Delirium 101

Acute Brain Failure

Overview

- Disorder of attention and develops acutely and fluctuates
- All delirious patients require a thorough evaluation
- Delirium is associated with numerous poor outcomes
- Very limited role for pharmacologic interventions in delirium
- Prevention of delirium is more effective than treatment
- Often under recognized
- Easily confused with Dementia

Case

Mrs. Delee Reema is a 78 y/o female who presents to the hospital after being found on the kitchen floor by her neighbor who called 911. EMS reports that it looked like she had been there for a while but hadn’t pushed the life alert she was wearing. The patient is awake and alert following simple commands occasionally but is only oriented to her name and does not know date, location and cannot give any meaningful information about what happened. She frail, disheveled and malnourished has a small bump on her head and right leg is extremely painful.

Exam

- Afebrile, pulse 111, bp 93/50, sat 93% on room air
- General: Awake alert, moderate distress from pain, thin, sarcopenic
- HEENT: small bruise right forehead, PERRL, dry mouth and tongue
- Neck: non-tender, appropriate ROM
- Chest: symmetric, no tenderness, no respiratory distress, CTA b/l
- Cardiac: Tachycardic, no murmur rub or gallop, no edema, peripheral pulses present
- Abdomen: soft nontender, non-distended, no guarding or rebound tenderness
- Extremities: right leg shortened and externally rotated.
- Skin: b/l upper extremity rash over hands and forearms
- Neuro: AAOx1, no focal weakness, CN II-XII intact, sensation intact
- Psych: underweight, distractible playing with pulse ox, Slow to answer questions, keeps bringing up her garden when asked where she is and what is going on.

Diagnostic and statistical manual of mental disorders (DSM-5)

A. A disturbance in attention and awareness
B. The disturbance develops over a short period of time, represents a change from baseline, tends to fluctuate
C. An additional disturbance in cognition
D. The disturbances in Criteria A and C are not explained by another preexisting, established, or evolving neurocognitive disorder
E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition

The Confusion Assessment Method (CAM) Diagnostic Algorithm

Feature 1: Acute Onset or Fluctuating Course

This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?

Feature 2: Inattention

This feature is shown by a positive response to the following question: Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?

Feature 3: Disorganized thinking

This feature is shown by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

Feature 4: Altered Level of consciousness

This feature is shown by any answer other than "alert" to the following question: Overall, how would you rate this patient's level of consciousness? (alert [normal]), vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable])

The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4.

Inouye, S., van Dyck, C., Alessi, C., Balkin, S., Siegal, A. & Horwitz, R. (1990). Clarifying confusion: The confusion assessment method. *Annals of Internal Medicine, 113*(12), 941-948.

The Confusion Assessment Method Instrument:

1. ***[Acute Onset]*** Is there evidence of an acute change in mental status from the patient's baseline?

2A. ***[Inattention]*** Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?

2B. ***(If present or abnormal)*** Did this behavior fluctuate during the interview, that is, tend to come and go or increase and decrease in severity?

3. ***[Disorganized thinking]*** Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

4. ***[Altered level of consciousness]*** Overall, how would you rate this patient's level of consciousness? (Alert [normal]; Vigilant [hyperalert, overly sensitive to environmental stimuli, startled very easily], Lethargic [drowsy, easily aroused]; Stupor [difficult to arouse]; Coma; [unarousable]; Uncertain)

5. ***[Disorientation]*** Was the patient disoriented at any time during the interview, such as thinking that he or she was somewhere other than the hospital, using the wrong bed, or misjudging the time of day?

6. ***[Memory impairment]*** Did the patient demonstrate any memory problems during the interview, such as inability to remember events in the hospital or difficulty remembering instructions?

7. ***[Perceptual disturbances]*** Did the patient have any evidence of perceptual disturbances, for example, hallucinations, illusions or misinterpretations (such as thinking something was moving when it was not)?

8A. ***[Psychomotor agitation]*** At any time during the interview did the patient have an unusually increased level of motor activity such as restlessness, picking at bedclothes, tapping fingers or making frequent sudden changes of position?

8B. ***[Psychomotor retardation]*** At any time during the interview did the patient have an unusually decreased level of motor activity such as sluggishness, staring into space, staying in one position for a long time or moving very slowly?

9. ***[Altered sleep-wake cycle]*** Did the patient have evidence of disturbance of the sleep-wake cycle, such as excessive daytime sleepiness with insomnia at night?

Attention and Disorganized Thinking

- Days of the week backwards
- Months of the year backwards
- Spell a word backwards
- CASABLANCA- squeeze on A
- Logical flow of ideas
- Unpredictable switching
- Do rocks float on water
- Is 1 lb more than 2lb

- The CAM demonstrates sensitivities from 94–100%, specificities from 90–95%, positive predictive accuracy of 91– 94%, negative predictive accuracy of 90–100%, high inter-rater reliability

Wei LA, Fearing MA, Sternberg EJ, Inouye SK. The Confusion Assessment Method: a systematic review of current usage. J Am Geriatr Soc. 2008;56(5):823-830. doi:10.1111/j.1532-5415.2008.01674.x

Delirium is often unrecognized and undocumented by clinicians. Rates of unrecognized delirium, which is defined as the diagnosis of delirium after being unrecognized by a primary physician or nurse is estimated to be about 60% of all cases

-DDIMER of Delirium. Day of the week. Months backwards. strong NNP

Oh, E.S., Fong, T.G., Hshieh, T.T., & Inouye, S K. (2017). Delirium in older persons: Advances in diagnosis and treatment. JAMA, 318(12), 1161-1174.

We really want background but in the meantime lets look for underlying causes

- ED is going to rule out everything big bad
- CBC, CMP, urinalysis, chest xray, drug screen, imaging of leg
- Head CT? not very helpful in diagnosis of delirium maybe 5% if no focal deficits
- but she hit her head, altered mental status she gets a head CT

Electrolytes Sodium, Potassium, acid base disturbances, kidney and liver function, anemia, infection-(bladder/kidney and lung)

- Sodium is a little low, cr 1.9 BUN 40 (kidneys aren't working great)
- UA shows some WBC and few bacteria (infection?)
- Drug screen negative
- Cxray no pneumonia
- Imaging of her hip show femoral neck fracture
- Head CT- "no acute intracranial process" chronic microvascular ischemic changes

- So she is started on fluids, antibiotics, pain control(IV opiate) and is in the ED until bed ready

- So she is started on fluids, antibiotics, pain control and is in the ED until bed ready
- Few hour later she becomes acutely agitated. Ripped out her IV. Attacked a nurse trying to take vitals and seem to be hallucinating.
- -20 goedon and 5 of Haldol and ends up in physical restraints so we can give her fluids and antibiotic

Crazy case?

Table 1
A comparison of the incidence of psychiatric disorder in the general population and delirium among medically ill patients

Selected Medical Populations	Incidence of Delirium (%)
Medical Services	
At admission to inpatient medicine ward	10–31
New delirium: general medicine wards	3–29
HIV-AIDS	20–40
Poststroke	13–48
Medical: ICU	60–87
Sepsis	9–71
CCU	26

Surgical Services	
General surgical wards	11–46
Postoperative delirium	4.7–74
Post-CABG	13–32
Vascular surgery	22
Abdominal aneurysm repair	33
Orthopedic surgery	12–41
Postorthotopic liver transplant	45.2
Postcardiotomy	32–67

Critical Care Setting	
Coronary care units	26
Medical ICU	60–87
ARDS	70–73
Survivors of stupor or coma	Up to 89

Elderly	
In nursing homes	15–70
Delirium present at hospital admission	10.5–39
In-hospital delirium	15–31
Frail-elderly patients	Up to 60
Postsurgery	20–65

END ACUTE BRAIN FAILURE

Things have escalated

Table 2
END ACUTE BRAIN FAILURE: predisposing and precipitating risk factors for delirium

Risk Factors	Examples
Electrolyte imbalance & dehydration	Electrolyte disturbances (eg, hyperammonemia, hypercalcemia, hypokalemia or hyperkalemia, hypomagnesemia, hyponatremia or hypernatremia)
Neurologic disorder & injury	All neurologic disorders: CNS malignancies, abscesses, CVA, intracranial bleed, meningitis, encephalitis, neoplasms, vasculitis, MS, epilepsy, Parkinson disease, NPH, TBI, DAI, paraneoplastic syndrome Of the various forms of sensory impairment, only visual impairment has been shown to contribute to delirium Visual impairment can increase the risk of delirium 3.5-fold
Deficiencies (nutritional)	Nutritional deficiencies (eg, malnutrition, low serum protein or albumin, low caloric intake, failure to thrive), malabsorption disorders (eg, celiac disease), and hypovitaminosis: specifically deficiencies in cobalamin (B12), folate (B9), niacin (B3, leading to pellagra), thiamine (B1, leading to beriberi & Wernicke disorder)

Age & gender	Age >65 y & gender male > female Old age is likely a contributor due to increased number of medical comorbidities: ↑ overall frailty, ↓ volume of ACH producing cells, ↓ cerebral oxidative metabolism, ↑ cognitive deficits, ↑ risk of dementia, ↑ age-related cerebral changes in stress-regulating neurotransmitter, intracellular signal transduction systems, chronic neurodegeneration with an increased production of inflammatory mediators, including cytokines and acute phase proteins
Cognition	Baseline cognitive deficits, even subtle ones, have been associated with an increased the risk of developing delirium The presence of dementia more than doubles the risk for postoperative delirium
U-Tox (intoxication & withdrawal)	Substance abuse: acute illicit substance intoxication (eg, cocaine, PCP, LSD, hallucinogens) and substance withdrawal, particularly abstinence syndromes from CNS-dep agents (eg, alcohol, benzodiazepines, muscle relaxants, opioids)
Trauma	Physical trauma & injury: heat stroke, hyperthermia, hypothermia, severe burns, surgical procedures
Endocrine disturbance	Endocrinopathies such as hyperadrenal or hypoadrenal corticoid, hyperglycemia or hypoglycemia, hyperthyroidism or hypothyroidism

Behavioral, psychiatric	Certain psychiatric diagnoses, including undue emotional distress, a history of alcohol and other substance abuse, and depression, schizophrenia, and bipolar disorder
Rx & other toxins	Several pharmacological agents have been identified as highly deliriogenic, including prescribed agents (eg, narcotics, GABA-ergic agents, steroids, sympathomimetics, dopamine agonists, immunosuppressant agents, some antiviral agents) & various OTC agents (eg, antihistaminic and anticholinergic substances), and polypharmacy Also consider the toxic effects of pharmacologic agents (eg, serotonin syndrome, neuroleptic malignant syndrome, anticholinergic states) and the deleterious effects of toxic levels of various therapeutic substances (eg, lithium, VPA, carbamazepine, immunosuppressant agents) Various toxins, including carbon dioxide & monoxide poisoning, solvents, heavy metals (eg, lead, manganese, mercury), insecticides, pesticides, poisons, biotoxins (animal poison), can also manifest with delirium

Anemia, anoxia, hypoxia, & low perfusion states	Any state that may contribute to decreased oxygenation (eg, pulmonary or cardiac failure, hypotension, anemia, hypoperfusion, intraoperative complications, hypoxia, anoxia, carbon monoxide poisoning, shock)
Infections	Pneumonia, urinary tract infections, sepsis, encephalitis, meningitis, HIV/AIDS
Noxious stimuli (pain)	Data suggest that pain and medications used for the treatment of pain have been associated with the development of delirium Studies have demonstrated that the presence of postoperative pain is an independent predictor of delirium after surgery On the other hand, the use of opioid agents has been implicated in the development of delirium

Failure (organ)	End organ failure (eg, hepatic, cardiac, renal failure) may lead to a delirious state
APACHE score (severity of illness)	Evidence shows that the probability of transitioning to delirium increases dramatically for each additional point in the APACHE II severity of illness score
Isolation & immobility	Social isolation, decreased intellectual stimulation, physical immobility, and increased functional dependence (eg, requiring assistance for self-care and/or mobility)
Light, sleep, & circadian rhythm	Sleep deprivation, sleep disorders (eg, obstructive sleep apnea, narcolepsy), & disturbances in sleep-wake cycle
Uremia & other metabolic disorders	Acidosis, alkalosis, hyperammonemia, hypersensitivity reactions, glucose, acid-base disturbances
Restraints	The use of restraints, including endotracheal tubes (ventilator), soft and leather restraints, intravenous lines, bladder catheters, and intermittent pneumatic leg compression devices, casts, and traction devices all have been associated with an increased incidence of delirium
Emergence delirium	Emergence from medication-induced sedation, coma, or paralysis, which may be associated with CNS-dep withdrawal, opioid withdrawal, REM-rebound, sleep deprivation

We need background information

Characteristic	Delirium	Dementia
Onset	Acute	Insidious
Course	Fluctuating	Gradual deterioration
Awareness	Impaired	Often clear until advanced stages
Attention	Disturbed	Often good until advanced stages
Memory	Poor working memory and immediate recall	Poor short-term memory
Delusions	Often short-lived or changing	More fixed
Sleep disturbances	Fragmented sleep	Sleep-wake reversal

Background/baseline information

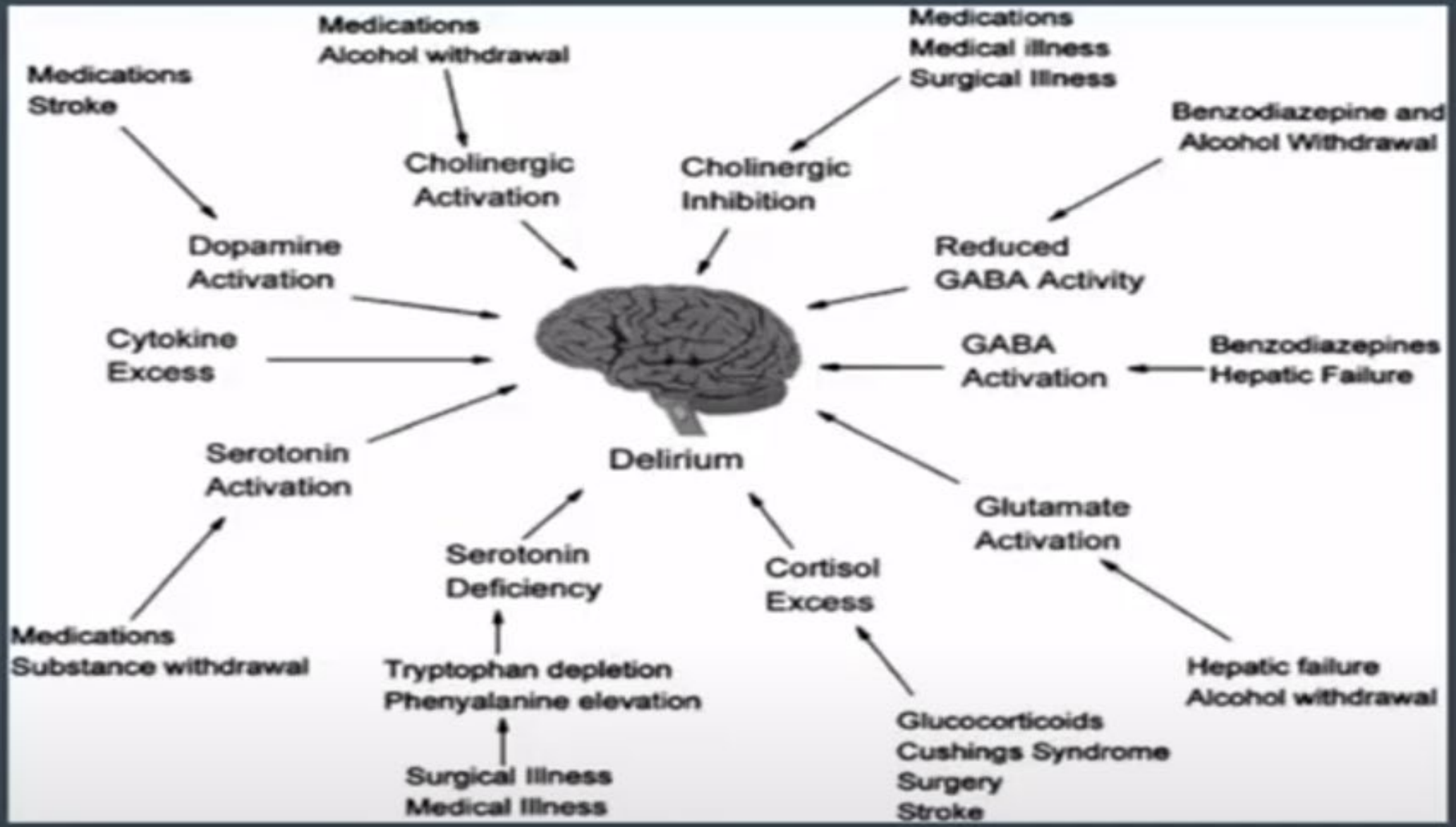
Finally get a hold of the daughter who lives Palm beach, but talks to her mother multiple times a week. She tells you about her past medical history. She is living alone since losing her husband 3 years. She has a history of HTN, hypothyroidism, depression. Daughter has some concerns that she has been declining, losing weight, not as active in the community and asked her to move in with her, but mother refuses.
She has been more forgetful but she is still independent at home manages her finances and medications. She hasn't mentioned any new medical issues. She enjoys gardening and actually got into some poison ivy recently and was very itchy so I told her to pick up some Benadryl.

Table 3
Theorized neurochemical mechanisms associated with conditions leading to delirium

Delirium Source	ACH	DA	GLU	GABA	5HT	NE	Trp	MEL	Phe	His	Cytok	HPA Axis	Cort	NMDA activity	RBF Δ	Inflam	EEG
Anoxia or hypoxia	↓	↑	↑	↑	↓	↓	⇔	↓	↑	↑↓	⫩↑	⫩	↑	↑	⫩	↑	↓
Aging	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	⫩↑	⫩	↑	↓	⫩	↑	↓
TBI	↑	↑	↑	↑	↑	↑	↑	↓	↑	↓	↑⫩	↑	↑	↑	↑	↑⫩	↓
CVA	↓	↑	↑	↑	↑	↑	↑	↓	↑	↓	↑⫩	↑	↑	↑	⫩	↑⫩	↓
Hepatic encephalopathy	⇔	↓	↑	↑↑	↑	↓	↑	↓	↑	↑	↑⫩	⫩	↑	↑	⫩	↑	↓
Sleep deprivation	↓	↓	⫩	↑	↑	↑	↓	↓⫩	↑	↑	↑	⫩	↑	↑	↑	↑⫩	↓
Trauma, Sx, & Postoperative	↓	↑	↑	↑	↓	↑	↓	↓	↑	↑	↑	↑	↑	↑	⫩	↑	↓
ETOH & CNS-Dep withdrawal	↑	↑	↑	↓	↑	↑	↓	↓	↑	↑	↑	↑⫩	↑	↑	↓	↑	↑
Infection or sepsis	↓	↓	↑	↑	↓	↓	↓	↓	↓	↓	↑	↑⫩	↑	↑⫩	⫩	↑	↓
Dehydration & electrolyte imbalance	⇔	↑	↑	↑	↓	↑	?	↓	?	↑	↑	⫩	↑	↑	↓	⫩↑	⫩
Medical illness	↓	↑	↑	⫩	↓	↑	↓	↓	↑	↑	↑	↓	↑	↑	⫩	⫩	⫩

Abbreviations: (–), likely not to be a contributing factor; ⇔, no significant changes; (⫩), likely a contributor, exact mechanism is unclear; ↑, likely to be increased o activated; ↓, likely to be decreased; Cort, cortisol; Cytok, cytokine; EEG, electroencephalograph; ETOH, alcohol; GABA, gamma-aminobutyric acid; His, histamine HPA axis, hypothalamic-pituitary-adrenocortical axis; Inflam, inflammation; NMDA, N-methyl-D-aspartic acid; Phe, phenylalanine; RBF, regional blood flow; Sx surgery; Trp, tryptophan.

Data from Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. Am J Geriatr Psychiatr 2013;21:1190–222; and Maldonado J. Delirium pathophysiology: current understanding of the neurobiology of acute brain failure. Int J Geriatr Psychiatry, in press



Flacker, J.M., & Lipsitz, L.A. (1999). Neural mechanisms of delirium: current hypotheses and evolving concepts. *The Journal of Gerontology Series A: Biological Sciences and Medical Sciences, 54(6)*, B239-B246.

Pharmacotherapy

- Data is limited
- Underlying theory abnormally elevated levels of dopamine
- Dopamine antagonist
- restoration of hippocampal functions (eg, short-term memory) and reversal of other regional brain disturbances (eg, agitation, psychosis),
- protect neurons against hypoxic stress and injury
- I’m not really convinced. Control not treatment

Dopamine antagonist

- Haloperidol-most research, has more side effects and contraindications, no other atypical have demonstrated superiority
- Risperidone-less sedating
- Quetiapine more sedating shorter half-life 7hrs
- Olanzapine better qt effect long half-life, anticholinergic potential
- Aripiprazole less sedating may be better in hypoactive delirium

❖ Black box warning related to dementia-related psychosis. Increase mortality risk in elderly dementia patients

❖ Check EKG, correct electrolytes K,Mg, review other qt prolonging agents, watch for EPS

Acetylcholinesterase inhibitor

- Eg, rivastigmine, donepezil for patients with a history of recurrent delirium or delirium superimposed on known cognitive deficits

Regulation of sleep wake cycles

- Melatonin or melatonin agonists (eg, ramelteon 8 mg every HS) to help promote a more natural sleep and management of all types of delirium
- If that is ineffective, consider trazodone (eg, 25–100 mg every HS) or mirtazapine (eg, 3.75–7.5 mg every HS)

Supportive therapies

- Maintain hydration/nutrition
- Avoid restraints
- Mobilize patients early
- Reduce noise
- Orienting stimuli
- Reassurance
- Beside sitter encourage family visit
- Manage pain

Hospital Elder Life Program Model

- Screen 70 and old for cognitive impairment, sleep deprivation, immobility, dehydration, vision and hearing impairment
- Team of nurses, volunteers, and geriatricians implement simple strategies to target specific risk factors
- Making sure pain is controlled, patient has their glasses, socialization with meal, quite time
- Widespread hospital use, Up to 30% reduction in the incidence of delirium and reduced readmission rate

Case: Treat the underlying condition!

- Started scheduled low dose quetiapine and melatonin at night with PRN quetiapine for acute agitation-more cooperative
- Treated underlying dehydration, UTI, and electrolyte abnormalities.
- Make sure we eliminated any medication that could be deliriogenic
- We start her thyroid medication +/- antidepressant
- We get PT/OT, dietary, invite family to sit with her, get her glasses, play music
- Manage pain with opioid sparing medication and lowest dose opioids
- Topical management of her contact dermatitis

Enormous Impact

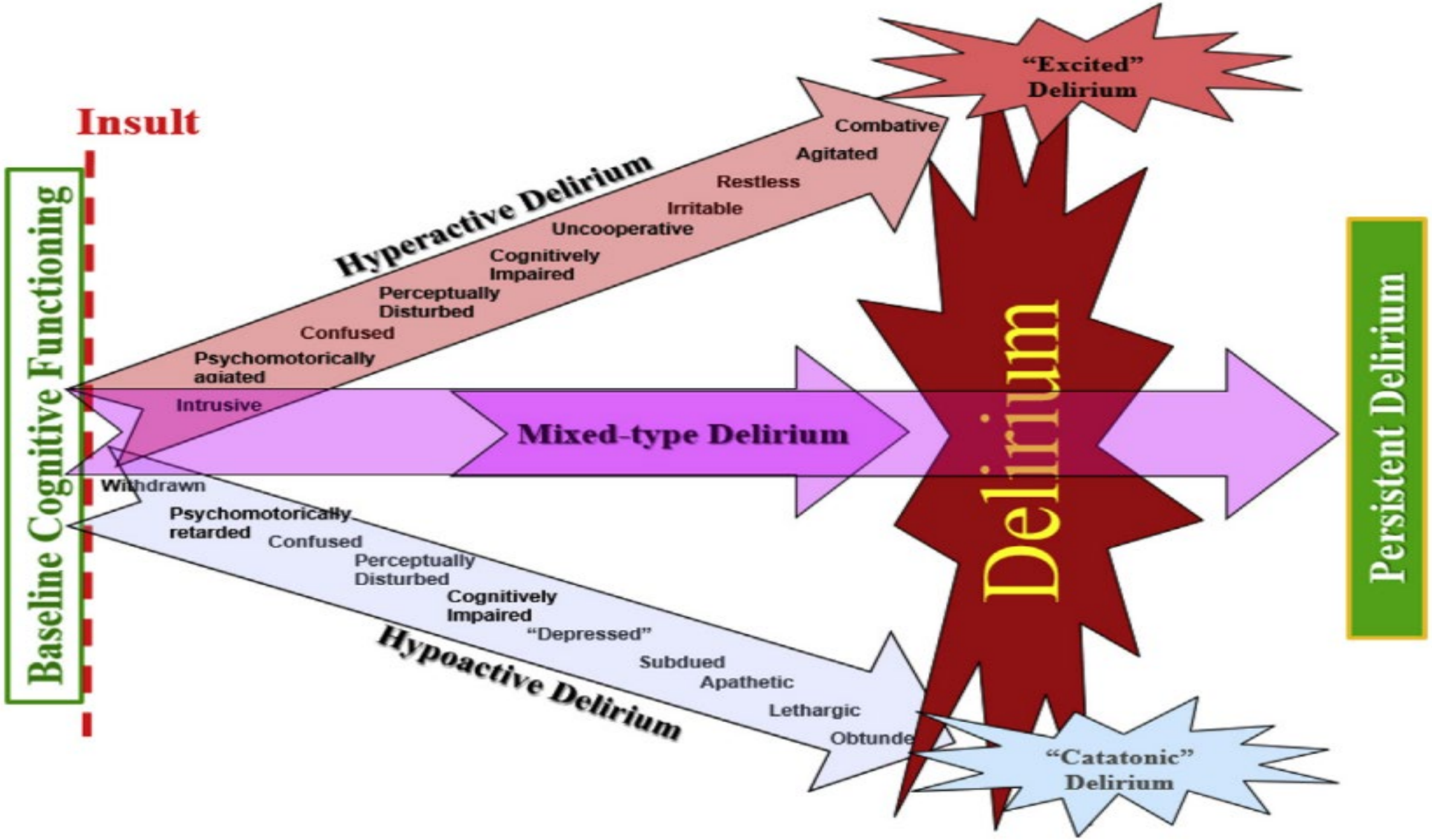
- Prolong hospitalization
- Functional and cognitive decline
- Higher risk for institutionalization
- 1-6 month mortality estimates 14-22% 2x
- Persistent cognitive dysfunction

Case

- Patient improved enough to go to surgery.
- We maintained the supportive delirium treatment/prevention
- Pain and mobility improved and she was able to leave the hospital

What happened?

- Baseline decline after loss of husband, lives alone with depression/decreased nutritional status and reserves
- Poison Ivy causing severe itching and sleeping difficulties
- Decreased liver metabolism associated with aging
- Use of Over the counter anticholinergic/antihistamine, perhaps UTI
- Delirium before the fall, didn’t know how to use her life alert
- Prolonged period on the ground with dehydration and kidney injury


Insult
Baseline Cognitive Functioning
Hyperactive Delirium
Combative
Agitated
Restless
Irritable
Uncooperative
Cognitively Impaired
Perceptually Disturbed
Confused
Psychomotorically agiated
Intrusive
"Excited" Delirium
Mixed-type Delirium
Delirium
Persistent Delirium
Withdrawn
Psychomotorically retarded
Confused
Perceptually Disturbed
Cognitively Impaired
"Depressed"
Subdued
Apathetic
Lethargic
Obtunde
Hypoactive Delirium
"Catatonic" Delirium

Take away

- This diagnosis is missed often
- Use the CAM exam. It doesn’t take long
- Implement Delirium preventative strategies early.

- Very common, very scary and difficult to treat