Calming the Storm: Antipsychotic Strategies in the ICU

A presentation for HealthTrust Members
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Gabriella Young, PharmD

PGY1 Pharmacy Resident

Tristar Skyline Medical Center

Preceptor: Deanna Pouliot, PharmD, BCPS, Clinical Pharmacy Manager & Residency Program Director, Tristar Skyline Medical Center

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Objectives

1. Recognize the pharmacologic profiles of commonly used antipsychotic therapies in the Intensive Care Unit (ICU)

2. Recall current evidence-based guidelines regarding clinical indications for antipsychotic pharmacologic therapies for delirium and agitation in critically ill patients

3. Identify patient-specific factors during interdisciplinary discussions and management when recommending antipsychotic pharmacologic therapy

Background

- Common challenges in ICU:
  - Delirium and agitation
  - Increased risk of infection
  - Contribute to increased morbidity, prolonged mechanical ventilation, greater healthcare cost
- Antipsychotics are often used in the ICU setting to treat:
  - Acute psychosis
  - Substance withdrawal
  - Delirium
  - Agitation (when not responding to other therapies)

Delirium

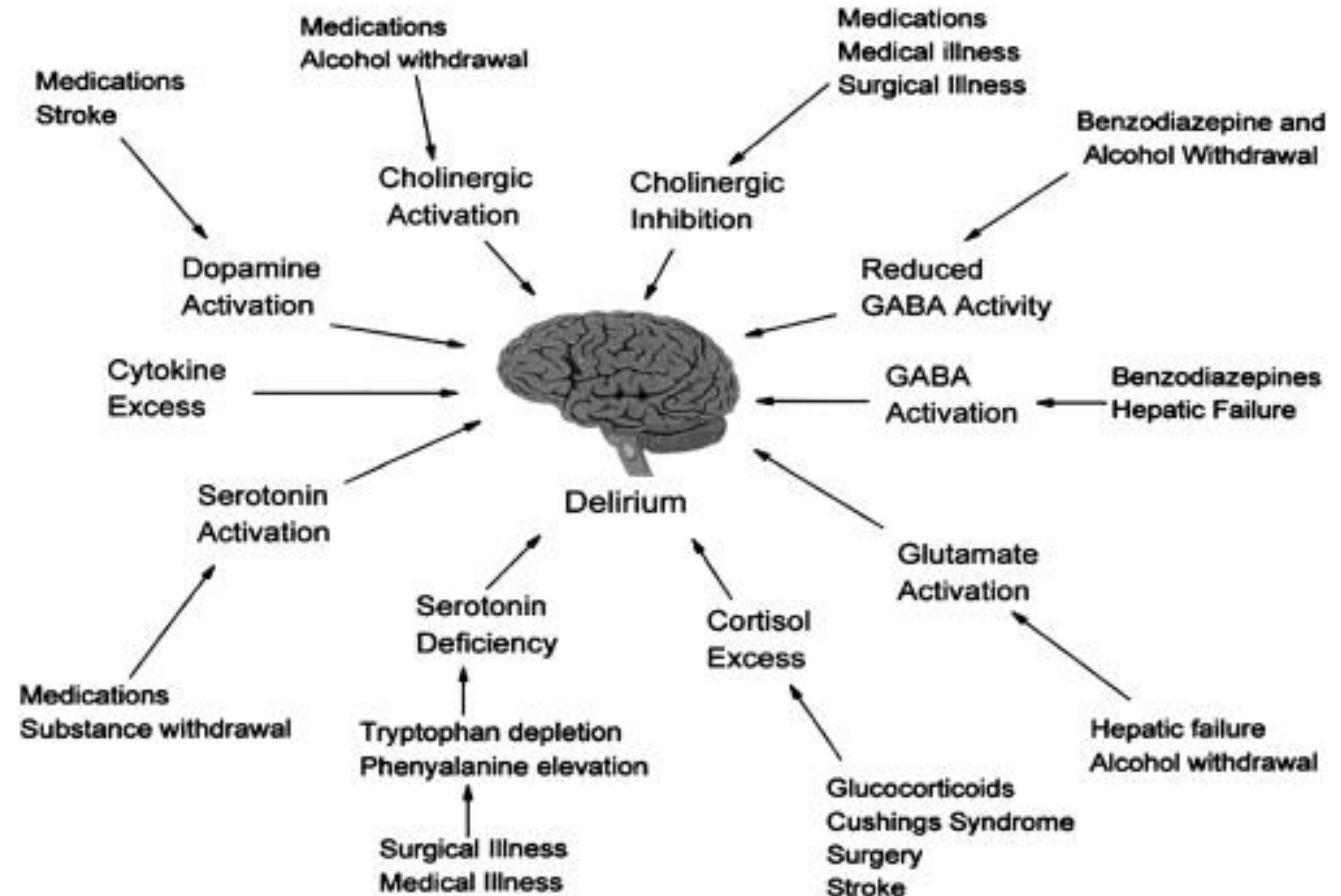
- Delirium: acute, generalized brain dysfunction that tends to wax and wane
  - Hyperactive—agitation
  - Hypoactive—withdrawn, mute, drowsy
  - Mixed—periods of both hyperactive and hypoactive
- Common features:
  - Increased sympathetic activity
  - Emotional symptoms
  - Psychotic symptoms
  - Sundowning

Source: Image accessed April 14, 2026 at Alzheimer's Association The Delirium Connection

Farkas, Josh. (2022, July 18). Antipsychotic use in acute care. *EMCrit Project IBCC*.https://emcrit.org/ibcc/dirium/

Pathophysiology of Delirium

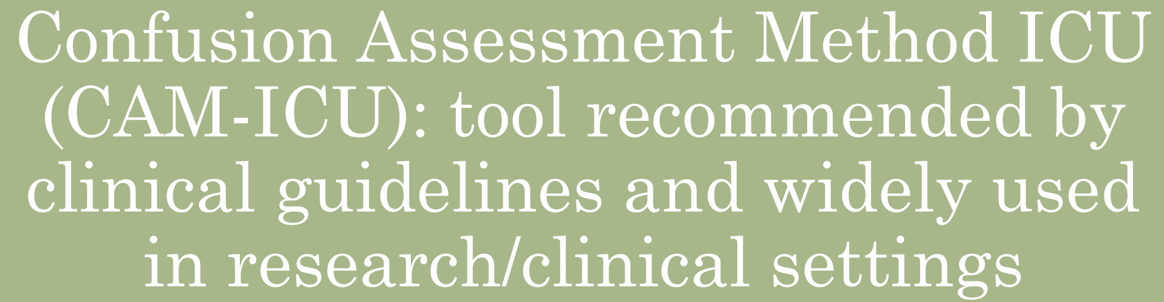
- Change in receptor regulation
- Multiple different receptors responsible for delirium
  - Cholinergic
  - GABA
  - Glutamate
  - Cortisol
  - Serotonin
  - Cytokine
  - Dopamine



Source: Chart accessed April 14, 2026 at [Chapter 2 – Postoperative Delirium - Anesthesia Key]

Gunther ML, Morandi A, Ely EW. Pathophysiology of delirium in the intensive care unit. *Crit Care Clin*. 2008;24(1):45-viii. doi:10.1016/j.ccc.2007.10.002

Assessing Delirium



Features Assessed:

1. Acute onset of mental status change	2. Inattention	3. Altered levels of consciousness	4. Disorganized thinking

Common Causes of Delirium

- Infection
- Trauma
- Withdrawal:
  - Alcohol
  - Benzodiazepines
  - Gabapentin
  - Baclofen
- Medications
  - Benzodiazepines
  - Antihistamines (especially first generation)
  - Anticholinergics
  - Opioids

Source: Farkas, Josh. (2022, July 18). Antipsychotic use in acute care. *EMCrit Project IBCC*.https://emcrit.org/ibcc/dirium/

Treatment Approaches

- Treat underlying cause
- Stop causative medication or give withdrawing agent
- Sedation (agitation)
  - Precedex
  - Propofol
  - Ketamine
- Antipsychotics

Source: Farkas, Josh. (2022, July 18). Antipsychotic use in acute care. *EMCrit Project IBCC*.https://emcrit.org/ibcc/dirium/

Clinical Application Question #1

Which of the following is a guideline-supported clinical indication for considering antipsychotics in critically ill patients?

A. Sedation
B. Anxiety
C. Depression
D. Delirium

Clinical Application Question #1: Correct Response

Which of the following is a guideline-supported clinical indication for considering antipsychotics in critically ill patients?

A. Sedation

B. Anxiety

C. Depression

D. Delirium

What are antipsychotics?

- Primarily classified by generation
- Classification comes from receptor-binding and side effect profile

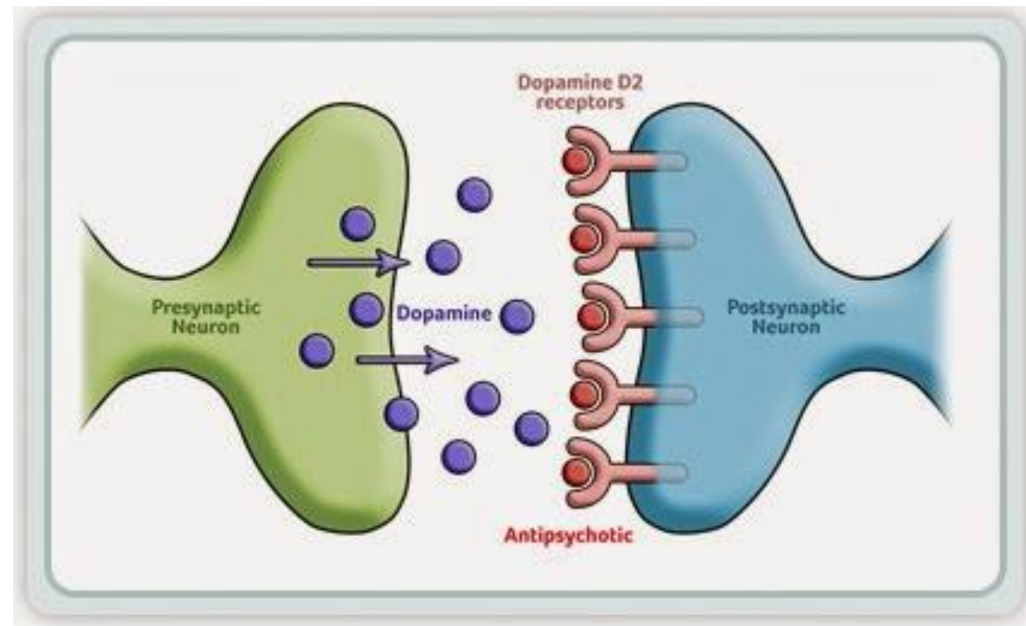
First-Generation (Typical)
Haloperidol
Droperidol
Chlorpromazine

What are antipsychotics?

Second-Generation (Atypicals)
Quetiapine
Ziprasidone
Clozapine
Aripiprazole
Olanzapine
Risperidone
Lurasidone

How do antipsychotics work?

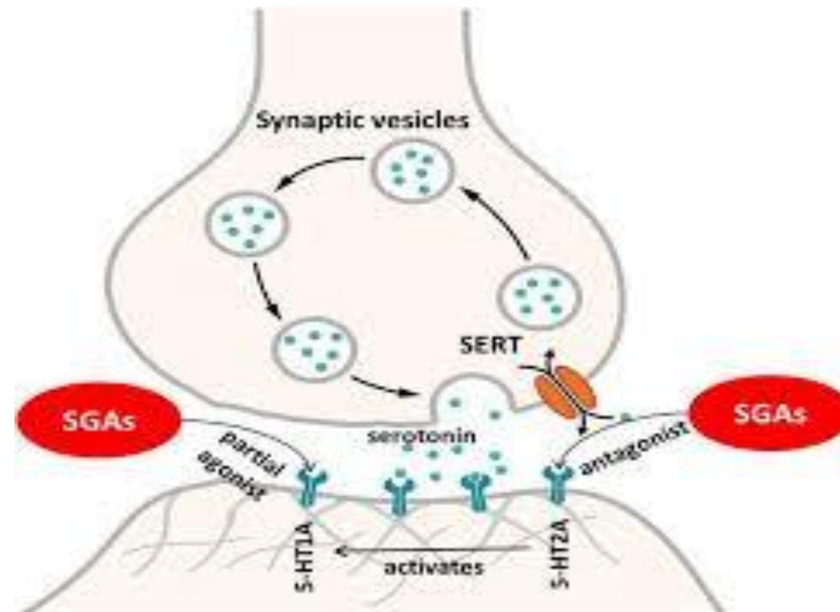
- First generation: high affinity for dopamine (D2) receptors
  - Developed in 1950s
  - First developed for treatment of psychosis(schizophrenia)
  - Haldol most studied in ICU setting



Source: Image Accessed at April 14, 2026 at [1.3 NEUROLEPTICS – English 301 99C Technical Writing]
Abou-Setta AM, Mousavi SS, Spooner C, et al. First-Generation Versus Second-Generation Antipsychotics in Adults: Comparative Effectiveness [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 Aug. (Comparative Effectiveness Reviews, No. 63.) Introduction. Available from: https://www.ncbi.nlm.nih.gov/books/NBK107237/

How do antipsychotics work?

- Second generation: serotonin receptor antagonists (5HT2a)
  - Developed in 1980s
  - Treat variety of psychiatric conditions



Source: Image Accessed at April 14, 2026 at Mechanisms of serotonin syndrome. Depiction of the actions of the... | Download Scientific Diagram

Abou-Setta AM, Mousavi SS, Spooner C, et al. First-Generation Versus Second-Generation Antipsychotics in Adults: Comparative Effectiveness [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 Aug. (Comparative Effectiveness Reviews, No. 63.) Introduction. Available from: https://www.ncbi.nlm.nih.gov/books/NBK107237/

Side Effect Profile

QTC prolongation

First generation are more likely to produce EPS

- More potent inhibition of D2 receptors

Anticholinergic effects

Sedative effects

Source: Shafiekhani M, Mirjalili M, Vazin A. Psychotropic drug therapy in patients in the intensive care unit - usage, adverse effects, and drug interactions: a review. *Ther Clin Risk Manag*. 2018;14:1799-1812. Published 2018 Sep 28. doi:10.2147/TCRM.S176079

Clinical Application Question #2

Which monitoring parameter is most critical when initiating antipsychotic therapy in the ICU?

A. Glucose

B. QTC interval

C. Renal function

D. WBC

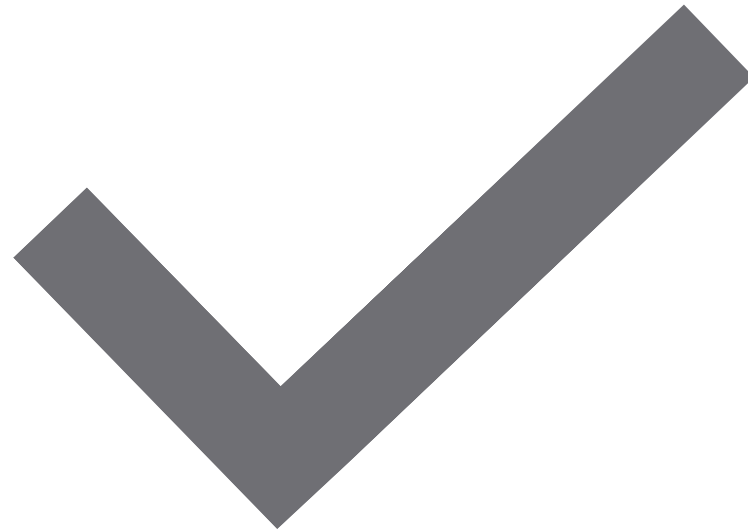
Clinical Application Question #2

Which monitoring parameter is most critical when initiating antipsychotic therapy in the ICU?

A. Glucose
B. QTC interval
C. Renal function
D. WBC

Comparative Considerations

- Non-pharmacological is first-line treatment
- No strong evidence one agent improves delirium duration
- Many factors contribute to selection agent
  - Route available
  - Side effect profile
  - Patient specific factors



Source: Farkas, Josh. (2022, July 18). Antipsychotic use in acute care. *EMCrit Project IBCC*.https://emcrit.org/ibcc/dirium/

Routes of Administration

IV	IM	PO
Haloperidol	Haloperidol	Haloperidol
Olanzapine	Olanzapine	Olanzapine
Droperidol	Ziprasidone	Ziprasidone
		Quetiapine

Dosing Strategies

Avoid prolonged therapy

Metabolism/Drug-Drug Interactions

- Primarily hepatically metabolized
  - CYP3A4
  - CYP2D6
  - CYP1A2
- Antipsychotics block sodium and potassium
  - Affect cardiac conductivity

Source: Image Accessed on April 14, 2026 at The Liver – Your Body's Greatest Multitasker | El Camino Health

Patient Specific Factor Considerations

- Liver Injury: Cirrhosis, Hepatitis
  - Cautious of accumulation

Lowest Risk	Highest Risk
Aripiprazole	Chlorpromazine
Ziprasidone	Olanzapine
	Clozapine

Source: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Antipsychotic Agents. [Updated 2023 Jun 10]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548317/

Patient Specific Factor Considerations

- Elderly population
  - Major anticholinergic effects
  - Cerebrovascular adverse events
- Prior treatment response/psych history
- Current home medications
- Comorbidity conditions:
  - Diabetes—weight gain consideration
  - Pre-existing heart conditions—arrythmias, QTC prolongation
  - Parkinson's

Source: Robyn Pauline Thom, MD, Clare Kelleher Mock, MD and Polina Teslyar, MD. Cleveland Clinic Journal of Medicine August 2017, 84 (8) 616-622; DOI: https://doi.org/10.3949/ccjm.84a.16077

MIND-USA Trial

- Published in 2018
- Clinical question: Does administration of the antipsychotic medications haloperidol or ziprasidone improve the number of days alive without delirium or coma when compared to placebo?
  - Critically ill patients with hypoactive or hyperactive delirium
- Interventions
  - Haloperidol IV 1.25mg or 2.5mg q12h prn x14d or until discharged from ICU
  - Ziprasidone IV 2.5mg or 5mg q12h prn x14d or until discharged from ICU
  - Placebo

MIND-USA Trial Results/Conclusions

- Administration of the antipsychotic medications haloperidol or ziprasidone did not improve the number of days alive without delirium or coma
- Major discussion points:
  - High proportion with hypoactive delirium (90%) may have been less likely to benefit from antipsychotic medications compared to hyperactive delirium
  - Use of ziprasidone is not as widespread

AID-ICU Trial

- Published in 2022
- Clinical question: Does scheduled and as needed intravenous haloperidol as compared to placebo affect the number of days alive and out of the hospital?
- Interventions:
  - Haloperidol 2.5mg IV TID + prn 2.5mg IV up to max 20mg daily
  - Placebo—matched both scheduled and prn

AID-ICU Trial Results/Conclusions

- In patients with hyperactive or hypoactive delirium, scheduled + PRN haloperidol did not lead to greater number of days alive and out of hospital at 90 days
- Haloperidol was associated with lower all-cause mortality
- Major discussion points:
  - Underreporting of medical comorbidities including other pharmacological medications
  - Might have underrecruited individuals with hypoactive delirium as individuals

Current Guideline Recommendations

No published evidence that treatment with haloperidol reduces duration of delirium in adult ICU patients

Atypical antipsychotics may reduce the duration of delirium in adult ICU patents (low/very low recommendation)

Antipsychotics do not appear to be effective in the treatment of hypoactive delirium

Not appropriate for routine sleep promotion

Source: Page VJ, Casarin A. Use of antipsychotics for the treatment of intensive care unit delirium. *Rev Bras Ter Intensiva*. 2014;26(2):86-88. doi:10.5935/0103-507x.20140016Page VJ, Casarin A. Use of antipsychotics for the treatment of intensive care unit delirium. *Rev Bras Ter Intensiva*. 2014;26(2):86-88. doi:10.5935/0103-507x.20140016

Current Guideline Recommendations

Appropriate for hyperactive delirium with dangerous agitation

Appropriate if failure of non-pharmacologic measures

Current Guideline Recommendations:
Society of Critical Care Medicine

We are unable to issue a recommendation for or against the use of antipsychotics over usual care for the treatment of delirium in adult patients admitted to the ICU.
Certainty of evidence: Low

Conditional For **Delirium** **Antipsychotics**

Source: Lewis K, Balas MC, Stollings JL, et al. *A focused update to the clinical practice guidelines for the prevention and management of pain, anxiety, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med.* 2025 Mar;53(3):e711-e727.

Clinical Application Question #3

According to the critical care guidelines, which of the following is the recommended first-line strategy for managing ICU delirium?

A. First-generation antipsychotic
B. Second-generation antipsychotic
C. Non-pharmacologic management
D. Benzodiazepines

Clinical Application Question #3

According to the critical care guidelines, which of the following is the recommended first-line strategy for managing ICU delirium?

A. First-generation antipsychotic

B. Second-generation antipsychotic

C. Non-pharmacologic management

D. Benzodiazepines

Consequences of Antipsychotic Use

- Antipsychotics do not fix the delirium but manage symptoms
- Important to differentiating delirium vs anxiety
- Continued use on transition (including discharge from hospital)

Source: Farkas, Josh. (2022, July 18). Antipsychotic use in acute care. *EMCrit Project IBCC*.https://emcrit.org/ibcc/dirium/

Key Takeaways

- Understanding patient specific factors should be driving therapy selection for delirium
- Antipsychotics are classified by generation and differentiate by mechanism of action and side effect profile
- Antipsychotics are noneffective in hypoactive delirium
- Choosing dosing strategy is patient specific and multifactorial
- Antipsychotics should not be used for sleep promotion

References

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Thank you!!

Gabriella Young, PharmD
PGY1 Pharmacy Resident
Gabriella.Young@hcahealthcare.com