



DELIRIUM

Pathophysiology, Prevention, and Treatment

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DISCLOSURES

No relevant disclosures to report

Off-label uses of medications will be discussed during this talk

**By the end of this
talk, you will be
able to:**



1

RECOGNIZE

Identify the clinical manifestations of delirium across its subtypes

2

EXPLAIN

Describe the converging pathophysiological pathways underlying acute brain failure

3

MITIGATE

Apply multicomponent, evidence-based strategies to reduce delirium incidence in hospitalized patients

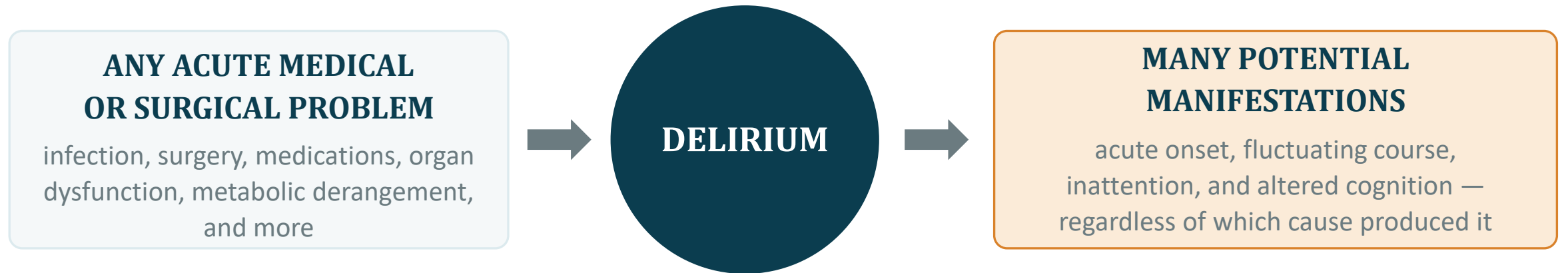
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MANAGE

Identify when pharmacotherapy is and is not indicated, and select safe, evidence-based management strategies

Delirium as a Syndrome, Not a Specific Diagnosis

Constellation of symptoms suggestive of global (diffuse) brain dysfunction



DSM-5-TR Criteria

- A** Disturbance in attention and reduced awareness
- B** Develops over a short period (hours to days), represents an acute change, and tends to fluctuate
- C** An additional disturbance in cognition (memory, disorientation, language, visuospatial, perception)
- D** Not better explained by a pre-existing, established, or evolving neurocognitive disorder
- E** Evidence that it is a direct physiological consequence of another medical condition(s)

Delirium is a medical emergency

It signals an acute physiological insult that requires urgent identification and treatment

Five Core Domains



These domains define the phenotype, not the etiology: the mix varies by patient, driven by neurotransmitter, sensory, and network breakdown

Delirium Motoric Subtypes



HYPERACTIVE

Agitation, restlessness, hypervigilance, hallucinations, combativeness — most easily recognized, least common

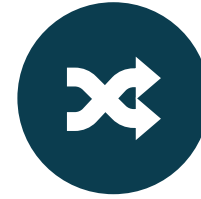
~23%



HYPOACTIVE

Lethargy, withdrawal, reduced responsiveness, quiet confusion — most underrecognized, most common, associated with worse outcomes

~50%



MIXED

Fluctuates between hyperactive and hypoactive features within the same day, sometimes hour to hour

~28%



60–70% of delirium cases go unrecognized by clinicians overall

And the rate is higher still for the hypoactive subtype

Differential Diagnosis



HYPOACTIVE DELIRIUM

Depression

Psychomotor slowing without inattention; gradual onset

Dementia with apathy

Chronic baseline; collateral history is key

Oversedation / medication effect

Can mimic or directly cause hypoactive delirium

Catatonia

Immobility, mutism, and staring; screen with Bush-Francis scale

Nonconvulsive status epilepticus

Unexplained unresponsiveness; requires EEG



HYPERACTIVE DELIRIUM

Mania / bipolar disorder

Agitation and sleep disruption; prior psych history; cognition intact

Primary psychosis

Hallucinations/delusions overlap; no attention deficit

Alcohol or substance withdrawal

DT = hyperactive delirium; distinguished by history and toxicology

Anxiety / panic

Restlessness and autonomic arousal; no true inattention

Akathisia (medication-induced)

Motor restlessness without cognitive deficit

Three features point back to delirium:

Acute onset (hours to days), fluctuating course, and deficit in attention

Why Delirium Matters



36%

of hospitalized adults ≥75
experienced delirium
during admission



3.4×

increase in 90-day
mortality risk associated
with delirium



60–70%

of delirium cases go
unrecognized by the
treating clinical team



+7.8 days

excess hospital length of
stay associated with
incident delirium

Delirium drives complications: infections, pressure injuries, GI bleed, and ICU transfers

Delirium occurrence rises sharply with baseline cognitive impairment:

16% (normal cognition) → 27% (MCI) → 59% (mild dementia) → 77% (moderate–severe dementia)

Why Delirium Matters



~3×

increased risk of incident dementia after a hospital delirium episode



2.4×

increased risk of nursing home placement (33% vs. 11% of controls)



~1 in 5

experience PTSD symptoms; delirium is a well-documented risk factor



3.15×

higher odds of self-removing medical devices

Patient safety: Major driver of self-extubation, device removal, and leading contributor to inpatient falls

Staff safety: Delirium is the strongest patient-level predictor of aggression towards healthcare workers

Clinical Assessment



No blood test or imaging study can confirm delirium

The diagnosis rests entirely on history and bedside clinical observation



Collateral History Is Essential

- Patients cannot reliably self-report
- Ask family, caregivers, or nursing staff
- Establishing a true cognitive baseline is often the most useful diagnostic step



Pattern of Onset and Course

- Was the change genuinely acute — hours to days, not weeks to months?
- Does it fluctuate — often worse at night?
- This temporal pattern separates delirium from dementia

Exam, labs, and imaging still matter

- Physical exam and targeted labs (CBC, BMP, LFTs, TSH, UA) help identify the underlying medical or surgical cause
- Neuroimaging is reserved for focal signs, trauma, or unexplained findings

The Neurological Examination in Delirium

No neurological finding is pathognomonic for delirium

AROUSAL & ATTENTION

Level of consciousness, digit span or months-of-year-backward for attention

CRANIAL NERVES

Pupillary response, extraocular movements, facial symmetry

MOTOR & TONE

Strength, tone, and symmetry

FRONTAL RELEASE SIGNS

Grasp, glabellar, palmomenta — reflect diffuse cortical dysfunction

MULTIFOCAL MYOCLONUS

Tremor, asterix, and multifocal myoclonus can signal toxic-metabolic encephalopathy

Red flag: any focal deficit (asymmetric weakness, gaze deviation, new aphasia) warrants urgent neuroimaging to rule out stroke, hemorrhage, or mass effect

Cognitive Dysfunction: Bedside Testing

Attention & Orientation Tests

Digit Span

Months Backward

Orientation

Clock Drawing Task

"Draw a clock showing 10 past 11"



Normal



Neglect



Stimulus-Bound



Perseveration

Luria's 3-Step Sequence

Sequencing errors suggest frontal/executive dysfunction



1. Fist (horizontal)



2. Edge



3. Palm

- Cognitive testing alone can't separate delirium from dementia
- Formal MMSE/MoCA testing is unreliable until delirium clears

The Role of EEG



Classic EEG Findings in Delirium

- Generalized, diffuse theta/delta slowing
- Slowing or loss of the posterior dominant rhythm
- Poor organization of the background rhythm
- Degree of slowing correlates with severity
- Triphasic waves
- **Important:** EEG normal or fast if delirium in GABA withdrawal

These changes are non-specific; the diagnosis remains clinical



WHEN TO ORDER IT

- If unsure if patient is delirious
- If suspected seizure – fluctuating unresponsiveness
- If there is concern for nonconvulsive status epilepticus
- If delirium is refractory to treatment of identified precipitants

Bedside Screening Tools

Validated, brief tools are helpful, but exam remains the **GOLD STANDARD**

Confusion Assessment Method (CAM)

1. Acute onset AND fluctuating course
2. Inattention
3. Disorganized thinking
4. Altered level of consciousness

Diagnosis requires: Features 1 + 2, and either 3 or 4

Sensitivity 0.80 • Higher specificity than 4AT/Nu-DESC

Best for confirmation; requires brief training

The 4 "A"s Test (4AT)

1. Alertness
2. AMT4 (age, DOB, place, year)
3. Attention (months backward)
4. Acute change or fluctuating course

No special training required; ~2 minutes

Sensitivity 0.76 • Fast, scalable front-line screen

Widely used in ED and general ward settings

Conditions Associated with Delirium: I WATCH DEATH

I WATCH

I

Infection

encephalitis, meningitis, UTI, pneumonia, sepsis

W

Withdrawal

alcohol, benzodiazepines, barbiturates

A

Acute metabolic

electrolyte imbalance, hepatic or renal failure, acidosis

T

Trauma

head injury, burns, postoperative state

C

CNS pathology

stroke, hemorrhage, tumor, seizure, NPH, abscess

H

Hypoxia

anemia, cardiac or lung failure, PE, CO poisoning

DEATH

D

Deficiencies

vitamin B12, folate, thiamine, niacin

E

Endocrinopathies

thyroid, glucose, parathyroid, adrenal

A

Acute vascular

shock, hypertensive encephalopathy, vasculitis

T

Toxins / drugs

medications, pesticides, solvents

H

Heavy metals

lead, mercury, arsenic, manganese

01



PATHOPHYSIOLOGY

Two-Hit Model

PREDISPOSING FACTORS

(baseline brain vulnerability)

- Advanced age
- Pre-existing dementia / cognitive impairment
- Frailty and multimorbidity
- Sensory impairment (vision, hearing)
- Prior stroke or neurodegenerative disease
- Polypharmacy at baseline



PRECIPITATING FACTORS

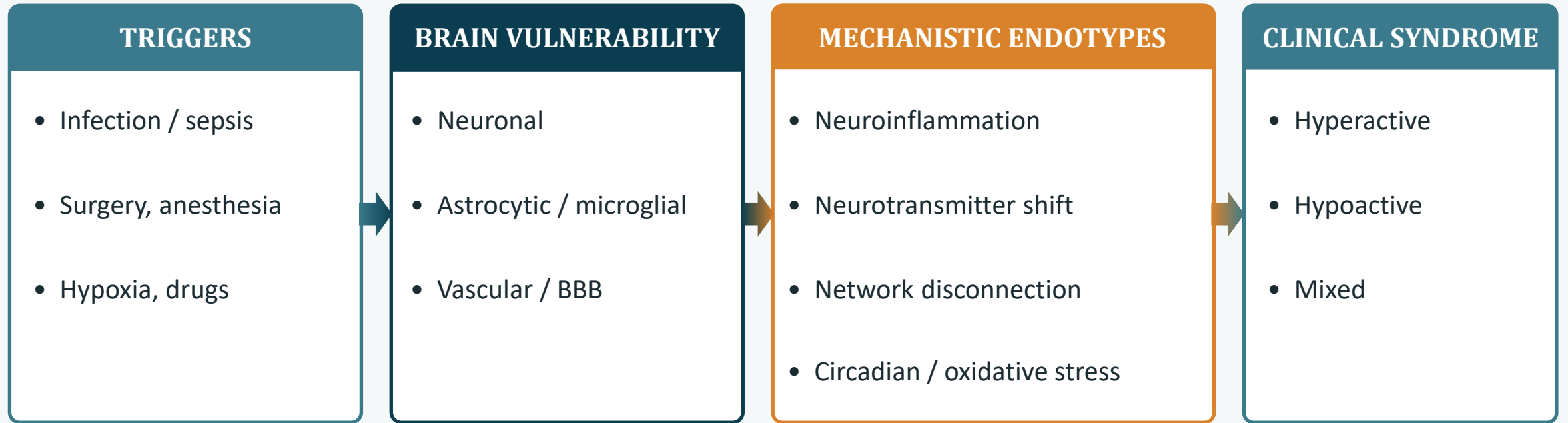
(acute triggering insult)

- Infection / sepsis
- Surgery and anesthesia exposure
- Hypoxia, metabolic derangement
- Psychoactive and anticholinergic drugs
- Immobility, sleep disruption, restraints
- Pain, urinary retention, constipation

The largest systematic mapping of delirium risk factors to date identified 33 predisposing and 112 precipitating factors

A highly vulnerable patient may develop delirium from a minor insult (e.g., a single dose of a sedating medication)

The Pathophysiologic Cascade



Systems Integration Failure Hypothesis: each pathway contributes variably per patient, shaping the clinical phenotype

Core Pathophysiologic Mechanisms



Neuroinflammation

- Systemic cytokines and NLRP3 inflammasome activation increase blood–brain barrier permeability
- Microglial activation drives neuronal injury and synaptic dysfunction
- Emerging link: gut microbiota dysbiosis may amplify the cascade



Neurotransmitter Dysregulation

- Acetylcholine deficiency impairs attention and arousal
- Explains why anticholinergic drug burden is a key, reversible precipitant
- Dopamine / glutamate excess drives hyperactive, excitotoxic features



Network Disconnection

- fMRI shows weakened connectivity between posterior cingulate and prefrontal cortex (Default Mode Network)
- EEG shows diffuse slowing and reduced connectivity, correlating with attentional deficits
- Explains why diverse insults converge on one clinical picture

Contributing Mechanisms



Circadian (Diurnal) Dysregulation

- Sleep–wake cycle disruption is both risk factor and consequence
- ICU/ward environments exacerbate it
- Suppressed melatonin drives circadian failure and correlates with delirium subtype



Oxidative Stress

- Reactive oxygen species accumulate with mitochondrial dysfunction
- Amplifies the neuroinflammatory cascade and promotes neuronal apoptosis
- Aging and neurodegeneration reduce antioxidant reserve, heightening vulnerability



Neuroendocrine / Stress Response

- Aberrant HPA-axis activation and cortisol dysregulation in acute illness
- Chronic stress-response activation intersects with neuroinflammatory signaling
- Part of a broader "neuronal aging" vulnerability model

02



Risk Stratification

SCREEN AT ADMISSION

- Age $\geq$ 65
- Known dementia or cognitive impairment
- Severe illness / high comorbidity burden
- Hip fracture or high-risk surgery
- Baseline sensory impairment
- Prior delirium episode

PREVENT AND MONITOR

- Enroll in the multicomponent prevention bundle — orientation, mobility, sleep, sensory aids, med review, family
- Document baseline cognitive and functional status, for comparison if delirium develops
- Increase delirium screening frequency (e.g., every shift)

Modifiable vs. Non-Modifiable Risk Factors

NON-MODIFIABLE

(fixed at the time of admission)

- Advanced age
- Pre-existing dementia or baseline cognitive impairment
- Prior stroke or neurodegenerative disease
- History of a previous delirium episode
- Genetic factors (e.g., APOE ε4 status)
- Severity of the acute illness itself

MODIFIABLE

(the targets of prevention)

- Uncorrected vision or hearing impairment
- Sleep deprivation / circadian disruption
- Immobility
- Dehydration and malnutrition
- Polypharmacy — anticholinergic and sedative burden
- Undertreated pain, restraints, and unnecessary catheters/lines

HELP trial targeted six modifiable risk factors — cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration — and reduced delirium incidence by 53% (OR 0.47)

Multicomponent Non-Pharmacologic Prevention



Orientation

Frequent reorientation, visible clocks/calendars, familiar objects and photos



Early Mobility

Minimize immobilization; ambulate as early as safely possible



Sleep Protocol

Non-pharmacologic sleep hygiene: reduce night-time noise/light, cluster care



Sensory Aids

Ensure glasses, hearing aids, and dentures are in place and functioning



Med Review

Minimize anticholinergic, sedative-hypnotic, and psychoactive drug burden



Family Engagement

Involve family in orientation, comfort, and monitoring

Multicomponent programs -> ~30–40% relative reductions in delirium incidence in perioperative populations

ICU-Specific Approach: ABCDEF

A

Assess, prevent,
and manage pain

B

Both spontaneous
awakening and
breathing trials

C

Choice of analgesia
and sedation

D

Delirium: assess,
prevent, and
manage

E

Early mobility and
exercise

F

Family
engagement and
empowerment

Evidence from a systematic meta-review:



Delirium incidence & duration

Significantly reduced by the ABCDEF bundle, multicomponent interventions, and early mobilization



Mortality

Multicomponent non-pharmacologic care nearly halved mortality; the ABCDEF bundle alone showed no mortality benefit



ICU / hospital length of stay

Reduced by approximately 1–2 days with non-pharmacologic interventions

Pharmacologic Prevention: A Limited Role

Not recommended

- Prophylactic antipsychotics — SCCM guidance suggests against routine use for delirium prevention or treatment
- Perioperative pharmacologic prophylaxis in general shows limited and inconsistent efficacy across trials



Mixed or Preliminary Evidence

Dexmedetomidine

Alpha-2 agonist; reduces delirium in mechanically ventilated ICU patients; role beyond sedation remains unclear

Melatonin / Ramelteon

Targets circadian dysregulation; conditionally recommended by SCCM, but RCT data for delirium prevention remain nonsignificant

NSAIDs / COX-2 inhibitors

Target neuroinflammation; parecoxib and NSAIDs reduced postoperative delirium but evidence remains limited — GI/renal/CV risk trade-offs

Orexin antagonists (suvorexant, lemborexant)

Promotes physiologic sleep; pooled RCTs show ~40% delirium reduction — larger confirmatory trials are needed

Non-pharmacologic multicomponent prevention has the strongest evidence; all pharmacologic approaches remain adjunctive or investigational

03

 TREATMENT

Treatment Principles: Detect, Correct, Support the Brain



1. Identify the cause

Systematically evaluate for infection, metabolic derangement, hypoxia, medication effect, withdrawal, pain, and urinary retention/constipation



2. Remove precipitants

Discontinue or minimize deliriogenic medications (anticholinergics, benzodiazepines, opioids); treat the underlying medical cause



3. Non-pharmacologic support

Reorientation, mobilization, sleep protocol, sensory aids, family involvement — the cornerstone of management



4. Targeted pharmacotherapy

Reserve medications for agitation or symptoms that threaten safety

Non-Pharmacologic Management

D.E.L.I.R.I.U.M



Drugs

Remove any deliriogenic medications



Light

Appropriate day/night lighting; visible clocks and calendars for orientation



Routine

A 24-hour approach: functional tasks, structured timetables, consistent staff assignment



Under-hydration / Nutrition

Monitor food/fluid intake; correct dehydration, constipation



Environment

Reduce noise/stimulus, minimize room changes, encourage family presence



Initiate Cognitive Tasks

Early OT referral; cognitive stimulation; ensure sensory aids are in place



Integrate the MDT

PT/OT, pharmacy, speech therapy



Mobility

Early mobilization as soon as safely feasible; avoid restraints when possible

The Antipsychotic Evidence: MIND-USA

A landmark trial reshaped guideline recommendations

MIND-USA Trial

Multicenter, double-blind, placebo-controlled RCT — IV haloperidol vs. ziprasidone vs. placebo in critically ill adults with delirium (~89% hypoactive subtype)

No difference

in delirium/coma-free days, survival, or ICU length of stay vs. placebo

No long-term benefit

in cognitive function, functional disability, psychological outcomes, or quality of life at follow-up

No difference

in QTc prolongation between haloperidol, ziprasidone, and placebo (exclusion threshold was QTc > 550ms)

Current SCCM guidance: suggest AGAINST routine antipsychotic use for treatment of delirium in critically ill adults.

When Are Antipsychotics Still Appropriate?



Reasonable, targeted use

- Severe agitation posing immediate danger to patient or staff
- Distressing hallucinations or delusions causing significant distress
- Lowest effective dose, shortest duration, with a clear stop date / reassessment plan
- QTc monitoring in at-risk patients



Not appropriate

- Routine / prophylactic use to prevent delirium
- As first-line treatment for hypoactive delirium – no evidence of benefit
- Long-term or indefinite continuation without reassessment
- As a substitute for identifying and treating the underlying cause

Choosing an Antipsychotic

What to Consider When Choosing

- **Sedation goal**

Olanzapine/chlorpromazine if sedation is desired

- **Cardiac risk / baseline QTc**

Baseline ECG, correct electrolytes; avoid if QTc already prolonged

- **Route available**

Parenteral option needed

- **Anticholinergic load**

Avoid high-anticholinergic-burden agents (if already elevated)

- **Age and frailty**

"Start low, go slow" — elderly patients are far more sensitive



What to Watch For

- **QTc prolongation**

Monitor, especially in patients on other QTc-prolonging drugs

- **Extrapyramidal symptoms**

Akathisia, rigidity, and acute dystonia; monitor regularly

- **Neuroleptic malignant syndrome**

Rare but life-threatening — rigidity, fever, and autonomic instability

- **Orthostatic hypotension**

Especially with chlorpromazine — a real fall risk in older patients

- **Oversedation**

Can mask a worsening mental status and clinical deterioration

Black-box warning: all antipsychotics carry an increased risk of **mortality** in elderly patients with dementia-related psychosis

Across every agent: lowest effective dose, shortest duration, and a clear stop date or reassessment plan.

Choosing an Antipsychotic

When symptom control is truly needed — no agent has proven superior; the choice is about side-effect fit

	Haloperidol	Olanzapine	Quetiapine	Chlorpromazine
Sedation	Low — calming, not sedating; potentiates other sedatives	Moderate–high	Moderate–high	High
EPS risk	High PO/IM; lower with IV	Moderate	Lowest	Low–moderate
Anticholinergic burden	Low	Moderate	Moderate	High
Typical dosing (delirium)	1–5mg IV q4–6h PRN	2.5–5mg PO/SL/IV q6–8h PRN	12.5–50mg PO q6h PRN	25–50mg PO/IV q6h PRN
Potential risks	QTc prolongation, dose-dependent	Avoid IM/parenteral form with benzodiazepines — cardiorespiratory depression risk	Modest QTc risk	Orthostatic hypotension (α 1-blockade), often dose-limiting; QTc prolongation with torsades risk
Available route	PO / IM / IV — IV preferred: faster, avoids IM pain/CK elevation, ~2x potent as oral	PO / IM / SL / IV (off-label)	PO only	PO / IM / IV (off-label, slow administration)
Best suited for	First-line for acute hyperactive delirium; rapid titration; preserves arousal	When sedation is desired; flexible routes; avoid with parenteral benzodiazepines	Delirium with Parkinson's/Lewy body dementia (lowest EPS); PO only limits use in acute agitation	Refractory agitation when deep sedation is acceptable; requires hemodynamic stability

Melatonin and Alpha-2 Agonists



Melatonin & Melatonin Agonists

(e.g., ramelteon)

- Useful in restoring the sleep-wake cycle — targets circadian dysregulation directly
- Hypothesized anti-inflammatory effects – insufficient evidence
- Relatively benign safety profile
- Some evidence that melatonergic agents reduce delirium incidence and shorten duration



Alpha-2 Agonists

Dexmedetomidine

- Strongest pharmacological evidence for delirium prevention in ICU
- Reduces ICU length of stay and mechanical ventilation duration vs. propofol/benzodiazepines
- Main risks: bradycardia and hypotension

Clonidine (Oral)

- Slower onset — not suited for acute agitation control
- Often used to transition patients off IV dexmedetomidine once stabilized
- Far less costly; available in long-acting patch form

Trazodone and Valproic Acid



Trazodone

- Used for agitation and insomnia in delirium and dementia
- Useful in older patients who cannot tolerate antipsychotics
- Associated with lower mortality and lower delirium rehospitalization

Caution: α 1-mediated orthostatic hypotension, serotonergic load, fall risk, and hyponatremia risk



Valproic Acid

- Proposed for refractory agitation when other agents have failed; can be useful for impulsivity in TBI
- Shown to reduce concomitant psychoactive medication burden
- Important caveat: not recommended for dementia-related agitation

Caution: monitor LFTs, ammonia, and platelets; avoid in hepatic impairment

Cholinesterase Inhibitors and Stimulants

Acetylcholinesterase Inhibitors

- Mechanistically appealing: cholinergic deficiency is a core proposed mechanism of delirium
- RCT of rivastigmine added to haloperidol was halted early for increased mortality (22% vs. 8%) with no reduction in delirium duration
- Smaller donepezil trials in non-ICU surgical settings have also failed to show clear benefit

Stimulants

- Aimed at increasing arousal in hypoactive delirium
- Methylphenidate in terminally ill/geriatric palliative care patients – improved alertness, communication, and MMSE scores
- Modafinil evidence is limited to isolated case reports only

Key Takeaways

- 1 Delirium is a syndrome, not a single disease
- 2 It is common and severely under-recognized
- 3 Diagnosis is a bedside diagnosis
- 4 Prevention beats treatment
- 5 Medications play a narrow, adjunctive role
- 6 The stakes are high and lasting

References

1. Al Huraizi AR, Al-Maqbali JS, Al Farsi RS, et al. Complications associated with delirium in hospitalized patients. *J Clin Med*. 2023;12(16):5346.
2. Azimaraghi O, Hammer M, Santer P, et al. Study protocol for a randomised controlled trial evaluating the effects of the orexin receptor antagonist suvorexant on sleep architecture and delirium in the intensive care unit. *BMJ Open*. 2020;10(7):e038474.
3. Bachu A, Kotapati P, Kainth T, et al. Use of methylphenidate for hypoactive delirium: a comprehensive systematic review. *Psychoactives*. 2023;2(4):337-345.
4. Beach SR, Gomez-Bernal F, Huffman JC, Fricchione GL. Alternative treatment strategies for catatonia: a systematic review. *Gen Hosp Psychiatry*. 2017;48:1-19.
5. Beach SR, Gross AF, Hartney KE, Taylor JB, Rundell JR. Intravenous haloperidol: a systematic review of side effects and recommendations for clinical use. *Gen Hosp Psychiatry*. 2020;67:42-50.
6. Brenner RP. Utility of EEG in delirium: past views and current practice. *Int Psychogeriatr*. 1991;3(2):211-229.
7. Cerejeira J, Mukaetova-Ladinska EB. A clinical update on delirium: from early recognition to effective management. *Nurs Res Pract*. 2011;2011:875196.
8. Chakraborti D, Tampi DJ, Tampi RR. Melatonin and melatonin agonist for delirium in the elderly. *Am J Alzheimers Dis Other Dement*. 2015;30(2):119-129.
9. CHANGE Study Investigators. Delirium prevalence, incidence, and outcomes in acutely admitted older patients: a prospective cohort study. *Age Ageing*. 2026;55(4):afag081.
10. Cheng SL, Hsu TW, Kao YC, et al. Haloperidol in treating delirium, reducing mortality, and preventing delirium occurrence: Bayesian and frequentist meta-analyses. *Crit Care*. 2025;29(1):112.
11. Crowley KE, Urben L, Hacobian G, Geiger KL. Valproic acid for the management of agitation and delirium in the intensive care setting: a retrospective analysis. *Clin Ther*. 2020;42(4):e65-e73.
12. Culhane J, Okeke R, Bushe K, Freeman C. Self-removal of medical devices in the ICU: a retrospective study. *Cureus*. 2025;17(6):e86865.
13. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018;46(9):e825-e873.
14. Ding XY, Zhang MH, Liu J, Wu D. Recent advances in postoperative delirium in elderly patients: pathophysiological mechanisms, risk prediction, and therapeutic strategies. *Front Neurosci*. 2026;20:1759910.
15. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology*. 2000;55(11):1621-1626.
16. Eknoyan D, Hurley RA, Taber KH. The clock drawing task: common errors and functional neuroanatomy. *J Neuropsychiatry Clin Neurosci*. 2012;24(3):260-265.
17. Fagiolini A, González Pinto A, Miskowiak KW, et al. Trazodone in the management of major depression among elderly patients with dementia: a narrative review and clinical insights. *Neuropsychiatr Dis Treat*. 2023;19:2819-2831.
18. Fan Z, et al. Delirium as an acute, global cognitive disorder syndrome. *Front Aging Neurosci*. 2024;16:1446523.
19. Finsterer J, Gama Marques J. The non-specificity of EEG slowing in delirium: a critical appraisal. *J Intensive Care Soc*. 2025. Published online ahead of print.
20. Gagnon B, Low G, Schreier G. Methylphenidate hydrochloride improves cognitive function in patients with advanced cancer and hypoactive delirium: a prospective clinical study. *J Psychiatry Neurosci*. 2005;30(2):100-107.
21. Girard TD, Exline MC, Carson SS, et al. Haloperidol and ziprasidone for treatment of delirium in critical illness. *N Engl J Med*. 2018;379(26):2506-2516.

References

22. Hatta K, Kishi Y, Wada K, et al. Preventive effects of suvorexant on delirium: a randomized placebo-controlled trial. *J Clin Psychiatry*. 2017;78(8):e970-e979.
23. Hodge H, Ullahansari S, Berry B. Zolpidem for catatonia refractory to benzodiazepines in resource-limited settings. *BJPsych Open*. 2025;11(Suppl 1):S303.
24. Inouye SK. The dilemma of delirium: clinical and research controversies regarding diagnosis and evaluation of delirium in hospitalized elderly medical patients. *Am J Med*. 1994;97(3):278-288.
25. Inouye SK, Bogardus ST, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med*. 1999;340(9):669-676.
26. Kim SW, Yoo JA, Lee SY, et al. Efficacy and safety of atypical antipsychotic medications in the treatment of delirium. *BMC Psychiatry*. 2013;13:240.
27. Krishnan V, Leung LY, Caplan LR. A neurologist's approach to delirium: diagnosis and management of toxic metabolic encephalopathies. *Eur J Intern Med*. 2014;25(2):112-116.
28. Kundakci B, Jones KL, Booth A, et al. A systematic meta-review of interventions to prevent and manage delirium in the intensive care unit: part 2 — non-pharmacological and multicomponent interventions. *Crit Care*. 2025;29(1):434.
29. la Cour KN, Andersen-Ranberg NC, Weihe S, et al. Distribution of delirium motor subtypes in the intensive care unit: a systematic scoping review. *Crit Care*. 2022;26(1):53.
30. Lee JH, Suzuki J. N-methyl-D-aspartate (NMDA) receptor antagonists for treatment of catatonia in adults: narrative review. *Gen Hosp Psychiatry*. 2024;91:60-65.
31. Leucht C, Kitzmantel M, Chua L, Kane J, Leucht S. Haloperidol versus chlorpromazine for schizophrenia. *Cochrane Database Syst Rev*. 2008;2008(1):CD004278.
32. Lewis K, Alshamsi F, Carayannopoulos KL, et al. Dexmedetomidine vs other sedatives in critically ill mechanically ventilated adults: a systematic review and meta-analysis of randomized trials. *Intensive Care Med*. 2022;48(7):811-840.
33. Lu X, Yan R, Song S. Neurobiological mechanisms of postoperative delirium at neural molecular and cellular levels. *Acad Med Health*. 2025;2(4).
34. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *Am J Geriatr Psychiatry*. 2013;21(12):1190-1222.
35. Maldonado JR. Delirium pathophysiology: an updated hypothesis of the etiology of acute brain failure. *Int J Geriatr Psychiatry*. 2018;33(11):1428-1457.
36. Mart MF, Boehm LM, Kiehl AL, et al. Long-term outcomes after treatment of delirium during critical illness with antipsychotics (MIND-USA): a randomised, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2024;12(8):599-607.
37. McCusker J, Cole M, Dendukuri N, Belzile E, Primeau F. Does delirium increase hospital stay? *J Am Geriatr Soc*. 2003;51(11):1539-1546.
38. Mormando C, Reinfeld S, Genova N, et al. Catatonia and delirium in a general medical setting: prevalence and naturalistic treatment outcome. *J Acad Consult Liaison Psychiatry*. 2026;67(1):26-34.
39. Mu DL, Zhang DZ, Wang DX, et al. Parecoxib supplementation to morphine analgesia decreases incidence of delirium in elderly patients after hip or knee replacement surgery: a randomized controlled trial. *Anesth Analg*. 2017;124(6):1992-2000.
40. Nuti O, Merchan C, Ahuja T, Arnouk S, Papadopoulos J, Katz A. Valproic acid for hyperactive delirium and agitation in critically ill patients. *J Intensive Care Med*. 2025;40(5):519-527.
41. Oh ES, Fong TG, Hsieh TT, Inouye SK. Delirium in older persons: advances in diagnosis and treatment. *JAMA*. 2017;318(12):1161-1174.
42. O'Keeffe F, Cervoni I, Ganau M, Prisco L. Serum biomarkers of delirium in critical illness: a systematic review of mechanistic and diagnostic evidence. *Intensive Care Med Exp*. 2025;13(1):90.

References

43. Ormseth CH, LaHue SC, Oldham MA, Josephson SA, Whitaker E, Douglas VC. Predisposing and precipitating factors associated with delirium: a systematic review. JAMA Netw Open. 2023;6(1):e2249950.
44. Paternò DS, Via L, Putaggio A, et al. Perioperative neurocognitive disorders: a narrative review of pathophysiology, prevention, and management strategies. J Clin Med. 2026;15(3). Published online 2026 Feb 4.
45. Queiroz I, Barbosa LM, Gallo Ruelas M, et al. Effect of peri-operative pharmacological interventions on postoperative delirium in patients having cardiac surgery: a systematic review and Bayesian network meta-analysis. Anaesthesia. 2025;80(9).
46. Rains J, Chee N. The role of occupational therapy and physiotherapy in the multimodal management of delirium in the intensive care unit. J Intensive Care Soc. 2017;18(4):318-322.
47. Righy C, Rosa RG, da Silva RTA, et al. Prevalence of post-traumatic stress disorder symptoms in adult critical care survivors: a systematic review and meta-analysis. Crit Care. 2019;23(1):213.
48. Stollings JL, Boncyk CS, Birdrow CI, et al. Antipsychotics and the QTc interval during delirium in the intensive care unit: a secondary analysis of a randomized clinical trial. JAMA Netw Open. 2024;7(1):e2350186.
49. Subedi B, Louzon PR, Masood A, Recksieck S. Prolonged refractory ICU delirium successfully treated with valproic acid: case report and literature review. J Pharm Pract. 2021;34(6):984-987.
50. Tachibana M, Inada T, Ishigooka J. Catatonia and delirium: similarity and overlap of acute brain dysfunction. Front Psychiatry. 2022;13:876727.
51. Tampi RR, Tampi DJ, Ghorl AK. Acetylcholinesterase inhibitors for delirium in older adults. Am J Alzheimers Dis Other Dement. 2016;31(4):305-310.
52. Teri L, Logsdon RG, Peskind E, et al. Treatment of agitation in AD: a randomized, placebo-controlled clinical trial. Neurology. 2000;55(9):1271-1278.
53. Terry KA, Blum R, Szumita PM. Evaluating the transition from dexmedetomidine to clonidine for agitation management in the intensive care unit. J Intensive Care Soc. 2015;16(3):229-233.
54. Tieges Z, MacLulich AMJ, Anand A, et al. Diagnostic accuracy of the 4AT for delirium detection: a systematic review and meta-analysis. Am J Psychiatry. 2018;175(12):1157-1160.
55. van Eijk MMJ, Roes KCB, Honing MLH, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. Lancet. 2010;376(9755):1829-1837.
56. van Montfort SJT, van Dellen E, Stam CJ, et al. Brain network disintegration as a final common pathway for delirium: a systematic review and qualitative meta-analysis. Neuroimage Clin. 2019;22:101789.
57. van Montfort SJT, van Dellen E, Stam CJ, et al. Predisposition circuits for delirium and their EEG characteristics: a systematic review. Clin Neurophysiol. 2020;131(5):1051-1058.
58. Veauthier B, Hornecker JR, Thrasher T. Recent-onset altered mental status: evaluation and management. Am Fam Physician. 2021;104(5):461-470.
59. Waefler N, Abid I, Montaut V, et al. Neurological diagnostic tests for patients with and without delirium: a prospective observational study. GeroScience. 2024;46(6):5887-5895.
60. Wilson JE, Mart MF, Cunningham C, et al. Delirium. Nat Rev Dis Primers. 2020;6(1):90.
61. Witlox J, Eurelings LSM, de Jonghe JFM, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. JAMA. 2010;304(4):443-451.