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- Joseph Mauro, MD
- Christina Waite, MD
- Dana Mackert
- India Myers

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CME CREDIT EVALUATION

The link to complete the evaluation will be shared at the end of the presentation:

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For questions, please contact Dana Mackert.

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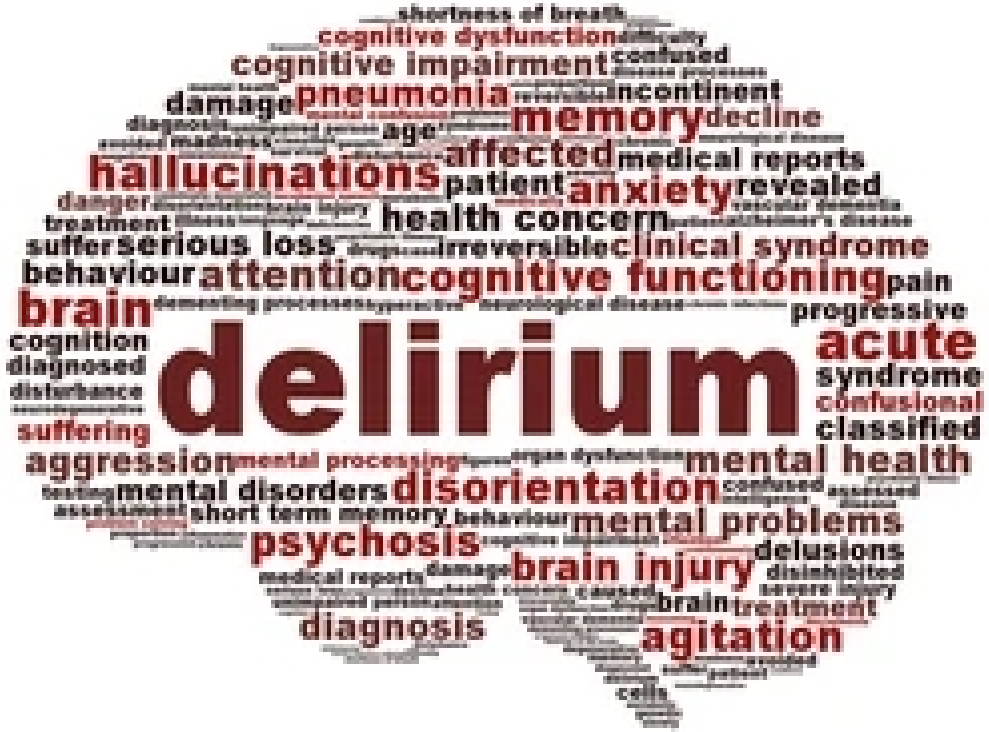
Delirium

February 1, 2024

Christina Waite, MD
Psychiatry



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Goals of Presentation

- Highlight Delirium as Medical Emergency
- Devastation of Impact
- Prevention
- Best Management
- Attending to Delirium is Cost Effective

Topics

- Impact
- Detection
- Pathophysiology
- Literature key points
- Protective factors vs Risk factors
- Interventions
- Case Presentation
- Pharmacologic management-general principles, reconciling medications and medication options

Impact of Delirium

- A Medical Emergency
- Impacts Patient Outcomes
- Impacts Health Care System
- Impacts Costs

Delirium is a Medical Emergency

- Serious Medical Condition
- Mortality
- Permanent Damage
- Urgent and Complete work-up
- History and Medication Reconciliation
- Physical exam, including Neurologic
- Labs, Imaging, EEG

Patient Outcomes

- Mortality Risk increases 25% during admission
- Mortality doubles in subsequent year
- Institutionalization risk increased by 2.5- fold
- Dementia risk increased by 12.5 -fold
- 1/3-1/2 of cases, regardless of age, experience cognitive decline

Mental Health Outcomes

- 1/3 Develop Depression and Anxiety
- 1/3 Develop PTSD After ICU or Critical Illness

Clinical Complications

- Aspiration
- Ulcers
- Weakness, falls
- Malnutrition, dehydration, electrolyte Imbalance

Health Care Cost

- US $164 billion per year spent in total healthcare cost
- Length of stay increases by an average of 5 to 10 acute care days
- Subsequent admission cost is 2.5 times more in following year

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Prevalence and Identification

- 50 to 60% prevalence on General Medical units
- Average ICU patient has >10 risk factors- 60 to 80% Developing delirium
- 40% of Consults to Psychiatry for "depression" meet delirium criteria
- Nurses identify 31% of cases (compared to research staff)(miss 70%)
- Physicians miss 80% of cases,
- Emergency department physicians -85% missed!(Han, Wilson and Ely 2013)
- Research estimates- total of 1/3 -1/2 cases missed

Identifying Delirium

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“Delirium”

- Altered Mental Status
- Metabolic encephalopathy
- Organic brain syndrome
- Toxidrome
- Acute confusional syndrome

DSM-V Definition

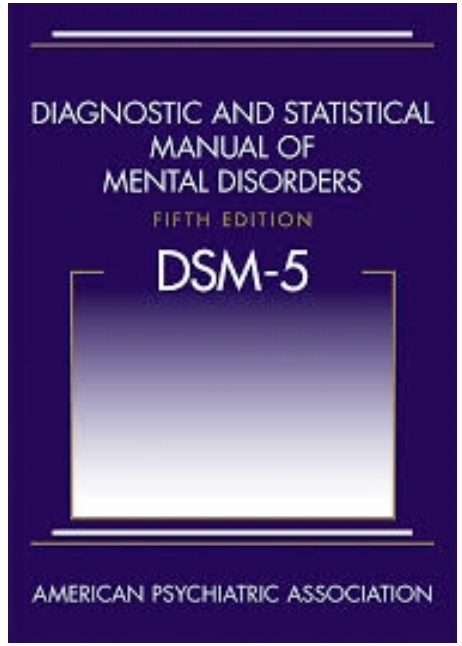
- Acute disturbance in Attention and Awareness that fluctuates in severity.
- At least one additional cognitive disturbance; disorientation, memory, perception, visuospatial , language
- Not better explained by underlying dementia
- Not during severely reduced LOC/coma
- Evidence of underlying organic cause(s)

Clinical Phenotypes

- Hyperactive
- Hypoactive -worst prognosis
- Mixed type - risky to treat treat and not convert to hypoactive
- Young with unexpected delirium- suspect serious illness
- In older, may herald dementia (five- fold risk)

Differential Diagnosis

- Dementia/ Sundowning
- Focal Syndrome
- Non-convulsive epilepticus
- Autoimmune encephalitis
- Central nervous system malignancy
- Psychosis, Mania, Catatonia, Coma



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Delirium vs Primary Psychosis vs Dementia

Delirium	Dementia	Primary Psychosis
<u>Rapid Onset</u> Fluctuates Visual and tactile hallucinations Confusion /poor orientation	<u>Slow onset</u> Stable LOC level (Unless LBD) Confabulate but not acutely confused	<u>Gradual onset</u> Stable LOC Auditory hallucinations predominate, often paranoid delusions Orientation often intact

CAM- Confusion Assessment Method: Gold Standard

From literature review and expert consensus

Sensitivity 94% to 100%, Specificity 90% to 95%

Features 1 and 2 Plus Either 3 or 4 Required for Dx

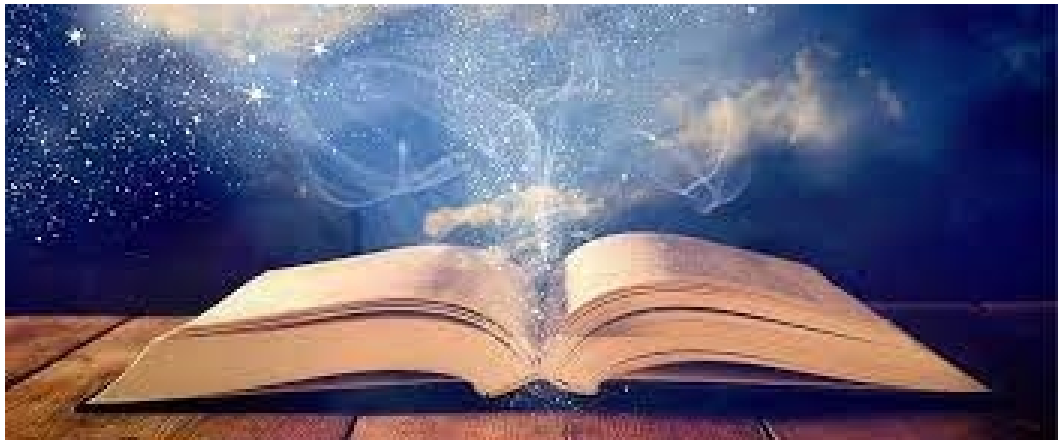
1. Acute Onset and Fluctuating Course
2. Inattention
3. Disorganized Thinking and
4. Altered Level of Consciousness

Pathophysiology

- Delirium -Final Common Pathway
- Inflammation, Hypoxia- leaky Blood Brain Barrier
- Toxins and medications invade brain
- Abnormal Glucose metabolism
- Abnormal Neurotransmitter production and Network Disconnection
- Functional abnormalities correlate closely with anatomy and symptoms of delirium

Literature Key Points

- Hard to detect and study
- Prevention is critical
- Non-Pharmacological approaches are effective



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Detection and Study is Difficult

- Multitude of predisposing and precipitating factors
- Difficulty assessing agitated, cognitively impaired patients
- Baseline unknown
- Signs and Symptoms fluctuate
- Conditions overlap-Complex Case Presentation

Current Research Observations

- Little evidence for effective pharmacologic treatment
- Majority of randomized controlled trials- negative or mixed results
- Current understanding from prospective observational studies, provide epidemiologic information.
- No FDA approved treatment for Delirium (except dexmedetomidine, restricted to ICU)
- Prevention and Non-Pharmacologic Approach

Prevention

- "An ounce of PREVENTION is worth a pound of cure“
- Evidence is for prevention a Non-pharmacologic multicomponent, individualized approach
- Requires broad understanding of medicine, pathophysiology, nursing science, and baseline functioning

Non-Pharmacologic Treatment is Effective

- 30-40% of cases preventable with non-pharmacologic approach
- One study -nonpharmacologic, multi component approach decreased delirium episodes (from 90 to 62 and number of delirium days from 161 to 105)
- Manage predisposing and precipitating factors
- Manage underlying disease states
- Manage Environment

Protective Factors

- Cognitive and social engagement
- Oral opioids and regional anesthesia instead of PCA pumps
- Slower acting agents , minimize confusion
- Supportive environment, including TV, radio and private room, night sleep
- Tissue oxygenation
- Blood pressure control

Risk Factors

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Non-modifiable risk factors

- Age > 65
- History of delirium or dementia
- Prior stroke, neurologic conditions
- Cardiovascular Surgeries
- Emergency surgeries
- Medical comorbidities
- Terminal illness
- Genetics

Clinical Precipitating Factors

- Infections
- Depth of Sedation and Anesthesia
- EOTH/ Substances
- Lorazepam use
- Organ failure, including CNS issues , HTN
- Metabolic abnormalities
- Hypoxia, Respiratory complication
- Dehydration, Malnutrition
- Obstipation, Urinary retention

Environmental Precipitating Factors

- Restraint Use
- Sensory Impairment
- Immobility
- Pain
- Polypharmacy
- Invasive Lines
- Decreased Family Communication

Interventions

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Interventions

- Avoid or minimize problematic medications
- Individualized considerations when choosing
- Target symptoms in circadian fashion
- Periodic Hold and Re-assess
- Mobilize patient
- Adequate Rest and Stimulation
- Periodic Hold and Re-assess
- Sleep/Circadian Rhythm
- Orientation
- Visual and hearing aids
- Educate and support, family and caregivers
- Avoid Restraints-Remove once calm!

Case Presentation

Multifactorial Delirium

Complex Management

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Complex Case Presentation

- 58 y/o female Adm for “decubiti and gangrene LEs” , Etoh hx.
- Presentation-Cachectic, paranoid-hostile, dysphoric- (acute withdrawal not seen)
- Dx 1.Bipolar mixed episode , life long-untreated 2.Delirium 2/2 suspected thiamine deficiency, malnutrition ,suspected alcohol induced dementia, chronic infection,
- Tx – High dose Thiamine, folate, Vitamin D , Nutrition/PEG, hydration,
- Antipsychotics – poorly tolerated (akathisia/dyskinesia)- -low dose Abilify
- Antidepressant –Discontinued 2/2 increased irritability and psychosis (due to Bipolar condition)
- VPA discontinued 2/2 Hyperammonemia
- Lithium – improved mood and cognition quickly

Complex Case Presentation

- Lucid intervals for four days- patient herself agreed to AKA
- Dry Gangrene spreading up leg-delirious again
- NOK surrogate decision maker consented to AKA
- High fever + COVID -surgery postponed
- COVID cleared without complications, cognitively significantly improved
- Nearly discharged, then increasing pain, high fevers/rigors, hypotensive. C& L advocated for surgery
- 5 months after admission – AKA
- Normal mood ,cognition significantly improving

Pharmacologic Management

- Principles of Management
- Reconciling ALL Medications
- Medication treatment options

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Pharmacologic Management

- Indications
- Patient or Staff Safety is at Risk
- Agitation prevents Treatment and Management of patient
- Research shows Use of medication Aligns more with Caregiver Distress than patent distress

Principles of Pharmacologic Agitation Management

- Avoid Polypharmacy
- Choice of Sedation, Depth and Duration
- Use Safest medication- Lowest Effective dose
- Under-medicating as harmful as Over-medicating!
- Target Symptoms (understand medications)
- Hold medications and Reassess
- How Treatment impacts Risk factors
- Continually Manage Predisposing /Precipitating /Exacerbating factors

Principles of Pharmacologic Management

- All medications, except Dexmedetomidine are off label
- When, why and how to use and not use medications
- Know medications- onset and duration of action of benzodiazepines, opioids!
- Carefully reconcile and analyze all historic and current medications (AI)
- Anticholinergic burden
- Other deleterious effects (neuroleptic induced side effects, excess serotonin, steroids.)

Reconciling Home Medications

- Both Over-the-Counter and Illicit
- Be aware of discontinuing home medications without analysis
- Withdrawal - antidepressants, sedatives, opiates, and levodopa
- Reduce dosing or change agent instead ?
- Hold all unnecessary medications during overdose states /toxidromes

Consider-New/Changed/Toxic Levels/Interactions

- Anticholinergic burden
- Antihistamines
- Antibiotics
- Keppra
- Steroids
- Opioids
- Muscle Relaxers
- Antipsychotics
- Antidepressants

Current Evidence for Medication Use in Delirium (Up-To-Date)

- Thiamine (Cofactor for neurotransmitter production, and proper Glucose Metabolism)
- Dexmedetomidine and possibly Oral Alpha Agonists
- Quetiapine in very small doses
- Haloperidol IM or IV - very small doses
- Careful use of Benzodiazepines as indicated by primary and comorbid conditions
- Gentle use of Analgesics –Try non-opioids
- Risperidone - most evidence besides Haloperidol in Dementia.

Medication Use in Agitation

- Thiamine
- Benzodiazepine
- Typical Antipsychotics
- Atypical Antipsychotics
- Phenobarbital
- Alpha Agonist
- (Antidepressants-Ramelteon, Trazodone)

Thiamine-Anti inflammatory?

- Essential for normal Glucose metabolism
- Improves endothelial function
- Reduces oxidative stress
- Cofactor in converting Glutamate to GABA
- Cofactor in synthesis of Acetylcholine
- Preliminary research resulted in 42% odds reduction of delirium
- Glucose without adequate thiamine-anaerobic metabolism of glucose – lactic acidosis..

Risks of Benzodiazepines

- Increase confusion
- Prolong delirium
- Reduce respiratory drive
- Lorazepam use equaled risk factors of old age and severe illness !
- (Pandaraharipande P et al anesthesiology 2006;104:21-26)

Indications for Benzodiazepines

- Stimulant intoxication
- Sedative or alcohol withdrawal
- Neuroleptic malignant syndrome
- Acute dystonic reactions
- Akathisia and catatonia
- Acute anxiety states - increase oxygen demands, make management of underlying conditions difficult or impossible

Benzodiazepines for Alcohol Withdrawal

- Chlordiazepoxide and Clonazepam
- Slow onset – not for acute withdrawal/CIWA
- Very long half-lives
- Good outpatient medications with responsible adult assisting.

Diazepam

- Rapid onset, very long half-life, (up to a week) good agent in acute severe withdrawal
- If fails, need phenobarbital.

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Lorazepam

- No oxidative metabolism - hepatic safety
- Rapid onset intravenously, fairly long half-life- 10 to 20 hours
- Suitable for Acute withdrawal management (CIWA)

Sedative-Alcohol Withdrawal Treatment

- Use longer acting agent than the agent the patient has tolerance to
- Rapid enough onset to be effective and use with q 1 h reassessments.
- Same agent for PRN use as in scheduled one
- Short acting ones are not helpful in withdrawal treatment

Benzodiazepines –Impact GABA Receptors

- Do not treat CNS delirium from excitotoxicity secondary to Glutamate
- Beta Blockers and dexmedetomidine mask withdrawal
- Inadequate use of benzodiazepine- Seizures/ Korsakoff

Phenobarbital for Delirium Tremens

- Treats down regulated GABA receptors- Autonomic Nervous System hyperactivity AND Treats Upregulated NMDA receptors -Glutamate hyperexcitability/Delirium

OSU Phenobarbital Protocol

- Do not use Phenobarbital with other CNS depressants
- Day #1 -Initial Loading- use IBW, 6 -10 mg per kilogram, depending on host vulnerability.
- Divide Loading dose in three divided doses 6 to 8 hours apart
- First dose -40% of the total loading
- Second and third doses-each 30% of the total

Tapered Oral Scheduled Maintenance Doses

- Second day 65.4 mg BID
- Third day 32.4 mg BID
- Fourth day 32.4 mg QD
- Can reduce or hold if indicated
    - i.e. large preceding benzodiazepine trial

PRN DOSING- 65 mg IM for 2 or More the Following

- Heart rate>110
- Systolic blood pressure > 160
- Diastolic blood pressure > 110
- Hallucinations
- Tremors
- Significant agitation (RASS over 2)

OSU Phenobarbital Protocol

- Consider use if on Beta Blocker, or h/o severe withdrawal
- IM safer and as effective as IV
- Oxygen saturation monitoring
- Adequate treatment protects the brain and prevents relapse of withdrawal, DT and Wernicke's- Korsakoff Syndrome.

Alpha Agonists

Dexmedetomidine

- Reduces Epinephrine Release in CNS and Peripherally in Sympathetic Nervous System
- <u>High-Quality Evidence Supporting Use in ICU</u>

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Dexmedetomidine Drawbacks

- Dose dependent bradycardia and hypotension
- Requires ICU
- Does not address
    - NMDA activation/Glutaminergic hyperactivity , or GABA Receptors

Dexmedetomidine Drawbacks

- Can mask alcohol, or sedative withdrawal, causing serious consequences to the brain IF NO OTHER Tx PROVIDED.
- Not indicated as a standalone agent in moderate or severe alcohol withdrawal
- Clonidine and Guanfacine - little research

Memantine - NMDA Receptor Antagonist

- Decreases excess glutamic drive during alcohol withdrawal(modulator of ion channel)

Gabapentin

- Mechanism -inhibition of subunit of voltage gated Calcium channels, neuropathic pain
- Pilot study, postoperative delirium declined -? due to decrease in pain and reduced need for narcotics?
- Add-on in alcohol withdrawal
- Avoid in AKI and CKD
- Does not affect GABA receptors

Valproic Acid-Possibly Beneficial

- Reversal of neuronal processes involved in delirium , involving;
- Dopamine, serotonin, acetylcholine, GABA, and NMD/glutamate
- Withdrawal seizures not prevented
- Add on with benzodiazepines
- Reduces impulsivity and aggression.
- Treats Bipolar depression/mania
- Helpful in traumatic brain injury
- Reduces need for sedation and antipsychotics

Opioid Analgesics

- Beneficial if selected properly
- Long acting -chronic pain (unless contraindicated)
- Short acting -separate ,or add-on for acute pain
- Short acting tends to increase delirium and confusion

Antipsychotics

- Use Antipsychotics Sparingly and in the Short-Term
- Reduce Need for Benzodiazepines, Sedatives or Narcotics
- Increase Hypotension and Causes Respiratory Suppression
- All Antipsychotics- Potential to Prolong QT Interval

Severe Side Effects

- Cardiac dysrhythmias
- Neuroleptic malignant syndrome
- Acute dystonic reactions – including dysphasia and dysphagia
- Aspiration and respiratory compromise (Can involve diaphragm)
- Catatonia
- Anticholinergic /Bowel obstruction

Typical antipsychotics - most EPS risk

- Haldol, Typical Antipsychotic – traditionally used
- No evidence Haloperidol improves delirium, severity, or duration.
- Ensure QTc <450msec, and no major cardiac risk factors
- Low dose 0.5-1 mg, max 5 mg/ 24 hours, as safe as low-dose quetiapine or risperidone
- IV use circumvents first pass through the liver and avoids extrapyramidal symptoms, unless large doses (100 mg /24 h)

Atypical Antipsychotics

- Quetiapine
- Aripiprazole
- Risperidone
- Paliperidone
- Ziprasidone
- Olanzapine

Quetiapine

- Reasonable side effect profile in very low doses
- Large RCT revealed no adverse effects in low doses
- One small PCR revealed positive outcome
- Higher doses can cause akathisia and hypotension.
- Best in Parkinsonism due to weak DA- antagonism
- May combine short acting with rapid acting at bedtime for hypnotic use and 24/7 symptoms
- Does not exist in parenteral form

Aripiprazole

- Best, cardiac side effect profile
- QTc up to 550 msec
- Less anticholinergic
- Does not exist in IM or IV form except LAI
- Add on for depression

Risperidone

- Low dose use 0.25-2 mg/24 h
- Most evidence besides Haldol
- Dementia with behavioral disturbance.
- Does not exist in parental form, but in meltable tablet and LAI
- Paliperidone, (Metabolite of Risperidone) renal metabolism-best in LF

Ziprasidone

- Most cardiotoxic (not ideal in stimulant intoxication)
- Prolongs QT most of all AAPs
- Intramuscular form or tablet
- Akathisia can be pronounced-Prevented by co-administration with benzodiazepine

Olanzapine

- Respiratory arrest, if given with benzodiazepines in parenteral form
- Strong antipsychotic /anti-dopamine effect -contraindicated in Parkinsonism)
- Hypotension
- Off label use intravenously-must heart monitor
- FDA approved for intramuscular use,(is used IV off label)

Other Medications

- Melatonin
- Ramelteon
- Trazodone
- Rozerem

Melatonin Agonists and Antidepressants

- Melatonin -Inconsistent research results, safe for Circadian Rhythm disturbance
- Ramelteon - melatonin agonist-post operative delirium
- Mirtazapine- antidepressant alpha2 and 5HT-antagonism -can be used as a sleep aid
- Trazodone-Anticholinergic AD , prolongs QT
- No high-quality evidence in delirium
- Trazodone

Contraindicated Medications

- Ketamine increases hallucinations and nightmares, exacerbates delirium
- Acetylcholinesterase inhibitors- increase risk of death in studies

Summary of Current Evidence Regarding Pharmacologic Treatment

- Reconcile Medications CAREFULLY
- Thiamine (cofactor for neurotransmitter production, and proper glucose metabolic)
- Dexmedetomidine (ICU) and possibly clonidine
- Quetiapine in very small doses
- Haloperidol IM or IV - very small doses (avoid oral)
- Risperidone has most evidence ,besides haloperidol
- Careful use of Benzodiazepines as Indicated by primary and comorbid conditions
- Gentle use of analgesics

Recap and Summary
Psychiatry Cl - here to help!

- Delirium is a medical emergency
- Impact is devastating
- Clinical screening and recognition is vital
- Prevention is important
- Optimize management -repeatedly
- Use of AI for medication reconciliation and risk stratification?
- Attending to Delirium time consuming , but cost effective

Summary and Conclusions

Attending to Delirium is cost effective

More research needed (larger, accurate)

Clinical Screening and recognition

More emphasis on prevention

-Use of AI for medication reconciliation and prognostics

Education regarding best practices

Help is available

Attending to Delirium is cost effective

More research needed (larger, accurate)

Clinical Screening and recognition

More emphasis on prevention-Use of AI for medication reconciliation and prognostics

Education regarding best practices

No Financial Interest

The author of this presentation has no conflicts of interest regarding the subject matter contained herein.

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Dr. Fadi Tayim
Clinical Neuroscience Institute
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Evaluation

Using the QR code or the link placed in the chat on the Teams Live Event please complete the evaluation to receive the CME credit being offered.

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Contact Dana Mackert, dlmackert@premierhealth.com, for any questions.

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