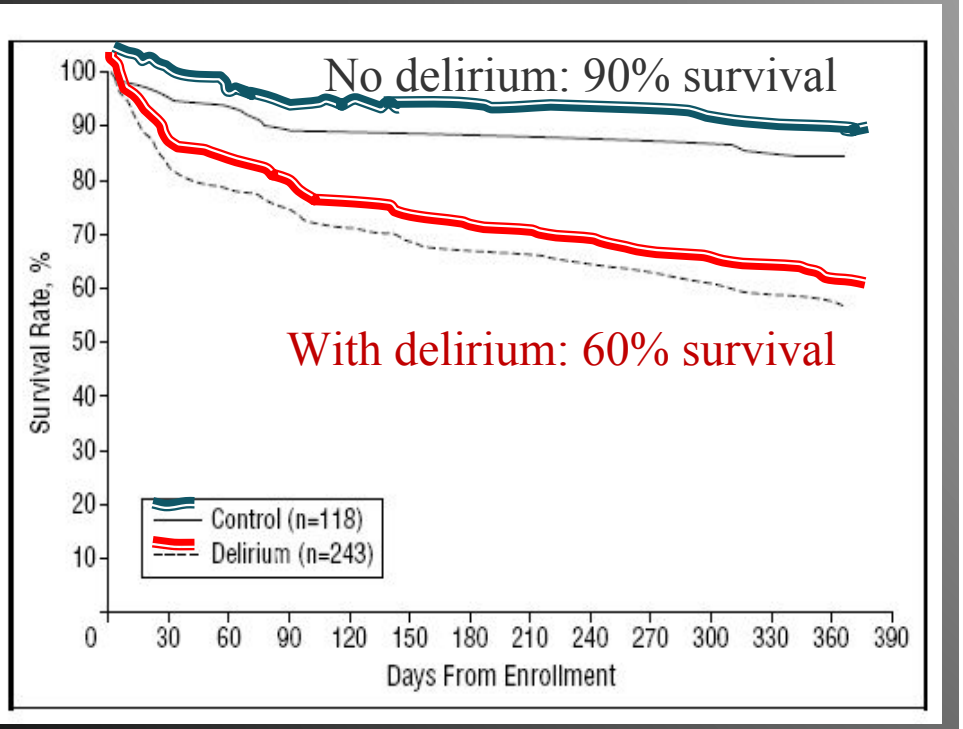


Table 2. Results of Proportional Hazards Analyses of 1-Year Mortality*

Variable	Statistical Model: Univariate	Statistical Model: Multivariable
Delirium/control	3.44† (2.05-5.75)	2.11‡ (1.18-3.77)
Age, y	1.01 (0.99-1.04)	1.04§ (1.01-1.07)
Male/female	1.80§ (1.25-2.58)	1.48 (0.98-2.24)
Married/single‖	1.10 (0.75-1.62)	0.61‡ (0.38-0.99)
Institution/home	1.33 (0.91-1.96)	1.14 (0.74-1.75)
Charlson Comorbidity Index	1.31† (1.23-1.40)	1.27† (1.18-1.38)
Acute Physiology Score	1.18† (1.13-1.24)	1.14† (1.08-1.20)
Clinical severity of illness	1.57† (1.38-1.79)	1.28§ (1.09-1.50)
Dementia (present)/absent	1.03 (0.69-1.55)	0.62‡ (0.40-0.97)
Dementia (missing)/absent	1.09 (0.52-2.28)	1.86 (0.85-4.09)
Medical/geriatric	2.33† (1.50-3.63)	1.13 (0.68-1.89)
Likelihood ratio statistic¶	. . .	123.38†

McCusker J, Cole M, Abrahamowicz M, et al.. Arch Intern Med 2002; 162:457.

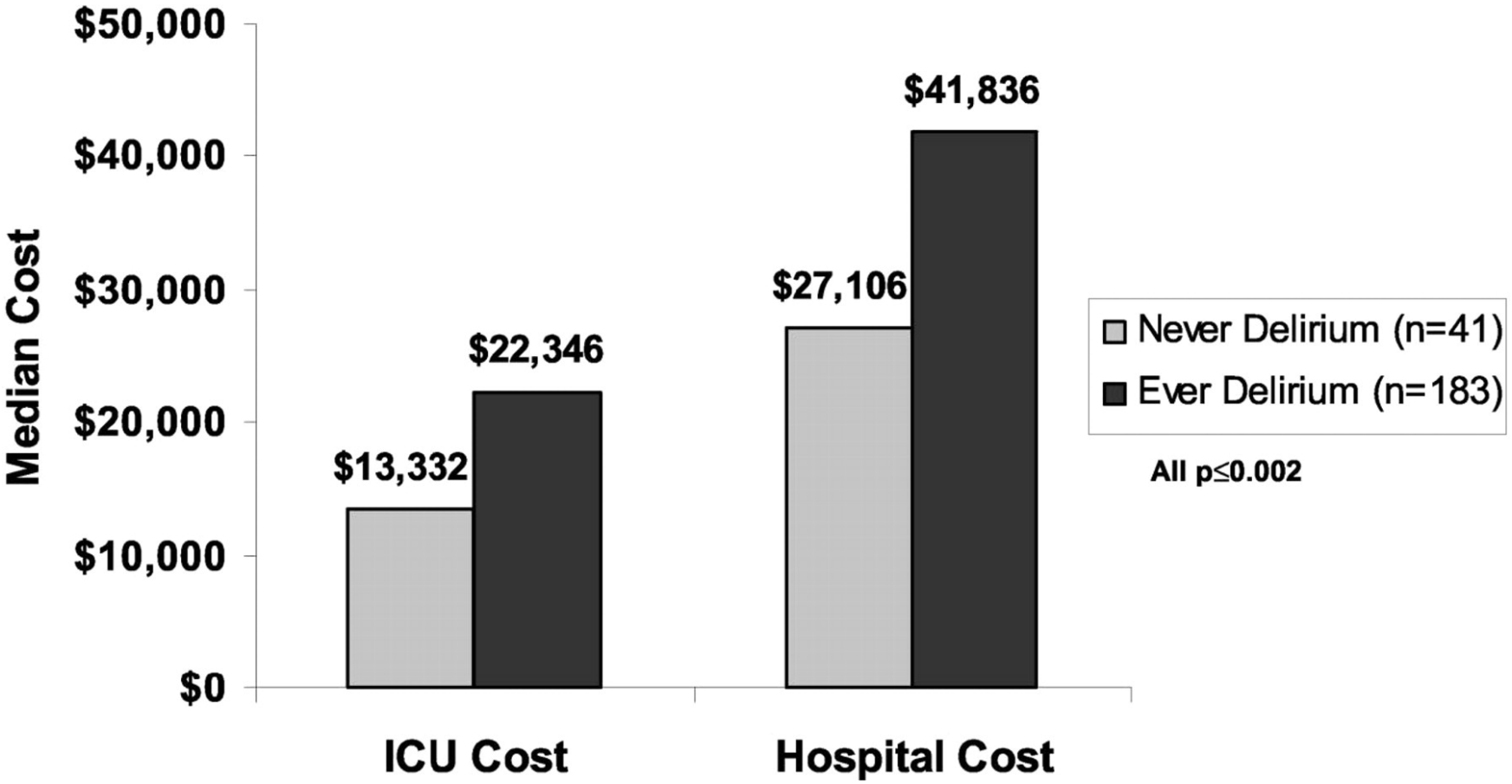
- *350+ Medical patients 65 and older*
- *243 with delirium*
- *118 without delirium*
- *Delirium had stronger effect on mortality in patients without baseline dementia!*

$$$ Delirium is EXPENSIVE $$$

- Adds $2500 to hospital cost per patient
- $6.9 billion of CMS expenditures due to delirium and $164 billion total costs annually
  - Re-hospitalization, ED visits
  - Institutionalization
  - Rehabilitation
  - Home care
  - Caregiver burden

Leslie DL, et al. Arch Intern Med 2008;168:27-32

Increased Cost of Delirium



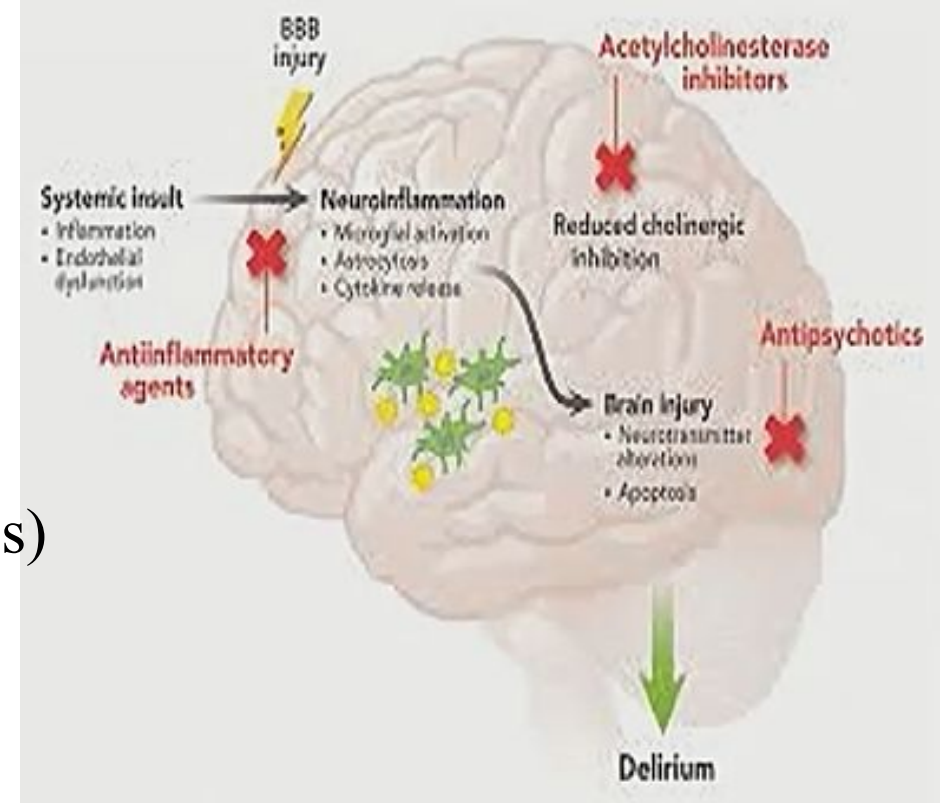
Milbrandt EB. Crit Care Med 2004

224 mechanically vent. patients

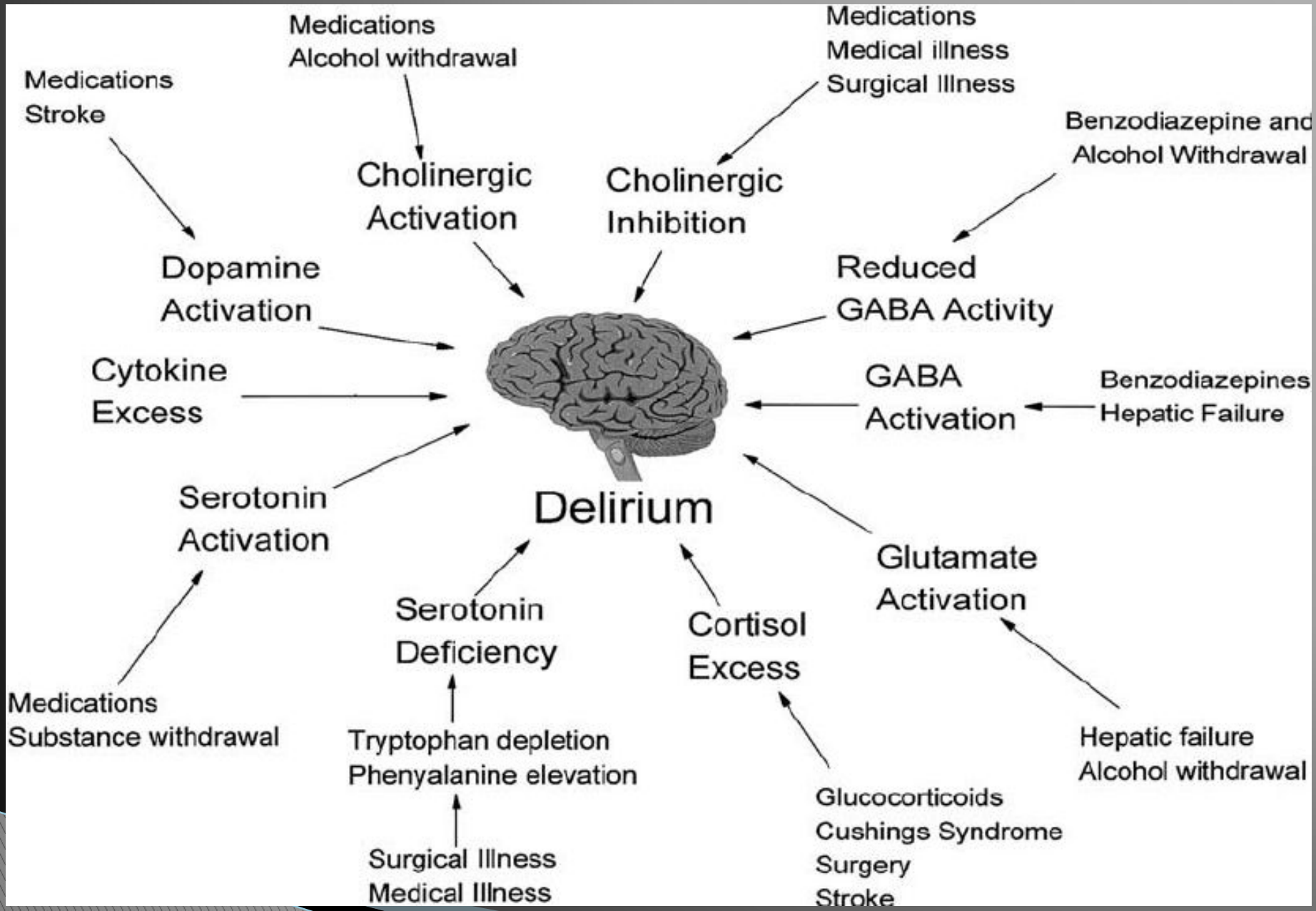
80% delirious, adjusted for age, comorbidity, severity

Mechanisms

- Neuro-Inflammation
- Neuro-aging (homeostenosis)
- Neuro-endocrine (aberrant stress)
- Neurotransmitter dysregulation
  - Anticholinergic and dopamine toxicity
- Oxidative Stress
- Sleep/wake dysregulation (melatonin)
- Network disconnectivity
- Direct Neurotoxicity



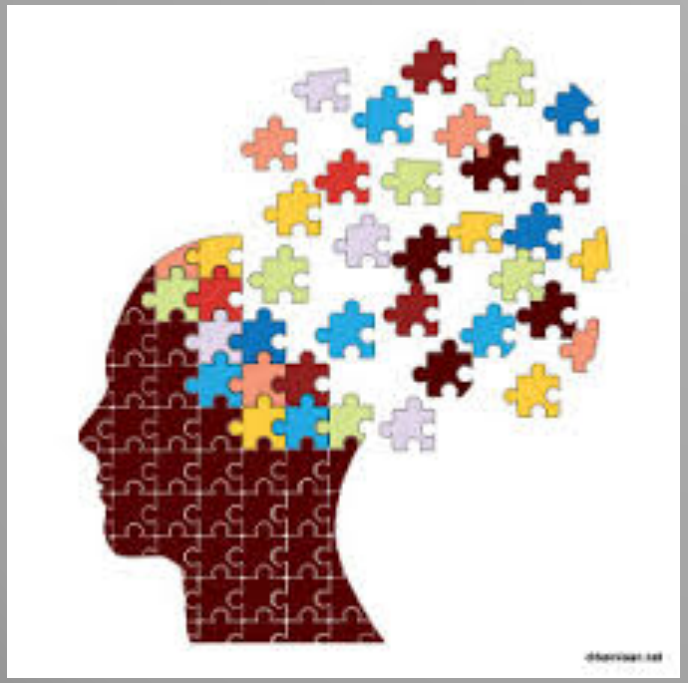
Maldonado, Am J GeriPsych, 2013


Medications
Stroke
Medications
Alcohol withdrawal
Medications
Medical illness
Surgical Illness
Benzodiazepine and
Alcohol Withdrawal
Cholinergic
Activation
Cholinergic
Inhibition
Dopamine
Activation
Reduced
GABA Activity
Cytokine
Excess
GABA
Activation
Benzodiazepines
Hepatic Failure
Serotonin
Activation
Delirium
Glutamate
Activation
Serotonin
Deficiency
Cortisol
Excess
Medications
Substance withdrawal
Tryptophan depletion
Phenyalanine elevation
Hepatic failure
Alcohol withdrawal
Glucocorticoids
Cushings Syndrome
Surgery
Stroke
Surgical Illness
Medical Illness

Anticholinergic Effect and Delirium

- Cholinergic transmission declines with age
- Cerebral cortex widely innervated by cholinergic neurons in basal forebrain
- Risk of delirium correlates with serum anticholinergic levels
- Anticholinergic levels associated with diminished ability to perform ADLs
- Anticholinergic levels normalize as delirium resolves

DELIRIUM

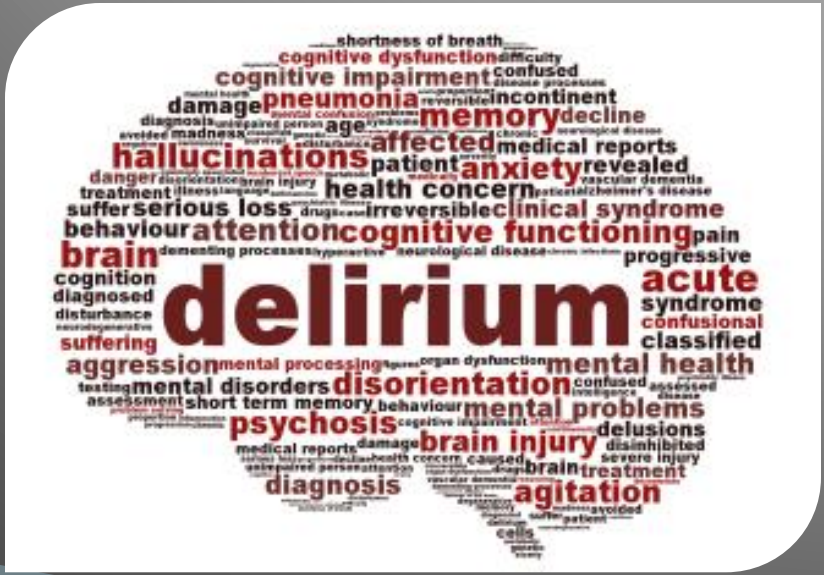


Symptom and **Syndrome…**

NOT a diagnosis!!!

Presentation

- **Core Symptoms**
  - Consciousness
  - Attention (1/3 hypoactive)
  - Cognition
  - Perception
- **Associated features**
  - Sleep-wake cycle
  - Psychomotor
  - Affective
  - Autonomic
  - Neurophysiologic



Remember…

Delirium presents in more than one type!

- **Hyperactive or agitated delirium**
  - Hallucinations, agitation

- **Hypoactive delirium**
  - Lethargy, somnolence
  - "Pleasantly confused"
  - Easily overlooked!
  - **Same adverse outcomes as the hyperactive form!**

Diagnosis Mnemonic: "IADL"

Confusion Assessment Method (CAM)

1) **I**nattention
2) **A**cute onset / fluctuating course
   - **AND**
3) **D**isorganized thinking
   - **OR**
4) **L**evel of consciousness change

- *Must have first 2 features plus either 3 or 4*
- *Sensitivity 94%, Specificity 89% (95% CI)*

Inouye Ann Intern Med1990 Dec 15;113(12):941-8

Inattention in Delirium

Tests of attention

- Digit span backward: give a series of numbers, ask pt to repeat forward and backward (should be able to repeat 5 forward and 4 backward)
- Days of week or months of year backward
- Serial 7's
- Spell WORLD backward

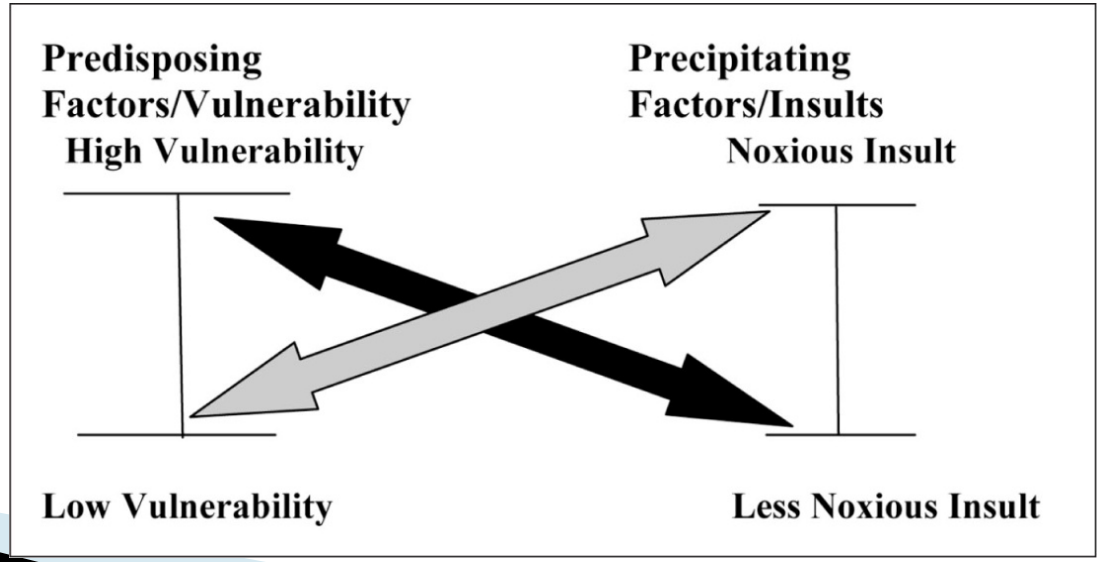
A Model of Delirium

A multifactorial syndrome that arises from an interrelationship between:

- **Predisposing factors** – a patient's underlying vulnerability

AND

- **Precipitating factors** – noxious insults



Inouye SK JAMA 1996 :275:852-857

So, who's vulnerable???

- **Predisposing Factors**
  - Older age (>70)
  - Male gender (???)
  - Dementia (5x risk)
  - ADL impairment (4x risk)
  - Sensory impairment
  - Mental illness
  - Chronic illness (CKD, CHF)
  - Past EtOH Abuse

- **Precipitating Factors**
  - Acute illness + bedrest
  - Surgery
  - Environmental changes
  - Uncontrolled pain
  - Urinary retention/ catheter
  - Dehydration/e-lyte abn.
  - Constipation/Fecal imp.
  - Infection
  - **Medications (40%, >3 new meds incr. 4-fold)**
  - *And so many more!*

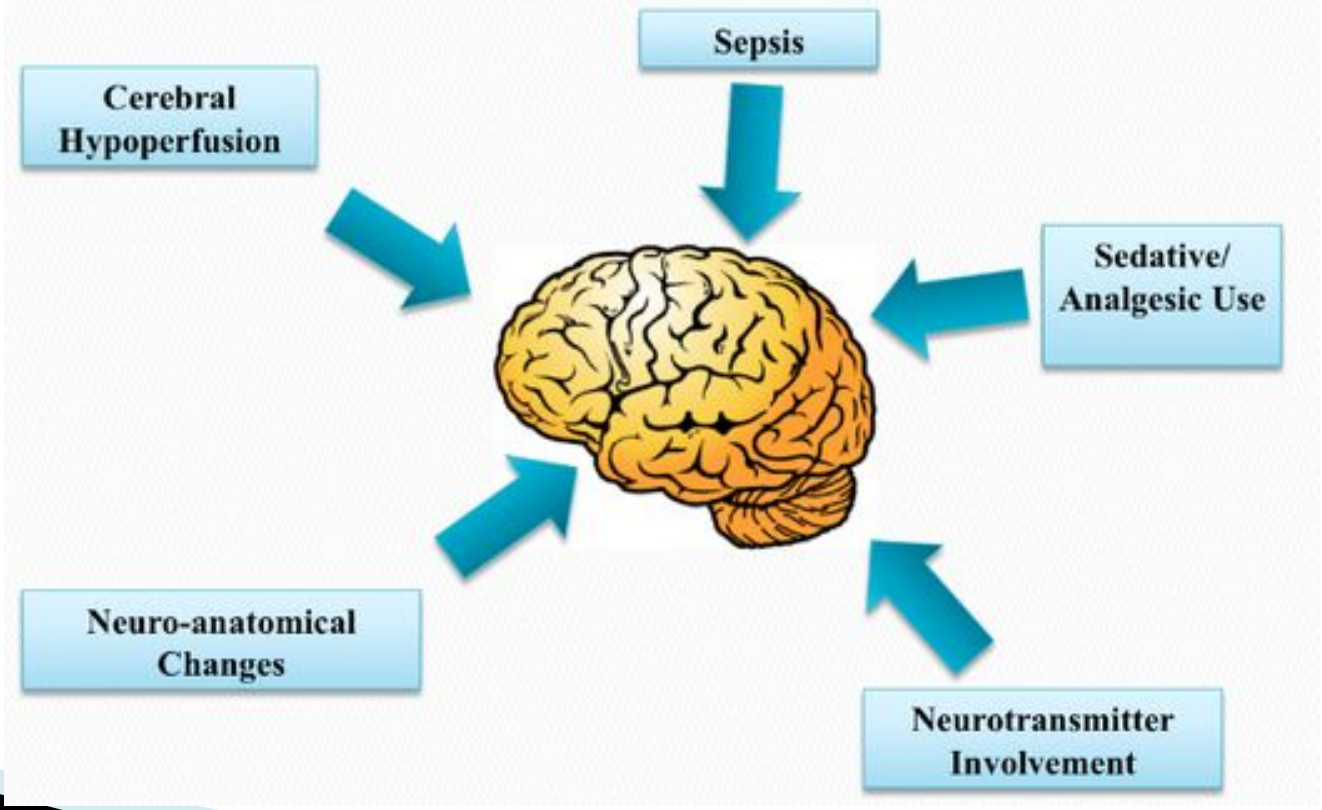
Elie M et al.. J Gen Intern Med. 1998; 13(3): 204-212.

Case: Back to Mr. M…

- 71 yo male Vietnam Veteran with “acute confusion & A/V hallucinations” & also significant quads/trunk weakness, hasn’t left same chair in 40 yrs
- Findings: Mild AKI; B12 287; CTH neg.; UR/FI ruled out; most meds held or decr.; SLUMS 10/30; CAM +
- Prescribed Home Meds: gabapentin 1800mg, hydroxyzine 50 mg, sertraline 100 mg, melatonin 10 mg, oxycodone 15 mg, ranitidine 300 mg, simvastatin 80 mg

Case: Back to Mr. M…

- *Is he delirious???*
- *WHY might he be delirious???*



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- Prescribed Home Meds: gabapentin 1800mg, hydroxyzine 50 mg, sertraline 100 mg, melatonin 10 mg, oxycodone 15 mg, ranitidine 300 mg, simvastatin 80 mg
- AND using something at home to help with "*head congestion caused by attempts to wear CPAP…*"

Mr. M's Predisposing/Precipitating Factors

- **Predisposing Factors**
  - Older age
  - Male gender
  - ? baseline cogn. imp.
  - ADL impairment
  - Sensory impairment
  - Chronic illness (CKD)
  - Possible mild viral GE (in retrospective history)
  - Strong Family History
- **Precipitating Factors**
  - Use of diphenhydramine
  - Mild dehydration
  - Bedrest (or, "chair rest")
  - Environmental changes
  - Pain
  - Electrolyte abnormalities (mildly low Na); low B12
  - AKI superimposed on CKD
  - Polypharmacy/GBP reten.
  - Soft wrist restraints (Vet)

Diagnosis: *Why is it so difficult?*

Serious

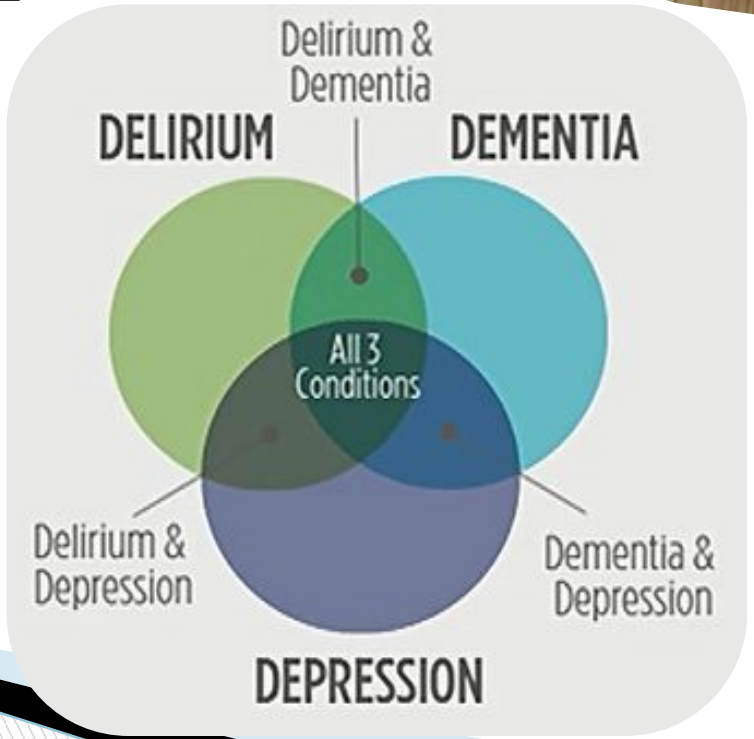
Common

Late Effects

Overlooked!

Delirium can Masquerade…

- Depression
- Dementia
- Delirium



Plus….

- Over reliance on technology
- Not systematically assessing mental status
- Lack of knowledge of patient's baseline
- Unawareness of seriousness of delirium

	DELIRIUM	DEMENTIA	DEPRESSION
ONSET/DURATION	Acute (hours-days)	Insidious (months-years)	Sub-acute (weeks-months)
ATTENTION	Impaired	Normal except in severe dementia	May be decreased
MOVEMENT		Slow, needs pr... mis...	...w esp. if severe, no prompting
HALLUCINATIONS	Common		...ally none
CONSCIOUSNESS/ ATTENTION	Impaired	Att... wrong ... sev...	No/little effort
SLEEP CYCLE	Sleepy, difficult to keep awake/ Does not sleep, awake for days	Sleeps during day, awake at night/ Can fall asleep, wanders at night	Sleeps more than usual day & night/ Trouble falling and staying asleep
SYMPTOM COURSE	Fluctuates	Progresses over time	Stable day to day, may be chronic
TREATMENT/ REVERSIBILITY	No known medication cure	Eventually worsens, despite medication	Reversible with medication

1/3 to 1/2 pts w/ delirium have dementia

Pts w/ dementia have up to 5X higher risk for delirium

Workup

- **Confirm**
  - Symptoms/history/thorough exam as warranted
  - Review meds!!!!!
  - R/o insidious substance use
  - Neuroimaging usually very low yield unless recent falls/head trauma, focal neuro changes, high fever and s/s encephalitis
- **Risk Assessment**
  - Safety, agitation/restlessness
  - Tethers (telemetry)
- **Management**
  - Medical
  - Environmental
  - Psychological

Drugs and Delirium

- Most common reversible cause
- Cause in up to 40% cases
- Adding >3 drugs in hospital increases risk 4-fold

Drug Class	Increased Risk Factor
Psychoactive agents	3.9
Sedative hypnotics	3-11.7
Opiates	2.5-2.7
Anticholinergics	4.5-11.7

Management: Non-Pharmacological

- Treat primary disease process
- Avoid other causes of delirium
- Optimize environment: coordinate staff, music, glasses/hearing aids, reorientation, family, lighting, keep patient busy to alleviate boredom
- Rehabilitate patient despite delirium
- Counsel/support family

Use Your Fellow Interprofessional Team!

- Nurse
- Pharmacist
- Provider
- Dietician
- Therapists
- SW/CM
- Family

An Ounce of Prevention…HELP!!!

RISK FACTOR	IDT INTERVENTION
Cognitive impairment	Orientation protocol, cognitively stimulating activities 3x/day
Sleep deprivation	Nonpharmacologic protocol, noise reduction, schedule adjustments
Immobility	Ambulation or active ROM exercises; minimize equipment
Visual impairment	Glasses or magnifying lens, adaptive equipment
Hearing impairment	Portable amplifying devices, earwax disimpaction
Dehydration	Early recognition and volume repletion

Reduced Delirium by 40%

Inouye SK et al. NEJM. 1999;340:669-76.

- RCT, prospective individual matching, 852 pts (426 matched pairs)
- Age >= 70 yrs, not delirious at admission but with int/high risk
- Intervention (HELP) - $300/pt - vs. usual care
  - Geriatric nurse, 2 elder life specialists, recreation therapist, PT, geriatrician, trained volunteers

Management: Pharmacological

- Paucity of evidence
- Haloperidol most studied
- Medications used to induce sedation; do NOTHING to treat underlying condition
- Use cautiously, in lowest doses needed to calm patient or restore sleep cycle

Medication Pointers

- Use only for severe agitation *when nothing else works*
- Lowest dose of shortest acting neuroleptic usually most effective over short term
  - Reduces agitation, BUT may prolong cognitive deficits & worsen clinical outcomes!
- AVOID benzodiazepines (except in EtOH w/d or really long QTc / no other options – paradoxical agitation)

Pharmacologic Management

- Haloperidol
  - 0.25-0.50 mg PO/IM (never IV!)
  - Can repeat @ 30 min intervals
  - Max. 3-5 mg/24 hrs
- Atypical antipsychotics
  - Risperidone 0.5 mg bid
  - Olanzapine 2.5-5 mg daily - BID
  - Quetiapine 12.5-25 mg daily-BID

Campbell et al. J Gen Intern Med. 2009
Yoon, et al. BMC Psychiatry. 2013
Inouye SK et al. NEJM. 2006;354:1157-65.

BUT… (another) word of caution with neuroleptics

- Risk of QT prolongation/torsades
- Extrapyramidal effects (which can be irreversible)
- Neuroleptic Malignant Syndrome
- Withdrawal Dyskinesias
- Increased risk aspiration, falls
- Black Box Warning – sudden death in those with CVD/vascular dementia

Restraints: LAST RESORT!!!

Medications for Delirium Prevention

- Antipsychotics: mixed evidence – not recommended
- BZDs – NO – Except in EtOH W/D
- Cholinesterase inhibitors – ineffective
- Melatonin/agonists (ramelteon) - ???
- Alpha 2 agonist (dexmedetomidine) - ??? In ICU setting
- Evidence:
  - NO: corticosteroids, statins, gabapentin
  - YES: reducing perioperative sedation

Take Home Points

- Delirium is common with serious long-term consequences
- End result of precipitating features imposed on predisposing factors
- Delirium CAM diagnostic mnemonic = “IADL”
- Will miss it if you don’t look for it; causation.
- Delirium *is* distinguishable from dementia and depression – *but might take some effort!*
- Delirium is preventable with IDT efforts targeting precipitating and predisposing factors; best treatment IS prevention.
- Interventions emphasize non-pharm. approach

Case: Outcome for Mr. M.

- Extensive family education about OTCs and anticholinergic/Beers meds
- DC'd ranitidine, decreased GBP, scheduled APAP, continued oxycodone, repleted B12
- Get hearing aids fixed and wear them
- Work with sleep medicine to titrate CPAP and mask to some level of tolerability
- PT: Inpatient short term rehab after hospital
- Follow up with Geriatrics in 3-4 mos for outpatient cognitive eval. when not delirious
- Repeat SLUMS at discharge (HD 5):
  - **26/30 (up from 10!); hallucinations gone.**

Questions?

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