

In the Clinic®

Delirium

Delirium is an acute confusional state that is common and costly and is associated with significant functional decline and distress. It is the manifestation of acute encephalopathy and is variably called *acute brain failure*, *acute brain dysfunction*, or *altered mental status*. All patients are at risk for delirium, although those with more vulnerabilities (such as advanced age, exposures to other stressors like infection, and certain medications) are at higher risk. The pathophysiologic cause of delirium is not well understood. It is important to recognize patients at risk for and those with delirium and to immediately identify and treat factors contributing to it. There is no single intervention or medication to treat delirium, making it challenging to manage. Therefore, risk mitigation and prompt treatment rely on a sophisticated strategy to address the contributing factors. Delirium may be prevented or attenuated when multimodal strategies are used, thereby improving patient outcomes.

CME/MOC activity available at [Annals.org](https://annals.org).

Screening and Prevention

Diagnosis

Treatment

Practice Improvement

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doi:10.7326/AITC202010060

CME Objective: To review current evidence for screening, prevention, diagnosis, treatment, and practice improvement of delirium.

Acknowledgment: The author thanks Edward R. Marcantonio, MD, author of the previous version of this In the Clinic.

Funding Source: American College of Physicians.

Disclosures: Dr. Mattison, ACP Contributing Author, has nothing to disclose. The form can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-0850.

With the assistance of additional physician writers, the editors of *Annals of Internal Medicine* develop **In the Clinic** using **MKSAP** and other resources of the American College of Physicians. The patient information page was written by Monica Lizarraga from the Patient and Interprofessional Partnership Initiative at the American College of Physicians.

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Delirium is an acute state of brain failure marked by sudden onset of confusion, a fluctuating course, inattention, and often an abnormal level of consciousness (1–3). The nomenclature of what is delirium versus encephalopathy versus an acute confusional state has recently been revised, with expert consensus recommending specific uses for each term. Specifically, the experts recommend using the term *acute encephalopathy* to refer to the pathophysiologic state of the central nervous system “process,” whereas the term *delirium* should be used to describe the symptoms observed at the bedside (4). The experts also recommend against use of the terms *acute confusional state*, *acute brain dysfunction*, *acute brain failure*, or *altered mental status* in clinical practice or research; although these terms might have relevance for educational purposes, they are believed to lack face or construct validity (4).

Delirium is extremely common but can be challenging to diagnose. Sometimes, patients are purely acutely agitated; however, this is much less common than the hypoactive or quiet variant (1, 5). Many patients have a mixed picture, with symptoms predominantly of hypoactive delirium and occasional agitation symptoms. Delirium is an acute change in mental status and must be differentiated from dementia, which is characterized as a chronic condition with slower progression of brain failure. However, delirium and dementia frequently coexist because preexisting cognitive failure is a risk factor for delirium.

Many older patients (11%–40%) have delirium when they are hospitalized or develop it during their admission (1, 6). Postoperative delirium rates among seniors range from 15%–25% after elective surgery, such as total joint replacement, to more than 50% after high-risk procedures, such as hip fracture repair and cardiac surgery (7–10). Among patients of any age admitted to intensive care units (ICUs) and requiring mechanical ventilatory support, the prevalence of delirium is as high as 80%, and the cumulative incidence at the end of life has been reported as high as 85% (11, 12).

Mounting evidence indicates that delirium is strongly and independently associated with poor patient outcomes. In the hospital, delirium has been associated with a 10-fold increased risk for death and a 3- to 5-fold increased risk for nosocomial complications, prolonged length of stay, and greater need for nursing home placement after discharge (1). Even after discharge, a patient who had delirium in the hospital is more likely to have poor functional and cognitive recovery.

In a study of critically ill adults, 74% had delirium during their hospitalization. Three months later, 40% of survivors had global cognition more than 1.5 SDs below the population mean, and a quarter of survivors were more than 2 SDs below the mean (13). Patients admitted to postacute care with delirium have an increased risk for 30-day mortality and readmission to the hospital and less chance of functional recovery (14).

Screening and Prevention

Which patients are at risk for delirium, and what are common precipitating factors?

Delirium is best understood as a multifactorial syndrome affecting

older patients. However, patients of any age can be affected. Like other organ systems that can fail, risk factors for delirium are multifactorial and often lie outside the presenting organ system—in the

case of delirium, the brain or central nervous system.

A common risk factor model for delirium distinguishes predisposing from precipitating factors; the former are chronic factors that increase a patient's vulnerability to delirium, whereas the latter are acute conditions or events that initiate delirium (see the Box: Common Risk Factors for Incident Delirium). Several large epidemiologic studies and systematic reviews have defined predisposing and precipitating factors for delirium. Based on this model, a person's risk for delirium is defined by the sum of predisposing and precipitating factors; the more predisposing factors present, the fewer precipitating events required to cause delirium (15). For example, a young person who is otherwise healthy may become delirious after having severe sepsis, respiratory failure, and mechanical ventilation in the ICU. In contrast, a frail older adult with cognitive impairment may become delirious after taking a low dose of acetaminophen with diphenhydramine for sleep. Emerging evidence suggests that a large proportion of hospitalized patients with coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) manifest neurologic and mental status changes; a subset of these changes may represent acute delirium (16, 17).

When and how should clinicians screen patients for delirium?

Although delirium is a common illness, 55%–80% of cases are unrecognized and undocumented by the treating clinical team (18–20). Thus, it is important to screen patients to improve recognition and prompt treatment. Trials that have assessed the effectiveness of sys-

Common Risk Factors for Incident Delirium

Predisposing conditions:

- Preexisting cognitive impairment
- Multiple comorbid conditions, including depression
- Polypharmacy
- Impaired sensation (e.g., vision, hearing)
- Impaired functional ability (i.e., activities of daily living diminished)
- History of alcohol misuse and/or malnutrition
- Anemia

Precipitating factors:

- Severe illness (e.g., sepsis, stroke)
- Presence of tethers (e.g., urinary catheter) and/or physical restraints
- Surgery/anesthesia
- New psychoactive medication
- Pain
- Environmental change
- Dehydration and/or electrolyte disturbances
- Urine retention/fecal impaction

tematic programs to improve findings and treatment of delirium have shown significantly improved detection rates and modest improvements in outcomes (21). Therefore, it seems prudent to screen hospitalized patients who are at risk for delirium (due to either predisposing factors or the acute situation), including those with preexisting cognitive impairment or multiple comorbid conditions or those admitted to the ICU. Patients transitioning from the hospital to postacute care, including to skilled-nursing facilities or outpatient primary care, warrant cognitive screening because any lingering delirium may hinder participation in the treatment plan and inhibit recovery.

Many screening and diagnostic tools are available to identify delirium (see the Box: Common Components of Delirium Screening Instruments). The briefest screening methods use the Confusion Assessment Method (CAM) diagnostic algorithm (22),

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which examines 4 key features of delirium: acute change in mental status and fluctuating course, inattention, disorganized thinking, and abnormal level of consciousness. The literature suggests that detecting delirium using routine observations from clinical care is likely not sufficient and that a standardized assessment should be done to improve timely detection (23). Diagnosis of delirium using the CAM requires the presence of the first and second features plus either the third or fourth. The CAM is an accurate approach for diagnosis of delirium; a review of a dozen articles published from 2001–2013 found sensitivity of 82% and specificity of 99% (24). It should be noted that the sensitivity of the CAM diminishes considerably when it is not accompanied by prior cognitive assessment. The Mini-Mental State Examination (which requires a license for use) takes up to 15 minutes, provides a limited assessment of attention and level of consciousness, and may be associated with high false-positive rates (25). Screeners can assess level of consciousness by using a standardized measure, such as the Richmond Agitation and Sedation Scale (26, 27), and attention by using 1 or more additional items (see the Box: Commonly Used Tests of Attention).

If delirium is suspected after an initial cognitive assessment, eval-

Common Components of Delirium Screening Instruments

- Test of attention (see the Box: Commonly Used Tests of Attention)
- Query of understanding (“Where are you?” “What has happened to you?”) to assess for disorganized thinking
- Assessment of psychomotor status (agitated vs. sedated vs. mixed)
- Estimate of timeline and course of symptom onset

uation should be followed by a delirium-specific diagnostic tool. The CAM is the most widely used instrument in the United States to identify patients with delirium, but special training is required to use it correctly for optimal performance (28). The 3-Minute Diagnostic Interview for Confusion Assessment Method (3D-CAM) has been described as a more user-friendly version for hospitalized patients, with sensitivity of 95% and specificity of 94% (29). The ultra-brief 2-item test, which assesses whether the patient can correctly identify the day of the week and recite the months of the year in reverse order, may be a reasonable screening instrument, with 93% sensitivity and 64% specificity (30). Another tool is the 4 A's Test (4AT), a brief instrument that requires no special training for clinical use. The 4AT is recommended in some countries for initial screening for delirium, with 76% sensitivity and 94% specificity (31).

The Confusion Assessment Method for the ICU (CAM-ICU) is a specific application of the CAM algorithm that uses nonverbal responses from the patient to assess attention, thinking, and level of consciousness (12). The CAM-ICU is valid and reliable and can be completed in a few minutes. Patients in the ICU are at such high risk for delirium that they should be screened at least daily.

Are there effective strategies for prevention?

Among all interventions for delirium, the strongest evidence supports use of a protocol aimed at reducing common risk factors for delirium. The effectiveness of prevention using this strategy can reduce the development of delirium by 40% (32).

The Yale Delirium Prevention Trial tested the effectiveness of the Hospital Elder Life Pro-

gram (33), which targeted 6 risk factors for delirium: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration. Risk factors were assessed at admission, and patients with 1 or more of these risk factors received targeted interventions to address them. The intervention was delivered by specially trained teams of volunteers under the guidance of specialized staff and included a nonpharmacologic sleep protocol that involved offering patients warm milk, back rubs, and soothing music at bedtime; this intervention substantially reduced the use of sedatives-hypnotics. Delirium in the intervention group was significantly reduced (odds ratio, 0.60 [95% CI, 0.39–0.92]; number needed to treat, 19) (33).

The approach used in the Yale trial has been implemented widely. Others have leveraged family members of patients at risk for delirium with similar success (34). The effect of nonpharmacologic strategies on improving sleep quality itself is less clear, with a paucity of good studies available (35, 36).

A recent meta-analysis of integrated models of care designed to prevent delirium found a pooled odds ratio of 0.56 (CI, 0.37–0.85; P = 0.006) for incidence of delirium in patients receiving these interventions compared with the control groups (37).

Implementation of commonly recommended measures to prevent delirium has been challenged by the COVID-19 pandemic. Hospitals and other care facilities have limited patients' in-person contact with family and friends, as well as hospital staff to reduce risk for transmission of SARS-CoV-2. Such contact is critical to delirium prevention strategies of offering reassurance, re-orientation, and other support. The personal protective equipment that members of the care team are required to wear for their own safety hinders communication and can be frightening, especially to a confused patient. Tethering devices (such as continuous cardiac telemetry and pulse oximetry) are used to keep

close—albeit remote—tabs on patients. These challenges undoubtedly create an environment ripe for delirium. As the health care system responds to the COVID-19 pandemic, it will be important to mitigate environmental challenges as much as possible and understand how SARS-CoV-2 contributes to encephalopathy (16, 17).

Despite the pandemic, additional measures can be taken to address and prevent delirium in hospitalized patients. Comanagement of patients with hip fracture and other vulnerable surgical populations by surgeons and geriatricians and/or internists improves overall geriatric patient outcomes, including delirium (38).

Medication trials to prevent delirium or reduce its severity have to date been unsuccessful. Recent systematic reviews found no evidence to support the use of antipsychotics for delirium prevention or treatment (39–41). Although haloperidol is commonly used in the ICU, it has not been shown to improve survival, even in patients at high risk for delirium (42). Moreover, nonpharmacologic preventive approaches reduce delirium severity and/or duration. These trials have tested new models of care that involve reorganization of nursing care and the hospital environment to focus on patient-centered care and the reduction of factors that commonly precipitate delirium (43). It has been suggested that antipsychotics can give the impression of improving symptoms of delirium by converting hyperactive symptoms to hypoactive features, resulting in an apparent reduction in delirium severity. Of note, studies suggest that patients with hypoactive delirium may have equal or worse outcomes compared with those with hyperactive delirium (44, 45).

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Screening and Prevention... Risk factors for delirium should be assessed on admission to the hospital. High-risk patients, including those in high-risk settings, such as the ICU, should also be screened for delirium on admission and at least daily thereafter using proven methods, such as the CAM. The most effective, proven approach to preventing delirium is proactive, multifactorial, nonpharmacologic interventions, such as the Hospital Elder Life Program, proactive geriatrics consultation, or careful comanagement for high-risk surgical patients.

CLINICAL BOTTOM LINE

Diagnosis

When should clinicians consider a diagnosis of delirium?

Delirium should be considered in any confused hospitalized patient and in high-risk patients with confusion in any setting. When in doubt, it is always better to rule out delirium first than to attribute confusion to an underlying chronic disorder, such as dementia, and fail to recognize delirium.

What elements of the history and physical examination indicate delirium?

The diagnosis of delirium is based entirely on the history and physical examination. **Table 1** summarizes the key history and physical examination components for the diagnosis and evaluation of delirium.

No laboratory tests, imaging studies, or other tests are more accurate than clinical assessment (1). The history and physical examination have 2 roles in the evaluation of delirium: confirmation of the diagnosis, and identification of potential causes and contributors.

Obtaining the history for delirium differs from that of other medical conditions in that it is primarily obtained from caregivers or family members rather than the patient. One key element is determining the timeline of the mental status changes; acute onset is most consistent with delirium. Whether there have been fluctua-

tions in mental status, such as the patient seeming normal at times and very confused at others, is also an essential element.

The key aspect of the physical examination is evaluation of mental status, and the most important aspect of this evaluation is determining the level of consciousness and attention (Box: Commonly Used Tests of Attention). Any abnormal level of consciousness, as well as the presence of inattention, is supportive of delirium. For patients with a normal level of consciousness, assessing their thinking, specifically whether there is evidence of disorganized thinking, such as rambling and incoherent speech, is also important.

Once the history is obtained from a family member and/or caregiver and the mental status examination

Commonly Used Tests of Attention

- Digit span (up to 5 forward and 4 backward)
- Recite the days of the week and the months of the year in reverse order
- Continuous performance task (instruct patient to raise hand when he or she hears a certain letter in a list)
- Attention screening examination (show pictures; ask patient to remember and recall)
- Recite a list of serial 7's or 3's
- Spell "world" backward

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is completed, the diagnosis of delirium can be determined using the screening tool of choice, incorporating key components (Box: Common Components of Delirium Screening Instruments).

Another important element of the history and physical examination is evaluating for causes and contributors (Box: Common Risk Factors for Incident Delirium). These include a medication history, vital signs, and a general medical examination.

What is the role of laboratory testing, brain imaging, and electroencephalography in the diagnosis and evaluation?

Laboratory testing, brain imaging, and electroencephalography (EEG) are not substitutes for history and physical examination in the diagnosis. However, these studies can be useful to identify possible causes of delirium and correctable contributing factors,

particularly when studies and tests are carefully selected on the basis of the history and physical examination (for a summary of the use of laboratory, imaging, and EEG studies in the evaluation of delirium, see the Box: Laboratory, Imaging, and Other Studies to Consider in the Evaluation of Delirium). When ordered as an unselected "delirium battery," the yield of these tests and procedures is low. In particular, cerebral imaging and EEG are usually not helpful, unless there is strong evidence of seizure activity or an intracranial cause based on the history (such as change in mental status after a blow to the head) or if focal neurologic signs or evidence of seizure activity is detected on physical examination (46). These studies are also not useful when a patient becomes delirious over the course of a hospitalization (47). Of note, delirium can occasionally be a pre-

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Table 1. Key History and Physical Examination Components for Delirium

Component	Notes
History	
Time course of the mental status or behavioral changes	New onset, fluctuating course suggestive of delirium; usually obtained from family member or caregiver rather than patient; patient may also have symptoms of depression or dementia, but an acute change should prompt an evaluation for potential delirium
Association of mental status changes with other events, including medication changes and development of physical symptoms	Obtained from review of the medical record or from a family member or caregiver
Medication history, including over-the-counter medications	Careful review of all medications taken, including pharmacy fill data and information from electronic health record to ensure an accurate list of medications is obtained
Sensory deprivation assessment	Absence of glasses or hearing aids normally worn by the patient
Pain assessment	Delirium has been associated with severe pain, especially in patients unable to effectively communicate; pain may be manifested only by agitation
Physical examination	
General medical examination, focusing on cardiac, pulmonary, and neurologic elements	Provides clues to causes of delirium; remember to look for transdermal patches
Cognitive examination, including attention testing (see the Box: Commonly Used Tests of Attention)	Inattention is the hallmark cognitive deficit in delirium; patients with Lewy body dementia may have symptoms at baseline that are similar to dementia (behavioral disturbances, fluctuating course); even in these patients, an acute change should be evaluated and managed as delirium

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senting sign of a stroke (48), so if the risk factors, history, and physical examination are suggestive, cerebral imaging may be warranted.

What other disorders should clinicians consider in patients with suspected delirium?

Major differential diagnoses of delirium are dementia; depression and other acute psychiatric syndromes; and subsyndromal delirium, also known as partial syndrome of delirium (1). In many cases, it is not truly a “differential” diagnosis because these syndromes can coexist and in some cases are risk factors for one another.

The most common diagnostic issue is whether a newly present-

ing confused patient has dementia, delirium, or both. To determine this, the physician must learn the patient's baseline status from either prior documentation or information provided by family members or others who know the patient. An acute change in mental status from baseline is not consistent with dementia and suggests delirium. It is important to note that a new major (or minor) neurocognitive disorder cannot be diagnosed during delirium. In addition, a rapidly fluctuating course (over minutes to hours) and an abnormal level of consciousness are highly suggestive of delirium. Of note, the incidence of delirium in hospitalized patients with dementia (chronic brain failure) is substantial. Pa-

Laboratory, Imaging, and Other Studies to Consider in the Evaluation of Delirium*

Basic laboratory assessment, including:

- Complete blood count: Infection and severe anemia
- Serum electrolytes: Electrolyte disorders, especially hyponatremia and hypernatremia
- Blood urea nitrogen, creatinine: Dehydration and occult renal failure (rare)
- Glucose: Hypoglycemia, severe hyperglycemia, hyperosmolar state
- Liver function tests (aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase): occult cholangitis, choledocholithiasis, hepatic injury

Infectious work-up:

- Chest radiography: Pneumonia if there is fever or physical findings
- Urinalysis, culture: consider urinary tract infection when associated with fever or other genitourinary symptoms
- Lumbar puncture: High suspicion of meningitis or subarachnoid hemorrhage based on history and physical examination or if delirium is persistent, unexpected, or unexplained or occurs in younger patients

Electrocardiogram: Myocardial infarction and arrhythmia

Venous blood gases: Hypercarbia in chronic obstructive pulmonary disease

Drug levels: Delirium can occur with “normal” serum levels of some drugs

Toxic screen: If ingestion is suspected, more common in younger patients

Cerebral imaging with CT, MRI: High suspicion of stroke or hemorrhage based on history and physical examination or if delirium is persistent, unexpected, or unexplained or occurs in younger patients

Electroencephalography: If occult seizure is suspected; often shows diffuse slow-wave activity, but is rarely helpful in evaluation and treatment of reversible causes

CT = computed tomography; MRI = magnetic resonance imaging.

** The evaluation should be targeted at predisposing and precipitating factors in the appropriate clinical context.*

tients with dementia have a 2–5 times increased risk for developing delirium (that is, delirium superimposed on dementia) (49); thus, a diagnosis of preexisting dementia does not rule out delirium and may make it more likely.

Depression may also be confused with hypoactive delirium. In one study, a third of patients undergoing psychiatric consultations for depression in the acute care setting had hypoactive delirium (50). Certain acute psychiatric syndromes, such as mania or acute psychosis, have a presentation like that of hyperactive delirium. Initially, it is best to evaluate and manage hyperactive patients as if they have delirium rather than attributing the presentation to psychiatric disease and missing a serious underlying medical disorder.

Patients who present with some but not all diagnostic features of delirium have subsyndromal delirium. These patients share a spectrum of outcomes like patients meeting full diagnostic criteria for delirium and should be evaluated and managed similarly, although the association of

subsyndromal delirium and progression to delirium or worse outcomes in critically ill patients is uncertain due to a paucity of evidence (51, 52).

When should clinicians consider subspecialty consultation for diagnosis of delirium?

Because the spectrum of contributing causes is broad and rarely involves the central nervous system, a general internist (preferably one who is familiar with the patient's baseline mental status) is usually best suited to guide the diagnosis and evaluation of delirium. If the cause of delirium is uncertain, consultation with experts in geriatric medicine, psychiatry, neurology, or medical/surgical intensive care may help guide evaluation. No data have evaluated whether particular specialists are superior to others in delirium evaluation and management. Therefore, whom to consult should be based on patient characteristics (geriatric medicine for very old patients) or setting (intensivists for ICU patients) and availability.

Diagnosis... For hospitalized patients with altered cognition, clinicians should assess for delirium first, followed by subsyndromal delirium, depression, and other acute psychiatric syndromes, and then dementia. This order is based on the reversibility and treatability of each disorder and the acute consequences of missing the diagnosis.

CLINICAL BOTTOM LINE

When should clinicians consider hospitalization for suspected delirium?

The decision to hospitalize a patient with suspected delirium requires consideration of several factors, including timeliness of the diagnostic evaluation, clinical

stability, and social support. Not all patients with delirium require hospitalization, and hospitalization may in fact exacerbate the condition. Outpatient management may be appropriate if the diagnostic work-up can be done in a timely and thorough fashion;

Treatment

63. Riker RR, Shehabi Y, Bokesch PM, et al; SED-COM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA*. 2009;301:489-99. [PMID: 19188334]
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68. Rudolph JL, Archambault E, Kelly B; VA Boston Delirium Task Force. A delirium risk modification program is associated with hospital outcomes. *J Am Med Dir Assoc*. 2014;15:957.e7-11. [PMID: 25306293]
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patient safety can be ensured; and treatment of the conditions causing delirium is straightforward, such as reversal of drug adverse effects or treatment of simple infections. It is also important that such outpatients have a dedicated caregiver who can alert the primary care physician promptly if the patient's status does not improve or acutely worsens. It is best to diagnose and treat the delirious patient in an environment they are familiar with, if possible. Hospitalization may be particularly traumatic for patients with underlying cognitive impairment or frailty.

However, hospitalization may be necessary when delirium is associated with a destabilizing medical illness, such as sepsis or myocardial infarction, or because of inadequate support at home. In making this decision, it is important to consider the high risk for nosocomial complications and that disorientation caused by an unfamiliar environment may exacerbate the delirium. A study found that carefully selected patients with acute conditions managed in a "home hospital" had a lower rate of delirium than similar patients managed in a traditional hospital setting (53, 54). Because adequate home clinical and social supports are often not available, many patients with delirium are hospitalized.

What nonpharmacologic measures are useful?

Nonpharmacologic measures are the cornerstone of delirium treatment. The primary therapy for delirium involves identification and treatment of its causative factors. Verbal comfort and reassurance by the hospital staff and provision of a companion are preferable to drug therapy. First and foremost, management involves identification and treat-

ment of underlying disease processes as well as removal and reduction of associated contributing factors. Such factors include psychoactive medications, fluid and electrolyte abnormalities, severe pain, hypoxemia, severe anemia, infections, sensory deprivation, and significant immobility. Particularly in elderly patients, it may not be possible to identify a single cause of delirium. Because there is a cumulative effect of many vulnerability factors at baseline and acute precipitating factors, small gains in several factors may yield positive results overall (1).

Psychoactive medications are among the most important and reversible contributors to delirium and therefore warrant particular attention. Medication classes associated with the highest risk include benzodiazepines, sedatives-hypnotics, medications with strong anticholinergic properties, opioid analgesics, and prodopaminergic agents (55, 56). In many cases, good alternatives exist and should be used if possible (**Table 2**). Benzodiazepines, in particular, are commonly used medications with strong associations with delirium.

When nonpharmacologic interventions are insufficient, should clinicians consider drug therapy? If so, which drugs are useful, and what are the adverse effects?

There is no medication to treat delirium; rather, there are medications that can cause sedation (for example, antipsychotics) when patients have agitation and other symptoms. Experts have suggested that the sedative effect of the medications converts the hyperactive/agitated delirium to a more hypoactive form, giving a false sense of positive response (57). Of note, hypoactive delirium portends a worse prognosis for the patient. Although antipsychotics are widely pre-

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78. Australian Commission on Safety and Quality in Health Care. Delirium Clinical Care Standard. July 2016.
79. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018;46:e825-e873. [PMID: 30113379]

scribed to delirious patients, they are not recommended unless the patient's symptoms are hindering their ability to receive treatment or are endangering themselves or those caring for them (40). In fact, patients prescribed an antipsychotic medication during hospitalization have a 4-fold increased risk for developing aspiration pneumonia (58). Thus, pharmacologic intervention must be used cautiously because it may prolong delirium and increase risk for complications by converting hyperactivity to stupor and increasing the risk for a fall or aspiration.

Medications to manage the agitation of delirium should be used sparingly and at the lowest effective doses for the shortest duration. Antipsychotics are the most common class of medications used for delirium symptoms, al-

though it is becoming increasingly clear that indications for their use are limited due to lack of efficacy and potential adverse effects (39–41). Few head-to-head trials have compared different types of antipsychotics, and it is not clear that one is consistently better than another. In the inpatient setting, trials have shown that haloperidol, when used to treat agitated symptoms of delirium, has efficacy similar to that of atypical antipsychotics. Both atypical and typical antipsychotics have a range of potential adverse effects, including oversedation, QTc prolongation, risk for aspiration, and increased risk for death.

In older patients with mild delirium who are in distress, are agitated, and cannot safely receive care otherwise, low doses of antipsychotics may be used for their sedative properties, with careful reassess-

Table 2. Drugs That May Cause Delirium and Potential Substitutes*

<i>Agent</i>	<i>Potential Mechanism Leading to Delirium</i>	<i>Potential Substitute</i>	<i>Notes</i>
Benzodiazepines (long- and short-acting)	CNS sedation	Nonpharmacologic sleep management; if required for patient safety, use short-acting in smallest effective dose	May be required for sedation in critical care setting; associated with precipitation of or worsening delirium
Alcohol	CNS sedation	If history of regular/significant intake, consider withdrawal syndrome and treat appropriately	-
Antidepressants (the tertiary amine tricyclic agents: amitriptyline, imipramine, doxepin)	Anticholinergic toxicity	Should be reserved for patients who do not respond to first-line treatment with SSRIs or SNRIs	-
Antihistamines, especially first-generation (e.g., diphenhydramine)	Anticholinergic toxicity	Nonpharmacologic sleep protocol; alternative decongestant strategies	Often included in over-the-counter preparations for sleep
Anticholinergics: bladder antispasmodics	Anticholinergic toxicity	Consider behavioral interventions	Newer agents may have fewer CNS adverse effects
Opioid analgesics	Anticholinergic toxicity, CNS sedation, constipation	Opiate-sparing analgesic regimens; use the lowest effective dose (opioid metabolites can accumulate in renal impairment) and provide supportive measures (e.g., to prevent constipation)	-
Antipsychotics	Anticholinergic toxicity, CNS sedation	Avoid use altogether; if use is necessary for patient safety and care delivery, use lowest effective dose	Discuss risks and potential benefits with patient or surrogate decision maker
Antibiotics, especially fluoroquinolones	GABA and NMDA receptor effects	Choose alternative antimicrobial agent when possible	Can also be associated with hypoglycemia, which may worsen delirium

CNS = central nervous system; GABA = γ -aminobutyric acid; NMDA = *N*-methyl-D-aspartate; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

* Almost any medication can cause or contribute to delirium if the time course is appropriate. Clinicians should consider the risks and benefits of all medications in older patients.

ment before increasing the dose. In more severe delirium, slightly higher doses may be used initially. Clinicians must be careful to assess for akathisia (motor restlessness), a potential adverse effect of high-potency antipsychotic medications that can be confused with worsening delirium. Haloperidol should be avoided in older persons with parkinsonism and Lewy body disease in favor of an atypical antipsychotic with fewer extrapyramidal effects.

For critically ill patients in the ICU setting, the risk-benefit ratio of medication adverse effects versus the removal of lines and devices often favors pharmacologic treatment. Nevertheless, routine use of antipsychotic medication to prevent or manage delirium is not recommended (39, 40). Recent guidelines suggest optimizing nonpharmacologic strategies and, when sedation is required, using dexmedetomidine in mechanically ventilated adults (59). Dexmedetomidine is an α -adrenergic agonist used for sedation in patients who are intubated and mechanically ventilated in the ICU. Some studies suggest that it can reduce the incidence and duration of ICU delirium, possibly because of its analgesic properties, reducing the exposure to higher doses of opiates (60–62). Because of this, dexmedetomidine is commonly used as an alternative to benzodiazepines for sedation in critically ill patients (63, 64). In contrast, despite the association of anticholinergic medications with delirium, trials of cholinesterase inhibitors have not shown favorable results (65). In all cases where such “pharmacologic restraints” are used, the health care team must clearly identify the target symptoms necessitating their use, frequently review the efficacy of these drugs in controlling the target symptoms, and

assess the patient for adverse effects and complications. In addition to identifying and addressing contributing factors, management of patients with delirium requires attentive supportive care and avoidance of iatrogenic complications (66) (see the Box: Key Steps in the Supportive Care of Delirious Patients).

Are physical restraints ever appropriate?

Physical restraints are always objectionable but may be required to control violent behavior or to

Key Steps in the Supportive Care of Delirious Patients

Enhance mobility

- Minimize indwelling catheters and other “tethers,” such as intravenous lines, cardiac telemetry, or continuous pulse oximetry
- Eliminate physical restraints
- Get patient out of bed for meals and provide mealtime assistance as needed to enhance nutrition and mobility and reduce risk for aspiration
- Ambulate the patient at least twice daily when the patient is able

Monitor urinary and bowel output; avoid urine retention and fecal impaction, which can contribute to delirium

Normalize patient's daily routine

- Provide adequate sensory input, including use of glasses and hearing aids and provision of clocks, calendars, and adequate lighting
- Provide frequent orientation and structured interpersonal contact to facilitate cognitive “reconditioning”
- Adopt healthy sleep-wake cycles: encourage nighttime sleeping by reducing environmental stimuli, including minimizing staff noise, using vibrating (silent) pagers, eliminating waking for vital signs except if essential, reducing hospital ward lighting, and turning off televisions and radios; bundle necessary care to minimize disruption and promote sleep

prevent the removal of important devices, such as endotracheal tubes, intra-arterial devices, and catheters, particularly in the ICU. In these cases, calm reassurance provided by a continuous observer or family member when possible may be more effective than restraints. When restraints are used, the indicators for use should be frequently reassessed, and the restraints should be removed as soon as possible. Physical restraints probably do not decrease the rate of falls among confused patients and may increase risk for injury (67). Reducing the use of restraints is associated with improved outcomes in patients at risk for delirium (68). Alarms are another form of restraint to limit patient freedom of movement; bed and chair alarms are frequently used in attempts to prevent unsupervised ambulation and decrease risk for falling. However, these types of alarms have not proved to be effective at decreasing fall risk and can cause distress for the patient (69).

When should clinicians consider subspecialty consultation for management of delirium?

As with diagnosis, most cases of delirium can be managed by the primary care physician or hospital-based generalist, and this is a core competency for hospital medicine attending physicians (70). Consultation may be helpful for persons who do not improve after obvious causes have been addressed. Medical/surgical intensivist consultation may be indicated for critically ill patients with delirium. Geriatrics consultation may be particularly helpful for management of vulnerable older persons with several medical problems, medications, or complex rehabilitative needs. At the end of life, palliative care consultation can be

helpful to manage distressing symptoms. Psychiatric consultation is particularly helpful for younger patients with extreme agitation or other life-threatening behavioral disorders requiring high-dose or alternative sedating medications. These patients are vulnerable to dangerous adverse effects; such drug administration should be guided by physicians experienced in the use of these medications at high doses.

What is the risk for recurrence after an initial episode, and how should clinicians follow patients?

Patients with delirium remain vulnerable, even after the initial confusion clears. A study found that postoperative cardiac surgical patients who developed in-hospital delirium had significant long-term cognitive impairment that remained at 1 month and 1

year after the surgery (71). This is also true for patients undergoing noncardiac major elective surgery (72). Clinicians should develop both short- and long-term monitoring plans for patients with delirium.

In the short term, patients with delirium require continued monitoring of medical, cognitive, and functional status until they return to baseline. The frequency of monitoring depends on the setting and ongoing instability. At a minimum, presence and severity should be monitored daily in the hospital; weekly in recently discharged patients, including those admitted to rehabilitation facilities; and monthly upon the patient's return to the community. More than a dozen tools that can be operationalized from many CAM-based

Key Recommendations of the NICE Guideline for Delirium

Assess delirium risk factors when patients are admitted to the hospital, especially those aged ≥ 65 years, those with cognitive impairment, those with a current hip fracture, and those with severe illness

Prevent delirium by addressing risk factors using a tailored 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

Diagnose delirium using a clinical assessment based on formal criteria and conducted by a trained health care professional; document in the medical record

Manage delirium by:

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

If a person with delirium is distressed or is 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 appropriate, consider short-term (usually ≤ 1 week) haloperidol at the lowest clinically appropriate dose and titrate cautiously according to symptoms
- Avoid using antipsychotic drugs if possible in patients with Parkinson disease or Lewy body dementia

NICE = National Institute for Health and Care Excellence.

instruments are used to measure delirium severity (73, 74). Those who are acutely delirious and are being managed as outpatients require frequent monitoring, perhaps daily on an initial basis, with reduced frequency as their status improves. Persistent or worsening symptoms may require further modifications of the treatment plan, hospitalization, or increased support services.

Medical conditions contributing to delirium may require follow-up testing, such as ensuring correction of electrolyte disturbances, heart failure, and infections.

Cognitive function can be monitored by using measures similar to those for delirium diagnosis. Assessment of activities of daily living (ADL) is particularly useful for monitoring functional recovery from delirium. Recovering patients will have an increased need for assistance that can be

tapered as delirium and function improve. Patients whose cognitive or ADL function does not return to baseline 1-2 months after an episode of delirium should be considered for comprehensive geriatrics assessment and/or neuropsychological testing.

Minimizing the duration of delirium is an important treatment goal. It is thought that the shorter the duration of delirium, the more fully a patient will recover, although it may take weeks to months. Patients with delirium lasting longer than 2 weeks are much less likely to return to baseline function (71).

Delirium, even if resolved, confers increased risk for poor long-term outcomes (14). Patients who have recovered completely from delirium remain vulnerable to repeated episodes, cognitive and functional decline, and death. Interventions to improve these long-term outcomes have not been well developed or studied and have been debated (75). At the very least, these patients should be considered to have high risk for delirium when rehospitalized or having surgery, and appropriate preventive measures should be implemented.

Treatment... The key elements of delirium treatment are identifying causative and contributing factors (for example, medications, infections, electrolyte disturbances), addressing or reversing these factors to the extent possible, and providing excellent supportive care to reduce risk for superimposed complications. Minimizing the duration of delirium is an important treatment goal.

CLINICAL BOTTOM LINE

Practice Improvement

What measures do stakeholders use to evaluate the quality of care for patients with delirium?

No formal federal guidelines or measures exist in the United States for patients with delirium. Many organizations in the United States and other countries have published best practice guidelines. A review from 2016 assessed the quality and validity of delirium guidelines and found wide variability. Specific limitations that were noted

include a reliance on expert opinion and limited evidence of evaluation studies of the guidelines themselves (76). However, guidelines have been widely disseminated and followed in Scotland and Australia (77, 78). In the United States, the Society of Critical Care Medicine's recommendations focus on caring for critically ill adult patients, including delirium management, and offer a framework that can be extrapolated to other care environments (79). A recent comprehensive

guideline was updated in 2019 by the National Institute for Health and Care Excellence (NICE) of the U.K. National Health Service (key contents of this guideline are summarized in the Box: Key Recommendations of the NICE Guideline for Delirium). A notable difference from the 2010 version is that olanzapine was removed for treatment of symptoms in delirious patients who are experiencing distress or pose a risk to themselves or others.

In the Clinic Tool Kit

Delirium

Patient Information

<https://medlineplus.gov/delirium.html>
<https://medlineplus.gov/ency/article/000740.htm>
<https://medlineplus.gov/spanish/ency/article/000740.htm>
Patient information and handouts on delirium in English and Spanish from the National Institutes of Health's MedlinePlus.

www.mayoclinic.org/diseases-conditions/delirium/symptoms-causes/syc-20371386
Information on delirium symptoms, causes, diagnosis, and treatment from the Mayo Clinic.

www.healthinaging.org/tools-and-tips/tips-managing-delirium-older-adults
Tips for managing delirium in older adults in English and Spanish from the American Geriatrics Society's Health in Aging Foundation.

Information for Health Professionals

www.nice.org.uk/guidance/cg103
National Institute for Health and Care Excellence 2019 updated guideline on prevention, diagnosis, and management of delirium.

www.sccm.org/Research/Guidelines/Guidelines/Guidelines-for-the-Prevention-and-Management-of-Pa
Society of Critical Care Medicine guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the intensive care unit.

www.sign.ac.uk/our-guidelines/risk-reduction-and-management-of-delirium
2019 guideline on risk reduction and management of delirium from the Scottish Intercollegiate Guidelines Network.

www.safetyandquality.gov.au/sites/default/files/migrated/Delirium-Clinical-Care-Standard-Web-PDF.pdf
2016 delirium clinical care standards from the Australian Commission on Safety and Quality in Health Care.

In the Clinic

WHAT YOU SHOULD KNOW ABOUT DELIRIUM

In the Clinic
Annals of Internal Medicine

What Is Delirium?

Delirium is a sudden change in mental state. It is marked by sudden onset of confusion that may come and go. The confusion may include disorientation, decreased consciousness, trouble focusing, or difficulty remembering recent events. Delirium may be hypoactive, where you are tired, sleepy, and less aware of your surroundings, or hyperactive, where you are restless or agitated and more aroused.

How Does It Differ From Dementia?

Delirium comes on suddenly, over a few hours or days. It is usually temporary and goes away once the cause is treated. Dementia is a chronic condition that develops over months or years and does not get better. However, dementia and delirium can coexist. In fact, having dementia is a risk factor for developing delirium.

What Are Some Symptoms?

- Sudden change in mental status
- Trouble paying attention or staying focused
- Disorganized thinking, rambling, or speaking incoherently
- Abnormal level of consciousness

What Are the Risk Factors?

Delirium usually affects older people; however, individuals of any age can be affected. It is common in people who are hospitalized, especially those in the intensive care unit. It is important to prevent, quickly diagnose, and treat delirium in order to reduce the risk for complications and death. Some common risk factors and triggers include:

- Preexisting cognitive impairment
- Vision or hearing impairment
- Severe illness
- Certain health conditions, such as depression or pain
- Recent surgery or anesthesia
- Certain medications, drugs, or alcohol
- Dehydration
- Sleep deprivation
- Immobility

How Is It Diagnosed?

- Your doctor will screen for delirium if you are hospitalized and have other conditions that affect the brain, have other medical conditions, or are admitted to the intensive care unit.
- Your doctor will take a medical history. This will include asking a family member or other



caregiver about your usual mental status to understand when mental changes began.

- Your doctor will ask for a list of the medicines you take and conduct a physical examination.
- Your doctor will ask you some questions to assess your mental state. These may include asking what day of the week it is or asking you to recite the months of the year in reverse order.
- Blood tests and brain scans are not needed to diagnose delirium. However, your doctor may need to use these tests to see what is causing the delirium (such as a seizure or low blood sugar).

How Is It Treated?

- Your doctor will identify and treat the cause of delirium. This may mean changing the type of medicine you take or treating a simple infection.
- It is important that you have a dedicated caregiver who can let your doctor know if your condition is getting worse and can stay with you while you are confused.
- Make sure that hearing and visual aids are available and used if needed.
- It is best to treat delirium at home or in an environment you are familiar with. Hospitalization is not always needed and can make delirium worse. However, it may sometimes be necessary when delirium is caused by certain medical conditions or when you do not have dedicated support at home.
- There is no medicine that can prevent or treat delirium. Medicine would typically only be used to calm you if you are endangering yourself or those caring for you.

Questions for My Doctor

- What can I do to prevent delirium?
- What medications cause delirium?
- What is the most likely cause of delirium?
- What interventions can help prevent delirium in the hospital?
- What can I do to prevent delirium from happening again?

For More Information



American College of Physicians
Leading Internal Medicine, Improving Lives

Health in Aging Foundation

www.healthinaging.org/a-z-topic/delirium/basic-facts

MedlinePlus

<https://medlineplus.gov/delirium.html>