



DELIRIUM

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Learning Objectives

1

Understand the definition of delirium and some of the reasons why it remains so underdiagnosed

2

Recognize how to screen for and identify delirium at the bedside

3

Think critically about possible approaches to the patient with delirium and understand the difference between treatment and management

What is Delirium?

- Delirium is a syndrome rather than a specific diagnosis
- A constellation of symptoms suggestive of global brain dysfunction or acute brain failure
- Many potential etiologies
- Many potential manifestations
- Pathophysiology
 - *Simplified version: Imbalance of dopamine and acetylcholine*
 - *Likely involves neuroinflammation, neuronal aging, oxidative stress, neuroendocrine dysregulation, circadian dysregulation*
- Vastly under-detected across clinical settings (55-86% of cases missed)

Traynor 2016, Maldonado 2018

Case

You are the hospitalist and are called to the ER to admit a 74yo female with a past medical history of CHF, COPD and remote breast cancer in remission x 10 years, now presenting with 2-3 days of “altered mental status.” When a patient is admitted to the hospital with “altered mental status,” the most common explanation is:

- A. Dementia
- B. Delirium
- C. Traumatic brain injury
- D. Normal aging
- E. Subdural hematoma

Terms Synonymous with Delirium

Encephalopathy

ICU Psychosis

Acute Brain
Failure

Acute brain
dysfunction

Altered mental
status

Sundowning?

Definition of Delirium: DSM-5-TR

A disturbance in attention and awareness

Develops over a short period of time (hours to days), represents a change from baseline, and tends to fluctuate in severity during the course of the day

An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception)

Disturbance is a direct physiological consequence of another medical condition(s)

Not better explained by another syndrome

Five Core Domains of Delirium

Cognitive deficits

Attentional deficits

Circadian rhythm dysregulation

Emotional dysregulation

Psychomotor dysregulation

Persistent Delirium

- Now a recognized subtype in the DSM-5-TR
- In hospital settings, delirium typically lasts days to 1 week, but may persist for weeks to months
- Not rare, especially in older individuals with dementia
 - Delirious symptoms persisted in 45% of elderly hospitalized patients at discharge
 - Symptoms were still present in 33% of elderly patients after 1 month, in 26% after 3 months, and in 21% after 6 months

Cole 2009

Non-Modifiable Risk Factors

Increasing age

Medical conditions

- *Setting (33% of ICU patients have delirium)*
- *Number of active medical issues*
- *Length of PMH*

Vulnerable substrate

- *Dementia, CVA, Inflammation, Space-occupying lesion, TBI*

Inflammatory States

- *Long bone fractures, burns, complex surgeries*

Modifiable Risk Factors

Medications

- Benzodiazepines
- Opioids
- Anti-cholinergic medications

Immobility

Metabolic disturbances

Poor oxygenation states

Case

If your patient does, in fact, have delirium, which of the following is most likely to describe her behavior over the next 24 hours:

- A. Near constant agitation, with attempts to kick and hit nursing staff, necessitating restraints
- B. Attempts to get out of bed every 1-2 hours, unresponsive to redirection, requiring 1:1 monitoring
- C. Long periods of calm, interspersed with unprovoked episodes of severe agitation, including yelling and screaming
- D. Calm, lying in bed, pleasant on brief interaction
- E. Several attempts to elope requiring security to intervene

Motoric Subtypes

Hypoactive (not prevalent, 15-80%)

- *Psychomotor retardation, apathy, slowed speech, decreased alertness*
- *Often confused with depression*

Hyperactive (least prevalent, 6-46%)

- *Agitation, insomnia, hypervigilance, irritability, wandering*
- *Perceptual disturbances may be more common*
- *Often confused with mania, schizophrenia or anxiety*

Mixed (11-55%)

Making the Diagnosis at Bedside

- Delirium is a bedside diagnosis
 - *No blood tests or imaging will confirm the diagnosis*
- Rely on history
 - *Look at pattern of onset and progression of symptoms*
 - *Patients often poor historians, so rely on family, staff*
 - *Physical therapists and nurses are the best at diagnosing delirium*
 - *Attending physicians are the worst*
- EEG
 - *Can help confirm the diagnosis*
 - *Classic EEG pattern is diffuse background slowing (delta-theta waves)*
 - *EEG will be normal or fast in delirium due to GABA withdrawal*

Case

If you only have time to do one bedside cognitive test to help determine if delirium is present, which is the highest-yield test?

- A. Orientation questions
- B. Luria sequence
- C. Days of the week backwards
- D. Naming items
- E. Delayed recall

Bedside Cognitive Testing



Orientation

Work orientation questions into interview

“Where is home for you? How far away is that?”

“What day did you come into the hospital? How long ago was that?”

“What are you watching on TV? What’s happening?”



Months of the Year Backwards

Test of sustained attention

More complex than days of the week backwards

Pay attention to speed, errors, omissions

Bedside Cognitive Testing

- Clock Draw
 - *No distraction, no help*
 - *Planning*
 - *Sequencing*
 - *Perseveration*
 - *Stimulus Bound*
- Luria Maneuvers
 - *Instructions: "I'm going to do a series of three movements with my hand. Watch what I do and then try to repeat it."*
 - *Deficits are analogous to those seen in the clock draw*

Both tests are meant to be used as a serial exam

Consequences of Delirium

- Increased Mortality
 - *3-year mortality for hospitalized elderly with index episode of delirium was 75% vs. 51% for non-delirious controls*
 - *Delirious patients experienced an adjusted risk of death of almost 2.0 compared to non-delirious controls*
- Increased Morbidity
 - *Poor functional recovery*
 - *Possible future cognitive decline*
 - *Increased risk of complications*
 - *Increased nursing home placement*
 - *Increased costs and LOS*
- 5-10% of patients never recover cognitive baseline – develop dementia

Curyto 2003, Inouye 1998

Sequelae of Delirium

Agitation

- *Increases risk of harm to patient and staff*
 - Pulling out IV's, central lines
 - Falling out of bed
 - Assaults on nursing and other staff

Perceptual Disturbances

- *Increase risk for post-delirium PTSD (Post-ICU syndrome [PICS])*

3 Main Questions

Can we prevent delirium with medications?

Can we treat delirium with medications?

Can we manage delirium with medications?

Prevention Strategies

- Choice of Analgesia and Sedation
 - *Compared with midazolam, patients that received dexmedetomidine for postoperative mechanical ventilation sedation had less risk of developing delirium*
 - *2021 study suggests no difference in risk between dexmedetomidine and propofol for mechanically-ventilated patients with sepsis*
 - *Among opioids, dilaudid and oxycodone may be associated with lower rates of delirium than morphine*
- Some evidence that melatonin and melatonin agonists like ramelteon may help to prevent delirium
- ABCDE Bundle
 - Awakening and breathing coordination, delirium prevention and management, and early physical mobility

Can We Prevent Delirium Using Other Medications?

- Evidence base is mixed but not robust for antipsychotic agents
- Prophylactic use of antipsychotics to prevent delirium is not currently supported by the literature

Kalisvaart 2005, Larsen 2010, Wang 2012, van den Boogaard 2013, Wu 2019

Can We Treat Delirium Using Medications?

- Conflicting evidence about whether medications can shorten the duration of delirium
- Conclusion – Antipsychotic agents do not treat delirium
- The only treatment for delirium is to reverse the underlying cause and treat the medical illness

*Devlin 2010, Breitbart 1996, Neufeld 2016,
Girard 2018, Nikooie 2019, Wu 2019*

Non-pharmacologic Management Strategies

Screen	Screen for delirium every shift
Create	Create a calm, orienting environment (clocks, calendars, familiar objects from home)
Encourage	Encourage normal sleep-wake cycles
Involve	Involve family members in supportive care
Place	Place patient near nursing station
Ensure	Ensure glasses and hearing aids available
Monitor	Monitor fluid input and output
Discontinue	Discontinue all non-essential medications • “Clean the patient up”

Case

In which of the following situations should you consider using antipsychotic medication to help manage your patient's delirium:

- A. She has difficulty sleeping at night
- B. She refuses to participate in PT
- C. She believes that rodents have infested her room and is very concerned about this
- D. She tries to get out of bed once without asking for assistance
- E. She does not eat most of her meals

Antipsychotics in Delirium

- Have been the mainstay of delirium management for decades
- Can be sedating
- In the 80's and 90's, intravenous haloperidol and chlorpromazine were used primarily
- In the past 20 years, second generation antipsychotics have been used with increased frequency
- Choice of antipsychotic often based on receptor profile, side effects, personal preference

Intravenous Haloperidol

- Use in delirium dates back to the 1970's
- Haloperidol has high affinity for D2 receptors and little effect on serotonergic, alpha, histamine or cholinergic receptors
 - *Also acts as a sigma-1 antagonist*
- IV route preferred due to being fast-acting, and avoidance of pain, fear, and elevation of creatinine kinase caused by repeated IM injections
- Twice as potent as oral form, faster time to onset, long-lasting effect
- Calming but not sedating
 - *Will potentiate sedative effects of other agents*
- IV haloperidol also causes EPS very infrequently
- Wide dose ranges have been reported (up to 1200 mg daily), and the use of continuous infusion is also described

Sos and Cassem 1980; Chang 1992

Intravenous Haloperidol and QT

- Concerns about QT prolongation with IV haloperidol may be overblown
- Current FDA recommendation is for telemetry at all doses
 - *Based on 70 reports of QTc prolongation or TDP; all had multiple other risk factors*
- Recent prospective studies indicate doses up to 20mg not associated with QT prolongation
- Revised Recommendations
 - *No ECG monitoring required if total dose <5 mg daily and less than 2 other risk factors present*
 - *Check a baseline ECG in a non-emergent situation and at least one follow-up ECG, preferably 30-60 minutes following administration, for doses >5 mg daily **OR** 2 or more risk factors*
 - *Consider daily ECG for total cumulative dose >25 mg*
 - *Consider continuous monitoring and/or alternative agents for QT_c > 500 ms **OR** total dose >100 mg*
 - *Minimal evidence to suggest that switching to another antipsychotic is safer*
 - *If there is enough concern about QT prolongation to stop using IVH, use a non-antipsychotic agent*

Beach 2020

Melatonin and melatonin- agonists

- Very useful in restoring sleep-wake cycle
- May also have immune modulating effects
- Relatively benign safety profile

Chakraborti 2015

Alpha-2 Agonists

- As discussed earlier, dexmedetomidine has been associated with reduced rates of delirium compared with other sedatives
- Clonidine has historically been used for agitation in TBI and more recently applied as a management strategy in delirium
- Available in long-acting patch form
- Also used for alcohol and opioid withdrawal
- Can cause hypotension and bradycardia

Maldonado 2017

Valproic Acid

- Can be useful for impulsivity, agitation, dysexecutive syndrome in TBI and dementia patients
- Has been associated in at least one study with decreased antipsychotic usage
- Available IV and can be loaded for rapid titration
- Wide dose range
- Can cause pancreatitis, fulminant hepatic failure and hyperammonemia

Sher 2015

Trazodone

- Helpful for anxiety, irritability in addition to sleep
- May be particularly useful in older patients who cannot tolerate antipsychotics
- Only available PO
- Wide dose range

Benzodiazepines

- Historic lore is that “Benzos are bad” for delirium
- May be necessary in certain causes of delirium (ETOH withdrawal, seizures)
- Low-dose benzos added to antipsychotics can enhance the effects and allow for lower dosing of antipsychotic agents
- 2019 meta-analysis suggested haloperidol and lorazepam combo may be ideal for managing delirium
- Available in a variety of forms, fast-acting

Wu 2019

Stimulants

- Used at times for hypoactive delirium with significant apathy
- Mild effects on heart rate, blood pressure
- Risk of worsening psychosis
- Typical agent is methylphenidate 5mg qam, with gradual titration by 5-10mg daily

Delirium in COVID-19

- Delirium is being frequently described in patients with COVID-19 (75-85% of ICU patients; 34% of older, hospitalized patients)
- Altered mental status is the 6th most common presenting sign for COVID
- Risk factors in COVID similar to general risk factors
- Increased mortality and increased risk for cognitive symptoms at 6 months
- Mixed evidence on motor subtypes
- Symptoms consistent with akinetic mutism (increased tone, mutism, immobility) are described more commonly in COVID delirium

Khan 2020; Kennedy 2020; Helms 2020; Beach 2020

Take Home Points

Delirium is greatly under-recognized, with 70% of cases being missed

Executive dysfunction is the most common cognitive deficit seen in delirium

Hypoactive delirium is the most common motoric subtype

Any process that affects the brain greatly increases the risk of delirium

Delirium is a bedside diagnosis, and basic bloodwork and imaging may be normal in many cases

The only treatment for delirium is to reverse the underlying cause

Medications are used to manage the sequelae of delirium

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