CLINICAL PRACTICE

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Delirium in Hospitalized Older Adults

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

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A 75-year-old man is admitted for scheduled major abdominal surgery. He is functionally independent, with mild forgetfulness. His intraoperative course is uneventful, but on postoperative day 2, severe confusion and agitation develop. What is going on? How would you manage this patient's care? Could his condition have been prevented?

THE CLINICAL PROBLEM

Although delirium has been described in the medical literature for more than two millennia, the condition is still frequently not recognized, evaluated, or managed appropriately.[1,2] Delirium is also known as acute confusional state, altered mental status, and toxic metabolic encephalopathy, among more than 30 descriptive terms.[3] Delirium can be thought of as acute brain failure[4] and is the final common pathway of multiple mechanisms, similar to acute heart failure. The official definition of delirium in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5),[5] requires a disturbance in attention and awareness that develops acutely and tends to fluctuate (Table 1). The pathophysiological mechanisms of delirium remain poorly understood; leading models include neurotransmitter imbalance and neuroinflammation.[1,2,7,8]

An audio version of this article is available at NEJM.org

Delirium is extremely common in hospitalized older adults. One third of general medical patients who are 70 years of age or older have delirium; the condition is present in half of these patients on admission and develops during hospitalization in the other half.[7] Delirium is the most common surgical complication among older adults, with an incidence of 15 to 25% after major elective surgery and 50% after high-risk procedures such as hip-fracture repair and cardiac surgery.[8] Among patients undergoing mechanical ventilation in the intensive care unit (ICU), the cumulative incidence of delirium, when combined with stupor and coma, exceeds 75%.[9] Delirium is present in 10 to 15% of older adults in the emergency department.[10] The prevalence of delirium at the end of life approaches 85% in palliative care settings.[1]

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.[1,7,8] Hypoactive delirium is associated with a poorer prognosis, potentially because it is less frequently recognized.[11,12] The features of delirium range from mild to extremely severe, with greater severity associated with worse outcomes.[1,2,7,8]

KEY CLINICAL POINTS

DELIRIUM IN HOSPITALIZED OLDER ADULTS

- 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.
- 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.
- 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.
- Behavioral disturbances should be managed with nonpharmacologic approaches first. If required for patient safety, low doses of high-potency antipsychotic agents are usually the treatment of choice (off-label use). Treatment should be targeted to specific behaviors and stopped as soon as possible.
- Proactive, multifactorial interventions and geriatrics consultation have been shown to reduce the incidence, severity, and duration of delirium.

Risk factors for delirium have been classified into two groups: predisposing and precipitating factors.[13] Older age, dementia (often not recognized clinically), functional disabilities, and a high burden of coexisting conditions are common predisposing factors. Male sex, poor vision and hearing, depressive symptoms, mild cognitive impairment, laboratory abnormalities, and alcohol abuse have also been associated with increased risk.[1,14-16] Among precipitating factors, drugs (especially sedative hypnotic agents and anticholinergic agents), surgery, anesthesia, high pain levels, anemia, infections, acute illness, and acute exacerbation of chronic illness are the most commonly reported.[1,13,17-19] The more predisposing factors that are present, the fewer precipitating factors that are needed.[13] This explains why delirium often develops in older, frail adults who have precipitants that would not cause delirium in younger adults.

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 and 1 month later in 33% of cases.[20] Risk factors for the persistence of delirium include advanced age, preexisting dementia, multiple coexisting conditions, delirium severity, and the use of physical restraints.[21,22] (Restraints could be an etiologic factor or a proxy for severity.)

In the hospital, delirium is a potent risk factor for complications, a longer length of stay, and discharge to a postacute nursing facility.[1,7,8,23] With respect to long-term outcomes, a meta-analysis that included almost 3000 patients who were followed for a mean of 22.7 months showed that delirium was independently associated with an increased risk of death (odds ratio, 2.0; 95% confidence interval [CI], 1.5 to 2.5), institutionalization (odds ratio, 2.4; 95% CI, 1.8 to 3.3), and incident dementia (odds ratio, 12.5; 95% CI, 11.9 to 84.2).[24] A number of studies have examined the relationship between delirium and long-term cognitive function.[25-27] A study involving patients undergoing cardiac surgery[26] showed that delirium was associated with acute cognitive decline and slow recovery; among patients in whom delirium developed, cognitive function remained significantly below baseline at 1 month and never fully recovered (although changes from baseline at 6 and 12 months did not differ significantly between those with delirium and those without delirium). Another study in an ICU population[27] did not measure baseline cognition but showed post-delirium dysfunction at the level of mild cognitive impairment even in patients younger than 50 years of age, among whom baseline impairments are unlikely.

STRATEGIES AND EVIDENCE

DIAGNOSIS

Studies comparing clinical documentation with research assessments suggest that only 12 to 35% of delirium cases are recognized.[1] Systematic reviews support the Confusion Assessment Method (CAM) as the most useful bedside assessment

Table 1. Diagnostic Criteria for Delirium.

Source of Criteria
DSM-5*
The presence of delirium requires all the criteria to be met:
Disturbance in attention and awareness
Disturbance develops acutely and tends to fluctuate in severity
At least one additional disturbance in cognition
Disturbances are not better explained by a preexisting dementia
Disturbances do not occur in the context of a severely reduced level of arousal or coma
Evidence of an underlying organic cause or causes
Confusion Assessment Method (CAM)†
The presence of delirium requires features 1 and 2 and either 3 or 4:
Acute change in mental status with a fluctuating course (feature 1)
Inattention (feature 2)
Disorganized thinking (feature 3)
Altered level of consciousness (feature 4)

* The criteria are adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5).[5]
† The criteria are adapted from Inouye et al.[6]

tool (Table 1).[6,28,29] 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. Rating the presence of CAM features with observations from routine care results in low sensitivity.[30] Alternatively, brief CAM-based instruments that incorporate mental-status testing show better sensitivity; these include the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU),[31] the Brief Confusion Assessment Method (bCAM) for emergency department patients,[32] and the 3-Minute Diagnostic Interview for Delirium Using the Confusion Assessment Method (3D-CAM) for general medical patients[33] (Table 2). The 4AT[34] — a test that examines alertness, cognition (orientation and attention), and acute change in mental status — is another brief tool for assessing delirium that is not based on the CAM algorithm. (For a comparison of these instruments, see the Supplementary Appendix, available with the full text of this article at NEJM.org.) These instruments can be used by clinicians to confirm delirium in suspected cases and for case finding in high-risk patients. Shorter "ultra-brief" screenings may be used for case finding in lower-risk patients; these include attention tests, such as digit span backward and days of the week and months of the year backward.[35] Barriers to implementation of broad-based screening for delirium include time, cost, competing demands, and the current absence of evidence that such screening improves patient outcomes.

Dementia, depression, and acute psychiatric syndromes should all be considered in the differential diagnoses for delirium; these syndromes often co-occur, and patients may have more than one.[7] The most common scenario is sorting out whether an older adult presenting with confusion has delirium, dementia, or both. 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.[6] Severe hypoactive and hyperactive delirium can be confused with depression and mania, respectively. It is prudent to evaluate these patients for delirium rather than attributing the presentation to psychiatric disease[7] and missing important medical problems.

EVALUATION

Newly diagnosed delirium can herald a life-threatening emergency, and affected patients require a prompt and appropriate evaluation, including history taking, physical and neurologic examination, and laboratory tests.[1,7,8] Table 3 outlines the most common reversible contributors to delirium. Acute brain disorders (e.g., stroke and seizure) can cause delirium, but in older adults, most treatable contributors lie outside the brain. More than one etiologic factor is often present; therefore, a thorough review of all elements of the DELIRIUM mnemonic (Table 3) should be performed.

Clinicians should ask when the changes in mental status started and whether they co-occurred with other symptoms (e.g., dyspnea and dysuria) or medication changes. A thorough medication review is required for all patients with delirium; this should include the consumption of alcohol and the use of nonprescription drugs and dietary supplements. The physical ex-

Table 2. 3-Minute Diagnostic Interview for Delirium Using the Confusion Assessment Method (3D-CAM).*

Type of Assessment	Feature 1: Acute Change in Mental Status with a Fluctuating Course†	Feature 2: Inattention	Feature 3: Disorganized Thinking	Feature 4: Altered Level of Consciousness
Patient responses: any positive symptom report, incorrect response, lack of response, or nonsense response indicates that the feature is present	Ask whether patient has experienced the following in the past day: Being confused Thinking that he or she is not in the hospital Seeing things that are not really there	Ask patient to do the following: Digit span (3 digits) backward Digit span (4 digits) backward Days of the week backward Months of the year backward	Ask patient to state the following: The current year The day of the week The type of place (hospital)	None
Interviewer observations: any "yes" indicates that the feature is present	Were there fluctuations in the level of consciousness? Fluctuations in attention? Fluctuations in speech or thinking?	Did the patient have trouble keeping track of the interview? Was the patient easily distractible?	Was the patient's flow of ideas unclear or illogical? Conversation rambling or tangential? Speech unusually limited or sparse?	Was the patient sleepy?‡ Stuporous or comatose? Hypervigilant?

* The CAM algorithm requires the presence of features 1 and 2 and either 3 or 4 to diagnose delirium. Adapted from Marcantonio et al.[33]
† A supplemental assessment of feature 1 is to be performed only if feature 2 and either feature 3 or 4 is present but feature 1 is not present: on the first 3D-CAM assessment, any evidence of an acute change in mental status from the medical record or from a family member or health care provider indicates that feature 1 is present; on the second or later assessment, any new incorrect answer or positive symptom or observation since the previous 3D-CAM assessments indicates that feature 1 is present.
‡ The patient must actually fall asleep during the interview.

amination should evaluate vital signs (including oxygen saturation) and the heart, lungs, and abdomen. The neurologic examination should evaluate new focal findings that suggest an intracranial cause (e.g., stroke).

Laboratory tests and imaging should be selected on the basis of the history and examination.[1,7,8] Tests that are routinely required include a complete blood count and measurement of electrolytes, blood urea nitrogen, and creatinine. A urinalysis, urine culture, liver-function tests, chest radiography, and electrocardiography are also often helpful. Additional tests that are useful in select situations include blood and urine toxicology studies, blood cultures, arterial blood gas analysis (if hypercapnia is suspected), cerebral imaging (in patients with head trauma or new focal neurologic findings), lumbar puncture (if findings suggest meningitis or encephalitis), and electroencephalography (if seizures are suspected).

MANAGEMENT

General Principles

Well-integrated care by physicians, nurses, other providers, and even family members helps to prevent the complications and poor outcomes often seen in delirium. Addressing all modifiable contributors to delirium that are identified in the evaluation is critically important, and multiple small interventions can yield substantial benefit.[1,7,8] Medications are the most common modifiable contributors; Table 4 lists common precipitating medications and potential alternatives.

Environmental factors are also important in delirium management. The hospital ward should be well lit during the day and dark and quiet at night. Interventions to improve orientation and reduce sensory deprivation include clocks, calendars, and encouragement of patients to wear eyeglasses and hearing aids. Family members should be encouraged to visit and provide orientation and reassurance.

Complications often prolong or worsen the course of delirium, and surveillance and prevention are critical elements of management (Table 3).[37] Such approaches include monitoring of bowel and bladder output, preferably without urinary catheters unless required for treating urinary retention. Constipation can be prevented by judicious use of laxatives, and prophylaxis is

Table 3. Evaluation and Management of Delirium.

Step and Key Issues	Proposed Evaluation and Treatment
Evaluate and treat common modifiable contributors to delirium*	
Drugs	Consider the etiologic role of newly initiated drugs, increased doses, interactions, over-the-counter drugs, and alcohol; consider especially the role of high-risk drugs: lower the dose, discontinue the drug, or substitute a less psychoactive medication
Electrolyte disturbances	Assess for and treat, especially dehydration, sodium imbalance, and thyroid abnormalities
Lack of drugs	Assess possible symptoms of withdrawal from long-term use of sedatives, including alcohol and sleeping pills; assess for and treat poorly controlled pain (lack of analgesia): use local measures and scheduled treatment regimens that minimize the use of opioids (avoid meperidine)
Infection	Evaluate and treat, especially urinary tract, respiratory tract, and soft-tissue infections
Reduced sensory input	Address issues involving vision (e.g., encourage use of eyeglasses) and hearing (e.g., encourage use of hearing aids or a portable amplifier)
Intracranial disorders	Consider such disorders (e.g., infection, hemorrhage, stroke, or tumor) if there are new focal neurologic findings or a suggestive history or if diagnostic evaluation for causes outside the central nervous system is unrevealing
Urinary and fecal disorders	Assess for and treat urinary retention (so-called cystocerebral syndrome) and fecal impaction
Myocardial and pulmonary disorders	Assess for and treat myocardial infarction, arrhythmia, heart failure, hypotension, severe anemia, exacerbation of chronic obstructive pulmonary disease, hypoxia, and hypercarbia
Prevent or manage complications	
Urinary incontinence	Implement a scheduled toileting program
Immobility and falls	Avoid physical restraints; mobilize the patient with assistance; use physical therapy
Pressure ulcers	Mobilize the patient; reposition an immobilized patient frequently and monitor pressure points
Sleep disturbance	Implement a nonpharmacologic sleep-hygiene program, including a nighttime sleep protocol; avoid sedatives; minimize unnecessary awakenings (e.g., for measuring vital signs)
Feeding disorders	Monitor dietary intake; provide feeding assistance if needed, aspiration precautions, and supplementation as necessary
Maintain patient comfort and safety	
Behavioral interventions	Teach hospital staff de-escalation techniques for patients who have hyperactive or agitated delirium; encourage family visitation
Pharmacologic interventions	Use low doses of high-potency antipsychotic agents only if necessary
Restore function	
Hospital environment	Reduce clutter and noise; provide adequate lighting; encourage family to bring in familiar objects from home
Cognitive reconditioning	Staff should reorient patient to time, place, and person at least three times daily
Ability to perform activities of daily living	Use physical and occupational therapy; as delirium clears, match performance to ability
Family education, support, and participation	Provide education about delirium, its causes and reversibility, the best ways to interact with affected patients, and the role of the family in restoring function
Discharge planning and education	Provide increased support for activities of daily living as needed at discharge; teach family members to follow mental status as a barometer of recovery

* The first letters of these eight items form the mnemonic DELIRIUM.

essential in those with standing orders for opioid analgesics. Getting the patient out of bed to a chair, and preferably walking, can prevent atelectasis, deconditioning, and pressure ulcers. Monitoring of food and fluid intake can identify those at risk for malnutrition and dehydration, in whom assisted feeding may be helpful. Some patients with delirium may require aspiration precautions and monitoring.

Behavioral Disturbances

On the basis of clinical experience as well as a lack of evidence of benefit (and the recognized potential harms) of drug treatment, nonpharma-

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; nonpsychoactive 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.

cologic interventions are the cornerstone of managing behavioral problems in delirium.[1,7,8] Nurses should be trained in de-escalation techniques, and when necessary, sitters can be employed to ensure patient safety.

Physical restraints, which staff often use to reduce the risk of patient self-harm, are actually associated with increased injury.[38,39] On general medical and surgical wards, the use of restraints should be minimized, if not eliminated. In the ICU, restraints may be required to prevent the removal of endotracheal tubes, intraarterial devices, and central intravenous catheters. If restraints are applied, they should be carefully monitored to reduce the risk of patient injury and discontinued as soon as they are no longer indicated.[1,7,8]

Pharmacologic treatment may be required for distressing perceptual disturbances or delusional thoughts when verbal reassurance is not successful or for behavior that is dangerous to the patient or others.[1,7,8] Benzodiazepines should be reserved for specific indications, such as delirium associated with alcohol or benzodiazepine withdrawal, in which preventive administration may also be indicated. For other cases, antipsychotic agents have a more favorable risk–benefit ratio. However, all such use in the United States is off-label; there are no Food and Drug Administration–approved drugs for delirium.

A recent meta-analysis reviewed 12 randomized trials of antipsychotic agents for delirium treatment and concluded that they did not reduce the duration or severity of delirium, the length of stay in the ICU or hospital, or mortality.[40] Thus, the decision whether to use such agents must consider the trade-off between an immediate reduction of agitation, hallucinations, and delusions versus the risks of sedation and antipsychotic-induced complications.[7]

Table 5 reviews antipsychotic agents used in treatment; small noninferiority trials have shown that these agents are similarly effective, and the choice among them is often made on the basis of adverse effects.[7] Haloperidol is the least sedating but confers the greatest risk of extrapyramidal symptoms, whereas quetiapine is most sedating and has the least extrapyramidal effects. The availability of intravenous administration may be important for ICU patients. Regardless of the drug selected, the initial dose should be low, because there is wide variability in response. Additional doses can be administered every 30 to 60 minutes until the desired behavioral end point is achieved (e.g., the patient is no longer hallucinating).[1,7] Thereafter, doses can be administered on an as-needed basis.

Patients with prolonged delirium may need continual scheduled dosing (e.g., once, twice, or three times daily). As with physical restraints, these drugs should be stopped as soon as possible. In the rare circumstance in which antipsychotic agents are needed beyond hospital discharge, a clear time frame and conditions for discontinuation should be included in the discharge paperwork.

PREVENTION

In a 1999 study, a unit-based proactive multifactorial intervention, the Hospital Elder Life Program (HELP), reduced the incidence of delirium among hospitalized patients who were 70 years of age or older.[41] Interventions that were implemented by trained volunteers on the basis of risk factors for delirium that were present at hospital admission included reorientation, a nonpharmacologic sleep protocol,[36] getting the patient out of bed and walking, encouraging the use of eyeglasses and hearing aids, and encouraging fluid intake. A 2015 meta-analysis examined the effectiveness of HELP-like multifactorial nonpharmacologic interventions for delirium.[42] A total of 14 high-quality intervention studies (most of which were randomized trials) were identified. Of these, 11 studies that measured delirium showed a significant reduction in incidence (odds ratio, 0.47; 95% CI, 0.38 to 0.58), and 4 studies that measured falls showed an even greater significant reduction in in-hospital falls (odds ratio, 0.38; 95% CI, 0.25 to 0.60).

Another effective nonpharmacologic approach for delirium prevention is proactive geriatrics consultation in surgical patients at high risk for delirium. Consultation begins before surgery and continues until discharge. A structured protocol is used to formulate daily recommendations — for example, using round-the-clock acetaminophen and local pain management to reduce opioid use and discontinuing standing orders for sleeping pills. Two studies involving older patients with hip fracture showed that the use of this model reduced the incidence of delirium[43,44]; in one randomized trial, the consultation group had a 36% lower incidence of delirium than the usual-care group (number needed to treat to

Table 5. Pharmacologic Therapy of Agitated Delirium.*

Agent	Drug Class	Dosing†	Routes	Degree of Sedation	Risk of EPS	Adverse Effects	Comments
Haloperidol	Typical antipsychotic	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 antipsychotic	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 antipsychotic	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 antipsychotic	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 antipsychotic	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.

prevent one case of delirium, 5.6).[43] Geriatrics–orthopedics services have been widely adopted for patients with hip fracture, and similar protocols can be implemented by trained hospital medicine physicians.

Reducing the use of psychoactive medications is an important component of the prevention strategies described above.[41,43] Observational studies have suggested a potential benefit of reducing the use of sedating medications, such as sleeping pills,[36] and reducing the use of deep sedation in the ICU.[45] In a small randomized trial, patients who received light sedation during spinal anesthesia for hip-fracture repair had a lower incidence of postoperative delirium than those who received deep sedation.[46]

The effectiveness of pharmacologic approaches for delirium prevention remains unclear. The meta-analysis of antipsychotic agents that is cited above also examined seven randomized trials that tested preventive administration of low doses of these agents in surgical patients at high risk for delirium.[40] The incidence of delirium appeared to be lower in the intervention groups than in the control groups, but there was considerable heterogeneity among studies, and the between-group difference was not significant (pooled odds ratio, 0.56; 95% CI, 0.23 to 1.34). This meta-analysis also showed no significant effect of the preventive use of antipsychotic agents on the length of stay in the ICU or hospital or on mortality.

Melatonin and its analogues have also been proposed to reduce the incidence of delirium. One small, randomized trial of the preventive administration of ramelteon (a melatonin analogue) involving 67 patients showed a significant benefit with respect to the risk of delirium (3% vs. 32% with placebo, $P=0.003$),[47] a finding that requires replication. However, a recent Cochrane review that pooled data from three trials involving 529 patients concluded that there is no clear evidence that the use of melatonin or melatonin agonists reduces the incidence of delirium as compared with placebo.[48]

AREAS OF UNCERTAINTY

It remains unclear whether systematic case finding of delirium improves patient outcomes, particularly in hypoactive delirium. It is also unclear whether measures of delirium severity, phenotype, or biomarkers can improve prognostication of outcomes after an episode of delirium. More data from randomized trials are needed to determine the effects of antipsychotic agents and other medications for the prevention and treatment of delirium. In addition, trials are needed of multifactorial approaches (similar to those successful for prevention) for the treatment of delirium.

GUIDELINES

Guidelines for the prevention and management of delirium in hospitalized elders have been developed by the United Kingdom National Institute for Health and Care Excellence (NICE)[39] and the American Geriatrics Society Section for Enhancing Geriatric Understanding and Expertise among Surgical and Medical Specialists.[38] The recommendations in this article are generally consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient in this vignette had severe hyperactive postoperative delirium. After confirmation of the diagnosis with the use of a validated CAM-based strategy, the next steps would be conducting a careful evaluation for reversible causes and addressing as many of these as possible. Agitation should be managed with nonpharmacologic strategies first. Physical restraints should be avoided. Antipsychotic agents should be reserved for unremitting symptoms that threaten patient safety; if required, haloperidol (initial dose, 0.25 mg), olanzapine (2.5 mg), or quetiapine (12.5 mg) would be reasonable first choices, depending on the amount of sedation desired. Had this patient's mild forgetfulness been recognized preoperatively, he could have been identified as being at high risk for delirium, and proactive strategies could have been implemented to reduce his risk.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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