In the Clinic

Delirium

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

The information contained herein should never be used as a substitute for clinical judgment.

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Screening and Prevention

Delirium is an acute state of confusion marked by sudden onset, fluctuating course, inattention, and at times an abnormal level of consciousness (1). Delirium is extremely common but can be challenging to diagnose. Its manifestations range from acute agitation, which accounts for less than 25% of all cases (1), to the much more common but less frequently recognized hypoactive, or quiet, variant. Delirium, which is an acute change in mental status, must be differentiated from dementia, which is usually characterized by a slower progression. However, delirium and dementia frequently coexist. Approximately one third of patients aged 70 years or older admitted to the general medical service of an acute care hospital experience delirium: One half of these are delirious on admission to the hospital; the other half develops delirium in the hospital (1). Postoperative delirium rates among seniors range from 15% to 25% after elective surgery (2), such as total joint replacement, to over 50% after high-risk procedures, such as hip fracture repair and cardiac surgery (3, 4). Among patients of any age admitted to intensive care units (ICUs), the prevalence of delirium may exceed 75% (5), and the cumulative incidence of delirium at the end of life is reported to be as high as 85% (6).

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 and is at increased risk for death for up to 2 years.

A recently published meta-analysis that included almost 3000 patients followed for a mean 22.7 months showed that delirium was independently associated with an increased risk for death (odds ratio [OR], 2.0 [95% CI, 1.5 to 2.5]), institutionalization (OR, 2.4, [CI, 1.8 to 3.3]), and dementia (OR, 12.5, [CI, 11.9 to 84.2]) (7). Further, another recent systematic review found that the persistence of delirium may play an important role in its association with poor long-term outcomes (8). In this review, delirium persistence rates at discharge, 1, 3, and 6 months were 44.7%, 32.8%, 25.6%, and 21%, respectively, and outcomes (mortality, nursing home placement, function, cognition) of patients with persistent delirium were consistently worse than those of patients who recovered.

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

Delirium is best understood as a multifactorial geriatrics syndrome, although patients of any age can be affected. Geriatrics syndromes, including delirium, falls, incontinence, and failure to thrive, share several characteristics (9). Most notably, risk factors are multifactorial and often lie outside of the presenting organ system, which in the case of delirium is the 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. Several large epidemiologic studies and systematic reviews have defined predisposing and precipitating factors for delirium. Based on this model, an individual'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 (10) (Box: Common Risk Factors for Delirium). For example, a young,

Common Risk Factors for Delirium

Predisposing
- Advanced age
- Preexisting dementia
- History of stroke
- Parkinson disease
- Multiple comorbid conditions
- Impaired vision
- Impaired hearing
- Functional impairment
- Male sex
- History of alcohol abuse

Precipitating
- New acute medical problem
- Exacerbation of chronic medical problem
- Surgery/anesthesia
- New psychoactive medication
- Acute stroke
- Pain
- Environmental change
- Urine retention/fecal impaction
- Electrolyte disturbances
- Dehydration
- Sepsis

otherwise-healthy person may become delirious after being subjected to 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.

Should clinicians screen hospitalized patients for delirium, and if so, how?

Delirium is a common, morbid condition; however, 50% to 80% of cases go unrecognized and undocumented by the treating clinical team (11). Trials that have assessed the effectiveness of systematic programs to improve case findings and treatment of delirium have shown significantly improved detection rates and modest improvements in outcomes (12). Therefore, it seems prudent to screen hospitalized patients who are at risk for delirium (either due to predisposing factors or the acute situation), including those with preexisting cognitive impairment or multiple comorbid conditions or those admitted to the ICU.

Screening methods are similar to those for diagnosis. The briefest screening methods use the Confusion Assessment Method (CAM) diagnostic algorithm (13) (Box: Confusion Assessment Method Diagnostic Algorithm), which examines 4 key features of delirium: acute change in mental status and fluctuating course, inattention, disorganized thinking, and abnormal level of consciousness. Diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4. Although CAM is considered to be an accurate approach for diagnosis of delirium, sensitivity varies depending on the assessment methods used (14, 15). The literature suggests that completing CAM by using routine observations from clinical care is probably *not* sufficient and that a standardized mental status assessment should be done to improve its sensitivity (16).

The 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 (17). The CAM-ICU is valid, reliable, and can be completed in a few minutes. Patients in the ICU are at such high

The Confusion Assessment Method Diagnostic Algorithm

Feature 1. Acute change in mental status and fluctuating course
- Is there evidence of an acute change in cognition from baseline?
- Does the abnormal behavior fluctuate during the day?

Feature 2. Inattention
- Does the patient have difficulty focusing attention (e.g., easily distracted, has difficulty keeping track of what is being said)?

Feature 3. Disorganized thinking
- Does the patient have rambling or irrelevant conversations, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

Feature 4. Abnormal level of consciousness
- Is the patient anything besides alert—hyperalert, lethargic, stuporous, or comatose?

The diagnosis of delirium requires features 1 and 2 and either 3 or 4.

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risk for delirium that they should be screened daily, if not more frequently. There are several options for assessing mental status before completing the CAM diagnostic algorithm in non-ICU patients. The Mini-Mental State Examination (which requires a license for use) (18) takes up to 15 minutes and provides a limited assessment of attention and level of consciousness. The CAM-ICU can be used, but sensitivity may be lower than that of CAM in verbal patients (19). Alternatively, screeners can assess level of consciousness by using a standardized measure, such as the RASS (Richmond Agitation Sedation Scale) (20), and attention by using 1 or more additional items (see Box in Diagnosis section).

A recent review that summarized multiple assessment methods concluded that CAM has the best available supportive evidence as a bedside delirium instrument (16).

Are there effective strategies for prevention?

Among all the interventions for delirium, the strongest evidence supports the effectiveness of prevention. The Yale Delirium Prevention Trial tested the effectiveness of the Hospital Elder Life Program (HELP), 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 one or more of these risk factors received targeted interventions to address them. The interventions were delivered by specially trained teams of volunteers under the guidance of specialized staff. Among these, the most creative and successful was a nonpharmacologic sleep protocol that involved trained volunteers offering patients warm milk, back rubs, and soothing music at bedtime; this intervention substantially reduced the use of sedative–hypnotic medication (21). Delirium in the intervention group was significantly reduced (OR, 0.60, [CI, 0.39-0.92], number needed to treat [NNT] = 19) (22). This approach has been implemented widely.

Another approach with proven benefit for prevention of delirium is proactive geriatrics consultation in elderly patients undergoing hip fracture repair. In a randomized, controlled trial, the proactive geriatrics consultation group achieved a 36% reduction [CI, 10% to 62%], NNT = 6) in the incidence of delirium (3). Consultation began before surgery and continued throughout the duration of hospitalization. Daily recommendations were based on a structured protocol that addressed 10 key risk factors for delirium, such as limitation of psychoactive medications and timely removal of indwelling urinary catheters. Co-management of hip fracture patients and other vulnerable surgical populations by surgeons and geriatricians and/or internists is increasing in popularity.

Recently, several preventive approaches have not reduced the incidence of delirium but have reduced 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 (23, 24). A very different approach involved administration of low-dose haloperidol (0.5 mg 3 times daily for 3 days) in high-risk hip surgery. This strategy also reduced the severity and duration (but not incidence) of postoperative delirium (25). It is important to note that all of these models were preventive—that is, they were started before the onset of delirium.

One methodological issue may limit the clinical utility of prevention trials that have reduced delirium severity alone. Delirium severity scales often disproportionately weight "positive" symptoms, such as agitation, perceptual disturbances, or delusions (26, 27). Reduction of these symptoms through interventions that use sedating or antipsychotic medication may result in an apparent reduction in delirium severity. However, studies suggest that patients with hypoactive delirium may have equal or worse outcomes than those with hyperactive delirium (28).

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Screening... The most effective, proven approach to prevent delirium is proactive, multifactorial, nonpharmacologic interventions, such as the HELP program or proactive geriatrics consultation for high-risk surgical patients. 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 CAM.

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 the presence of delirium.

What elements of the history and physical examination indicate delirium?

The diagnosis of delirium is based entirely on the history and physical examination. 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 (sudden) onset is most consistent with delirium. Whether there have been fluctuations in mental status, such as the patient seeming normal at some times and very confused at others, is also an essential element of the history.

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 rambling and incoherent speech, is also important.

Once the history is obtained from a family member and/or caregiver and the mental status examination is completed, the diagnosis of delirium can be determined using the CAM Diagnostic Algorithm (see the Box) (13).

Another important element of the history and physical examination is evaluating for underlying causes. These include a medication history, vital signs, and general medical examination. Table 1 summarizes the key history and physical examination components for both the diagnosis and evaluation of delirium.

Commonly Used Tests of Attention

- Digit span—up to 5 forwards and 4 backwards
- Days of the week, months of the year backwards
- Continuous performance task—raise hand when hears a certain letter in a list
- Attention screening examination—show pictures; ask patient to remember and recall
- Recite a list of serial 7s or 3s
- Spell W-O-R-L-D backwards

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

Laboratory testing, brain imaging, and electroencephalography (EEG) do not substitute for history and physical examination in the diagnosis of delirium. However, these studies can be useful to identify possible causes of delirium and correctable contributing factors, particularly when they are carefully selected on the basis of history and physical examination. When ordered as an unselected "delirium battery," the yield of these tests and procedures is apt to be low. In particular, cerebral imaging and EEG are usually not helpful in the evaluation of delirium, unless there is strong evidence of 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 seizure activity is detected on physical examination (29). Notably, delirium can be a presenting sign of a stroke (30), so if the risk factors, history, and physical examination are suggestive, cerebral imaging may be warranted. The Box: Laboratory, Imaging, and Other Studies summarizes the use of laboratory, imaging, and EEG studies in delirium.

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

Major differential diagnoses of delirium are dementia; depression; other acute psychiatric syndromes; and subsyndromal delirium, also known as the partial syndrome of delirium (1). In many cases, it is not truly a "differential" diagnosis, since these syndromes can coexist and indeed are risk factors for one another. Instead, it should be considered a series of independent questions: Does this patient have delirium? . . . dementia? . . . depression?

The most common diagnostic issue is whether a newly presenting confused patient has dementia,

Table 1. Key History and Physical Examination Elements for Delirium

Variable	*Notes*
History	
Time course of the mental status changes	Relatively abrupt onset, fluctuating course suggestive of delirium; usually obtained from family member or caregiver, not from the patient
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. Key medication classes on which to focus: sedative-hypnotics, barbiturates, alcohol, antidepressants, anticholinergics, opioid analgesics, antipsychotics	A "brown bag" test, in which all medicines, including over the counter, are brought in for review; may be helpful in the outpatient setting
Sensory deprivation	Absence of glasses or hearing aids normally worn by the patient
Pain assessment	Delirium has been associated with severe pain as a contributing factor Pain may be manifested only by agitation
Physical examination	
Vital signs, including oxygen saturation	Provide clues to underlying causes of delirium
General medical examination, focusing on cardiac and pulmonary examination	Provides clues to underlying causes of delirium
Neurologic examination, including mental status examination and examination for focal findings	Intracranial events rarely present with delirium in elderly patients
Cognitive examination, including attention testing (see the Box: Commonly Used Tests of Attention)	Inttention is the hallmark cognitive deficit in delirium

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

- Complete blood count: Infection and severe anemia
- Serum electrolytes: Electrolyte disorders, especially hyper- and hyponatremia
- BUN, creatinine: Dehydration and occult renal failure (rare)
- Glucose: Hypoglycemia, severe hyperglycemia, hyperosmolar state
- Albumin, bilirubin, international normalized ratio: Only if liver failure and hepatic encephalopathy are suspected (rare)
- Urinalysis, culture: Urinary tract infection (common in very frail elders)
- Chest x-ray: Pneumonia or congestive heart failure if there is fever or physical findings
- Electrocardiogram: Myocardial infarction and arrhythmia
- Arterial 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, unexplained, or occurs in younger patients
- Lumbar puncture: High suspicion of meningitis or subarachnoid based on history and physical examination or if delirium is persistent, unexpected, unexplained, or occurs in younger patients
- Electroencephalography: Often shows diffuse slow wave activity but is rarely helpful in evaluation and treatment of reversible causes

BUN = blood urea nitrogen; CT = computed tomography; INR = international normalized ratio; MRI = magnetic resonance imaging.

delirium, or both. To make this determination, the physician must know the patient's baseline status. In the absence of documentation of a baseline evaluation, information from family members, caregivers, or others who know the patient is essential. An acute change in mental status from baseline is not consistent with dementia and suggests delirium. In addition, a rapidly fluctuating course (over minutes to hours) and an abnormal level of consciousness are highly suggestive of delirium. Diffuse Lewy body dementia, which has among its features a fluctuating course and an abnormal level of consciousness, may be particularly difficult to distinguish from delirium. Even in these patients, however, acute changes should be evaluated and managed as delirium. Notably, the incidence of delirium in hospitalized dementia patients exceeds 65% (31), so a diagnosis of dementia does not rule out delirium in these patients—indeed, it makes it more likely.

Depression may also be confused with hypoactive delirium. In 1 study, a third of patients undergoing psychiatric consultations for depression in the acute care setting actually had hypoactive delirium (32). Certain acute psychiatric syndromes, such as mania or acute psychosis, have a presentation similar to 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 so-called subsyndromal delirium. There is a growing body of evidence that these patients may have a spectrum of outcomes similar to patients who meet the full diagnostic criteria for delirium and should be evaluated and managed similarly (33, 34).

When should subspecialty consultation be considered for patients with delirium?

The primary care physician usually is best suited to guide the

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diagnosis and evaluation of delirium, because knowledge of the patient's baseline mental status is key in the diagnosis and because the spectrum of contributing causes is broad and rarely involves the central nervous system. However, given the rapid pace of primary care practice, a consultant may have more time to review the data required to diagnose and evaluate delirium. Therefore, if needed, consultation with experts in geriatric medicine, psychiatry, neurology, or medical/surgical intensive care may be helpful with the differential diagnosis of delirium and to evaluate contributing factors. These consultants may also be helpful in guiding delirium treatment. No data have currently evaluated whether particular specialists are superior to others in delirium evaluation and management. Therefore, decisions about which discipline to consult are based primarily on patient characteristics (geriatric medicine for very old patients) or setting (intensivists for ICU patients).

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

CLINICAL BOTTOM LINE

Treatment

When should clinicians consider hospitalization for suspected delirium?

The decision to hospitalize a patient with suspected delirium requires consideration of multiple factors, including timeliness of the diagnostic evaluation, clinical stability, and social support. Not all patients with delirium require hospitalization, and in fact hospitalization may exacerbate the condition. Outpatient management may be appropriate if the diagnostic workup can be done in a timely and thorough fashion; patient safety can be assured; and treatment of the conditions causing delirium is straightforward, such as reversal of drug side effects or treatment of simple infections. It is also important that such outpatients have a dedicated family member who can alert the primary care physician promptly if the patient's status does not improve or acutely worsens. Nonhospital management may be particularly appropriate for nursing home residents, for whom diagnostic, therapeutic, and monitoring resources are greater than outpatients and for whom hospitalization may be particularly traumatic.

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 a new, unfamiliar environment may exacerbate the delirium. A study of 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 (35). However, because adequate home clinical and social supports are

often not available, many patients with delirium are hospitalized.

What nonpharmacologic measures are useful in treatment?

Nonpharmacologic measures are the cornerstone of delirium treatment. First and foremost, management involves identification and treatment 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 for delirium. Because there is a cumulative effect of many vulnerability factors at baseline and acute precipitating factors, small gains in several factors may yield impressive 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 the benzodiazepines, sedative-hypnotics, medications with strong anticholinergic properties, opioid analgesics, and pro-dopaminergic agents (36–39). In many cases, good alternatives exist and should be used if possible (Table 2). Meperidine has the strongest anticholinergic properties of any opioid analgesic and also has active metabolites that accumulate in the bloodstream; it has been associated with a high risk for delirium, and an alternative opioid should be used whenever possible (38). Benzodiazepines are another commonly used psychoactive medication class with strong associations with delirium.

Recently, the α-adrenergic agonist dexmedetomidine has been identified as a less delirium-causing alternative to benzodiazepines for sedation in critically ill patients (40). On the other hand, despite the association of anticholinergic medications with delirium, recent trials of cholinesterase inhibitors have not shown favorable results (41, 42).

In addition to searching for and addressing contributing factors, management of delirious patients requires attentive supportive care to meet their needs and to avoid iatrogenic complications (43, 44) (Box: Key Steps in Supportive Care).

Randomized trials of intervention programs that have adopted some or all of the measures described in the Box have shown a significantly reduced duration of delirium, length of stay for delirious patients, and a trend toward reduction in hospital mortality (45, 46).

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

The primary therapy for delirium involves the identification and treatment of its causative factors. Moreover, there are no Food and Drug Administration–approved drugs to treat delirium. However, drug therapy (off-label) is frequently used for such symptoms of delirium as delusions or hallucinations that are frightening to the patient or for patient behaviors that are dangerous to him- or herself or others. Even in these cases, verbal comfort and reassurance by the hospital staff and provision of a sitter or family companion may be preferable to drug therapy. Pharmacologic intervention must be used cautiously, as it may prolong delirium and increase the risk for complications by converting a hyperactive patient into a stuporous one whose risk for a fall or aspiration is increased.

Recently, several meta-analyses have examined pharmacologic treatment of agitation in delirium (47–50), although they contained few studies. One of these studies, done in young patients with AIDS, established the superiority of haloperidol to benzodiazepines (51). All of the other studies in

Key Steps in the Supportive Care of Delirious Patients

- Minimize indwelling catheters and other "tethers," such as intravenous lines, electrocardiography leads
- Eliminate physical restraints and mobilize the patient as soon as possible
- Monitor urinary and bowel output; avoid urine retention and fecal impaction, which can contribute to delirium
- Address nutritional needs, including assistance with meals and possible hand-feeding—delirious patients may have difficulty attending to food and are at risk for acute malnutrition
- Provide adequate sensory input, including use of glasses and hearing aids, provision of clocks, calendars, and adequate lighting
- Provide frequent orientation and structured interpersonal contact to facilitate cognitive "reconditioning"
- Adopt healthy sleep–wake cycles, encouraging night 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.

45. *Lundström M, Edlund A, Karlsson S, Brännström B, Bucht G, Gustafson Y. A multifactorial intervention program reduces the duration of delirium, length of hospitalization, and mortality in delirious patients. J Am Geriatr Soc. 2005;53:622-8. [PMID: 15817008]*
46. Pitkälä KH, Laurila JV, Strandberg TE, Tilvis RS. Multicomponent geriatric intervention for elderly inpatients with delirium: a randomized, controlled trial. J Gerontol A Biol Sci Med Sci. 2006;61:176-81. [PMID: 16510862]
47. Campbell N, Boustani MA, Ayub A, Fox GC, Munger SL, Ott C, et al. Pharmacological management of delirium in hospitalized adults—-a systematic evidence review. J Gen Intern Med. 2009;24:848-53. [PMID: 19424763]

the meta-analyses showed that the new generation of antipsychotics were equivalent to haloperidol. None of the studies used a placebo-control group. Based on this limited evidence, high-potency antipsychotics are considered the treatment of choice for agitation in delirium because of their low anticholinergic potency and minimal risks for hypotension or respiratory depression (49, 50).

In older patients with mild delirium, low doses of haloperidol (0.5 to 1 mg orally or 0.25 to 0.5 mg parenterally) should be used initially, with careful reassessment before increasing the dose. In more severe delirium, somewhat higher doses may be used initially (0.5 to 2 mg parenterally), with additional

Table 2. Drugs That May Cause Delirium and Potential Substitutes

Agent	*Potential Mechanism Leading to Delirium*	*Potential Substitute (Reference)*	*Notes*
Benzodiazepines, especially long-acting, including diazepam, flurazepam, chlordiazepoxide	Central nervous system sedation	Nonpharmacologic sleep management, intermediate agents (lorazepam); dexmedetomidine can be used as a sedative in the intensive care unit (40)	Associated with delirium in medical, surgical, and intensive care unit patients
Benzodiazepines: ultra–short-acting, including triazolam, alprazolam, midazolam	Central nervous system sedation and withdrawal	Nonpharmacologic sleep management, intermediate agents (lorazepam) (21)	Associated with delirium in case reports and series
Barbiturates	Severe withdrawal syndrome	Avoid inadvertent discontinuation, or substitute benzodiazepine	
Choral hydrate	Central nervous system sedation	Nonpharmacologic sleep protocol (21)	No better for delirium than benzodiazepines
Alcohol	Central nervous system sedation; withdrawal syndrome	If history of heavy intake, carefully monitor and use benzodiazepines if withdrawal symptoms occur	Alcohol history is imperative
Antidepressants, especially the tertiary amine tricyclic agents: amitriptyline, imipramine, doxepin	Anticholinergic toxicity	Secondary amine tricyclics: nortriptyline, desipramine. Selective serotonin reuptake inhibitors or other agents.	Secondary amines as good as tertiary for adjuvant treatment of chronic pain
Antihistamines, including diphenhydramine	Anticholinergic toxicity	Nonpharmacologic protocol for sleep (21); decongestants for colds	Obtain history of over-the-counter drug use
Anticholinergics: oxybutynin, other bladder antispasmodics	Anticholinergic toxicity	Lower dose, behavioral measures	Even newer agents may have central nervous system side effects
Opioid analgesics, especially meperidine	Anticholinergic toxicity; central nervous system sedation; fecal impaction	Consider using local, regional, and nonopioid analgesics as opioid-sparing strategies. Use scheduled rather than PRN dosing when possible. Use prophylactic strategies to prevent opioid side effects, such as fecal impaction.	Higher risk in patients with renal insufficiency. Must balance the risks from opioid use against the risks from pain.
Antipsychotics, especially low-potency agents	Anticholinergic toxicity; central nervous system sedation	Eliminate, or if necessary use low-dose, high-potency agents	
Anticonvulsants, especially primidone (Mysoline), phenobarbital, phenytoin	Mysoline is converted to phenobarbital, which is a sedating long-acting barbiturate	Consider alternative agent	Toxic reactions can occur despite "therapeutic" drug levels
Histamine-2 blocking agents	Anticholinergic toxicity	Lower dosage. Consider antacids or proton-pump inhibitors.	Usually seen with high-dose and/or intravenous use
Antiparkinsonian agents: levodopa-carbidopa, dopamine agonists, amantadine	Dopaminergic toxicity	Lower dose. Adjust dosing schedule.	Usually with end-stage disease and high doses.
Antiarrhythmics	Interfere with neuronal metabolic physiology	Lower dose; consider need for alternative agent	Highly lipophilic and cross blood–brain barrier
Almost any medication if time course is appropriate		Consider risks and benefits of all medications in the elderly	

dosing every 60 minutes as required for symptom management. One must be careful to assess for akathisia (motor restlessness), which may be an adverse effect of high-potency antipsychotic medications and can be confused with worsening delirium. Haloperidol should be avoided in older persons with parkinsonism and Lewy body disease—an atypical antipsychotic with less extrapyramidal effects may be substituted. The pharmacologic management of agitation in delirium is summarized in Table 3.

Higher-dose intravenous haloperidol may be the drug of choice for critically ill patients in the ICU setting. For such patients, the risk–benefit ratio of medication adverse effects versus the removal of lines and devices often favors pharmacologic treatment. Such therapy must be used with special caution in older persons. In addition to extrapyramidal effects, the potential for QT interval prolongation and torsade de pointes, neuroleptic malignant syndrome, and withdrawal dyskinesias are important concerns (52). 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.

Are physical restraints ever appropriate?

Physical restraints are always objectionable but may be required to control violent behavior or to 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 sitter or family member may be more effective than the use of restraints. Whenever 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 by confused patients and may increase the risk for injury. Restraints may also prolong delirium; their use has been shown to be an independent predictor of persistence of delirium to hospital discharge (53).

When should clinicians consider specialty consultation?

Similar to diagnosis, most cases of delirium can be managed by the primary care physician or hospital-based generalist. Consultation may be helpful for persons whose cause of delirium remains obscure or who do not improve after obvious causes have been addressed. Medical/surgical intensivist consultation may be indicated for delirious critical care patients. Geriatrics consultation may be particularly helpful for management of frail, older persons with several medical problems, medications, or complex rehabilitative needs. Psychiatric consultation is particularly helpful for younger patients with extreme agitation or other life-threatening behavioral disorders requiring high-dose or alternative sedating medications (Table 3). These patients are vulnerable to dangerous side effects, and such drug administration should be guided by physicians experienced in the use of these medications at high doses. Trials of specialty consultation for delirium have been mixed, with some showing no benefit, and others showing a reduction in the delirium severity and duration (12, 46). While such mixed evidence should not preclude consultation in complex cases, it does suggest that prevention is more effective than treatment, even when done by specialists.

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

An increasing body of evidence suggests that patients with delirium

48. Lacasse H, Perreault MM, Williamson DR. Systematic review of antipsychotics for the treatment of hospital-associated delirium in medically or surgically ill patients. Ann Pharmacother. 2006;40:1966-73. [PMID: 17047137]
49. Lonergan E, Britton AM, Luxenberg J, Wyller T. Antipsychotics for delirium. Cochrane Database Syst Rev. 2007:CD005594. [PMID: 17443602]
50. Seitz DP, Gill SS, van Zyl LT. Antipsychotics in the treatment of delirium: a systematic review. J Clin Psychiatry. 2007;68:11-21. [PMID: 17284125]
51. Breitbart W, Marotta R, Platt MM, Weisman H, Derevenco M, Grau C, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry. 1996;153:231-7. [PMID: 8561204]
52. Lawrence KR, Nasraway SA. Conduction disturbances associated with administration of butyrophenone antipsychotics in the critically ill: a review of the literature. Pharmacotherapy. 1997;17:531-7. [PMID: 9165555]
53. Inouye SK, Zhang Y, Jones RN, Kiely DK, Yang F, Marcantonio ER. Risk factors for delirium at discharge: development and validation of a predictive model. Arch Intern Med. 2007;167:1406-13. [PMID: 17620535]

remain vulnerable, even after the confusion clears. Clinicians should develop both a short-term and long-term monitoring plan for patients with delirium.

In the short term, delirious patients 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, it should be done daily in the hospital; weekly in recently discharged patients, including those admitted to rehabilitation facilities; and monthly upon the patients' return to the community. 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, which can be tapered as delirium and function improves. Patients whose cognitive or ADL function does not return to baseline 1 to 2 months after an episode of delirium should be considered for comprehensive geriatrics assessment and/or neuropsychological testing.

Table 3. Pharmacologic Management of Agitated Delirium

*Agent**	*Drug Class*	*Dosage*	*Benefits*	*Adverse Effects*	*Comments*
Haloperidol	Typical antipsychotic	0.25–1 mg PO or IV q 4 h prn agitation	Relatively nonsedating; few hemodynamic effects	EPS, especially if > 3 mg per day	Usually, agent of choice†
Olanzapine	Atypical antipsychotic	2.5–10 mg PO daily; dissolving tablet IV: 2.5–10 mg PO qd OR IM: 2.5–10 mg daily	Fewer EPS than haloperidol	More sedating than haloperidol	Small trials‡PO route less effective for acute management
Quetiapine	Atypical antipsychotic	25–50 mg PO bid	Fewer EPS than haloperidol	Most sedating of atypical antipsychotics Hypotension	Small trials‡
Risperidone	Atypical antipsychotic	0.25–1 mg PO or IV q 4 h prn agitation	Relatively nonsedating; few hemodynamic effects	Might have slightly fewer EPS than haloperidol	Small trials‡
Lorazepam	Benzodiazepine	0.25–1 mg PO or IV tid prn for agitation	Use in sedative and alcohol withdrawal, and history of the neuroleptic malignant syndrome	More paradoxic excitation, respiratory depression than haloperidol	Second-line agent, except in specific cases noted

bid = twice a day; EPS = extrapyramidal symptoms; h = hour; IV = intravenously; prn = as needed; PO = by mouth; q = each; tid = three times a day.

**Use for delirium is an off-label indication. Due to the small number and size of trials investigating the use of these agents for agitation in delirium, the recommendations above are Class B.*

†In a randomized trial comparing haloperidol, chlorpromazine, and lorazepam in the treatment of agitated delirium in young patients with AIDS, all were found to be equally effective; however, haloperidol had the fewest side effects or adverse sequelae (51).

‡All atypical antipsychotics have been tested only in small equivalency trials with haloperidol. The Food and Drug Administration has attached warnings to these agents because of the increased risk for stroke and mortality that has been associated with long-term use, primarily for agitation in dementia.

As discussed, minimizing the duration of delirium is an important treatment goal. Patients with delirium that persists for less than 2 weeks will probably fully 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 (54).

There is a growing body of evidence that delirium, even if resolved, confers an increased risk for poor long-term outcomes (7). Patients who have recovered completely from delirium remain vulnerable to repeated episodes, cognitive decline, functional decline, and death. Interventions to try to improve these long-term outcomes have not been well-developed or studied. At the very least, these patients should be considered 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 (e.g., 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 quality measures for delirium have been adopted by U.S. stakeholders. Incident delirium in the hospitalized patient was considered by the Center for Medicare & Medicaid Services as a "no-pay" condition, but was ultimately not included because of insufficient evidence supporting preventability of most cases by using current state-of-the art methods (the most effective preventive strategies reduce delirium by 30% to 40%). In addition, such "no-pay" status might lead to a potential disincentive to diagnose delirium, which could exacerbate current poor recognition and documentation (see above). The ACOVE guidelines (55) include a single delirium quality indicator within its indicators for hospital care: If a hospitalized vulnerable elder has a suspected or definite diagnosis of delirium, then potentially precipitating factors should be evaluated for and identified causes treated.

What do professional organizations recommend with regard to prevention, screening, diagnosis, and treatment?

Several clinical practice guidelines for delirium have been published by diverse groups, such as the American Psychiatric Association, the American Medical Directors Association (for nursing home patients), and international organizations. The most recent, comprehensive guideline was published in 2010 by the National Institute for Health and Clinical Excellence (NICE) of the United Kingdom Health Service, based on "systematic reviews of the best available evidence and explicit considerations of cost-effectiveness" (56, 57). Key contents of this guideline are summarized in the Box: Key Recommendations of the NICE Guideline for Delirium.

54. Kiely DK, Jones RN, Bergmann MA, Murphy KM, Orav EJ, Marcantonio ER. Association between delirium resolution and functional recovery among newly admitted postacute facility patients. J Gerontol A Biol Sci Med Sci. 2006;61:204-8. [PMID: 16510867]
55. Shekelle PG, MacLean CH, Morton SC, Wenger NS. Acove quality indicators. Ann Intern Med. 2001;135:653-67. [PMID: 11601948]
56. Young J, Murthy L, Westby M, Akunne A, O'Mahony R; Guideline Development Group. Diagnosis, prevention, and management of delirium: summary of NICE guidance. BMJ. 2010;341:c3704. [PMID: 20667955]
57. O'Mahony R, Murthy L, Akunne A, Young J; on behalf of the Guideline Development Group. Synopsis of NICE Guideline for prevention of delirium. Ann Intern Med. 2011;154:746-51.

Key Recommendations of the NICE Guideline for Delirium

Assess delirium risk factors when patients are admitted to the hospital.

Prevent delirium by addressing risk factors using a multicomponent intervention.

Screen for incident delirium by assessing recent changes or fluctuations in cognitive function, perception, physical function, and social behavior on admission and at least daily thereafter.

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

Manage delirium by:

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

If a person with delirium is distressed or 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, playing relaxing music
- If these are not effective or are inappropriate, consider short-term antipsychotics at the lowest clinically appropriate dose and titrate cautiously according to symptoms.

In the Clinic Tool Kit

Delirium

PIER Modules

http://pier.acponline.org

PIER module on delirium and postoperative delirium. PIER modules provide evidence-based, updated information on current diagnosis and treatment in an electronic format designed for rapid access at the point of care.

Patient Information

www.annals.org/intheclinic/toolkit-delirium.html

Patient Information material that appears on the following page for duplication and distribution to patients.

www.nlm.nih.gov/medlineplus/ency/article/000740.htm

www.nlm.nih.gov/medlineplus/spanish/ency/article/000740.htm

Information on delirium in English and Spanish from the National Institutes of Health's MedlinePlus.

www.uptodate.com/patients/content/topic.do?topicKey=~V0VnMxZiE1

Patient information on delirium from UpToDate, an online, evidence-based, peer-reviewed information resource.

www.hpna.org/pdf/teachingsheet_managingdelirium.pdf

Handout for patients and their families on managing delirium from the Hospice and Palliative Nurses Association.

Clinical Guidelines

www.health.vic.gov.au/acute-agedcare/delirium-cpg.pdf

Recommendations to guide the clinical assessment and management of delirium in older Australians in hospital and across health care settings, prepared in 2006 for the Australian Health Ministers' Advisory Council.

www.bmj.com/content/341/bmj.c3704.full

Guidelines on the diagnosis, prevention, and management of delirium from the British National Institute for Health and Clinical Excellence (NICE) in 2010.

www.psychiatryonline.com/pracGuide/pracGuideTopic_2.aspx

American Psychiatric Association Practice Guidelines on treatment of patients with delirium.

Diagnostic Tests and Criteria

www.hospitalelderlifeprogram.org/private/camdisclaimer.php?pageid=01.08.00

The CAM tool can be used to screen for overall cognitive impairment.

www.annals.org

Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113:941-8.

www.ncbi.nlm.nih.gov/pubmed/18293243

Nursing Delirium Screening Scale

www.medscape.com/viewarticle/581322_appendix3

Delirium Detection Score

THINGS YOU SHOULD KNOW ABOUT DELIRIUM

In the Clinic
Annals of Internal Medicine

What is delirium?

- A state of severe confusion that may come and go.
- The confusion may include difficulty staying focused and fully alert and conscious.
- It may include disorientation and inability to remember recent events.

What are risk factors for delirium?

- Being older than 65.
- Having severe, chronic, or terminal illness.
- Having previous brain disease or damage, such as dementia, Parkinson disease, or stroke.
- Having vision or hearing impairment.
- Being malnourished or dehydrated.

What are the common triggers for delirium?

- Having multiple medical procedures.
- Sudden, severe illness, particularly infection.
- Admission to the ICU.
- Certain medications, particularly narcotics, antidepressants, anticonvulsants, or sleep medications, or taking multiple medications.
- Drug or alcohol abuse.
- Emotional stress.

How does delirium differ from dementia?

- Delirium develops suddenly, over a few hours or days.
- Dementia develops over many months or years.
- Delirium is usually temporary and goes away once the cause is treated
- Dementia is usually long-lasting and usually does not get better.

What should you do if a family members has delirium?

- Seek immediate medical attention.
- Try to provide information to the doctor about the patient's medications and medical conditions.
- The doctor will ask when the symptoms of delirium started and how behavior has changed specifically.

For More Information

www.mayoclinic.com/health/delirium/DS01064
Information on delirium from Mayo Clinic.

www.nlm.nih.gov/medlineplus/delirium.html
Information resources on delirium from the National Institutes of Health's MedlinePlus.

www.healthinaging.org/aginginthenow/chapters_ch_trial.asp?ch=57
Information on delirium, including how it differs from dementia, from the Foundation for Health in Aging.

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Patient Information

CME Questions

MKSAP
MEDICAL KNOWLEDGE Self-Assessment Program

1. A 79-year-old woman was hospitalized 4 days ago after sustaining a right hip fracture in a fall. She underwent surgical repair with right hip replacement 3 days ago and did not awaken from general anesthesia until 12 hours after extubation. As her alertness has increased, she has become increasingly agitated, yelling at the nurses and flailing her arms; mechanical 4-limb restraints were placed 2 days ago. The patient has a 4-year history of progressive cognitive decline diagnosed as Alzheimer dementia. She also has chronic atrial fibrillation treated with chronic warfarin therapy. She has no other pertinent personal or family medical history. Current medications are donepezil, memantine, atenolol, warfarin, and low-molecular-weight heparin.

   On physical examination today, temperature is 37.2 °C (99.0 °F), blood pressure is 100/68 mm Hg, pulse rate is 100/min and irregular, respiration rate is 18/min, and BMI is 21. The patient can move all 4 limbs with guarding of the right lower limb. She is inattentive and disoriented to time and place and exhibits combativeness alternating with hypersomnolence. The remainder of the neurologic examination is unremarkable, without evidence of focal findings or meningismus.

   Which of the following is the most likely diagnosis?

   A. Acute cerebral infarction
   B. Acute worsening of Alzheimer dementia
   C. Meningitis
   D. Postoperative delirium

2. An 85-year-old terminally ill woman is evaluated in a home hospice setting. She has metastatic breast cancer to the spine, lungs, and liver. She has had progressive anorexia and weight loss and is dependent on family for all activities of daily living. She has an advance directive stating she does not want cardiopulmonary resuscitation or artificial nutrition. Her pain has been well controlled on a fentanyl transdermal patch and immediate-release morphine as needed for pain. These medications have been stable over the past month. Last night, the patient became confused and agitated, trying to get out of bed and repeatedly stating she needed to look for her deceased husband. There is no dyspnea, fever, dysuria, chest discomfort, or abdominal discomfort. She rates her back pain as 1 on a scale of 1 to 10. She continues to require immediate-release morphine.

   Vital signs are normal. The patient is alert and oriented to name and place but cannot remember the year or date. The patient is still agitated and confused, picking at her clothes during the examination.

   Which of the following is the most appropriate management for this patient?

   A. Discontinue fentanyl patch
   B. Initiate haloperidol
   C. Initiate lorazepam
   D. Measure serum electrolytes, calcium, and renal and hepatic function
   E. Schedule an MRI

3. A 75-year-old woman with a history of chronic obstructive pulmonary disease is evaluated in the ICU for delirium. She had a median sternotomy and repair of an aortic dissection and was extubated uneventfully on postoperative day 4. Two days later she developed fluctuations in her mental status and inattention. While still in the ICU, she became agitated, pulling at her lines, attempting to climb out of bed, and asking to leave the hospital. Her arterial blood gas values are normal. The patient has no history of alcohol abuse. Frequent orientation cues, calm reassurance, and presence of family members have done little to reduce the patient's agitated behavior.

   Which of the following is the most appropriate therapy for this patient's delirium?

   A. Diphenhydramine
   B. Haloperidol
   C. Lorazepam
   D. Propofol

4. A 68-year-old man with chronic obstructive pulmonary disease, hypertension, and hyperlipidemia is being weaned from mechanical ventilation after an exacerbation. The patient's current medications are ipratropium bromide and albuterol (both by metered-dose inhaler through the ventilator), prednisone, lisinopril, and atorvastatin.

   He is started on a spontaneous breathing trial, which he initially tolerates well but later shows evidence of oxygen desaturation and agitation. He is given increasing doses of lorazepam to cause sedation, and assist-control ventilation is resumed. The following day he is calm but is not focused and fails to follow commands consistently.

   Which of the following is the best test to assess the patient's mental status?

   A. Beck Depression Inventory
   B. Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)
   C. CT scan of the head
   D. Metabolic profile
   E. Mini-Mental State Examination

5. A 78-year-old woman is evaluated in the ICU for disorientation. The patient recently developed the acute respiratory distress syndrome secondary to community acquired pneumonia, and mechanical ventilation was started 2 days ago. She lives alone and functions well independently.

   The patient is on a ventilator; she has received small doses of lorazepam over the past 48 hours and appears comfortable. She has recently become disoriented, is not interacting as well with her family as she had before, and has had fluctuations in mental status over the past 24 hours.

   On physical examination, pulse rate is 92/min, but vital signs are otherwise normal. Neurologic examination shows no focal abnormalities, and cranial nerve examination is normal. She is calm and awake but cannot follow directions to do the ‚Äúrandom letter A test,‚Äù by squeezing the examiner's hand only on hearing the letter ‚ÄúA,‚Äù; she also cannot organize her thinking to answer simple questions. When asked whether she is seeing things or hearing things that are not there, she shakes her head ‚ÄúNo.‚Äù Laboratory studies show hemoglobin of 9.9 g/dL (99 g/L) and a leukocyte count of 11,000/¬µL (11 √ó 109/L) with a normal differential. Metabolic panel reveals plasma glucose of 180 mg/dL (10.0 mmol/L); serum total thyroxine and thyroid-stimulating hormone levels are normal.

   Which of the following is the most likely diagnosis?

   A. Delirium
   B. Dementia
   C. Psychosis
   D. Stroke

Questions are largely from the ACP's Medical Knowledge Self-Assessment Program (MKSAP, accessed at http://www.acponline.org/products_services/mksap/15/?pr31). Go to www.annals.org/intheclinic/ to complete the quiz and earn up to 1.5 CME credits, or to purchase the complete MKSAP program.