DELIRIUM DIFFERENTIALS: “SPECIAL CASES”

DAVID GALARNEAU, M.D.

DISCLOSURES – NONE

BREAKOUT GROUP FACILITATORS

- Ariya Beitollahi, M.S.
- Adam Mauricio, B.S.
- Jacob Park, B.S.
- Marlie Winslow, B.A.
- Laura Yuan, B.A.

ACKNOWLEDGEMENTS

- I would like to thank the following individuals, who contributed to the development of this symposium:
  - *Ariya Beitollahi, M.S*
  - *Adam Mauricio, B.S.*
  - *Jacob Park, B.S.*
  - *Andrew Teodorczuk, M.D.*
  - *Marlie Winslow, B.A.*
  - *Isabel Yoon, M.D.*
  - *Laura Yuan, B.A.*

THE CASE OF MR. E

THE CASE OF MR. E – DAYS 1-3

- 74-year-old retired fisherman
- Lives alone, independent, still driving
- PMHx: hypertension and dyslipidemia – on medications
- Admitted for severe kidney infection with associated vomiting, severe pelvic/back pain, and dehydration
- Received IV fluids and narcotic pain meds on admit
- On the ward:
  - At night: poor sleep
  - During day: pleasant and cheerful, though tired
- Mild periodic confusion, coherent majority of the time

THE CASE OF MR. E – DAY 4

- Abrupt change on fourth night
- Anxious, pacing, waving his arms in the air, and mumbling to himself
- Verbally abusive to nursing staff
- Inattentive, not able to engage in sensible conversation
- When questioned, inappropriate answers and repetitive responses
- Accuses you of trying to steal his keys and move his car out of garage
- Attempts to hit you during physical exam

DELIRIUM

PROVISIONAL & DIFFERENTIAL DIAGNOSIS

- Provisional diagnosis: delirium
- Primary differential: delirium vs dementia
  - Delirium: acute in onset – abrupt change – problems not identified at admission
  - Dementia: insidious in onset – significant cognitive dysfunction prior to admission
- *Of note:* delirium can be superimposed on dementia
- Less commonly – primary psychotic disorder
- Also consider MDD – “pseudodementia”

DSM-5-TR CRITERIA – DELIRIUM

A. Disturbance in attention and awareness
B. Develops over short period of time, represents a change from baseline, and fluctuates in severity
C. An additional disturbance in cognition
D. Not better explained by another preexisting, established, or evolving neurocognitive disorder
E. The disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, exposure to a toxin, or due to multiple etiologies

DSM-5-TR CRITERIA – DELIRIUM

- *Specify* whether:
  - Substance intoxication
  - Substance withdrawal
  - Medication-induced
  - Due to another medical condition
  - Due to multiple etiologies
- *Specify* if:
  - Acute
  - Persistent
- *Specify* if:
  - Hyperactive
  - Hypoactive
  - Mixed

DELIRIUM – CAUSE AND EFFECT

- Delirium is a marker, like fever
- Signals an underlying derangement
- Of utmost importance: determine then correct underlying cause
- Significant morbidity/mortality
  - Medical emergency – treat as such!
- Assessment and management of medical problems on their merits
- *Setting:* medical not psychiatric unit

WORK UP

- Extensive and integral
- Etiology likely multifactorial – exhaustive search
- Appropriate labs and imaging to assess all potential causes
- Fall sustaining subdural hematoma?
  - *Consider head imaging*

INVESTIGATIONS

- History and physical exam
- Serum electrolytes
- Creatinine
- Glucose
- Calcium
- Complete blood count
- Urinalysis and urine culture
- Urine and blood toxicology screens
- Drug levels
- Arterial blood gas
- Liver function tests
- Thyroid function tests
- B12 and folate levels
- Cardiac enzymes
- D-Dimer
- Neuroimaging
- EEG, LP
- CT of chest, abdomen, pelvis
- CXR
- EKG

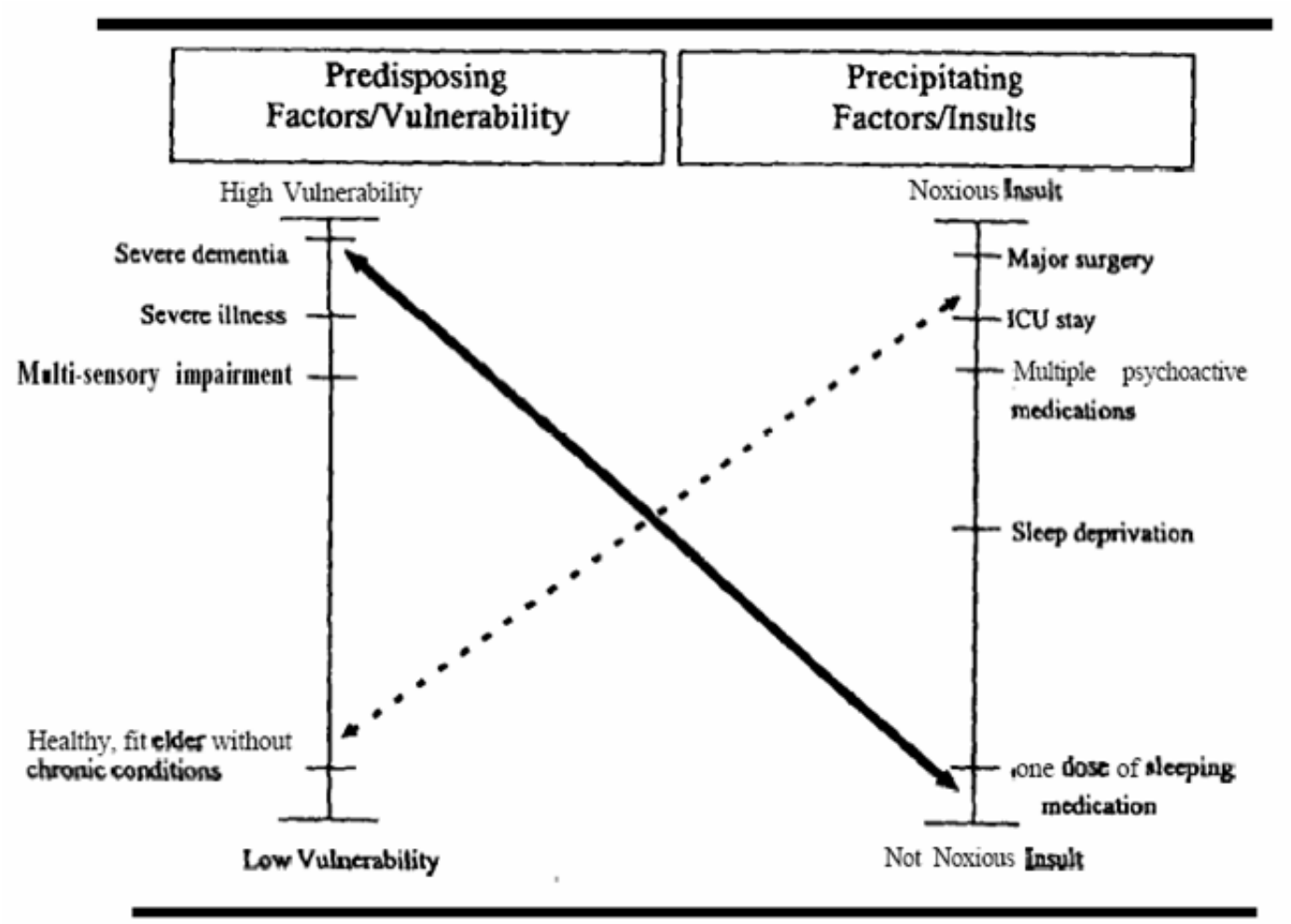
COMMON CAUSES

“I WATCH DEATH”

Infections
Withdrawal
Acute metabolic
Trauma
CNS pathology
Hypoxia
Deficiencies (vitamins)
Endocrinopathies
Acute vascular
Toxins
Heavy metals

Infection	HIV, sepsis, Pneumonia
Withdrawal	Alcohol, barbiturate, sedative-hypnotic
Acute metabolic	Acidosis, alkalosis, electrolyte disturbance, hepatic failure, renal failure
Trauma	Closed-head injury, heat stroke, postoperative, severe burns
CNS pathology	Abscess, hemorrhage, hydrocephalus, subdural hematoma, Infection, seizures, stroke, tumors, metastases, vasculitis, Encephalitis, meningitis, syphilis
Hypoxia	Anemia, carbon monoxide poisoning, hypotension, Pulmonary or cardiac failure
Deficiencies	Vitamin B12, folate, niacin, thiamine
Endocrinopathies	Hyper/hypoadrenocorticism, hyper/hypoglycemia, Myxedema, hyperparathyroidism
Acute vascular	Hypertensive encephalopathy, stroke, arrhythmia, shock
Toxins or drugs	Prescription drugs, illicit drugs, pesticides, solvents
Heavy Metals	Lead, manganese, mercury

PREDISPOSING & PRECIPITATING FACTORS: VULNERABILITY VERSUS INSULT



ASSESSMENT

- MMSE – Folstein Exam
- MoCA
- CAM-ICU
- Mini-Cog
- SAVEAHAART
- Note: WORLD backwards and serial 7s both assess attention
- *Clinical Pearl:* waxing and waning course, easy to miss with single assessment
  - Inquire with family and nursing staff, assess on multiple occasions

MANAGEMENT – SAFETY

- Room next to nursing station for closer monitoring
- Falls precaution
- Family/friend at bedside for support, comfort, and reorientation
- Consider 1:1
- Technology – video monitoring, bed alerts
- PRN for agitation
- Last resort – restraints

MANAGEMENT – NON-PHARMACOLOGIC APPROACHES

- Rehydration and correction of electrolyte abnormalities
- Address malnutrition and constipation
- Mobility activities
- Oxygen therapy
- Pain assessment and management
- Regular reassurance
- Activities to stimulate cognition
- Assistance with hearing and visual aids
- Discontinuing foley catheter or IV *when/if feasible*

MANAGEMENT – NON-PHARMACOLOGIC APPROACHES

- Reorientation
  - Calendar/clock
  - Day: lights on/shades up
  - Night: lights off/shades down
  - Minimize disruptions at night
  - Key information on white board
  - English second language – employ an interpreter – may lose fluency

MANAGEMENT – PHARMACOLOGIC REVIEW

- Review and cull medication regimen, as appropriate
- Common offenders:
  - Benzodiazepines
  - Anticholinergics
  - Antihistamines
  - Steroids
  - Opiates
- *Of note:* untreated pain also deliriogenic – may not be able to eliminate opioids

MANAGEMENT – PHARMACOLOGIC APPROACHES

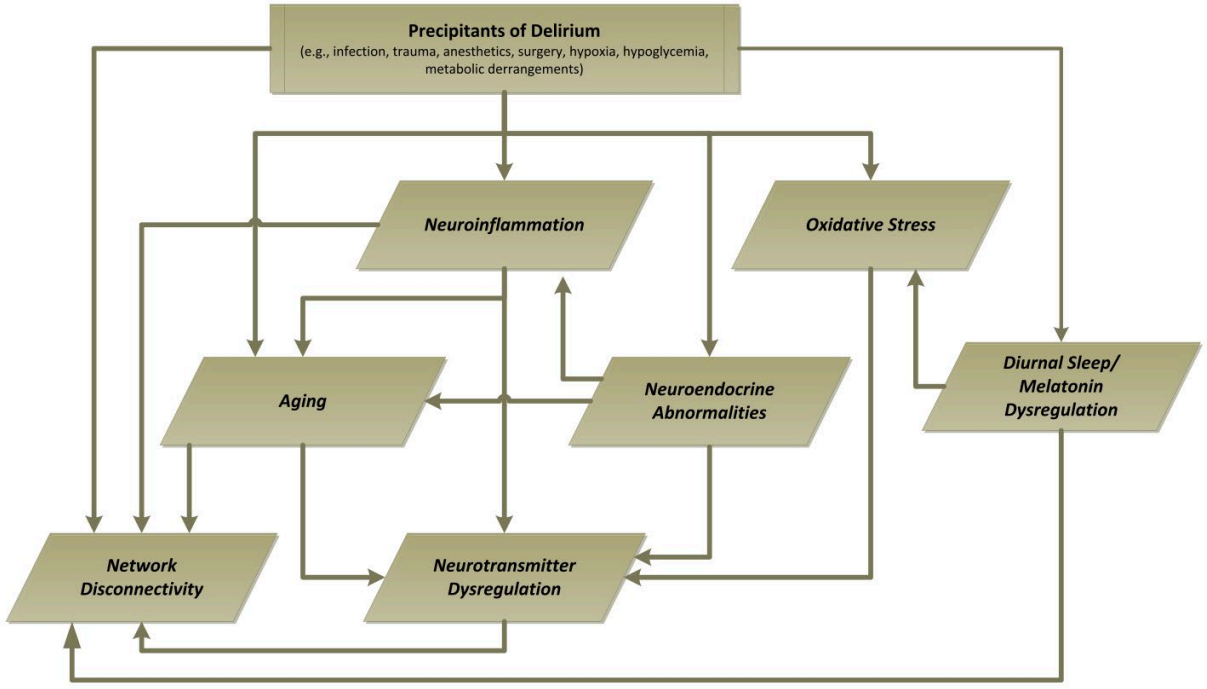
- Most commonly: neuroleptics
  - Start low, go slow!
  - e.g., Haldol 0.5mg, Risperdal 0.5mg, Zyprexa 2.5mg, Seroquel 25mg
  - *Remember:* medically frail, neuroleptic naïve – more sensitive to side effects
  - **DO NOT ORDER** Haldol 5mg, Ativan 2mg, and Benadryl 50mg
    - This is delirium, not schizophrenia!
  - Monitor QTc
    - Haldol IV – best to avoid, despite easy access

MANAGEMENT – PHARMACOLOGIC APPROACHES

- *Goal:* manage behavior – delirium itself only resolves with identification and correction of underlying cause(s)
- New approaches:
  - Valproic Acid (Depakote)
  - Dexmedetomidine (Precedex)
- Benzodiazepines – to be avoided
  - Exception: Alcohol/Benzodiazepine Withdrawal

ETIOLOGY: THEORETICAL MODELS

- Neuroinflammatory
- Neuronal aging
- Oxidative stress
- Neurotransmitter deficiency
- Neuroendocrine
- Diurnal dysregulation
- Network disconnectivity



Maldonado 2013

- Theories are complementary, not competing, with many intersections and reciprocal influences

A CLOSER LOOK AT NEUROTRANSMITTERS

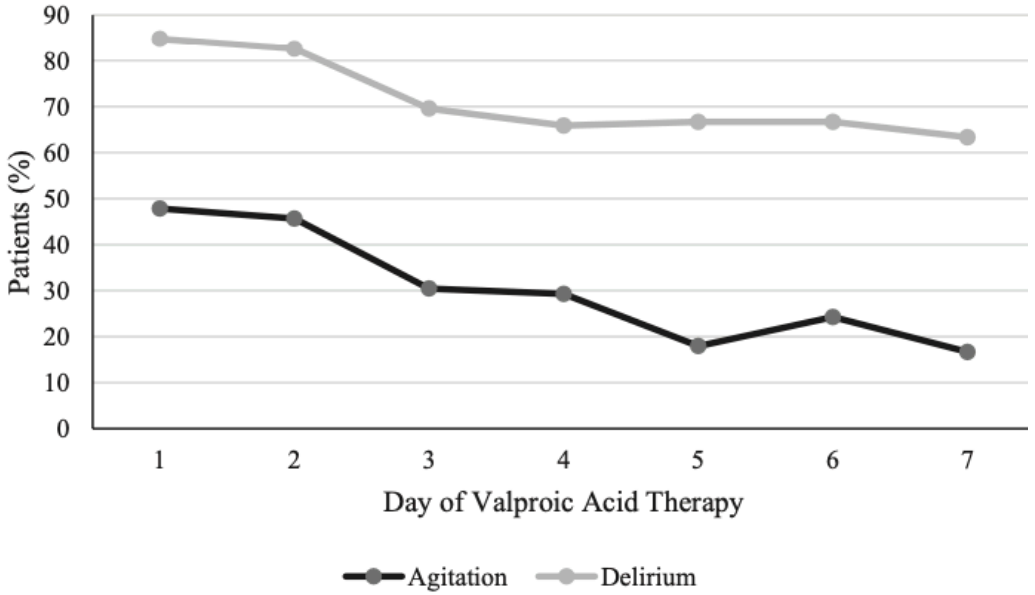
- Delirium can arise from neurotransmitter imbalance
- The most common neurotransmitter derangements:
  - Ach ↓
  - DA, NE, GLU ↑
  - 5HT, H1, H2, GABA ↑ ↓ *
    - * Variable – based on underlying etiology
- Implicated in Delirium:
  - Excitatory amino acid (e.g., glutamate) toxicity
  - Gamma-aminobutyric acid (GABA) agonism
  - Acetylcholine deficiency

VALPROATE AND DEXMEDETOMIDINE: PHARMACOLOGIC RATIONALE IN DELIRIUM

- Valproate:
  - Decreases glutamate release
  - Increases GABA in synaptic cleft
  - Increases acetylcholine efflux in hippocampus
- Dexmedetomidine:
  - Highly selective α^2 agonist – reduces norepinephrine release
  - Significant opioid-sparing effect
  - Decreases glutamate release
  - Lack of GABA receptor modulation or cholinergic receptor activity
  - Promotes natural sleep patterns
    - Inhibition of noradrenergic neurons – locus coeruleus
    - Disinhibition of GABA neurons – ventrolateral preoptic nucleus

EVIDENCE FOR VALPROATE IN DELIRIUM

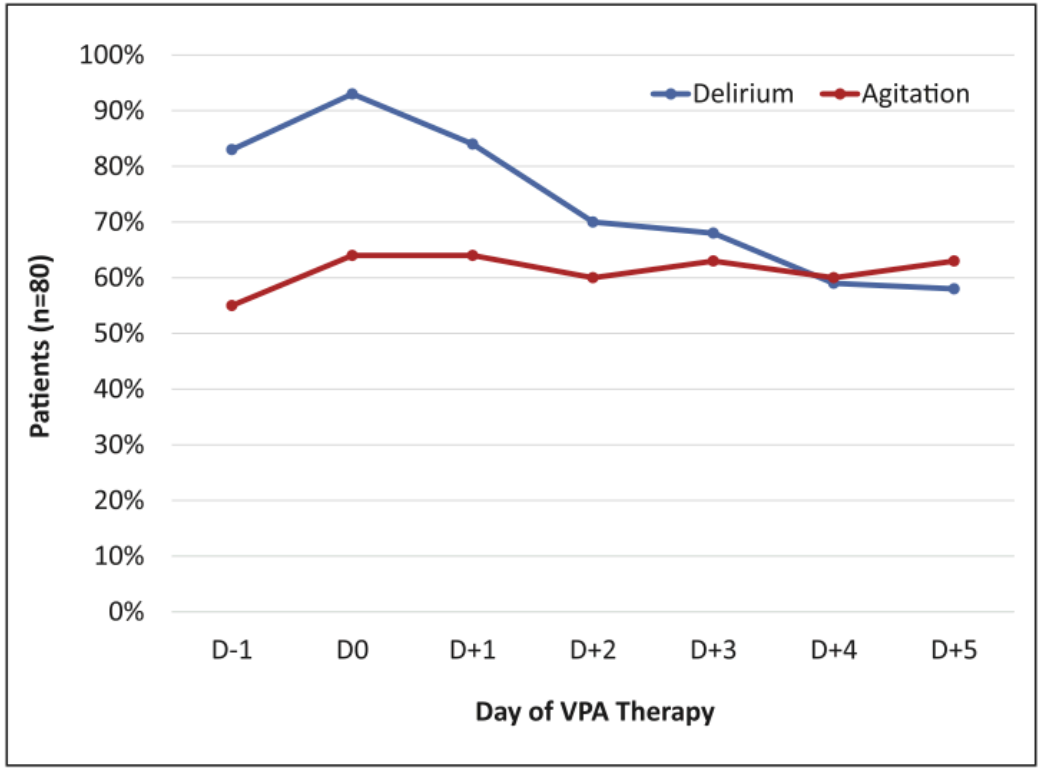
- Retrospective analysis
- Study size: 47 patients
- Downward trend in prevalence of agitation (47% to 16%) and delirium (83% to 68%)
- Decreased need for neuroleptics, benzos, and dexmedetomidine



Crowley et al. 2020

EVIDENCE FOR VALPROATE IN DELIRIUM

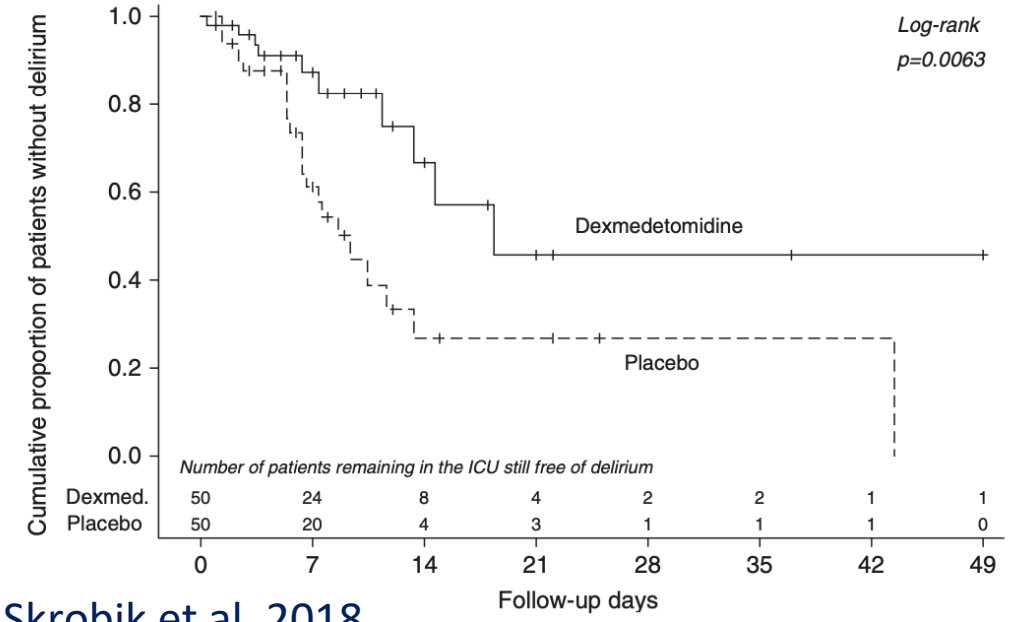
- Retrospective cohort study of ICU patients
- 80 patients
  - 35 valproic acid alone
  - 45 in conjunction with neuroleptics
- Delirium resolution in 55%
- Significant decreases in incidence of delirium
  - Day 0 to 3 (93% vs 68%; P < 0.01)
- No change in agitation (64% vs 63%; P = 0.28)



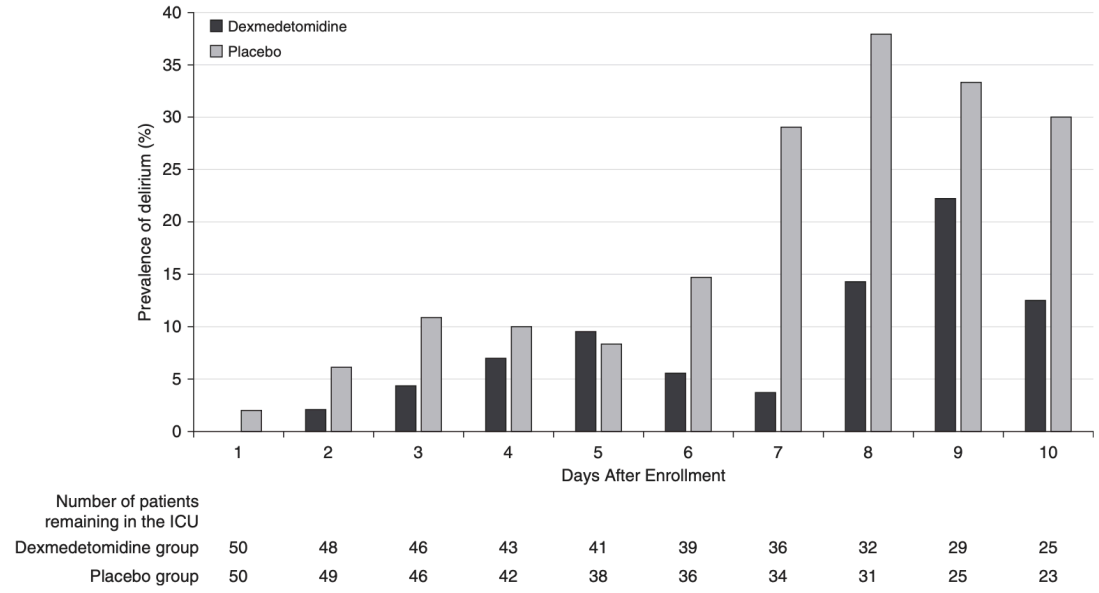
Quinn et al. 2021

EVIDENCE FOR DEXMEDETOMIDINE IN DELIRIUM

- Prospective, double-blinded, randomized, placebo-controlled trial
- 100 ICU patients: 50 receiving dexmedetomidine, remainder placebo



Skrobik et al. 2018



EVIDENCE FOR DEXMEDETOMIDINE IN DELIRIUM

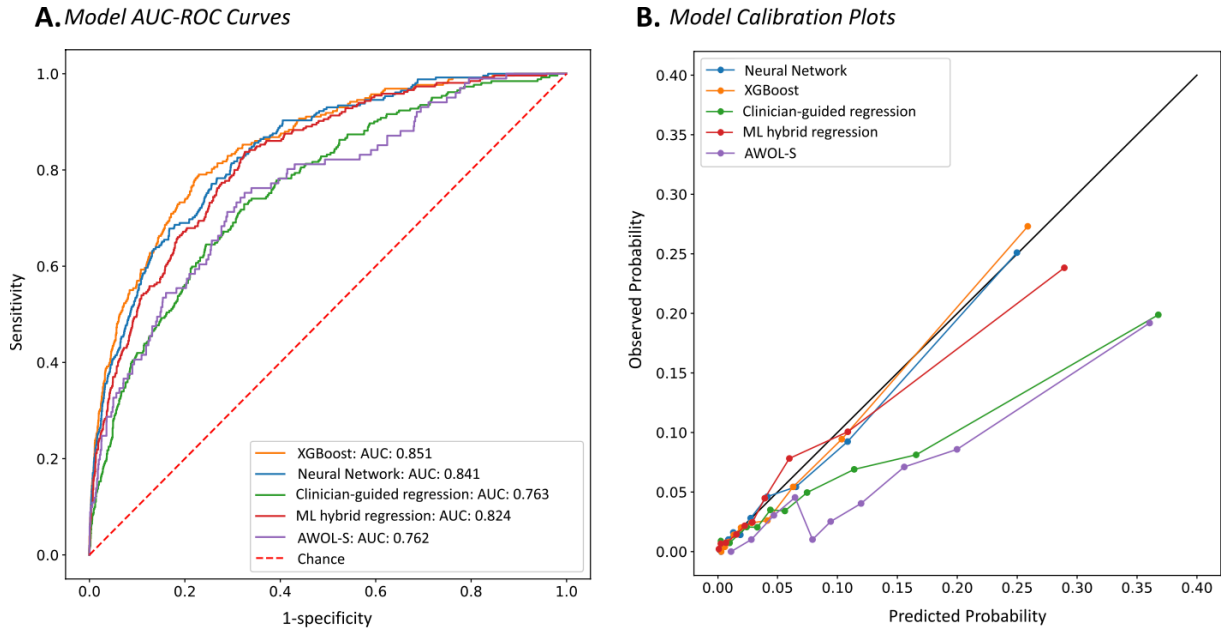
- Prospective, single-blinded, randomized, controlled trial
- Comparing dexmedetomidine to propofol for prevention of post-op delirium
- 91 patients receiving dexmedetomidine and 92 receiving propofol
- Decreased incidence of postoperative delirium in group receiving dexmedetomidine (16 vs 29), with additional significance in other categories observed (e.g., onset, duration, time to extubation)

	Dexmedetomidine Group (n = 16)	Propofol Group (n = 29)	*P* Value
Onset of delirium, d, median (range)	2 (1–4)	1 (1–4)	0.027
Duration of delirium, d, median (range)	2 (1–4)	3 (1–5)	0.04
Extubation time, h, median (range)	5.5 (3.5–14.2)	7.6 (3.8–202.2)	0.0007
Intensive care unit length of stay, h, median (range)	67.8 (20–214)	76.5 (17.8–956.5)	0.38
Hospital length of stay, d, median (range)	7.5 (5–32)	10 (6–74)	0.054

Djaiani et al. 2016

MACHINE LEARNING PREDICTION MODELS

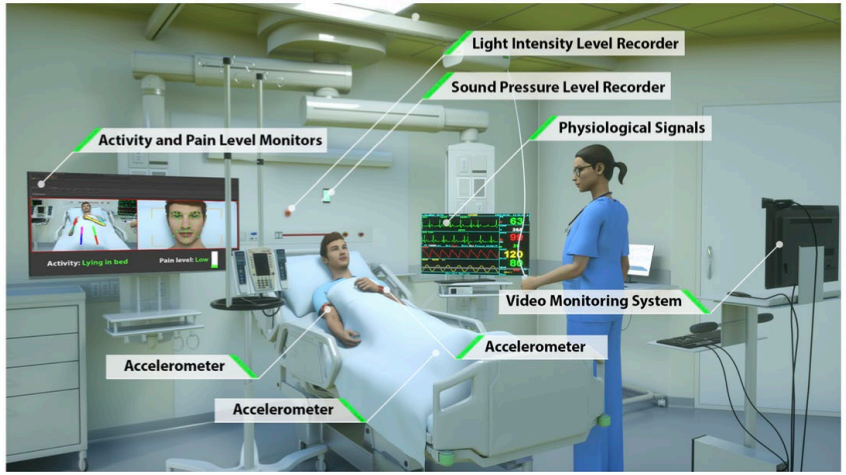
- Multicenter EHR database of 22,000+ ICU patients
- Program screens data for risk factors of post-op delirium
- Machine learning identifies higher-order interactions difficult to identify through traditional data analysis techniques
- Predicts delirium with AUC-ROC of 0.84-0.85

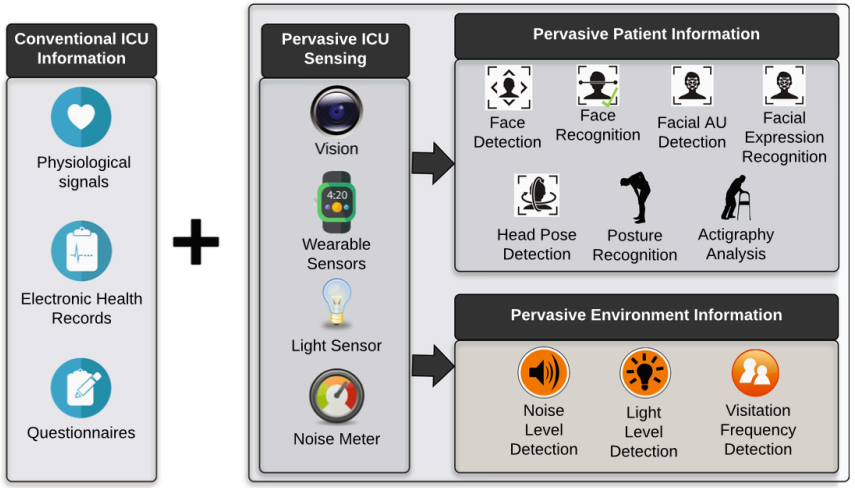


Ocagli et al. 2021

INTELLIGENT ICU – AUTONOMOUS PATIENT MONITORING

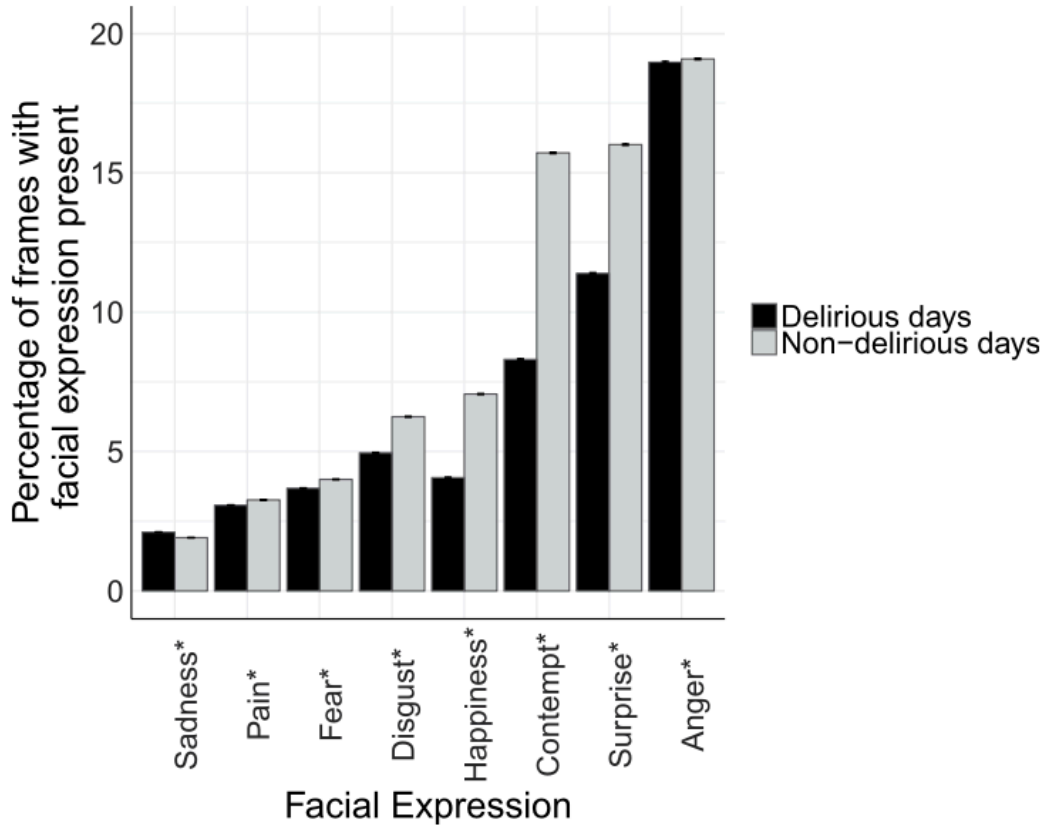
- Pilot study – 22 patients recruited in a surgical ICU
- Data on patients and environment collected via sensors (wearable, light, and sound) and cameras
- Data analyzed to detect and recognize:
  - Patient's face and postures
  - Facial action units/expressions
  - Head pose variation
  - Extremity movements
  - Sound pressure/light intensity level
  - Visitation frequency





INTELLIGENT ICU – AUTONOMOUS PATIENT MONITORING

- Significant differences between delirious and non-delirious patients:
  - Facial expressions
  - Functional status entailing extremity movement and postures
  - Environmental factors including visitation frequency, light/sound levels at night
- Results showed that autonomous monitoring of patients and their environment is feasible using a noninvasive system



Davoudi et al. 2019

BREAKOUT GROUP: DISCUSSION QUESTIONS

- What are the distinguishing features of the case?
- What additional information would you like, and why?
- What are your provisional and differential diagnoses?
- *If time permits,* what is your initial management plan?
- *If time permits,* any clinical pearls for the group?

THE CASE OF MRS. M

THE CASE OF MRS. M

- Married woman in mid 60s
- Presents to the ED with respiratory distress, somnolence, and “confusion”
- COVID+, admitted to floor
- PMHx: migraines and IBS – otherwise, reasonably healthy
- No previous admits
- Medications:
  - Mirtazapine 30mg PO bedtime
  - Topiramate 50mg PO bid
  - Amitriptyline 50mg PO bedtime
  - Sumatriptan 50mg PO PRN migraine

THE CASE OF MRS. M

- Nursing staff notes high level of dependency and unwillingness to attempt activities on her own
- However, no difficulty communicating her needs
- Quite forgetful upon direct questioning, but in casual conversation appears more cognitively intact
- Incontinent of urine and feces
- Declines repeatedly to work with PT/OT – “too tired”, “my breathing”
- At times, needs to be asked repeatedly before answering
- Commonly responds: “I don’t know”, “I’m just so confused right now”

THE CASE OF MRS. M

- Mini Mental State Examinations (MMSE) – 8/30
- Frequently answers: “I don’t know” or “I can’t do that”
- Apologizing often for her “terrible memory”
- Unable to obtain more extensive cognitive testing due to lack of cooperation and poor effort

THE CASE OF MRS. M

- Collateral obtained from husband:
- Describes wife as “high-strung”
- Sporadic somatic complaints throughout the years but generally healthy
- Distant psychiatric hospitalization for self-harm and depression – her father disappeared shortly prior; body never recovered
- Decline in memory beginning ~ 1 year ago
- Coincided with his retirement, which was precipitated by decline in his own health – “heart problems”

THE CASE OF MRS. M

- Further collateral from husband:
- Refuses to get out of bed or to attend to domestic tasks
- Withdrawn socially from her former friend group
- Needs aid with certain ADLs – others she manages alone
- Increasingly burdensome given his own infirmities
- He is scheduled for cardiac surgery in several weeks – scrambling for someone to look after her during his recuperation period
- Their only child (a son) frequently away for work

THE CASE OF MRS. M

- Further collateral from husband:
- He expresses frustration – normally active, now limited by his health and wife's condition
- Cannot motivate her to leave house even when son available to help
- Past month: insomnia and decreased appetite with 10lbs weight loss
- PCP prescribed Mirtazapine to address
- Several days ago: difficulty breathing, activity level decreased even further, listless
- Morning of presentation: fever, so he brought her in for evaluation

THE CASE OF MRS. M

- Vitals and labs consistent with mild dehydration
- Saturating in the high 80s/low 90s on room air
- CT of head – unremarkable
- MRI of head – notable for scattered periventricular white matter hyperintensities

”PSEUDODEMENTIA”

”PSEUDODEMENTIA”

- Apparent cognitive/behavioral problems, resembling but inconsistent with a neurodegenerative disorder
  - Colloquial term – *not* official DSM-5-TR nomenclature
- Heterogenous group of disorders:
  - Commonly: thinly veiled depressive episode
  - Occasionally: more akin to conversion disorder

FEATURES OF “PSEUDODEMENTIA”

- Regression and increasing physical dependency are common
- Tendency for past depressive symptoms/episodes in the history
- Premorbid personality often includes an inability to express emotions directly
- Objective cognitive testing limited by poor concentration/effort, failure to cooperate
- Frequent complaints of memory loss
- Staff and carers have intuitive impression that:
  - Cognition largely intact, inconsistencies in performance noted
  - Psychological (e.g., psychodynamic, dissociative) factors maintain impairment

PSYCHODYNAMIC FORMULATIONS

- The threatened *Ego* defends itself against the fear of fragmentation by “converting” the anxiety into something else (i.e., “dementia”)
- Regression and conversion triggered by losses associated with ageing in those with:
  - Emotional instability/repression
  - Diminished self-esteem
  - Insufficient social supports
  - Immature personality traits
  - Early abuse/trauma
  - Abandonment

DISTINGUISHING DEPRESSION FROM DELIRIUM

- Often challenging:
  - Hypoactive delirium versus psychomotor retardation?
  - Hyperactive delirium versus psychomotor agitation?
  - Early delirium – mood dysregulation can be sole presenting symptom
- Often preclude one another:
  - Depression is sequela of delirium
  - Previous depression common in delirious patients
- Lack of motivation and minimal effort mistaken for cognitive decline
- Memory impairments:
  - Delirium – more consistently forgetful of recent events
  - Depression – patchy, variable losses – recover with time/treatment
  - Implicit memory intact in depressed, not delirious, patients

“PSEUDODEMENTIA”: MANAGEMENT

- First-line treatment for MDD – meds, therapy, or combo of both
  - SSRI (or similar) and/or manualized psychotherapy (e.g., CBT)
  - Add augmenting agents as necessary
  - CBT once adequate engagement/participation – supportive psychotherapy initially
  - ECT for severe cases – memory may actually improve!
- Conversion syndromes respond better to psychotherapy than pharmacotherapy
  - However, must treat psychiatric comorbidities
  - Fostering the dependency worsens outcomes – unlike dementia/delirium

KEY DISTINGUISHING FEATURES

	HYPOACTIVE DELIRIUM	DEPRESSION
Course	Rapid, definable	Insidious, difficult to pinpoint exact onset/offset, may be worse in morning
Orientation	Fluctuates throughout day	Generally, fully oriented
Consciousness	Altered level of consciousness	Usually, unaltered
Thought Content	Confusion, but not persistent hopelessness or helplessness	Hopelessness and/or helplessness that persists throughout the day
Cognitive Functioning	Overall lower scores than depression, but higher effort level	Overall better scores than delirium, but lower effort level
Awareness/Acceptance of Memory Loss	Unaware or denies there is a problem	Frequently complains about the memory loss

DSM-5-TR CRITERIA: MAJOR DEPRESSIVE DISORDER

- Five or more of the following in the same two-week period
- At least one is *depressed mood* or *anhedonia*
  - Depressed mood
  - Anhedonia
  - Appetite/weight loss or gain
  - Insomnia or hypersomnia
  - PMA or PMR – observable
  - Fatigue
  - Worthlessness/guilt
  - Decreased concentration or indecisiveness
  - Suicidal ideation/behavior
- Symptoms must occur concurrently, be present near continuously, and be markedly impairing

THE CASE OF MS. F

THE CASE OF MS. F

- 55-year-old single woman
- Admitted for a UTI complicated by acute renal failure
- PMHx: well-managed schizoaffective disorder, type 2 diabetes, chronic renal failure, atrial fibrillation, arterial hypertension, previous CVA with right arm contracture, and aortic stenosis
- Psych Meds:
  - Invega Sustenna 234mg IM monthly (last administered a week ago)
  - Escitalopram 20 mg daily
- Numerous other medications to address her medical comorbidities

THE CASE OF MS. F

- When admitted, at chronic baseline, with no appreciable psychiatric symptoms
- Change noted seven days into hospitalization
- Developed altered level of consciousness, rigidity, and isolated temperature spike
- Exam notable for mutism, negativism, withdrawal, motor retardation, and new onset increased tone in her left arm
- Per night nurse: mobility had deteriorated, selective speech
- On pre-rounds: mouthed single word greeting then made no further attempt at verbal interactions; did not respond to questioning
- Staring out window, minimal facial expressions, inconsistently followed examiner's gaze
- Oral intake decreased over past 24 hours and breakfast is untouched

THE CASE OF MS. F

- Collateral obtained from family:
- Recent low mood in context of brother's death six months prior
- Two months ago, escitalopram titrated from 10mg to 20mg PO daily
- Collateral obtained from community mental health nurse:
- Patient well known, last checked on her 1 week prior to admission
- Briefly and appropriately tearful (i.e., brother's death)
- Otherwise, engaged and denied persistent depressed mood
- Fixed persecutory delusion involving neighbor's cat, does not routinely disclose outside of acute decompensations

THE CASE OF MS. F

- AM Vitals: afebrile, HR 105, BP 125/70
- Repeat labs given new symptoms:
  - No significant changes noted from previous values
  - Mild transaminitis and elevated WBC, normal creatinine kinase
- MRI brain showed no acute change
- EEG unremarkable
- LP deferred

CATATONIA

DSM-5-TR CRITERIA: CATATONIA

- Three (or more) of the following symptoms:
  - Stupor (i.e., no psychomotor activity; not actively relating to environment)
  - Catalepsy (i.e., passive induction of a posture held against gravity)
  - Waxy flexibility (i.e., slight, even resistance to positioning by examiner)
  - Mutism (i.e., no, or very little, verbal response [exclude if known aphasia])
  - Negativism (i.e., opposition or no response to instructions or external stimuli)
  - Posturing (i.e., spontaneous and active maintenance of a posture against gravity)
  - Mannerism (i.e., odd, circumstantial caricature of normal actions)
  - Stereotypy (i.e., repetitive, abnormally frequent, non-goal-directed movements)
  - Agitation, not influenced by external stimuli
  - Grimacing
  - Echolalia (i.e., mimicking another's speech)
  - Echopraxia (i.e., mimicking another's movements)

FEATURES OF CATATONIA

- Neuropsychiatric syndrome with motor, behavioral, and autonomic signs
- Notable for prominent psychomotor dysregulation:
  - Unable to move normally despite retained functional capacity to do so
  - Decreased motor activity/engagement vs excessive/peculiar motor activity
  - Marked decrease in reactivity to the environment
- Clinical presentation often puzzling:
  - Presentation can range from marked unresponsiveness to marked agitation
  - Symptoms can vary from mild to severe
- Seemingly opposing clinical features, variable manifestations, and overemphasis in teaching on rare, severe signs have led to lack of awareness and decreased recognition

ETIOLOGY AND RISK FACTORS

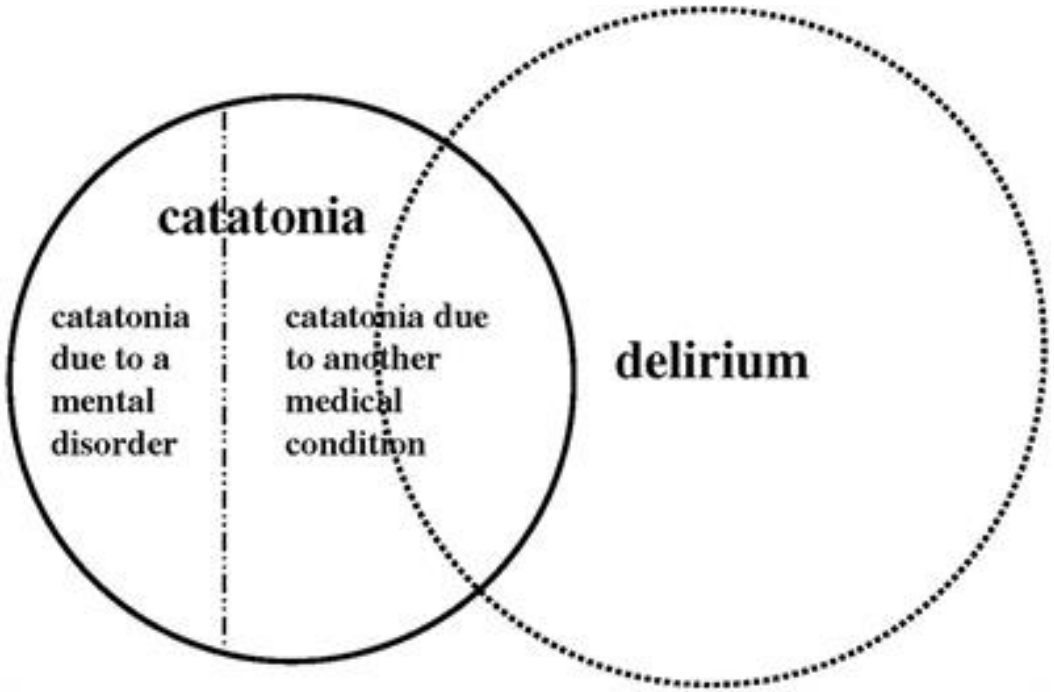
- Associated with:
  - Psychiatric, neurologic, and general medical conditions
  - Select medications (e.g., those affecting the extrapyramidal system)
- Although historically linked with schizophrenia, medical and mood disorders more common
- Previous delirium increases likelihood of developing catatonia
- Similar risk factors for catatonia and delirium

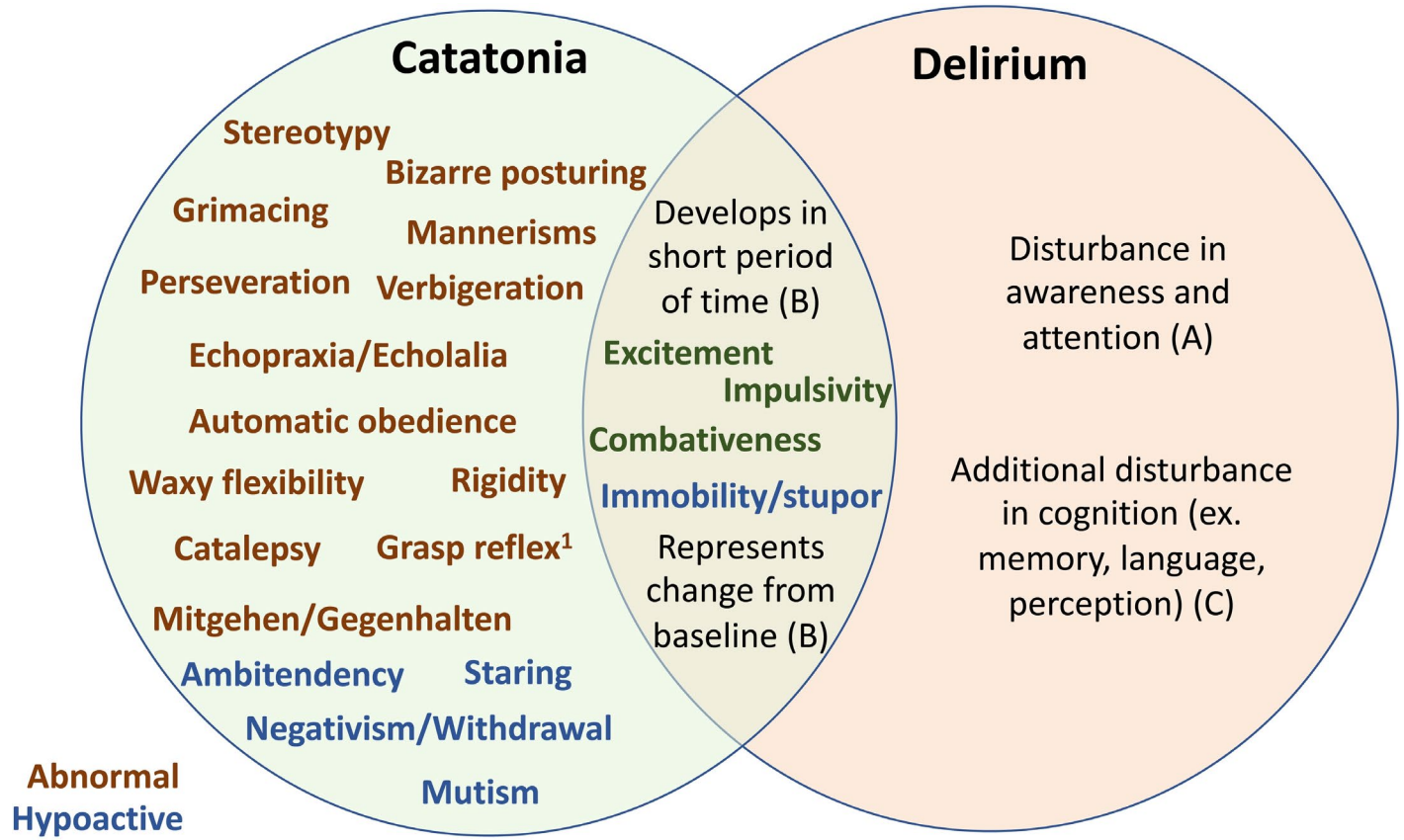
DELIRIUM VERSUS CATATONIA

- Per DSM-5-TR, catatonia cannot be diagnosed if delirium criteria met
  - However, catatonia symptoms occur in significant proportion of delirium cases
- Both can have hypoactive and hyperactive subtypes
  - Catatonia also has malignant subtypes
  - Distinguished by the presence of fever and associated with higher mortality
  - e.g., neuroleptic malignant syndrome and serotonin syndrome
- The mutism, stupor, and agitation of catatonia often mistaken for the changes in attention, awareness, and language deficits of delirium

DELIRIUM VERSUS CATATONIA

- Both present with apparent alterations in attention and awareness
  - However, recovered catatonic patients usually able to recall details of previous episodes
  - i.e., awareness intact despite inability to respond
- Stupor, agitation, and PMR are examples of shared symptoms
- For patients displaying the common features of both, observation over time and diagnostic tools (e.g., Bush-Francis scale) aid in differentiation
- EEG findings normal in catatonia, unlike delirium


catatonia
catatonia due to a mental disorder
catatonia due to another medical condition
delirium


Catatonia
Delirium
Stereotypy
Bizarre posturing
Grimacing
Mannerisms
Perseveration
Verbigeration
Echopraxia/Echolalia
Automatic obedience
Waxy flexibility
Rigidity
Catalepsy
Grasp reflex[1]
Mitgehen/Gegenhalten
Ambitendency
Staring
Negativism/Withdrawal
Mutism
Develops in short period of time (B)
Excitement
Impulsivity
Combativeness
Immobility/stupor
Represents change from baseline (B)
Disturbance in awareness and attention (A)
Additional disturbance in cognition (ex. memory, language, perception) (C)
Abnormal
Hypoactive
Hyperactive

CATATONIA: MANAGEMENT

- First step – trial of a benzodiazepine
  - Contraindicated in delirium (with exception of alcohol/benzodiazepine withdrawal)
  - Lorazepam – 1 to 2mg bid to tid to start, titrating as necessary
- If worsens or fails to respond – ECT
- Use of antipsychotics controversial
  - Clear advice against first-generation antipsychotics – shown to exacerbate condition
  - Second-generation antipsychotics not clear cut, case reports showing good outcomes
- Valproate or similar: possible replacement for antipsychotics to target agitation and reduce risk of NMS
- Premature discontinuation of benzos can cause relapse

NEUROLEPTIC MALIGNANT SYNDROME

- Life threatening emergency – must stop agent IMMEDIATELY!
- Symptoms include hyperthermia, confusion, rigidity, autonomic imbalance, diaphoresis, and tachycardia
- Elevated WBC and CPK common, also transaminitis
- Complications may include rhabdomyolysis, kidney failure, or seizures
- Ideally, manage in ICU: supportive measures, rapid cooling, IV hydration
- Medications: dantrolene and bromocriptine
- Risk of death: ~ 10%
- Many can eventually resume antipsychotic at lower dose – not until full resolution

THE CASE OF MR. A

THE CASE OF MR. A

- 65-year-old widowed man
- Admitted to orthopedic service for hip fracture
- Tripped and fell at home, does not recall the details
- PMHx: hypotensive episodes, frequent urination, and constipation
- No standing or PRN medication at home
- Does not follow regularly with PCP, eschewing routine medical visits

THE CASE OF MR. A

- Now 3 days post-op s/p internal fixation
- Altered mental status
- Shouting and flailing in his sleep and removed his IV catheter overnight
- Appears moderately agitated and has difficulty concentrating
- Unable to follow simple commands, easily distracted by surroundings
- Oriented to person and place, but not time
- CAM-ICU positive and scores 20/30 on MoCA
- Reports “vivid” dream of being chased by a car
- Well-formed visual hallucinations of a non-threatening nature (objects in room)
- Surgical site is clean with no drainage, and he reports his pain as manageable

THE CASE OF MR. A

- Chart review: urgent care visit for sprained right ankle, documented MMSE of 22/30
- Collateral obtained from daughter:
- Quite worried about her dad
- Gradual decline in cognitive function over the past year, with increasing difficulties in daily activities and memory loss
- Feels he is depressed but never treated
- Some days are better than others
- Experiencing visual hallucinations for several months
- This was not his first fall

THE CASE OF MR. A

- Dose of quetiapine given due to increased agitation, now calm
- However, you notice an obvious tremor in both hands and feet
  - Coarse, symmetrical, and perceptible at rest and on intentional movement
- Examination is positive for masked facies and cogwheel rigidity
- His speaking is barely audible
- His flow of thoughts is mildly slowed with absent delusional content
- Vitals, laboratory investigations, and CXR are all unremarkable
- CT of Head:
  - No acute neurological events or expansion process; cerebral atrophy noted

LEWY BODY DEMENTIA

DLB CONSORTIUM: REVISED CRITERIA (2017)

- *Essential for diagnosis*
  - Dementia (deficits on tests of attention, executive function, and visuospatial ability may be especially prominent and occur early)
- *Core features*
  - Fluctuating cognition with pronounced variations in attention and alertness
  - Recurrent visual hallucinations that are typically well-formed and detailed
  - REM sleep behavior disorder, which may precede cognitive decline
  - Spontaneous features of parkinsonism

DLB CONSORTIUM: REVISED CRITERIA (2017)

- *Supportive clinical features*
  - Severe neuroleptic sensitivity
  - Postural instability and repeated falls
  - Syncope or other transient episodes of unresponsiveness
  - Severe autonomic dysfunction (e.g., constipation, orthostatic hypotension, urinary incontinence)
  - Hypersomnia
  - Hyposmia
  - Hallucinations in other modalities
  - Systematized delusions
  - Apathy, anxiety, and depression

DLB CONSORTIUM: REVISED CRITERIA (2017)

- *Indicative biomarkers*
  - Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET
  - Abnormal (low uptake) ^{123}iodine0MIBG myocardial scintigraphy
  - Polysomnographic confirmation of REM sleep without atonia
- *Supportive biomarkers*
  - Relative preservation of medial temporal lobe structures on CT/MRI scan
  - Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity +/- the cingulate island sign on FDG-PET imaging
  - Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range

DLB CONSORTIUM: REVISED CRITERIA (2017)

- Probable DLB:
  - 2 or more core clinical features, with or without indicative biomarkers
  - 1 core clinical feature, with 1 or more indicative biomarker
- Possible DLB:
  - 1 or more core clinical feature, no indicative biomarker evidence
  - 1 or more indicative biomarker, no core clinical features
- A diagnosis is less likely:
  - In the presence of any other physical illness or brain disorder (including cerebrovascular disease) sufficient to account for the clinical picture
    - Of note: these do not exclude DLB – mixed or multiple pathologies may be present
  - If parkinsonism is the only core clinical feature, appearing for the first time at a stage of severe dementia

LEWY BODY DEMENTIA VERSUS DELIRIUM

- Lewy body dementia (LBD) is a common progressive neurodegenerative disorder, often co-existing with other dementia subtypes as part of a mixed presentation
- Differentiation important given LBD's low index of suspicion and overlap of symptoms with delirium
- If misdiagnosed and treated as delirium with neuroleptic – increased risk of irreversible parkinsonism and neuroleptic malignancy syndrome

LEWY BODY DEMENTIA VERSUS DELIRIUM

- Cognitive fluctuations in both LBD and delirium – changes in the level of arousal and excessive daytime drowsiness
- LBD insidious onset with progressive decline; delirium generally acute onset and reversible
- Visual hallucinations and falls in both, further complicating diagnosis
- Biomarkers from neuroimaging techniques can support the diagnosis
  - Differentiation of the diagnosis is possible using MRI and SPECT

LEWY BODY DEMENTIA VERSUS DELIRIUM

- Similarities make diagnosis challenging, but differences exist
  - Motor:
    - LBD: extrapyramidal symptoms such as hypokinetic movements, small shuffling gait, muscle rigidity, and resting tremor
    - Delirium: EPS not typically present
  - Sleep disturbances:
    - LBD: sleep-related vocalizations and/or complex motor behaviors during REM sleep with violent thrashing, punching, and kicking – injury to bed partner
    - Delirium: impairment of alertness, awareness, and arousal – secondary to derangements of sleep-wake cycle

LEWY BODY DEMENTIA: MANAGEMENT

- Cholinesterase inhibitors: effective for cognitive and behavioral symptoms, visual hallucinations
- Donepezil and rivastigmine both treat cognitive fluctuations and psychotic symptoms
- Rivastigmine available as TD patch – ideal if unable to take PO
- REM sleep behavior disorders – melatonin and clonazepam

LEWY BODY DEMENTIA: MANAGEMENT

- Levodopa may reduce motor disturbances for some, when titrated slowly
- However, others exhibit limited clinical response
- Levodopa can cause or exacerbate visual hallucinations
- Risks of treatment need to be carefully weighed against potential benefits
- There is a fine balance between treating parkinsonism and increasing psychotic symptoms

LEWY BODY DEMENTIA: MANAGEMENT

- Neuroleptics generally avoided
- More than 50% of patients – strong reaction with hypersensitivity (e.g., severe EPS, altered consciousness, pyrexia, and collapse)
- Heightened risk for typical as compared to atypical agents
- Can be irreversible and fatal – important implications for the management of psychotic symptoms
- If prescribed, quetiapine recommended – more favorable side effect profile, though limited evidence for efficacy

DSM-5-TR CRITERIA – NCD WITH LEWY BODIES

A. Major or mild neurocognitive disorder met
B. Insidious onset and gradual progression
C. Meets a combination of core diagnostic features and suggestive diagnostic features for either probable or possible neurocognitive disorder with Lewy bodies
D. The disturbance is not better explained by another condition

DSM-5-TR CRITERIA – NCD WITH LEWY BODIES

- For **probable** major or mild NCD with Lewy bodies – two core *or* one suggestive with one core
- For **possible** major or mild NCD with Lewy bodies – only one core *or* one or more suggestive
  1. Core diagnostic features:
     a) Fluctuating cognition with pronounced variations in attention and alertness
     b) Recurrent visual hallucinations that are well formed and detailed
     c) Spontaneous features of parkinsonism, with onset subsequent to cognitive decline
  2. Suggestive diagnostic features:
     a) Rapid eye movement sleep behavior disorder
     b) Severe neuroleptic sensitivity

DSM-5-TR CRITERIA – MAJOR NEUROCOGNITIVE DISORDER

A. Significant decline in one or more cognitive domains (i.e., complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition):
   1. Concern of individual or others for significant decline in cognitive function; AND
   2. Substantial impairment in cognitive performance
B. Interferes with independence in everyday activities
C. Does not occur exclusively in the context of a delirium
D. Not better explained by another mental disorder

DSM-5-TR CRITERIA – MINOR NEUROCOGNITIVE DISORDER

A. Modest decline in one or more cognitive domains (i.e., complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition):
   1. Concern of individual or others for mild decline in cognitive function; AND
   2. Modest impairment in cognitive performance.

B. Does not interfere with independence in everyday activities; accommodations may be required

C. Does not occur exclusively in the context of a delirium

D. Not better explained by another mental disorder

THE CASE OF MR. Z

THE CASE OF MR. Z

- 45-year-old twice-divorced man
- Brought to ED by neighbor: severe lower right quadrant pain
- States the pain started about 48 hours ago, accompanied by loss of appetite, nausea, and vomiting
- PMHx: chronic acid reflux on omeprazole
- Also takes over-the-counter melatonin nightly for insomnia
- Seen once before in ED s/p rib fracture sustained in a car accident

THE CASE OF MR. Z

- Tachycardic, diaphoretic, and hypertensive in the ED; clearly in considerable pain
- Found to have acute appendicitis and undergoes an emergency appendectomy that same evening
- No notable events during procedure and the patient appeared to be stable immediately afterwards, but staff mentions increasing restlessness and agitation overnight
- Observed this morning yelling at staff and refusing to get out of bed, exclaiming “I see spiders everywhere on the walls”
- No collateral is readily available

THE CASE OF MR. Z

- Current vital signs are as follows:
  - Temperature 38.6 °C (101.5 °F), BP 150/92, HR 120, RR 18
- Physical Exam:
  - Anxious, with bilateral hand tremors and diaphoresis
  - Surgical incision has minimal erythema and swelling, with some clear drainage at the margins
- Labs:
  - BMP and TSH unremarkable
  - CBC notable for a mildly elevated WBC
  - LFTs notable for a transaminitis: AST 260, ALT 124

THE CASE OF MR. Z

- During the next 2 hours, increasing agitation and confusion, with incoherent speech, diaphoresis, and combative behavior requiring restraints
- Lorazepam, haloperidol, magnesium sulfate, and IV fluids administered, leading to eventual sedation and decreased agitation
- Blood pressure and pulse remain elevated

DELIRIUM TREMENS

FEATURES OF DELIRIUM TREMENS

- Commonly observed in heavy drinkers with physiologic dependence
- Typically manifests ~ 3 days after sudden cessation or significant curtailing of drinking
- Chronic alcohol abuse can lead to medical comorbidities and nutritional/electrolyte derangements
  - Independent risk factors for delirium, which can be superimposed on DTs
- Knowledge of sequential development of alcohol withdrawal essential for prompt identification and rapid treatment

ALCOHOL WITHDRAWAL SYNDROMES

- Clinical features set it *(and benzodiazepine withdrawal, which presents/managed similarly)* apart from other forms of delirium
- If caught early and aggressively treated, can potentially prevent progression to delirium tremens
- Track with CIWA-Ar
- *Hallucinosis:* clear sensorium, distinguishing it from DTs
- *Seizures:* a symptom of complicated withdrawal, ominous and a frequent harbinger for DTs

ALCOHOL WITHDRAWAL SYNDROMES

SYNDROME	CLINICAL FINDINGS	ONSET AFTER LAST DRINK
Minor Withdrawal	Tremulousness, anxiety, headache, diaphoresis, palpitations, anorexia, gastrointestinal upset; normal mental status	6 to 36 hours
Seizures	Single or brief flurry of generalized tonic-clonic seizures, short postictal period; status epilepticus is rare	6 to 48 hours
Alcoholic Hallucinosis	Visual, auditory, and/or tactile hallucinations with intact orientation and normal vital signs	12 to 48 hours
Delirium Tremens	Confusion, agitation, tachycardia, hypertension, fever, diaphoresis, hyperarousal, hallucinations and delusions	48 to 96 hours

DELIRIUM TREMENS: MANAGEMENT

- Rule out or adequately address coexisting disorders
- Identify and correct metabolic derangements
- Aggressive supportive care:
  - Intravenous fluids
  - Nutritional supplementation
  - Correction of electrolyte/vitamin deficiencies
- Intravenous thiamine to prevent or treat Wernicke's encephalopathy and Korsakoff's syndrome

THE ROLE OF BENZODIAZEPINES

- Benzodiazepines first-line treatment
- No consensus as to the best benzo to use
  - Long-acting agents with active metabolite(s) – smoother course
    - Diazepam
  - Agents not requiring oxidative metabolism – safer with severe *(e.g., synthetic as opposed to enzymatic)* liver dysfunction
    - Lorazepam
- Administered by fixed-schedule or symptom-triggered regimens
  - Often a combination of the two is utilized
  - A withdrawal regimen should be constantly reassessed and revised, not set and forgotten

BENZODIAZEPINES: ROUTE AND DOSE

- Intravenous route for complicated withdrawal
  - Guaranteed absorption and rapidity of onset
  - IM: variable drug absorption
  - PO: when adequately managed
- Aggressive dosing often required
  - Give until calm and lightly sedated
  - In severe withdrawal, may require massive doses
    - >500mg of diazepam IV initially
    - >2000mg diazepam IV over first 48 hours

MIXED ETIOLOGIES AND REFRACTORY CASES

- If mixed picture suspected, benzos still employed, at least initially
  - e.g., delirium tremens in combination with hepatic encephalopathy
- Some will have refractory delirium tremens despite treatment with high-dose benzodiazepines
- General rule of thumb – refractory if symptoms not controlled adequately after:
  - >50mg of diazepam or 10mg of lorazepam IV during first hour
  - >200mg of diazepam or 40mg of lorazepam IV during initial 3-4 hours

REFRACTORY DELIRIUM TREMENS: MANAGEMENT

- Adjunctive treatments for refractory DTs
  - Barbiturates (e.g., phenobarbital) alone or in conjunction with a benzodiazepine – they are thought to work synergistically
  - Propofol
  - Dexmedetomidine – preliminary evidence supports, caution advised
  - Tracheal intubation and mechanical ventilation often required
- Unlike benzodiazepines, phenobarbital and propofol have action at NMDA receptors, in addition to $GABA_A$ receptors
  - Helps explain their efficacy in refractory cases
  - *Of note:* dexmedetomidine (α^2 agonist) hits neither

RISK FACTORS FOR DELIRIUM TREMENS

- A history of sustained drinking
- A history of alcohol withdrawal seizures
- A history of delirium tremens
- Age greater than 30 years
- The presence of concurrent illness
- Significant tolerance/withdrawal symptoms in the presence of an elevated blood alcohol concentration
- A longer period since the last drink before treatment initiated

DSM-5-TR CRITERIA: ALCOHOL WITHDRAWAL

A. Cessation of (or reduction in) heavy and prolonged alcohol use

B. Two (or more) of the following:
   1. Autonomic hyperactivity
   2. Tremor
   3. Insomnia
   4. Nausea or vomiting
   5. Transient VH/AH/TH or illusions
   6. Psychomotor agitation
   7. Anxiety
   8. Generalized tonic-clonic seizures

- *Specify if* with perceptual disturbances: hallucinations occur with intact reality testing, or illusions occur in absence of delirium

REFERENCES

- Bishara *et al*. Postoperative Delirium Prediction Using Machine Learning Models and Preoperative Electronic Health Record Data. *BMC Anesthesiology 2022; 22:8.*
- Bourgeois *et al*. Adjunctive Valproic Acid for Delirium and/or Agitation on a Consultation-Liaison Service: A Report of Six Cases. *J Neuropsychiatry Clin Neurosci 2005; 17:232–238.*
- Bouter *et al*. Case Report: The Role of Neuropsychological Assessment and Imaging Biomarkers in the Early Diagnosis of Lewy Body Dementia in a Patient With Major Depression and Prolonged Alcohol and Benzodiazepine Dependence. *Front Psychiatry 2020; 11:684.*
- Brake and Abidi. A Case of Adolescent Catatonia. *J Can Acad Child Adolesc Psychiatry 2020; 19:2.*
- Crowley *et al*. Valproic Acid for the Management of Agitation and Delirium in the Intensive Care Setting: A Retrospective Analysis. *Clinical Therapeutics 2020; 42:4.*
- Djaiani *et al*. Dexmedetomidine versus Propofol Sedation Reduces Delirium after Cardiac Surgery: A Randomized Controlled Trial. *Anesthesiology 2016; 124:362–8.*
- Davoudi *et al*. Intelligent ICU for Autonomous Patient Monitoring Using Pervasive Sensing and Deep Learning. *Scientific Reports 2019; 9:8020.*
- Doran and Sheehan. Acute Catatonia on Medical Wards: A Case Series. *Journal of Medical Case Reports 2018; 12:206.*

REFERENCES

- Erdoğan *et al*. A Challenging Hypoactive Delirium Case with Multiple Etiological Considerations. *Eur J Geriatr Gerontol 2019;1(2):67–69.*
- Gong *et al*. Predicting Intensive Care Delirium with Machine Learning: Model Development and External Validation. *Anesthesiology 2023; 138:299–311.*
- Hepple. Conversion Pseudodementia in Older People: A Descriptive Case Series. *Int J Geriatr Psychiatry 2004; 19:961–967.*
- Khotianov *et al*. Lewy Body Dementia: Case Report and Discussion. *J Am Board Fam Pract 2002;15:50–54.*
- Maldonado. Neuropathogenesis of Delirium: Review of Current Etiologic Theories and Common Pathways. *Am J Geriatr Psychiatry 2013; 21:1190–1222.*
- Mattoo *et al*. Refractory Delirium Tremens: A Case Report and Brief Review. *Innov Clin Neurosci. 2012; 9(3):19–22.*
- McKeith *et al.* Diagnosis and Management of Dementia with Lewy Bodies: Fourth Consensus Report of the DLB Consortium. *Neurology 2017; 89:88-100.*
- Nejad *et al*. Case 39-2012: A 55-Year-Old Man with Alcoholism, Recurrent Seizures, and Agitation. *N Engl J Med 2012; 367:2428-34.*

REFERENCES

- Nelson *et al*. Defining the Role of Dexmedetomidine in the Prevention of Delirium in the Intensive Care Unit. *BioMed Research International 2015; 635737.*
- Ocagli *et al*. A Machine Learning Approach for Investigating Delirium as a Multifactorial Syndrome. *Int J Environ Res Public Health 2021; 18:7105.*
- Orlović *et al*. The Enigma of Lewy Body Dementia: A Case Report. *Acta Clin Croat 2020; 59:4.*
- Quinn *et al*. Prescribing Practices of Valproic Acid for Agitation and Delirium in the Intensive Care Unit. *Annals of Pharmacotherapy 2021; 55(3):311–317.*
- Ratnakaran *et al*. A Case Series on Late-Onset Catatonia Misdiagnosed as Delirium. *Am J Geriatr Psychiatry 2020; 28:4S.*
- Sher *et al*. Valproic Acid for Treatment of Hyperactive or Mixed Delirium: Rationale and Literature Review. *Psychosomatics 2015; 56:615–625.*
- Sher *et al*. Adjunctive Valproic Acid in Management-Refractory Hyperactive Delirium: A Case Series and Rationale. *J Neuropsychiatry Clin Neurosci 2015; 27:365–370.*
- Skrobik *et al*. Low-Dose Nocturnal Dexmedetomidine Prevents ICU Delirium: A Randomized, Placebo-controlled Trial. *Am J Respir Crit Care Med 2018; 197(9):1147–1156.*
- Tobe. Pseudodementia Caused by Severe Depression. *BMJ Case Reports 2012.*

THANK YOU