

Delirium and complications of antipsychotics

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Clinical case

- 82-year-old woman who comes to the office with her daughter.
- "My mother has been acting strangely"
 - Especially confused at night
 - Struggles to stay awake in the daytime
 - Two nights ago I gave her Tylenol PM to help her sleep

She has not been as sharp over the past several years either.

Clinical case

- Past medical history
 - Hypertension
 - Hyperlipidemia
 - Atrial fibrillation
 - Stroke with minimal residual weakness
 - CKD
 - Diabetes mellitus type II

Clinical case

- Social history
 - Used to smoke cigarettes long time ago
 - Drinks one glass of wine most days of the week

Clinical case

- Medications
 - metoprolol, 50 mg twice daily
 - aspirin, 81 mg daily
 - rosuvastatin, 20 mg daily
 - escitalopram, 10 mg daily
 - metformin, 500 mg twice daily
 - glipizide, 5 mg daily

Clinical case

- Physical exam
 - Vital signs: within normal limits
 - General: Well-nourished, well dressed, makes fleeting eye contact
 - Skin: actinic keratosis lesions on backs of hands
 - HEENT: Oral mucosa moist, PERRL, EOMI, mild hearing loss, patient wears glasses, ear canals clear with normal appearing tympanic membranes
 - Heart: S1 and S2 normal, II/VI holosystolic murmur at apex, no peripheral edema, peripheral pulses 2+ bilaterally

Clinical case

- Physical exam
 - Lungs: Clear to auscultation; respirations unlabored
 - Abdomen: Soft, no tenderness to palpation, no palpable organomegaly.
 - Nervous system: AAO to self and place, residual mild left sided hemiparesis; weakness greater in left upper extremity than left lower extremity.

What is causing the acute confusional state in this patient?

- A. Dementia
- B. Change of environment
- C. Cognitive impairment as part of alcohol withdrawal
- D. Delirium from multifactorial causes, such as over-the-counter medications and undetected infection

What is delirium?

- Delirium is an acute confusional state that is extremely common among hospitalized elders and is strongly associated with poor short-term and long-term outcomes.
- Delirium can be thought of as acute brain failure and is the final common pathway of multiple mechanisms, similar to acute heart failure.
- Delirium is frequently not recognized, evaluated, or managed appropriately.

What is delirium?

- **Onset is acute** and condition lasts hours to days.
- Reduced clarity in the **patient's awareness** of the environment, with **impaired ability to focus, sustain, or shift attention**. The patient may be agitated, irritable, and emotionally labile or drowsy, quiet, and withdrawn.
- **Consciousness level fluctuates** over the course of the day.
- Delirium **cannot be explained by a patient's preexisting, established, or evolving dementia**.
- Delirium is conceptualized as a reversible illness, except in the last 24 to 48 hours of life.

Differential diagnosis

- Dementia, depression, and acute psychiatric syndromes (mania) should all be considered in the differential diagnoses for delirium.
- These syndromes often co-occur, patients may have more than one.
- In the absence of clear documentation from medical records or reports from family members that the patient's mental status is consistent with his or her baseline, it is always safest to assume delirium.
- Reports of an acute change in mental status, witnessed fluctuations over a period of minutes to hours, or an abnormal level of consciousness fulfill CAM criteria and make delirium more likely.

Delirium prevalence

- 1/3 of general medical patients who are 70 years of age or older have delirium.
- Delirium is the most common surgical complication among older adults, with an incidence of 15-25% after major elective surgery and 50% after high-risk procedures such as hip-fracture repair and cardiac surgery.
- Among patients undergoing mechanical ventilation in ICU, the cumulative incidence of delirium, when combined with stupor and coma, exceeds 75%.
- Delirium is present in 10-15% of older adults in ED.
- The prevalence of delirium at the end of life approaches 85% in palliative care settings.

Delirium

- Although many clinicians think of patients with delirium as being agitated, hyperactive delirium represents only 25% of cases, with the others having hypoactive (“quiet”) delirium.
- Hypoactive delirium is associated with a poorer prognosis, potentially because it is less frequently recognized.

Delirium = Predisposing + Precipitating

- The risk of delirium can be assessed according to the presence of predisposing (baseline) and precipitating (acute) factors.
- The more predisposing factors that are present, the fewer precipitating factors that are required to cause delirium.

Predisposing factors

- Older age
- Dementia (often not recognized clinically)
- Functional disabilities
- Male sex
- Poor vision and hearing
- Depressive symptoms
- Mild cognitive impairment
- Alcohol abuse

Precipitating factors

- Drugs (especially sedative hypnotic agents and anticholinergic agents)
- Surgery/anesthesia
- High pain levels
- Anemia
- Infections
- Acute illness, or acute exacerbation of chronic illness
- Restraints could be an etiologic factor or a proxy for severity

Which of the following tests would you perform to test her cognitive function?

- A. Mini-Mental State Examination (MMSE)
- B. Confusion Assessment Method (CAM)
- C. Clock-Drawing Test
- D. Mini-Cog

Delirium in Hospitalized Older Adults

- The first step in delirium management is accurate diagnosis; a brief validated instrument that assesses features in the Confusion Assessment Method algorithm is recommended.
- After receiving a diagnosis of delirium, patients require a thorough evaluation for reversible causes; all correctable contributing factors should be addressed.

CAM diagnostic

- Only 12 to 35% of delirium cases are recognized.
- Systematic reviews support the Confusion Assessment Method (CAM) as the most useful bedside assessment tool.
- The CAM algorithm establishes the diagnosis of delirium according to the presence or absence of four features: an acute change in mental status with a fluctuating course, inattention, and either disorganized thinking or an altered level of consciousness.

3D-CAM

- 3D-CAM question: Does patient have acute onset and fluctuating course?
 - During the past day have you felt confused? During the past day did you think that you were not really in the hospital? During the past day did you see things that were not really there?
- 3D-CAM test of disorganized thinking
 - Can you tell me the year we are in right now? Can you tell me the day of the week? Can you tell me what type of place is this?

3D-CAM

- 3D-CAM question: Does patient have inattention?
 - I am going to read some numbers. I want you to repeat them in backwards order from the way I read them to you. For instance, if I say "5-2-3," you would say "3-2-5." Okay?
 - Can you tell me the days of the week backwards, starting with Saturday? Can you tell me the months of the year backwards, starting with December?
- 3D-CAM question: Does patient have altered level of consciousness? Was the patient's speech unusually sparse or limited (such as yes/no answers)?

Feature and Assessment

1. Acute onset and fluctuating course

Fluctuation in level of consciousness
Fluctuation in attention during interview
Fluctuation in speech or thinking

AND

2. Inattention

Did the patient have trouble keeping track of what was being said during the interview?
Did the patient appear inappropriately distracted by environmental stimuli?

AND EITHER

3. Disorganized thinking
>2 errors

Was the patient's flow of ideas unclear or illogical; for example, did he/she tell a story unrelated to the interview (tangential)?
Was the patient's conversation rambling; for example, did he/she give inappropriately verbose and off-target responses?
Was the patient's speech unusually limited or sparse (such as yes/no answers)?

OR

4. Altered level of consciousness

Was the patient's speech unusually limited or sparse (such as yes/no answers)?

3D-CAM for our patient

- Disorganized thinking
- Not oriented to time or place
- Has inattention, with inability to say the months of the years backwards

Given that our patient's symptoms were of acute onset and had a fluctuating course and included both inattention and disorganized thinking, she meets criteria for the diagnosis of delirium.

DELIRIUM

- **D:** Drugs (opioids, anticholinergics, sedatives, steroids, benzodiazepines, chemotherapy and immunotherapies, some antibiotics)
- **E:** Eyes and ears (poor vision and hearing, isolation)
- **L:** Low flow states (hypoxia, MI, HF, COPD, shock)
- **I:** Infections
- **R:** Retention (urine/stool), restraints
- **I:** Intracranial (CNS metastases, seizures, subdural, CVA, hypertensive encephalopathy)
- **U:** Underhydration, undernutrition, undersleep
- **M:** Metabolic disorders (sodium, glucose, thyroid, hepatic, deficiencies of vitamin B12, folate, niacin, and thiamine) and toxic (lead, manganese, mercury, alcohol)

Evaluation

- Other symptoms (e.g., dyspnea and dysuria), focal weakness
- A thorough medication review is required for all patients with delirium
- Consumption of alcohol and the use of nonprescription drugs, dietary supplements.

Evaluation

- Tests that are routinely required include a CBC and BMP.
- A urinalysis, urine culture, liver-function tests, chest radiography, and EKG are also often helpful.
- Additional tests that are useful in select situations include blood and urine toxicology studies, blood cultures, ABG (if hypercapnia is suspected), cerebral imaging (in patients with head trauma or new focal neurologic findings), LP (if findings suggest meningitis or encephalitis), and EEG (if seizures are suspected).

Lab data for our patient

- CBC – unremarkable
- BMP – unremarkable other than glucose: 125 mg/dL
- TSH – 2.5 mU/L (0.5 to 5 mU/L)
- UA Leukocyte esterase: trace; hematuria: 1+; pH: 5.0; nitrites: positive
- Vitamin B12 – 640 pg/mL (200 to 800 pg/mL)

What is the next best step to further diagnose our patient's delirium?

Suspecting that the patient has a urinary tract infection, you order a urine culture.

- A. CT head
- B. LFT and ammonia levels
- C. Start empiric antibiotics
- D. Refer to a neurologist

Follow-up

The patient begins taking the empiric antibiotic therapy.

The urine culture reveals greater than 100,000 colonies and shows that the bacteria is sensitive to the prescribed antibiotic.

She completes a 3-day course.

In about a week, patient's condition has improved and she is sleeping through most of the night.

Delirium post discharge

The classic teaching is that delirium is transient; however, a growing literature shows that this is not always true.

A systematic review showed that incident hospital delirium persisted

- at hospital discharge in 45% of cases
- 1 month later in 33% of cases

Risk factors for the persistence of delirium include advanced age, preexisting dementia, multiple coexisting conditions, delirium severity, and the use of physical restraints.

Six months later...

The patient is admitted to the hospital with shortness of breath and cough.

In the emergency department she is found to have a temperature of 39°C.

Physical exam and data

RR of 24 breaths/min, HR of 100 beats/min

Rhonchorous breath sounds on the left side

She is disoriented to time and place, and, per her nurse, she has been trying to get out of bed and has not been keeping her oxygen nasal cannula on.

You also notice that she doesn't have her prescription glasses on.

Data

Chest radiography: Infiltrate in left lower lobe

CBC is significant for WBC of 14,000

BMP is significant for glucose of 130

Urinalysis: Leukocyte esterase: trace; hematuria: negative; pH: 5.0; nitrites: negative

Nursing concern

The nurse feels frustrated and is wondering whether applying restraints might help to keep her from falling and prevent her from pulling at her oxygen cannula.

- A. Order restraints and reevaluate her in 24 hours
- B. Recommend nonpharmacologic treatments
- C. Consult neurology
- D. Order floor mattress pads to decrease injury in the event of a fall

Recommendations

- Check the patient for urinary retention and fecal impaction, as these conditions can cause delirium.
- Ask the nurse to make sure that your patient has her glasses on and to provide clocks, calendars, and adequate lighting during the day.
- You also ask the nurse to provide frequent orientation, turn off televisions at night, reduce noise around her room, and decrease bright lights at night.

Follow-up

- The patient's condition slowly improves over the course of the next day.
- The nurse's aide helps her ambulate in the hallway and also provides frequent reorientation and day/night cuing.
- The patient's daughter also visits her and encourages her to eat her breakfast and lunch.

Recommendations

- Commonly ordered treatments in patients with delirium are not always sufficient or effective.
- Restraints can lead to unintended injury and have not been shown to shorten the course of delirium.
- Fall precautions, while important for safety reasons, do not help evaluate or treat the underlying delirium.
- Consultations to specialists can add expense due to unnecessary testing.

Follow-up

During the course of the evening, the patient becomes more agitated, restless, and combative. The float nurse calls the night physician and asks for medication to help the patient to sleep.

What should the night physician order?

- A. Intravenous diazepam
- B. Intravenous diphenhydramine
- C. Intravenous haloperidol
- D. Intravenous meperidine

Recommendations

- You prescribe IV haloperidol, 0.5 mg every 4 hours as needed for agitation.
- After the patient is prescribed haloperidol for delirium, her condition slowly improves.
- She becomes less agitated and sleeps at night. She still requires attention from staff during the day to help her with meals and to keep her stimulated and awake.

Recommendations - benzodiazepines

Benzodiazepines, both long-acting (such as diazepam) and ultra-short-acting (such as midazolam) are not optimal agents in attempts to induce sedation.

- causing excessive daytime sedation
- not providing sustained sleep, and thereby potentially worsening sleep
- potentially worsening delirium.

Thus, if nonpharmacologic sleep management is not adequate, use of an intermediate-acting medication, such as lorazepam, is preferred.

Lorazepam is recommended as a first-line agent only for alcohol and sedative withdrawal and in patients with a history neuroleptic malignant syndrome.

Recommendations

When considering starting new psychoactive medications in delirium, the following points should be kept in mind:

- Antidepressants, antihistamines, bladder antispasmodics, opioid analgesics (such as mepiridine), and low-potency antipsychotic medications have anticholinergic toxicity and therefore should be avoided in patients with delirium.
- Anticholinergic activity is associated with worsening delirium.

Recommendations

- For the pharmacologic treatment of agitated delirium, antipsychotic agents are recommended (Class B recommendation).
- While antipsychotic agents are not FDA–approved for this indication, these agents are commonly prescribed. In small trials, haloperidol, olanzapine, quetiapine, and risperidone were effective in reducing agitation.
- As a first-line agent, haloperidol ordered as needed is recommended.
- However, if there is concern that the patient may not receive it when ordered as needed, then haloperidol should be scheduled at a starting dose of 0.5 mg 3 to 4 times daily.
- An atypical antipsychotic agent, such as risperidone, can be used as an alternative.
- For hypoactive delirium, in which delirium may not be recognized, scheduled dosing is recommended.

Follow-up

- You consult physical therapy to assess her strength and ability to ambulate safely.
- Physical therapy recommends a short stay in a rehabilitation facility.

Follow-up

- At the skilled nursing facility, the rehabilitation medicine physician evaluates our patient's activities of daily living and her needs for physical therapy.
- The physician also discontinues her antipsychotic medications and lorazepam.
- During the first week, your patient seems to be making slow improvement.
- In the second week, she starts refusing to participate in physical therapy and prefers to sleep in bed all morning.

Follow-up

What is the next best step in managing your patient's behavioral change?

- A. Discharge her from skilled nursing and admit her to long-term care.
- B. Arrange for admission to hospice for failure to thrive.
- C. Increase the escitalopram dose from 10 to 20 mg daily.
- D. Evaluate for hypoactive delirium.
- E. Prescribe donepezil, 5 mg daily.

Lab data

CBC is unremarkable

BMP is significant for creatinine of 2.5 and glucose of 125

UA - leukocyte esterase: trace; hematuria: negative; pH: 5.0; nitrites: negative

Follow-up

The patient is admitted for dehydration and acute-on-chronic renal insufficiency.

She receives IV fluids, and physical therapy is continued in the hospital.

After a 3-day stay, her condition improves. Trazodone, 25 mg at night, is prescribed and is effective in helping her with sleep. She is discharged to the skilled nursing facility with instructions to monitor her closely for signs of dehydration.

Follow-up

She requires a 3-week stay at the skilled nursing facility, during which she recovers her activities of daily living. Upon discharge home, she still uses a walker, but on a follow-up visit, the daughter notes that she is more stable and has tried walking with the assistance of her daughter at home.

Table 5. Pharmacologic Therapy of Agitated Delirium.*

Agent	Drug Class	Dosing†	Routes	Degree of Sedation	Risk of EPS	Adverse Effects	Comments
Haloperidol	Typical anti-psychotic	Initial: 0.25–0.5 mg Maximum: 3 mg	Oral, IM, or IV	Low	High	Risk of EPS increases if daily dose exceeds 3 mg	Longest track record in delirium; several large trials are ongoing
Risperidone	Atypical anti-psychotic	Initial: 0.25–0.5 mg Maximum: 3 mg	Oral or IM	Low	High	Slightly less risk of EPS than with haloperidol at low doses	Small trials; considered to be very similar to haloperidol
Olanzapine	Atypical anti-psychotic	Initial: 2.5–5 mg Maximum: 20 mg	Oral, sublingual, or IM	Moderate	Moderate	More sedating than haloperidol	Small trials; oral route is less effective than other routes for management of acute symptoms
Quetiapine	Atypical anti-psychotic	Initial: 12.5–25 mg Maximum: 50 mg	Oral	High	Low	Much more sedating than haloperidol; risk of hypotension	Small trials; can be used, with caution, in patients who have parkinsonism
Ziprasidone	Atypical anti-psychotic	Initial: 5–10 mg Maximum: 40 mg	Oral or IM	Moderate	Moderate	More sedating than haloperidol; risk of cardiac arrhythmia, heart failure, and agranulocytosis	Owing to risks, used primarily in ICU; large trial is ongoing
Lorazepam	Benzodiazepine	Initial: 0.25–0.5 mg Maximum: 2 mg	Oral, IM, or IV	Very high	None	More paradoxical excitation and respiratory depression than with haloperidol	Second-line agent; use in sedative and alcohol withdrawal or if patient has a history of the neuroleptic malignant syndrome

* Use of all these drugs for delirium is off-label in the United States. Atypical antipsychotic agents have been tested primarily in small noninferiority trials with haloperidol and recently in small placebo-controlled trials in the intensive care unit (ICU). The Food and Drug Administration (FDA) requires a “black box” warning for all atypical antipsychotics because of increased risks of cerebrovascular events (e.g., stroke) and death among patients with dementia. Typical antipsychotic agents have an FDA “black box” warning because of an increased risk of death among patients with dementia. EPS denotes extrapyramidal symptoms, IM intramuscular, and IV intravenous.

† The doses recommended in this table are for older adults. “Initial” represents the initial dose for an acutely agitated older patient; the dose may need to be repeated. “Maximum” represents the maximum recommended cumulative daily dose — that is, the sum of all as-needed and scheduled doses over a period of 24 hours. Somewhat higher doses may be used in younger patients if the side-effect profile is acceptable.

Table 4. High-Risk Drugs in Delirium and Potential Substitutes.*

Drug	Mechanism of Adverse Effect	Substitutes or Alternative Strategies	Comments
Benzodiazepines	CNS sedation and withdrawal	Nonpharmacologic sleep protocol ³⁶	Associated with delirium in hospitalized patients; if patient is already taking, maintain or lower dose, but do not discontinue abruptly
Opioid analgesics (especially meperidine)	Anticholinergic toxicity, CNS sedation, and fecal impaction	Local and regional analgesic measures; non-psychoactive pain medications (e.g., acetaminophen and NSAIDs) around the clock; reserve opioids for breakthrough and severe pain	Consider risks versus benefits, since uncontrolled pain can also cause delirium; patients with renal insufficiency are at elevated risk for adverse effects; naloxone can be used for severe overdoses
Nonbenzodiazepine sedative hypnotics (e.g., zolpidem)	CNS sedation and withdrawal	Nonpharmacologic sleep protocol ³⁶	Like other sedatives, these agents can cause delirium
Antihistamines, especially first-generation sedating agents (e.g., doxylamine and diphenhydramine)	Anticholinergic toxicity	Nonpharmacologic sleep protocol, ³⁶ pseudoephedrine for upper respiratory congestion, and nonsedating antihistamines for allergies	Patients should be asked about the use of over-the-counter medications; many patients do not realize that drugs with names ending in “PM” contain diphenhydramine or other sedating antihistamines
Alcohol	CNS sedation and withdrawal	If patient has a history of heavy intake, monitor closely and use benzodiazepines for withdrawal symptoms	The history taking must include questions about alcohol intake
Anticholinergics (e.g., oxybutynin and benztropine)	Anticholinergic toxicity	Lower the dose or use behavioral approaches for urinary incontinence (e.g., scheduled toileting)	Delirium is unusual at low doses
Anticonvulsants (e.g., primidone, phenobarbital, and phenytoin)	CNS sedation	Use an alternative agent or consider stopping if patient is at low risk for seizures and has no recent history of them	Delirium can occur despite therapeutic drug concentrations
Tricyclic antidepressants, especially tertiary amines (e.g., amitriptyline, imipramine, and doxepin)	Anticholinergic toxicity	Serotonin-reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and secondary amine tricyclics (e.g., nortriptyline and desipramine)	Newer agents (e.g., duloxetine) are as effective as tertiary amines for adjuvant treatment of chronic pain
Histamine H ₂ -receptor blockers	Anticholinergic toxicity	Lower the dose or substitute antacids or proton-pump inhibitors	Anticholinergic toxic effects occur primarily with high-dose intravenous infusions
Antiparkinsonian agents (e.g., levodopa and amantadine)	Dopaminergic toxicity	Lower the dose or adjust dosing schedule	Dopaminergic toxic effects occur primarily in advanced disease and at high doses
Antipsychotics, especially low-potency typical antipsychotics (e.g., chlorpromazine and thioridazine)	Anticholinergic toxicity as well as CNS sedation	Discontinue entirely or, if necessary, use low doses of high-potency agents	Carefully consider risks vs. benefits of use in delirium
Barbiturates	CNS sedation and severe withdrawal syndrome	Gradual discontinuation or benzodiazepine substitution	In most cases, barbiturates should not be prescribed; avoid inadvertent or abrupt discontinuation

* In older adults, the risks and benefits of all medications should be considered carefully. Adverse effects should be monitored whenever any medication is started or the dose is adjusted. CNS denotes central nervous system, and NSAIDs nonsteroidal antiinflammatory drugs.

Take-home points

- Assess risk factors for delirium when patients are admitted to the hospital.
- Prevent delirium by addressing risk factors using a multicomponent intervention.
- Screen for incident delirium by assessing recent changes or fluctuations in cognitive function, perception, physical function, and social behavior on admission and at least daily thereafter.

Take-home points

- Diagnose delirium by carrying out a clinical assessment based on formal criteria conducted by a trained health care professional; document the results of the assessment in the medical record.

Take-home points

- Manage delirium by the following:
 - Identifying and managing possible underlying causes
 - Ensuring effective communication, reorientation, and providing reassurance
 - Considering the involvement of family, friends, and caregivers
 - Providing care in a suitable environment

Take-home points

- If patients with delirium are distressed or are a risk to themselves or others:
 - Use verbal and nonverbal deescalation techniques, such as quietly sitting at the bedside and engaging the patient in conversation or playing relaxing music.
 - If these are not effective or are inappropriate, consider short-term antipsychotic medication at the lowest clinically appropriate dose and titrate cautiously according to symptoms.

Take-home points

- If patients with delirium are distressed or are a risk to themselves or others:
 - If needed for insomnia, nonpharmacologic sleep management or use of an intermediate-acting medication, such as lorazepam, is preferred.
 - Avoid drugs with anticholinergic activity. Anticholinergic activity is associated with worsening delirium.
 - For hypoactive delirium, especially where agitation is not overt and delirium may not be recognized, scheduled dosing is recommended.

THANK YOU

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