



Delirium: New Ways to Understand and Manage It

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Self-Assessment Question 1

A 79 year old man with dementia, diabetes mellitus type II, coronary artery disease, COPD, and acute renal failure but no additional psychiatric history was admitted for treatment of pneumonia. After a 3 week hospital course complicated by delirium, hyponatremia, and UTI, he has been less agitated, more cooperative and more oriented for 2 days. Oxygen requirements have diminished and leukocytosis has decreased. You are consulted because of his acute suicidal ideation.

What *initial* plan would be best here?

- a. Assign a sitter (1:1), evaluate patient for antidepressant, provide supportive psychotherapy to address prolonged hospitalization
- b. Assign a sitter (1:1), check urinalysis, do a chest x-ray, begin SSRI
- c. Transfer to psychiatry for further assessment and care
- d. Evaluate for a sitter (1:1), check urinalysis, do a chest x-ray, discuss with primary team



Self-Assessment Question 2

- A 70 yo man with a history of severe alcohol abuse, life-threatening withdrawals (including DTs on one occasion), hepatitis, MI x 2, prior chronic renal insufficiency and hypertension is admitted for treatment of an acute cellulitis. He has been drinking two fifths of whiskey per day for the past 2 months. On admission he is delirious and agitated, with elevated pulse (105, RRR) and blood pressure 160/95) His last drink was 2 days earlier. What first approach would you take?
- A. Pt is high risk for severe withdrawal, which, given his baseline burden of illness and cellulitis, could complicate his medical recovery. Begin lorazepam at 2mg q 4 to prevent a serious withdrawal
 - B. Review medications and remove any with significant risk for delirium; review laboratories (comp, CBC, urinalysis) to assess overall risk factors for delirium; provide symptom triggered alcohol withdrawal regimen using lorazepam 2 mg q 2 hr prn P>110, BP >165/100
 - C. Interview the patient to determine whether he has any signs of delirium (inattention, fluctuation in any behavioral/affective/cognitive sphere), obtain history from collaterals re whether he has in fact been drinking recently, and to what extent; weigh the risk that benzos will worsen his delirium against the benefits they might have in treating alcohol withdrawal in his case.
 - D. Put patient on low dose beta blockers to control VS, treat other medical illnesses, provide symptom triggered lorazepam regimen (as above) for withdrawal prophylaxis, and put the patient into restraints to avoid having to use any CNS active agents



Self-Assessment Question 3

Which of the following medication used for the treatment of pain puts patients at the highest risk for iatrogenic delirium (in light of recent studies of neurotransmitter mechanisms involved in delirium)?

- A. Tramadol
- B. Gabapentin
- C. Morphine
- D. Nortriptyline



Self-Assessment Question 4

Choose the answer which best describes the most important risk factors in predicting delirium in frail patients:

- A. Frail patients often lack social support networks due to loss of mobility.
- B. Frail patients often lack nutritious diets due to poor mobility and loss of economic resources
- C. Baseline medical risk factors impair frail patients' response to the effects of additional acute medical illness.
- D. Adherence to a medical treatment regimen may be poor in a frail patient with chronic medical conditions.
- E. All of the above



Self-Assessment Question 5

Question: Which of the following is a good example of an inattentiveness in a patient?

- A. The patient interrupts the conversation to ask when he will be discharged.
- B. The patient is oriented and aware of his recent medical problems but falls asleep during the conversation.
- C. The patient suddenly bursts into tears when you are discussing his recent amputation.
- D. The patient watches a fly buzzing on the ceiling while you are discussing the prognosis for his lung cancer, then falls asleep.



Teaching Points

- Delirium, though common, is often missed or misdiagnosed
- Delirium is linked with bad outcomes: prolonged/complicated inpatient stays, loss of function, onset of dementia, and increased mortality.
- Detection can be improved by using the Confusion Assessment Method, assessing risk factors and frailty, and reviewing the nursing notes.
- Among delirium's many causes, one important mechanism may be imbalance between acetylcholine and dopamine systems.
- Multimodal treatment of delirium includes attention to environment, sleep, mobility, sensory function, hydration, and other metabolic factors.
- Psychopharmacologic implications: Reduce anticholinergic burden, consider use of antidopaminergic agents as appropriate with proper precautions and education. Avoid benzodiazepines when possible. Cholinesterase inhibitors have not been shown beneficial.
- Recognition of delirium facilitates more effective, safe, and cost-effective treatment of underlying conditions.



A Failing Grade for Recognition: D-

- 33-95% of cases are
 - MISSED altogether or
 - Misdiagnosed as
 - depression
 - psychosis
 - dementia



How Big a Problem is This?

DELIRIUM

- 10-40% Prevalence in acute settings
- 25-60% Incidence in acute settings
 - Up to 87% incidence in ICU
- VS DEPRESSION
- 10% Primary care; 25% Acute settings*

Inouye, 1998, J Ger Psy Neurol; Patel, 2009, Critical Care Med

Rates of Postoperative Delirium

- 9-13% overall in-hospital mortality
- AA Aneurysm repair: 41-54%
- CABG: 32-50%
- Peripheral Vascular: 10-48%
- Elective Orthopedic: 9-15%
- Hip Fracture: 52%

Rudolph et al, 2007 American J Med 120:9

Lundstrom et al. 2007 Aging Clin Exp Res 19:3



Outcomes of Delirium

- In most studies:
- Up to four times the length of stay
- 2-7x Rate of new institutionalization
- Single strongest predictor of in-hospital complications (UTI, falls, incontinence) (O'Keeffe,1997)
- Strong predictor of long term loss of function

Outcomes of Delirium in Nursing Homes (NH)

- 801 postdischarge patients (NH, or community based care) ≥ 70
- Patients who received multi-component targeted intervention to prevent delirium showed:
 - → Significantly lower total costs
 - → Shorter length of stay
 - → Lower cost per survival day
 - → 15.7% decrease in costs among those in nursing home settings (likely due to shorter length of stay)



Death?

- Prospective study of 2 cohorts of medical inpatients ≥ 65 ; 243 with prevalent or incident delirium, 118 without
- Adjusted Hazard Ratio for delirium =2.11 (CI=1.18-3.77) (age, marital status, comorbidity, clinical severity, acute physiology, baseline dementia, degree of institutionalization)
- Greater severity of delirium associated with higher mortality among non-demented



Does Delirium Predict Onset of Dementia?

- 203 patients >65 on a general medicine service (Halifax), no dementia at baseline
- During followup (median of 32.5 months), dementia was diagnosed in
 - 5.6% of those without delirium during index hospitalization
 - 18.1% of those with delirium during index hospitalization
- Adjusted OR: (sex, age, comorbid illness)=5.97 (CI=1.83-19.54); P=0.0003



Reversible? Not Necessarily...

- 325 Elderly patients ≥ 65 admitted to teaching hospital; pre-existing dementia included
- Six month followup study

Resolution of *All* New Symptoms of Delirium is Minimal at 6 months

	Full Syndrome	Partial Syndrome
Discharge	4.0%	17.3%
3 Months	20.8%	42.4%
6 Months	17.7%	37.4%

Impact of Resolution on Function

- 393 pts ≥ 65 referred to post acute facilities after delirium episode
- Delirium resolved by 2 weeks \rightarrow regaining of 100% prehospital functional level
- Slowly resolving delirium or recurrent delirium had intermediate return of function
- With no resolution of delirium, $< 50\%$ of prehospital functional level was achieved



Cost of Delirium

- \$4-\$16 Billion per year in US alone¹
- In ICUs, episodes of delirium average 39% higher ICU costs and 31% higher hospital costs, after adjusting for age, comorbidity, severity of illness, degree of organ dysfunction, nosocomial infection, hospital mortality, and other confounders²
- In other work LOS largely accounted for this difference

1. Inouye 1998 J Geriatr Psychiatry Neurol:11;
2. Milbrandt 2004 Critical Care Medicine 32:4



Clinical Features of Delirium

- Acute or subacute onset
- Fluctuating intensity of symptoms
 - *ALL* SYMPTOMS FLUCTUATE...not just level of consciousness
 - Clinical presentation can vary within seconds to minutes
 - Can be very subtle
- Inattention – aka “human hard drive crash”



Attention

Most basic cognitive organizing function;
underlies ALL other cognitive functions

- Not a static property: an active, selective, working process that should continuously adapt appropriately to incoming internal or external stimuli, primarily based in pre-frontal cortex with limbic, parietal, and brainstem contributions



Inattention

- A cognitive state that DOES NOT meet the requirements of the person's environment, resulting in a global disconnect: inability to fix, focus, or sustain attention to most salient concern
- Hypoattentiveness, hyperattentiveness
- Days of week backward, immediate recall are good bedside tests



Summary of Clinical Signs (1)

- Overall: GROSS DISTURBANCE OF ABILITY TO INTERACT WITH ENVIRONMENT
 - Poor executive function (poor insight, can't address own personal needs, can't plan and execute complex and rational behaviors, interpretation of and relationship with environment often impaired)



Summary of Clinical Signs (2)

- “Fuzzy interface”
- Patient appears withdrawn, uninterested, does not ask questions, no effort to be heard/understood (distinctly *dysfunctional* in modern hospital setting...does not reflect insightful behavior)
- Misdiagnosis: Examiner often *misinterprets* or “*normalizes*” such patient behavior, which results in failure to diagnose. Examples: examiner can’t hear patient, room “too noisy”, “I must just be tired”, patient is “sleepy” or worn out from PT, etc.



Summary of Clinical Signs (3)

Cognitive Signs:

- Inattention,
- Disorganized, fragmented thought patterns,
- Poor memory
- Disorientation
- Depressed level of consciousness



Summary of Clinical Signs (4)

- Affective Signs: Often not recognized as “part of delirium”
 - Lability
 - Anxiety (particularly premorbid)
 - Dysphoria
 - 60% dysphoric; 52% thoughts of death; 68% feel “worthless”



Summary of Clinical Signs (5)

- Perceptual Distortions
 - Hallucinations more often illusory/reflect misinterpretation of environmental cues than in psychosis
 - Interpretation of pain often faulty...over- and under-exaggeration



Summary of Clinical Signs (6)

- Sensory and Motor Impairments
 - Erratic
 - Capacity to speak, hear, ambulate, swallow, etc.
 - All of these can vary within seconds
 - Diagnostically very confusing
 - Wait for delirium to stabilize before final conclusions



Summary of Clinical Signs (7)

- Behavioral signs:
 - Withdrawn, uncommunicative, unmotivated;
 - Impulsive, irrational, agitated, with chaotic activity;
 - But most are mixed in presentation
 - Both may have day/night reversal

Delirium: A Spectrum Disorder

Prodrome

Disorientation
Irritability
Anxiety
Sensory hypersensitivity
Sleep/wake reversal
Nightmares

Levkoff, 1996

1-3 days

Full Syndrome

Resolving Phase

"Sundowning"
Dysphoria
Prolonged short term
memory loss
PTSD
Psychosis

Up to 6 months





Primary Differential: It is NOT Depression

- Quiet delirium:
 - Resembles depression: unmotivated, slow, withdrawn, undemanding; Up to 42% of cases referred for depression are delirious (Farrell, 1995)
 - Quiet delirium may be associated with worse outcomes (O'Keeffe 1999 Age Aging)
 - A MAJOR cause of poor recognition of delirium overall!



Misdiagnosis as Depression: Double Risk


- *Risks of misdiagnosing delirium as depression:*

- A. May *overlook medical cause(s) of the delirium itself*

- B. May add an additional and inappropriate CNS active agent (antidepressant) prematurely

It is NOT Dementia

- *Abrupt onset* can help distinguish; dementia is a chronic condition
- *Level of attention* in demented patients is better and they are *less globally dysfunctional and chaotic*
- Prolonged or unresolvable delirium is basically a new dementia, however



Delirium “Trumps” Other Diagnoses!

- When a patient is delirious, *no other psychiatric diagnosis can be made*. This is critically important to the management of delirious patients, both to focus on the delirium and to avoid adding other medications. Keeping other diagnoses off the chart during delirium will greatly assist with this.
- The patient will need to be *re-diagnosed* after resolution of the delirium, which may have had a major impact on brain neurotransmitter systems that formerly supported a psychiatric illness such as depression, anxiety, bipolar disorder, etc.



How Do We Improve Delirium's Dire Outcomes?

- I. Improving recognition of delirium itself
- II. Focused multidisciplinary efforts
- III. Prevention: Recognition of *vulnerable* patients



1. Improving Recognition

- A. Clinical examination
- B. Nursing staff notes/observations
- C. Prediction by risk factors



A. Clinical Examination

- Clinical interview is often difficult to interpret alone, and it usually represents a small slice of patient's presentation and behavior during 24 hrs
- Active delirium is often not recognized; quiet ones are usually unrecognized or misdiagnosed.
- ICU presents additional problems given difficulty communicating with patients



Operationalizing Recognition of Delirium: The Confusion Assessment Method (CAM)

- Assesses:
 - 1) Acute onset and fluctuating course
 - 2) Inattention
 - 3) Disorganized Thinking
 - 4) Altered Level of Consciousness

1 AND 2 necessary; and either 3 OR 4

Widespread Acceptance

- CAM has become standard assessment tool (originally designed as a screening tool); often used with MMSE to obtain data for scoring

CAM ICU

- Based on CAM; widely used in intensive care settings; provides pictorial memory items and problem solving questions to avoid difficulty with communication

Other Common Scales

- Cognitive Test for Delirium
- Delirium Rating Scale-98
- NEECHAM Confusion Scale
- Delirium Symptom Index
- Memorial Delirium Assessment Scale



B. Nursing's Contribution

- Much broader clinical exposure over 24 hour cycle
- Patient's interaction with challenges of environment and ability to problem solve much more readily observed
- Fluctuations in clinical presentation are much more easily put into context

Nurses' Notes

- Review of 24 hour nurses' notes is *critical* to making the diagnosis in most cases—particularly with quiet delirium. Notes will more accurately reflect evidence of variable levels of orientation, cooperativeness, judgment, and behavior

Evidence: Nursing Chart Notations/Nursing Input

- Perez noted that physicians indicated possible delirium in only 34% of referrals, but non-psychiatric health personnel recorded signs of delirium in 93% of cases – with the first recording made most commonly by nurses.

Chart Notations/Nursing Input

- Chart Screening Checklist (Kamholz, AAGP 1999)
- Composed of commonly charted behavioral signs
(Sensitivity= 93.33%, Specificity =90.82% vs CAM)
- 97.3% of diagnoses of delirium can be made by nurses' notes alone using CSC
- 42.1% of diagnoses made by physicians' notes alone using CSC



C. Prediction by “Risk Factor Analysis”

- Helps “narrow the field” : must be specific, not just the usual compendium
- Inouye’s work critical in devising a two phase model—baseline (“predisposing”)risk (population of interest) and “last minute”precipitating factors (potentially treatable causes) that push the patient over the threshold into delirium

Inouye: Risk Factor Study

- Inouye's initial study involved 281 patients in 2 cohorts, all over 70; 13 clinical variables were used; those involving relative risks of 1.5 or greater were used in the multivariable proportional hazards model.

Table 3. Predisposing Factors for Delirium (N = 107)

<i>Risk Factor</i>	<i>Adjusted Relative Risk (95% CI)</i>
Vision impairment	3.5 (1.2, 10.7)
Severe illness	3.5 (1.5, 8.2)
Cognitive impairment	2.8 (1.2, 6.7)
BUN/Cr ratio ≥ 18	2.0 (0.9, 4.6)

CI = confidence interval.

Adapted from Inouye et al.¹⁰

Table 5. Precipitating Factors for Delirium (N = 196)

<i>Precipitating Factor</i>	<i>Adjusted Relative Risk (95% CI)</i>
Use of physical restraints	4.4 (2.5–7.9)
Malnutrition	4.0 (2.2–7.4)
> 3 medications added	2.9 (1.6–5.4)
Use of bladder catheter	2.4 (1.2–4.7)
Any iatrogenic event	1.9 (1.1–3.2)

CI = confidence interval.

Adapted from Inouye and Charpentier.⁹

Table 8. Inter-relationship of Predisposing and Precipitating Factors in Development Cohort (N = 196)

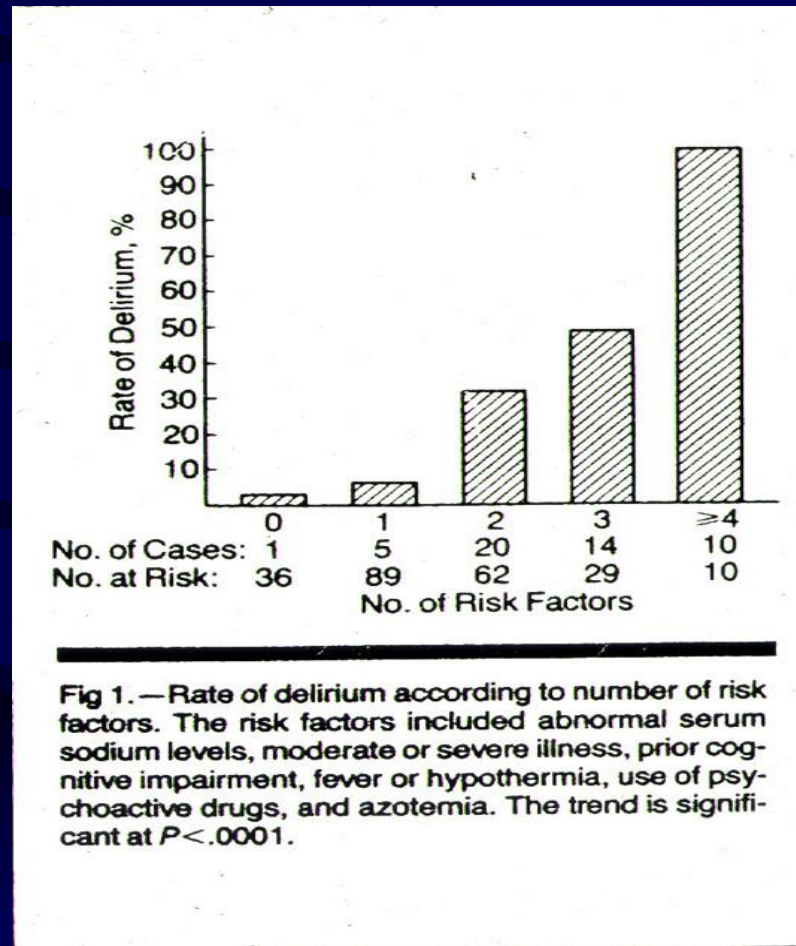
<i>Predisposing Factors Group</i>	<i>Rate of Delirium (per 100 Person-days)*</i>			
	<i>Precipitating Factors Group</i>			
	<i>Low</i>	<i>Intermediate</i>	<i>High</i>	<i>Total</i>
Low	0	0	0	0
Intermediate	0	3.2	13.6	1.6
High	1.4	4.9	26.3	5.6
Total	0.3	3.6	21.3	

*Corresponds with percentage of patients developing delirium per day.

Comments on 3 Prior Slides

- Note the *nonlinear* relationship between risk of delirium and cumulative risk burden (predisposing and precipitating) as you proceed from upper left to lower right in Inouye's slide, "Table 8"
- You can observe nearly the same interaction in the following slide, although it is not segregated by predisposing and precipitating factors.

And Again...





Main Observations

- Every “risk factor” study actually lists a different assortment of factors.....so:
- *Specific* risk factor(s) are less important than the burden of factors that may overcome the patient’s limited resilience, biological reserve, and (fragile) equilibrium...in a dose-dependent fashion. The more frail the patient, the less impact is required to precipitate a *disequilibrated* state (such as delirium or a fall.)



Frailty

- The concept of frailty has been invoked to identify individuals who are not just disabled but are approaching, at risk for, disequilibrium and deterioration
- 61% of frail patients in acute decompensation present with *delirium*

Physiological Definitions of Frailty

- 1) Recent weight loss, self reported exhaustion, poor grip strength, slow walking speed, low physical activity → 3/5 Predictor of hospitalization, disability, mortality¹
- 2) Primary component is sarcopenia (muscle weakening/wasting). Atherosclerosis, cognitive impairment, and malnutrition are its primary causes²

A Canadian Perspective

- If enough variables are considered (including social support, economic security, disease burden, prior disabilities, etc.) the specific ones do not matter. It is the percentage...that predicts “higher likelihood” of frailty
- Deficit accumulation, not chronological age
- Priorities in a national health system include a significant focus on global *prevention* of illness

Implications of Frail Patients in Disequilibrium

....these are patients who are broadly vulnerable, for whom “fixing one thing” will not do; they remain vulnerable at least through the course of delirium and often afterwards....generally with the length of recovery proportional to the degree of baseline frailty and size of impact of stressors.

How Do States of Global Vulnerability Develop?

- Age associated decrease in homeodynamism (decrease of dynamic range of physiological solutions, redundant systems, or “reserves”)
- Loss of dendritic branching, loss of variability of heart rate, decrease of latency, amplitude and range of EEG frequencies, trabecular loss in bone, etc.
- Too little variation=less ability to adapt



Age and Reduced Reserves

- Redundant numbers/circuits exist at birth
- Neurons can increase metabolism to produce more transmitters to compensate
- Terminals are able to increase in size and take over function of lost terminals, and receptors can increase their sensitivity
- BUT, with aging, these compensatory systems wane....and become exhausted

Disequilibrium, etc

- Evidence from other biosystem investigations that at about 70% loss of function or reserve there is an abrupt break with a homeodynamic state
- Result is an unstable, unpredictable system with significant vulnerability
- States “far from equilibrium” characterized by large reaction to small insults

Bortz WM “The Physics of Frailty” JAGS 1993

Que Cheng-Li “Equilibrium, Homeostasis and Complexity” Annales CRMCC 1998



The Relationship Between Frailty and Delirium

.... for many patients with delirium, it seems to be best to think about it as a manifestation of frailty. Older adults are frail when they have several, interacting medical and social problems that give rise to a loss of redundancy in their homeostatic capacity and, thus, an inability to withstand stress. In other words, they need most of their physiologic components and most of their environmental supports at or near maximum capacity to get through the day. When one component goes awry, the equilibrium of this complex system fails, and the system's highest-order functions (staying upright, maintaining focused cognition) fail first. This is why delirium and falls.... are common among frail elderly people when they become ill, even with seemingly trivial illnesses. This is why their apparent causes are so protean. This is why their outcomes are so poor, and why successful management requires a multidisciplinary approach. (It might also be why systematic assessment of mobility and balance could be a better indication of recovery from delirium than assessment of cognition.)

Graphic Images of Frailty

- In the following slide, note the great difference between Barthel's scores (measures of ADL, which are a proxy for medical burden) between frail elderly (bottom row) and well elderly (top row) before, during, and after hospitalization.
→ *Frail patients living in the community are as deteriorated as well patients upon acute admission to the hospital.*

Frailty

(Jarrett,P,Arch Intern Med. 155:1995)

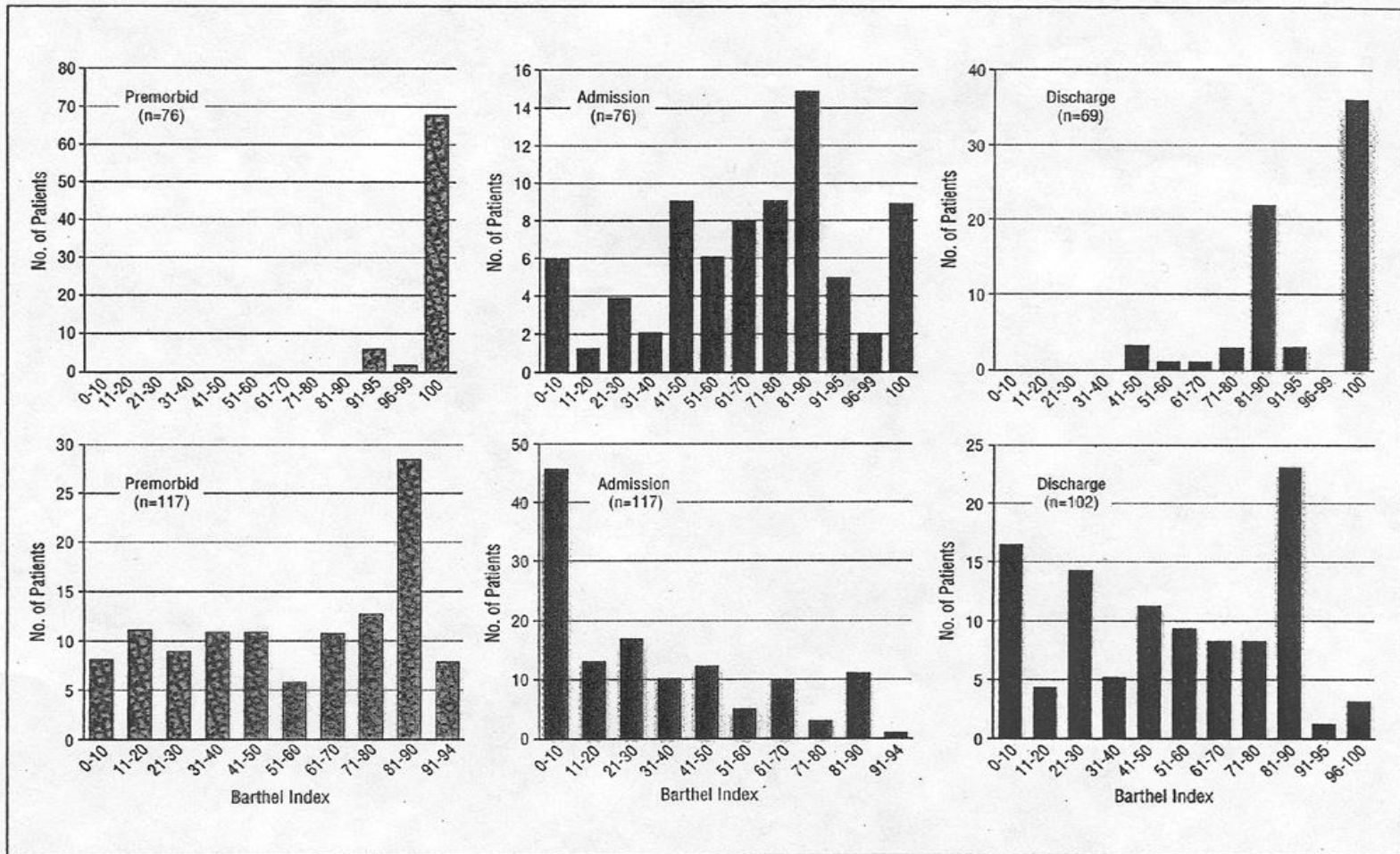


Figure 1. Distribution of Barthel Index scores before admission, at admission, and at discharge for the well elderly (top) and for the frail elderly (bottom).

How Frequent? How to Measure?

- 7% community dwellers¹
- Obstacle course/hip abduction strength, semi-tandem part of Romberg, coordination on pegboard test²
- One leg standing test³
- TAG: “Timed up and go”: rise from chair, walk³ meters, sit down, walk >4.5 seconds carrying glass of water=frail⁴

1. Fried et al. 2001; 2. Brown et al. 2000; 3. Vellas et al. 1997;
4. Lundin-Olsson et al 1998

Impact

- Loss of “internal complexity” found in delirium → need for caregiving environment to respond in increasingly complex and protective ways.

Implications for Delirium

- “Diffuse vulnerability” can account for the ‘multiple pathways’ to delirium
- In fact, delirium may be the **FIRST SIGN** of an underlying medical disorder (sometimes the **ONLY** sign)
- But it’s more than just a signal: independent impact on outcomes

LOWERING Risk: Education?

- Each yr of completed education associated with .91 lower odds of delirium
- Individuals with 7 years of education had 1.6 fold increased odds of delirium compared to those with 12 years

Pathophysiology: Basic Problem

- Diverse etiologies: metabolic, perfusion-based, medication-related, structural lesions
ALL result in same general phenomenon, implying that they all somehow feed OUT through the same neural circuit that determines this complex of behaviors



Prefrontal Cortex as “CEO”

- Prefrontal Cortex is ~ “CEO”: consolidates polymodal sensory information with limbic (amygdala, anterior temporal regions, thalamus, cingulate gyrus, hippocampus) inputs, and which enables focusing attention in on matters most relevant and away from “distractions”

Prefrontal Cortex

- Layer 3 is a huge association/abstraction/executive function area, takes very long time to develop (past adolescence (!)...and a main area of decline in Alzheimer's patients. Delirium in this population was found associated with significant declines in Layer 3, which is also very rich in acetylcholine



Neurochemical Findings: Most Useful Theories

- *Decrease in acetylcholine;*
- *Increase in dopamine (ECT, opiates, cocaine...);*
- *OR imbalance between these systems*
- Others....glutamate, GABA pathways, immune mediators...less unifying in explanation



Acetylcholine

- A primary neurotransmitter associated with arousal, learning, memory, attention, and sensory GATING at the thalamus
- Anticholinergic influences associated with increased agitation, slower EEG patterns, delirium (which may reverse with agonists)
- Decreases in acetylcholine associated with decrease in MMSE

Genesis of Acetylcholine

- Krebs/CAC: glucose and oxygen as substrates produce ATP as well as AcetylCoA, which is a precursor
- In hypoxic states, we know that AcChol is decreased and DOPA is increased
- With aging, synthesis of AcChol is decreased, but acetylcholinesterase activity is not decreased...net loss



Serotonin

- Synthesis dependent on availability of tryptophan
- BUT → Both *increased* serotonin (such as in hepatic encephalopathy) and *decreased* serotonin (such as in alcohol w/d) in brain have been associated with delirium

Dopamine

- Extracellular dopamine, which can reflect medication effects or hypoxia conditions, increased up to $> 1000\%$ in a rat model of hypoxic striatal injury.

Inflammatory Hypotheses (1)

- Tissue injury and inflammation increase cytokine activity, alter permeability of the blood brain barrier, and alter neurotransmitter function/release
- Cytokines (interleukins—IL1, IL2, IL6, IF-alpha, TNF) are released from glia under stressful circumstances (such as surgery, acute illness)

Inflammatory Hypotheses (2)

- Cytokines affect regulation of hormones and neurotransmitters -- especially resulting in decreases in DOPA and norepinephrine and increases in AcChol
- Treatment with cytokines may cause dose dependent cognitive, emotional, and behavioral disturbances, such as delirium

Neuroimaging

- Among the limited studies, SPECT findings are notable
- Frontal and parietal areas (likely right sided) and basal ganglia are areas of some consensus
- Delirium is likely associated with reduced blood flow and recovered blood flow after delirium resolves



Interventions: What's Available Now (1)

- Delirium rates increase with level of morbidity, so interventions must be multi-focused
- Currently the “gold standards” include multicomponent interventions

Inouye 1999 NEHM 340(9), Marcantonio 2001 JAGS 49:5,
Pitkala 2006 J Gerontol A Biol Sci Med Sci. 61(2)



Interventions: What's Available Now (2)

- Prophylactic low dose haloperidol may reduce duration and severity of delirium with decreased LOS in hip fracture patients¹
- Overall, only one has decreased incidence of delirium², but reductions in severity, duration, and length of hospital stay are more frequently achieved.

An Intervention Program That Works

- Decreased incidence
- Decreased length of stay
- Decreased days of delirium

Elder Life Program

- 852 patients >70, general medicine
- Interventions addressed cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration
- Multiple community and international replications

Results of Multicomponent Intervention Trial

	Control	Intervention
Incidence of delirium	15.0%	9.9% (matched odds 0.60, 95% confidence interval)
Days of delirium	161	105 (p=0.02)

Results of Multicomponent Trial

	Control	Intervention
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Number of days of delirium	161	105 (p=0.02)

Multicomponent Trial (2)

- Cost per patient, \$327; per case of delirium prevented, \$6,341 (however, volunteers were used)
- Severity not different
- Rate of recurrence not different
- PREVENTION is best strategy
- PREVENTION IS POSSIBLE



Outcomes of Delirium after Discharge

- Unfortunately, multidisciplinary interventions have *not* had a significant impact on survival, cognitive status, or institutionalization at 6 months and there are few reports at 12 months
- Is this due to the limited, inhospital intervention?

Outcomes of Delirium: NH

- 801 hospitalized patients ≥ 70
- Among patients with multi-component targeted intervention (“Elder Life” program), no impact on % needing long term care
- BUT, lower total costs, shorter LOS, lower cost per survival day (15.7% savings) among those receiving intervention



Interdisciplinary Comprehensive Care: One “Gold” Standard

- Prospective, Randomized, Blinded, 126 patients ≥ 65 ; Intensive geriatric consultation v. usual care
- 77% adherence to recommendations
- Recs: Adequate CNS Oxygenation, F/E Balance, Pain, Reduce medication burden, B/B Regulation, Nutrition, Early mobilization, Prevention of Medical Complications, Environmental Orientation/Stimuli, Treatment of Agitation with Low Dose Neuroleptics



Hip Fracture Trial Results

	<u>Interv</u>	<u>Usual</u>	<u>P</u>	<u>RR</u>
Incident Delirium	32%	50%	.04	.64
Severe Delirium	12%	29%	.02	.40
<u>Adj OR (dementia,ADL impairment)</u>				
Incident Delirium	0.60 (NS)			
Severe Delirium	0.40 (NS)			



Hip Fracture Trial (2)

- Hip fracture patients who did NOT fulfill CAM criteria for delirium, but who had *some symptoms* of delirium (subsyndromal) had outcomes *similar to, or even worse than*, those with mild delirium



What Guidance Do We Have?

- Cases involving moderate risk are more amenable to alterations in course of delirium¹ (partial syndromes present risk also²)
- Increased severity predicts worse outcome³
- Once delirium develops, it is harder to impact⁴

1. Inouye S 1998 NEJM 340(9); 2. Marcantonio 2001 JAGS 49:53;
3. McCusker 2002 J Arch Int Med 162; 4. Inouye 1999 NEJM 340(9)



So, to Practicalities....

- Modified risk factor model helps recognition, helps focus treatment in all phases despite variability of evidence-based risk factors identified
- “Consensus” Baseline Risks:
 - Age
 - Cognitive Impairment
 - Multiple Medical Problems



Precipitating Risk Factors: Systemic, Basic, *not* CNS

- Infections – UTI, Pneumonia
- Metabolic – Hyper, hyponatremia; high BUN, low H/H, low O₂ sats, high Ca⁺⁺
- Medications (39%) – *Anticholinergics* (*diphenhydramine*), Opiates (meperidine), Benzodiazepines (high dose/longer acting), Lithium, Antidepressants, High dose antipsychotics (>3 mg/d haloperidol equivalents), Steroids



Precipitating Risk Factors: *Systemic, not CNS (2)*

- Any new medical event (MI, PE, CHF, hip fracture, orthopedic injury)
- Pain (especially at rest)
- Alcohol/benzodiazepine withdrawal
- Use of restraints
- Dehydration, Malnutrition
- New interventions/tests: Intubation, surgery (particularly orthopedic/vascular), biopsy, BM transplant, neuroimaging



Goals of Treatment

- 1) EARLY intervention and screening for most common factors, taking med history into account
- 2) Maintain VIGILANCE (vulnerability appears to correlate with length of recovery)
- 3) Maintain adequate behavioral control
 - Assists with preventing functional decline while in hospital
 - Less chance of complications while hospitalized (broken limbs, self extubation, aspiration, etc.)

Ways that Delirium Can Prolong Itself When Ignored

- Increased risk of aspiration → pneumonia
- Agitation → Risk of falls, breakage, restraints
- Altered perceptions of pain → inadequate/increased use of opiates
- Poor oral intake → dehydration, malnutrition, hyponatremia, uremia

Further Ways that Delirium Prolongs Itself

- Inactivity/prolonged bedrest → decubiti, UTIs, phlebitis, poor conditioning, bony resorption (hypercalcemia)
- Impaired sensory awareness/poor communication → poor reporting of new sources of pathology (pain, infection, etc)



Medication Considerations

- Medications have historically not been used for disease modification so much as to modify *behavior*, however recent reports such as Kalisvaart, 2005, as well as newer findings relating to the impact of dopamine on cellular function, argue that dopamine blockade and modulation of the inflammatory response may have promise in mitigating delirium

Maldonado JR (2008): Crit Care Clin 24(4): 789-856.

Medication Trials

- Liptzin showed in a sample of younger old, cognitively intact patients undergoing elective joint replacement surgery that donepezil was not helpful with delirium prevention / cholinesterase inhibitors were not helpful with delirium resolution or prevention

Medication Trials (2)

- Kalisvaart et al found that among elderly hip surgery patients at risk for delirium, preoperative use of haloperidol 1.5 mg/day in combination with the same dose up to 3 days after hip surgery, resulted in decreased severity and duration of delirium episodes, as well as the number of days of delirium, but did not decrease the incidence of delirium postop.

Medication Trials (3)

- One pilot study (randomized, placebo controlled, double blinded) of 12 patients \geq 45 undergoing spinal surgery, demonstrated that none of 9 patients receiving 900 mg/day of gabapentin for 3 days postoperatively developed delirium; 5/12 on placebo+opiates did develop delirium.
- Opium sparing effect?

Few Double-Blind, Placebo-Controlled, Randomized Trials

- Few, and few replications, little consensus
- Benzodiazepines are to be avoided
- Antipsychotics are preferred; in general, avoid those with anticholinergic effects

Approaches to Medication

- For agitation
- Avoid benzodiazepines, trazodone, benadryl
- Lorazepam an independent risk factor for transition to delirium , even compared with fentanyl, morphine, and propofol in ICU patients ¹
- Provide safe prns
- **LOW DOSE NEUROLEPTICS**
 - Risperidone 0.25-0.5 po bid prn (unless hx CVA)
 - Quetiapine 25 mg po bid prn
 - Haloperidol 0.25-0.5 po bid/IM
 - Haldol IV:QTC>440, Normal K+, Under 40 mg/day
 - » Risk: Hypotension, Severe Ventricular Arrhythmias
 - » Drip is MOST effective, starting at very low dose

Sedating Agents in Critical Care Settings

- Analgesics and sedatives may help alleviate stress response in critically ill pts, improving outcomes as well as ability of staff to work effectively and safely with pts, as well as being essential (at times) for mechanical ventilation
- Agitation and anxiety may reflect physiological states such as pain, hypoxia, withdrawal

Sedating Agents (2)

--Propofol

- IV general anesthetic with sedative/hypnotic properties at lower doses; GABA a receptor agonist
- 1-2 minute onset; 26-32 hr half life;
5-80 ug/kg/min (>80, cardiac arrest adults)
- Hypotension (esp with initial bolus) bradycardia, elevated pancreatic enzymes
- Very rapid reawakening (11-13 minutes)
→ YOU CAN TAPER IT with better result
- May contribute less to delirium than benzos

Midazolam

- GABA-a receptor agonist/sedative/hypnotic/anxiolytic
- Respiratory depression, hypotension
- Strongly associated (as all benzos) with transition to delirium/worsening of delirium
- 3-12 hour half life but it *can accumulate*, especially in renal failure; Society of Critical Care Medicine recommends use <48 hours
- Complex metabolites; extensively metabolized in liver

Dexemedetomidine

- Alpha 2 adrenergic agonist
- 2-3 hour half life; easy to provide as IV infusion
- Negatives: Bradycardia, sinus pause, arrest
- Hypertension and hypotension (related to alpha 2 impacts)
- *Possible* decreased minute ventilation, response to CO2 challenge;
- Positives:
- Some analgesia
- Some anti-inflammatory impact
- ?Neuroprotective effect in ischemia?
- May address withdrawal from benzos, alcohol but peripheral alpha blockade may mask signs of sympathetic outflow

IV Haloperidol

- Haliperidol IV:QTC>440, Normal K+, Under 40 mg/day
 - » Risk: Hypotension, Fatal Ventricular Arrhythmias which (per case reports) appear most common >40 mg/day
 - » *Drip* is easiest to titrate; start (.25 mg/hr), SLOW titration; rarely need >40 mg/day
 - » Often prolongs QTc; patients **MUST** be monitored
 - » Some studies: up to 900/day/rare EPS



Environmental Factors

- Frequent reorientation
- Moderate level of sensory stimulus
- Minimize caregiver changes
- Provide hearing aids, glasses
- Family available
- QUIET at night—avoid VS, meds, etc.
- Avoid Restraints
- **AMBULATE! Emphasize FUNCTION!**

Delirium as a Symptom of Hospital Care

- “Delirium often results from hospital-related complications or inadequate hospital care and can be viewed as a symptom of broader problems in the delivery of hospital services.”
- “...the incidence of delirium...can serve as a window on aspects of the quality of hospital care that are not currently measured”

Inouye S, et al., “Delirium: A symptom of how hospital care is failing older persons and a window to improve quality of hospital care”, Am J Med 106:565-573, 1999



Example

- A 79 year old man with dementia, DMII, CAD, COPD, and acute renal failure but no other psychiatric history was admitted for pneumonia. After a 3 week hospital course complicated by delirium, hyponatremia, and UTI, he has been less agitated, more cooperative and more oriented for 2 days in association with decreased wbc and lessened oxygen requirements. You are consulted for acute suicidal ideation. What should you do?



Case #1 Discussion

- Delirium must be ruled out first here...it offers more morbidity than depression in this setting and this patient is very vulnerable to it. Suicidal ideation is common in delirium. Adding an antidepressant may worsen the picture—better to wait 2-3 days to r/o delirium, as that delay will not greatly impact treatment of depression anyhow. Mislabelling as depression may result in failing to search for the cause of the delirium.



Example #2

- A 59 year old man functional man with a lifetime history of bipolar disorder and no other medical comorbidities was initially treated 3 months PTA with lithium, valproate, and risperidone in slowly escalating doses. He has a 1 month history of steadily declining mental status, now being completely dependent in ADLs. He appears cognitively very slowed on admission, struggling with attention questions. Li⁺ level is 2.15. What do you do now?



Example #2 (2)

- Okay, lithium and risperidone are stopped and valproate is reduced to $\frac{1}{4}$ prior dose (500 mg/day). Over the next 10 days he improves only slowly and gradually.
- What do you do now?



Case #2 Discussion

- This relatively young, healthy patient should not have had such profound delirium, or such slow resolution, with just this one stressor (elevated Li^+) based on risk factor analysis. Therefore, medical investigation proceeded further...head CT revealed gross atrophy that had not otherwise been apparent. Treatment course had to be fundamentally different! “Manic” symptom presentation one month before might have been first sign of dementia.



Summary

- Delirium is a severe illness with many negative consequences that is very *rarely* completely recoverable
- The most effective approach is *prevention*, focusing on frail patients as the most important population of interest (less frail patients are more likely to recover)
- In the presence of delirium, your most important job is to identify and address *treatable* causes
- *Always* use very low dose neuroleptics, which may not modify disease but **will** allow behavioral control so the underlying causes can be addressed



Self-Assessment Question 1

A 79 year old man with dementia, diabetes mellitus type II, coronary artery disease, COPD, and acute renal failure but no additional psychiatric history was admitted for treatment of pneumonia. After a 3 week hospital course complicated by delirium, hyponatremia, and UTI, he has been less agitated, more Cooperative and more oriented for 2 days. Oxygen requirements have diminished and leukocytosis has decreased. You are consulted because of his acute suicidal ideation.

What *initial* plan would be best here?

- a. Assign a sitter (1:1), evaluate patient for antidepressant, provide supportive psychotherapy to address prolonged hospitalization
- b. Assign a sitter (1:1), check urinalysis, do a chest x-ray, begin SSRI
- c. Transfer to psychiatry for further assessment and care
- d. Evaluate for a sitter (1:1), check urinalysis, do a chest x-ray, discuss with primary team

Best Answer: d

Delirium must be ruled out first here...it offers more morbidity than depression in this setting and this patient is very vulnerable to it. Suicidal ideation is common in delirium. Adding an antidepressant may worsen the picture—better to wait 2-3 days to r/o delirium, as that delay will not greatly impact treatment of depression anyhow. Mislabelling as depression may result in failure to search for the cause of the delirium.



Self-Assessment Question 2

- A 70 yo man with a history of severe alcohol abuse, life-threatening withdrawals (including DTs on one occasion), hepatitis, MI x 2, prior chronic renal insufficiency and hypertension is admitted for treatment of an acute cellulitis. He has been drinking two fifths of whiskey per day for the past 2 months. On admission he is delirious and agitated, with elevated pulse (105, RRR) and blood pressure 160/95) His last drink was 2 days earlier. What first approach would you take?
- A. Pt is high risk for severe withdrawal, which, given his baseline burden of illness and cellulitis, could complicate his medical recovery. Begin lorazepam at 2mg q 4 to prevent a serious withdrawal
 - B. Review medications and remove any with significant risk for delirium; review laboratories (comp, CBC, urinalysis) to assess overall risk factors for delirium; provide symptom triggered alcohol withdrawal regimen using lorazepam 2 mg q 2 hr prn P>110, BP >165/100
 - C. Interview the patient to determine whether he has any signs of delirium (inattention, fluctuation in any behavioral/affective/cognitive sphere), obtain history from collaterals re whether he has in fact been drinking recently, and to what extent; weigh the risk that benzos will worsen his delirium against the benefits they might have in treating alcohol withdrawal in his case.
 - D. Put patient on low dose beta blockers to control VS, treat other medical illnesses, provide symptom triggered lorazepam regimen (as above) for withdrawal prophylaxis, and put the patient into restraints to avoid having to use any CNS active agents

Best answer: C

This patient is already at a high risk for delirium based on his age and severe comorbidities, including renal insufficiency. Use of benzos for withdrawal must be carefully weighed against the risk of worsening his delirium.

- B. Without adequate collateral history, providing a high dose prn regimen of potentially unnecessary benzos puts the patient at risk of worsened delirium. His elevated VS may reflect agitation or pain due to the cellulitis
- C. Beta blockers most often mask the sympathetic outflow signs of withdrawal, which are vital to monitor in determining whether this relatively frail, ill man should be exposed to the additional deliriogenic risk from the addition of benzos for treatment of a withdrawal syndrome.
 - *→Note that with additional trials of anticonvulsants for alcohol withdrawal, or dexmedetomidine for alcohol withdrawal delirium, benzos remain the standard of care.*



Self-Assessment Question 3

Which of the following medication used for the treatment of pain puts patients at the highest risk for iatrogenic delirium (in light of recent studies of neurotransmitter mechanisms involved in delirium)?

- A. Tramadol
- B. Gabapentin
- C. Morphine
- D. Nortriptyline

Best answer: (c), because morphine is BOTH anticholinergic and dopaminergic



Self-Assessment Question 4

Choose the answer which best describes the most important risk factors in predicting delirium in frail patients:

- A. Frail patients often lack social support networks due to loss of mobility.
- B. Frail patients often lack nutritious diets due to poor mobility and loss of economic resources
- C. Baseline medical risk factors impair frail patients' response to the effects of additional acute medical illness.
- D. Adherence to a medical treatment regimen may be poor in a frail patient with chronic medical conditions.
- E. All of the above

Best answer: E



Self-Assessment Question 5

Question: Which of the following is a good example of an inattentiveness in a patient?

- A. The patient interrupts the conversation to ask when he will be discharged.
- B. The patient is oriented and aware of his recent medical problems but falls asleep during the conversation.
- C. The patient suddenly bursts into tears when you are discussing his recent amputation.
- D. The patient watches a fly buzzing on the ceiling while you are discussing the prognosis for his lung cancer, then falls asleep.

Best answer is (d);

- A. Impulsive interruptions may or may not indicate inattentiveness.
- B. Falling asleep may indicate inattentiveness, but further information would be needed to rule out other explanations such as recent administration of a sedating medication.
- C. Sudden bursts of affect may or may not indicate inattentiveness.
- D. This patient seems distracted despite discussion of an issue of vital personal importance to him. In the context also of apparent drowsiness, the clinician should suspect the presence of delirium.



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