

Depression or delirium?

Juan Carlos Cleves-Bayon, MD, Kirsten M. Wilkins, MD, and Rajesh R. Tampi, MBBS

Confused and depressed, Mr. L, age 85, is admitted after threatening his wife. He has several medical conditions and receives multiple medications. What could be causing his mental status changes?



How would you handle this case?

Visit CurrentPsychiatry.com to input your answers and see how your colleagues responded

CASE Agitated and paranoid

Police bring Mr. L, age 85, to the emergency department (ED) because he threatened his wife, claiming she is having an affair. Two days earlier, he was discharged from a different hospital, where he was treated for progressive and fluctuating irritability, depressed mood, confusion, disorientation, inattention, and delusional thinking that had started 4 to 5 months earlier. He has no other psychiatric history.

Mr. L has a history of atrial fibrillation, hypertension, benign prostatic hypertrophy, and noninsulin-dependent diabetes mellitus. Several months ago, he had hip surgery, which was complicated by a surgical wound infection. Medications include digoxin, 0.125 mg/d; atenolol, 100 mg/d; warfarin, 1 mg/d on Monday, Wednesday, Friday, Saturday, and Sunday and 0.5 mg/d Tuesday and Thursday; lisinopril, 40 mg/d; tamsulosin, 0.4 mg/d; and glyburide, 1.25 mg/d. During the previous hospitalization, physicians discovered he had myasthenia gravis, which they treated with prednisone and pyridostigmine. Mr. L also was diagnosed with hyperaldosteronism. An adrenal mass was found in an abdominal CT. At that time, he also was diagnosed with major depressive disorder (MDD) with psychotic features and started on aripiprazole, 10 mg/d, mirtazapine, 30 mg/d, and trazodone, 50 mg/d for sleep.

Which diagnosis would you include in the differential?

- a) psychotic disorder due to a general medical condition
- b) delirium
- c) dementia
- d) all of the above

The authors' observations

When evaluating mental status changes in older patients, consider the time course and characteristics of the changes, especially if the patient's cognitive function changes. Acute mental status changes that occur over hours to days often represent delirium caused by a medical condition such as a coronary event or infection. Changes that develop over weeks to months often signal a primary psychiatric disorder such as depression, mania, or dementia. Mr. L's mood and psychotic symptoms developed over 4 to 5 months and were thought to be a result of MDD with psychotic features. However, his fluctuating cognitive symptoms, confusion, and lack of psychiatric history suggest that the differential diagnosis should include a cognitive disorder

Dr. Cleves-Bayon is a Geriatric Psychiatry Fellow, Department of Psychiatry, Yale School of Medicine, New Haven, CT. Dr. Wilkins is Assistant Professor, Department of Psychiatry, University of Oklahoma College of Medicine-Tulsa. Dr. Tampi is Associate Clinical Professor, Department of Psychiatry, Yale School of Medicine, New Haven, CT.

such as delirium or dementia. The hypoactive form of delirium often is unrecognized or misdiagnosed as sedation or depression, particularly in older patients.¹

Multiple medical conditions and polypharmacy are important factors to consider when evaluating mental status changes in geriatric patients. In Mr. L's case, atrial fibrillation, hypertension, and diabetes increase his risk of an acute cardiovascular or cerebrovascular event and chronic cerebrovascular disease. Hyperaldosteronism can lead to electrolyte abnormalities that may produce mental status changes. Treatment with an oral hypoglycemic raises the possibility that hypoglycemia is contributing to his mental status changes. Prednisone can cause psychosis, anxiety, and mania. Digoxin toxicity is associated with psychosis and irritability. Pyridostigmine also has been reported to cause psychosis. Use of an antidepressant, such as mirtazapine, could have exacerbated an underlying undiagnosed bipolar disorder. Antipsychotics, such as aripiprazole, may cause akathisia or activation. Substance intoxication or withdrawal should not be excluded solely because a patient is older. In older patients, medications with anticholinergic effects are common culprits for cognitive impairment (*Table 1*).^{2,3}

What is the best next step?

- continue aripiprazole and mirtazapine
- switch to a benzodiazepine
- switch to a selective serotonin reuptake inhibitor (SSRI)
- initiate electroconvulsive therapy
- complete your assessment, including history, physical examination, and laboratory workup

ASSESSMENT More problems

At admission to the medical unit, Mr. L's temperature is 36.7°C (98°F), with a heart rate of 77 beats per minute, respiratory rate of 24

Table 1

Medications that could contribute to mental status changes

Anticholinergics (atropine, benztropine, oxybutynin, some OTC medications)
Hypnotics/sedatives (benzodiazepines)
Opiate analgesics (meperidine)
Neuroleptics (clozapine, thioridazine, olanzapine)
Antiparkinsonian medications (levodopa, selegiline, pergolide, amantadine)
Antidepressants (amitriptyline)
Anticonvulsants (phenytoin)
Histamine H2 receptor antagonists (ranitidine, cimetidine, omeprazole)
Cardiac drugs (digoxin)
Nonsteroidal anti-inflammatory drugs (aspirin)
Corticosteroids (prednisolone)
Antibiotics (penicillins, cephalosporins, quinolones)
OTC: over the counter
Source: References 2,3

breaths per minute, and blood pressure of 164/84 mm Hg with oxygen saturation of 96% at room air. Physical exam is notable for 2+ pitting edema in the lower extremities. Mr. L is oriented to person, place, and time and is psychomotorically activated. Neurologic examination is within normal limits.

Laboratory data reveal a potassium level of 2.5 mEq/L. Other results, including complete blood count, comprehensive metabolic panel, thyroid-stimulating hormone, urinalysis, urine toxicology screen, B12, folate, venereal disease research laboratory, and ammonia are unremarkable. Chest radiography reveals an enlarged cardiomeastinum. A CT scan of the brain without contrast shows cortical volume loss and periventricular white matter disease without evidence of acute intracranial abnormality. ECG shows atrial fibrillation with a rate of 67 beats per minute.

Mr. L's hypokalemia is corrected with potassium chloride and his hyperaldosteronism is

Clinical Point

In older patients, medications with anticholinergic effects are common culprits for cognitive impairment

Clinical Point

Mental status changes caused by medical disorders or medications may not clear for days or weeks after the problem is corrected

Table 2

DSM-IV-TR criteria for delirium caused by a medical condition

A. Disturbance of consciousness (ie, reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention

B. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia

C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day

D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition

Source: Reference 4

treated with spironolactone, 25 mg/d. Physicians on the medical unit discontinue digoxin because Mr. L's heart rate is controlled with atenolol and he is anticoagulated with warfarin.

Mr. L continues to be depressed and irritable with delusional jealousy. Mirtazapine is continued at 30 mg/d at bedtime. Aripiprazole and trazodone are discontinued and Mr. L is started on olanzapine, 10 mg/d, and haloperidol, 1 mg 4 times a day as needed for agitation. He requires multiple "as needed" haloperidol doses because of intermittent episodes of agitation. Mr. L is then transferred to the inpatient psychiatric unit for continued evaluation and treatment.

Which medications would you use to treat Mr. L's psychiatric symptoms?

- continue olanzapine and trazodone
- continue haloperidol and trazodone
- continue haloperidol alone
- start risperidone
- start lorazepam

The authors' observations

The fact that Mr. L is alert and oriented is encouraging; however, it does not rule out

delirium because this condition is characterized by fluctuating levels of consciousness. Therefore, it is important to reassess him over time and perform a more thorough evaluation of cognitive function, especially attention and concentration, in addition to alertness and orientation. Psychomotor activation could suggest agitated depression, anxiety, mania, psychosis, substance intoxication, akathisia from antipsychotics, or delirium (Table 2).⁴ Initial evaluation—especially in older patients—should include a thorough history (including collateral sources) and be guided by the clinical presentation and physical examination, taking into consideration life-threatening conditions and common causes of mental status change such as infections, hypoxia, substance or medication effects, acute coronary syndromes, acute neurologic events, and metabolic conditions.

Reconsider the diagnosis

Even after being treated for hyperaldosteronism and discontinuing unnecessary medications, Mr. L continued to be treated for MDD with psychotic features despite intermittent confusion and agitation. At this point, it might have been useful to reconsider whether MDD with psychotic features was the most appropriate diagnosis to explain his mental status changes.

Mental status changes caused by medical disorders or medications do not immediately clear after the medical disorder is corrected or the medication is discontinued; it could take days or weeks for a patient to return to baseline. In Mr. L's case it may be useful to simplify his medication regimen because polypharmacy contributes to delirium. Finally, olanzapine could worsen his condition because of its anticholinergic effects.⁵

EVALUATION Poor cognitive status

Mental status examination upon admission to the psychiatric unit reveals a poorly coopera-

tive patient with irritable mood and affect with slowed psychomotor activity. Mr. L's thought process is organized with normal associations and thought content does not reveal suicidality or homicidality. However, he verbalizes delusions about his wife having an affair with a neighbor. He is partially oriented to time but believes he is in Germany. His insight is limited and he demonstrates impaired attention and concentration. We cannot complete a Mini-Mental State Exam (MMSE) because Mr. L does not cooperate.

After admission, Mr. L is intermittently confused, agitated, and disoriented. Between these episodes he is pleasant, cooperative, and oriented. Jealous delusions regarding his wife continue. Olanzapine and mirtazapine are tapered and discontinued. Haloperidol dose is changed to 1 mg 3 times a day, then to 1.5 mg in the morning and 3 mg in the evening. Prednisone is tapered and discontinued.

The authors' observations

Cognitive testing is essential for the diagnosis and treatment of patients with mental status changes and for evaluating their response to treatment. Although the MMSE is widely used, other scales—including the Confusion Assessment Method, the Organic Brain Syndrome Scale, the Memorial Delirium Assessment Scale, and the delirium severity index⁶—may be more sensitive for detecting delirium. All of these scales can be difficult to complete when evaluating confused and combative patients. Quick screening instruments for inattention, such as the digit span test and listing days of the week backwards, could be used as well.

HISTORY Surgical complications

Further questioning of Mr. L's family reveals that his behavior started to change 7 months

Clinical Point

Although the MMSE is widely used, other scales may be more sensitive for detecting delirium

Available Online Earn up to 1.5 Free CME credits

Schizophrenia e-newsletters from CURRENT PSYCHIATRY

Activity Chair: **Peter J. Weiden, MD**

Director, Psychotic Disorders Program, Center for Cognitive Medicine, Professor, Department of Psychiatry, University of Illinois at Chicago, Chicago, Illinois

- **Expanding the Treatment Paradigm in Patients With Schizophrenia: Beyond Psychotic Symptoms**
- **Long-Term Treatment of Schizophrenia: Minimizing Side Effect Burden to Improve Patient Outcomes**

These e-newsletters are sponsored by SciMed and supported by an educational grant from Merck. They are peer reviewed by *Current Psychiatry*.

The CME activities are part of a curriculum that includes the Virtual Patient Visits involving Jason. These interactive activities highlight the importance of patient-directed goals in managing patients attempting to achieve functional recovery from schizophrenia.

All activities are available at CurrentPsychiatry.com.
Click on [Supplements/CME](#).

Current
PSYCHIATRY

Clinical Point

Benzodiazepines should be avoided in older patients unless symptoms are secondary to CNS-depressant withdrawal

Table 3

Deconstructing delirium

Defining characteristics
Confusional state of fluctuating course
Acute or subacute onset
Inattention
Disorganized thinking
Alteration and fluctuation of level of consciousness
Other characteristics
Cognitive: Memory impairment, perseveration
Motor: Hyperactive, hypoactive, mixed
Psychiatric: Thought disorganization, mood changes, delusions, hallucinations
Etiologies*
Predisposing factors: Age, functional status (ie, immobility), nutritional status (ie, dehydration), sensory impairment, medical conditions, psychiatric conditions (ie, dementia, TBI), medications, illicit drugs
Precipitating factors: Acute neurologic conditions (ie, stroke), intercurrent illnesses (ie, infections, hypoxia, anemia), surgery, environmental factors (ie, ICU, restraints, pain), illicit drugs (alcohol withdrawal), medications (ie, polypharmacy, anticholinergics), sleep deprivation
*Usually >1 etiology
ICU: intensive care unit; TBI: traumatic brain injury
Source: References 4,7

ago; this was 1 month after undergoing hip replacement surgery, which was complicated by a surgical wound infection and worsened his medical illnesses. Within a month, Mr. L became withdrawn and appeared depressed. He was confused and intermittently disoriented to place and time. He became irritable and started reporting concerns about his wife having an affair. During this time different medications were introduced, including steroids and several antibiotics.

The authors' observations

A thorough history from the patient and caregivers, including the time course of mental status changes, new medication use, and history of medical and psychiat-

ric disorders—especially depression and dementia—are important to obtain, especially early in the evaluation.

Although Mr. L's irritability, delusions, and psychomotor slowing could be signs of psychotic depression, his fluctuating mental status, disorientation, poor attention, and impaired concentration suggest delirium (*Table 3*).^{4,7} This diagnosis is supported by the fact that Mr. L's symptoms emerged after orthopedic surgery. Delirium after orthopedic surgery is common among older patients.⁸ Contributing and perpetuating factors in Mr. L's case may have included postoperative complications, hypokalemia (hyperaldosteronism), medications (prednisone, digoxin, and olanzapine), and environmental unfamiliarity during hospitalization. A delirium diagnosis should be based on a high index of suspicion and a careful clinical assessment rather than diagnostic tests.

OUTCOME Return home

Mr. L's confusion and delusional jealousy decrease over time, as do his disorientation and inattention, as evidenced by improvement on MMSE scores. His last MMSE score is 27/30, failing mostly in attention and recall.

After sustained improvement in cognition and behavior, Mr. L is discharged home on haloperidol and the remainder of his nonpsychiatric medications with outpatient medical and psychiatric follow-up. Over several months, he continues to show improvement and haloperidol is discontinued.

The authors' observations

Delirium treatment should focus on prompt identification and management of precipitating and contributing factors.⁷ Antipsychotics are considered first-line treatment for patients with delirium, agitation, or psychosis who pose a risk to themselves or others. Benzodiazepines should be avoided in older patients unless symptoms are secondary to CNS-depressant withdrawal (ie, alcohol, benzodiazepines).⁹

Although there are no-FDA approved medications for delirium, haloperidol has been widely studied and used for treatment of agitation and psychosis in delirium. There is no evidence that low-dose haloperidol is any less effective than olanzapine or risperidone, or is more likely to cause adverse drug effects such as extrapyramidal syndrome.¹⁰ Antipsychotic use in a confused or agitated dementia patient increases risk of mortality compared with dementia patients who do not receive antipsychotics.¹¹ The use of typical or atypical antipsychotics for delirium should be guided by the patient's characteristics, such as cardiovascular status and presence or absence of underlying dementia. Atypical antipsychotics should be used carefully because—as in Mr. L's case—anticholinergic side effects of medications such as olanzapine could worsen delirium.⁵ Once delirium has resolved, antipsychotics should be tapered and discontinued.

Other components of delirium treatment and prevention include:

- reorientation (verbally, with clocks, calendars, etc.)
- safe ambulation
- adequate sleep, food, and fluid intake
- adaptive equipment for vision and hearing impairment
- adequate management of pain and other comorbidities.¹²

References

1. McAvay GJ, Van Ness PH, Bogardus ST Jr, et al. Depressive symptoms and the risk of incident delirium in older hospitalized adults. *J Am Geriatr Soc.* 2007; 55:684-691.
2. Mintzer J, Burns A. Anticholinergic side-effects of drugs in elderly people. *J R Soc Med.* 2000;93(9):457-462.
3. Moore AR, O'Keefe ST. Drug-induced cognitive impairment in the elderly. *Drugs Aging.* 1999;15(1):15-28.
4. Diagnostic and statistical manual of mental disorders.

Related Resources

- Khan RA, Kahn D, Bourgeois JA. Delirium: sifting through the confusion. *Curr Psychiatry Rep.* 2009;11(3):226-234.
- Maldonado JR. Delirium in the acute care setting: characteristics, diagnosis, and treatment. *Crit Care Clin.* 2008;24:657-722.
- Young J, Inouye SK. Delirium in older people. *BMJ.* 2007;334(7598):842-846.

Drug Brand Names

Amantadine • Symmetrel	Omeprazole • Prilosec
Amitriptyline • Elavil	Oxybutynin • Ditropan
Aripiprazole • Abilify	Pergolide • Permax
Atenolol • Tenormin	Phenytoin • Dilantin, Phenytek
Atropine • AtroPen	Prednisolone • Orapred, Prelone, others
Benzotropine • Cogentin	Prednisone • Deltasone, Meticorten
Cimetidine • Tagamet	Pyridostigmine • Mestinon
Clozapine • Clozaril	Ranitidine • Zantac
Digoxin • Lanoxicaps, Lanoxin	Risperidone • Risperdal
Glyburide • DiaBeta, Micronase	Selegiline • Eldepryl, Zelapar
Haloperidol • Haldol	Spironolactone • Aldactone
Levodopa/carbidopa • Parcopa, Sinemet	Tamsulosin • Flomax
Lisinopril • Prinivil, Zestril	Thioridazine • Mellaril
Lorazepam • Ativan	Trazodone • Desyrel
Meperidine • Demerol	Warfarin • Coumadin
Mirtazapine • Remeron	
Olanzapine • Zyprexa	

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

4th ed, text rev. Washington, DC: American Psychiatric Association; 2000.

5. Lim CJ, Trevino C, Tampi RR. Can olanzapine cause delirium in the elderly? *Ann Pharmacother.* 2006;40(1):135-138.
6. Woodford HJ, George J. Cognitive assessment in the elderly: a review of clinical methods. *QJM.* 2007;100:469-484.
7. Young J, Inouye SK. Delirium in older people. *BMJ.* 2007; 334(7598):842-846.
8. Bruce AJ, Ritchie CW, Blizard R, et al. The incidence of delirium following orthopedic surgery: a meta-analytic review. *Int Psychogeriatr.* 2007;19(2):197-214.
9. Attard A, Ranjith G, Taylor D. Delirium and its treatment. *CNS Drugs.* 2008;22:631-644.
10. Lonergan E, Britton AM, Luxenberg J, et al. Antipsychotics for delirium. *Cochrane Database Syst Rev.* 2007;(2):CD005594.
11. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA.* 2005;294(15):1934-1943.
12. Tabet N, Howard R. Non-pharmacological interventions in the prevention of delirium. *Age Ageing.* 2009;38(4):374-379.

Clinical Point

There is no evidence that haloperidol is any less effective than olanzapine or risperidone for treating agitation and psychosis in delirium

Bottom Line

Although psychiatric illnesses can manifest for the first time later in life, when a geriatric patient presents with acute or subacute psychiatric symptoms, first consider and rule out delirium. Antipsychotics are considered first-line treatment for delirium, but the risk of adverse effects in older patients necessitates a careful risk-benefit analysis.