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. Delirium is also known as acute confusional state, altered mental status, and toxic metabolic encephalopathy, among more than 30 descriptive terms. Delirium can be thought of as acute brain failure 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), 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.

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. 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. Among patients undergoing mechanical ventilation in the intensive care unit (ICU), the cumulative incidence of delirium, when combined with stupor and coma, exceeds 75%. Delirium is present in 10 to 15% of older adults in the emergency department. The prevalence of delirium at the end of life approaches 85% in palliative care settings.

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. The features of delirium range from mild to extremely severe, with greater severity associated with worse outcomes.
Risk factors for delirium have been classified into two groups: predisposing and precipitating factors. 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. 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. The more predisposing factors that are present, the fewer precipitating factors that are needed. 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. Risk factors for the persistence of delirium include advanced age, preexisting dementia, multiple coexisting conditions, delirium severity, and the use of physical restraints. (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. 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). A number of studies have examined the relationship between delirium and long-term cognitive function. A study involving patients undergoing cardiac surgery 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 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.
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

**Table 1. Diagnostic Criteria for Delirium.**

<table>
<thead>
<tr>
<th>Source of Criteria</th>
<th>DSM-5†</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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</tr>
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<td>Disturbances are not better explained by a preexisting dementia</td>
<td></td>
</tr>
<tr>
<td>Disturbances do not occur in the context of a severely reduced level of arousal or coma</td>
<td></td>
</tr>
<tr>
<td>Evidence of an underlying organic cause or causes</td>
<td></td>
</tr>
</tbody>
</table>

† The criteria are adapted from the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5).5

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 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
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- 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 Inouye et al.6

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**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-
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. 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. 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). 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
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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-

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Adverse Effect</th>
<th>Substitutes or Alternative Strategies</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>CNS sedation and withdrawal</td>
<td>Nonpharmacologic sleep protocol[^6^]</td>
<td>Associated with delirium in hospitalized patients; if patient is already taking, maintain or lower dose, but do not discontinue abruptly</td>
</tr>
<tr>
<td>Opioid analgesics (especially meperidine)</td>
<td>Anticholinergic toxicity, CNS sedation, and fecal impaction</td>
<td>Local and regional analgesic measures; nonpsychoactive pain medications (e.g., acetaminophen and NSAIDs) around the clock; reserve opioids for breakthrough and severe pain</td>
<td>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</td>
</tr>
<tr>
<td>Nonbenzodiazepine sedative hypnotics (e.g., zolpidem)</td>
<td>CNS sedation and withdrawal</td>
<td>Nonpharmacologic sleep protocol[^6^]</td>
<td>Like other sedatives, these agents can cause delirium</td>
</tr>
<tr>
<td>Antihistamines, especially first-generation sedating agents (e.g., doxylamine and diphenhydramine)</td>
<td>Anticholinergic toxicity</td>
<td>Nonpharmacologic sleep protocol[^6^], pseudoephedrine for upper respiratory congestion, and nonsedating antihistamines for allergies</td>
<td>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</td>
</tr>
<tr>
<td>Alcohol</td>
<td>CNS sedation and withdrawal</td>
<td>If patient has a history of heavy intake, monitor closely and use benzodiazepines for withdrawal symptoms</td>
<td>The history taking must include questions about alcohol intake</td>
</tr>
<tr>
<td>Anticholinergics (e.g., oxybutynin and benztpetine)</td>
<td>Anticholinergic toxicity</td>
<td>Lower the dose or use behavioral approaches for urinary incontinence (e.g., scheduled toileting)</td>
<td>Delirium is unusual at low doses</td>
</tr>
<tr>
<td>Anticonvulsants (e.g., primidone, phenobarbital, and phenytoin)</td>
<td>CNS sedation</td>
<td>Use an alternative agent or consider stopping if patient is at low risk for seizures and has no recent history of them</td>
<td>Delirium can occur despite therapeutic drug concentrations</td>
</tr>
<tr>
<td>Tricyclic antidepressants, especially tertiary amines (e.g., amitriptyline, imipramine, and doxepin)</td>
<td>Anticholinergic toxicity</td>
<td>Serotonin-reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and secondary amine tricyclics (e.g., nortriptyline and desipramine)</td>
<td>Newer agents (e.g., duloxetine) are as effective as tertiary amines for adjuvant treatment of chronic pain</td>
</tr>
<tr>
<td>Histamine H₂-receptor blockers</td>
<td>Anticholinergic toxicity</td>
<td>Lower the dose or substitute antacids or proton-pump inhibitors</td>
<td>Anticholinergic toxic effects occur primarily with high-dose intravenous infusions</td>
</tr>
<tr>
<td>Antiparkinsonian agents (e.g., levodopa and amantadine)</td>
<td>Dopaminergic toxicity</td>
<td>Lower the dose or adjust dosing schedule</td>
<td>Dopaminergic toxic effects occur primarily in advanced disease and at high doses</td>
</tr>
<tr>
<td>Antipsychotics, especially low-potency typical antipsychotics (e.g., chlorpromazine and thioridazine)</td>
<td>Anticholinergic toxicity as well as CNS sedation</td>
<td>Discontinue entirely or, if necessary, use low doses of high-potency agents</td>
<td>Carefully consider risks vs. benefits of use in delirium</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>CNS sedation and severe withdrawal syndrome</td>
<td>Gradual discontinuation or benzodiazepine substitution</td>
<td>In most cases, barbiturates should not be prescribed; avoid inadvertent or abrupt discontinuation</td>
</tr>
</tbody>
</table>

[^6^]: 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.
Pharmacologic interventions are the cornerstone of managing behavioral problems in delirium. Nurses should be trained in de-escalation techniques, and when necessary, sitter 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. 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.

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. 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. 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.

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. 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). 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. 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, 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. 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 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.*

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

* 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). 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. Observational studies have suggested a potential benefit of reducing the use of sedating medications, such as sleeping pills, and reducing the use of deep sedation in the ICU. 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.

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. 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), 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.

**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) and the American Geriatrics Society Section for Enhancing Geriatric Understanding and Expertise among Surgical and Medical Specialists. 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 non-pharmacologic 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.

No potential conflict of interest relevant to this article was reported. Disclosure forms provided by the author are available with the full text of this article at NEJM.org.


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