REVIEW ARTICLE

CURRENT CONCEPTS

Delirium in Older Persons

Sharon K. Inouye, M.D., M.P.H.

From the Department of Medicine, Harvard Medical School, Boston. Address reprint requests to Dr. Inouye at the Aging Brain Center, Hebrew Senior Life, 1200 Centre St., Boston, MA 02131.

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Delirium, an acute decline in attention and cognition, is a common, life-threatening, and potentially preventable clinical syndrome among persons who are 65 years of age or older. The development of delirium often initiates a cascade of events culminating in the loss of independence, an increased risk of morbidity and mortality, and increased health care costs.[1-6] Delirium in hospitalized older patients has assumed particular importance because the care of such patients accounts for more than 49 percent of all hospital days.[7] Delirium complicates hospital stays for at least 20 percent of the 12.5 million patients 65 years of age or older who are hospitalized each year and increases hospital costs by $2,500 per patient,[8-10] so that about $6.9 billion (value in U.S. dollars in 2004) of Medicare hospital expenditures are attributable to delirium. Substantial additional costs accrue after hospital discharge because of the need for institutionalization, rehabilitation services, formal home health care, and informal caregiving.

This report examines current clinical practice in delirium, identifies areas of controversy, and highlights areas for future research.

Epidemiology and Diagnostic Criteria

In direct contrast to dementia, which is a chronic confusional state, delirium is an acute confusional state. Rates of delirium are highest among hospitalized older patients, and the rates vary depending on the patients' characteristics, setting of care, and sensitivity of the detection method. The prevalence of delirium at hospital admission ranges from 14 to 24 percent, and the incidence of delirium arising during hospitalization ranges from 6 to 56 percent among general hospital populations.[11,12] Delirium occurs in 15 to 53 percent of older patients postoperatively[11] and in 70 to 87 percent of those in intensive care.[13] Delirium occurs in up to 60 percent of patients in nursing homes or post–acute care settings[14,15] and in up to 83 percent of all patients at the end of life.[16,17] Although the overall prevalence of delirium in the community is only 1 to 2 percent,[18,19] the prevalence increases with age, rising to 14 percent among those more than 85 years old. Moreover, in 10 to 30 percent of older patients presenting to emergency departments, delirium is a symptom[11] that often heralds the presence of life-threatening conditions. The mortality rates among hospitalized patients with delirium range from 22 to 76 percent,[20] as high as the rates among patients with acute myocardial infarction or sepsis. The one-year mortality rate associated with cases of delirium is 35 to 40 percent.[21]

The diagnosis of delirium is primarily clinical and is based on careful bedside observation of key features. Although the criteria continue to evolve,[22,23] the diagnostic algorithms that are most widely used are presented in the Supplementary Appendix (available with the full text of this article at www.nejm.org). Delirium is often unrecognized by the patients' physicians and nurses,[1,24] in part because of its fluctuating nature, its overlap with dementia, lack of formal cognitive assessment, underappreciation of its clinical consequences, and failure to consider the diagnosis important.

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CLINICAL CHARACTERISTICS

Because delirium remains a bedside diagnosis, understanding its clinical features (Table 1 and the Supplementary Appendix) is crucial to the diagnosis of delirium. Delirium has hypoactive and hyperactive forms (Table 1). The hypoactive form of delirium is more common among older persons and often goes unrecognized.

ETIOLOGIC AND RISK FACTORS

The cause of delirium is typically multifactorial.[25] In fact, the development of delirium involves the complex interrelationship between a vulnerable patient (one with predisposing factors) (Table 2) and exposure to precipitating factors or noxious insults (Table 3).[26,27] Thus, in patients who are highly vulnerable to delirium, such as those with dementia and multiple coexisting conditions, it may develop as a result of relatively benign insults, such as one dose of a sleeping medication. Conversely, in patients who are not vulnerable to delirium, it develops only after exposure to multiple noxious insults, such as general anesthesia, major surgery, and psychoactive medications. Addressing just one contributing factor is unlikely to resolve delirium in an older person; they should all be addressed when possible.

PATHOGENESIS

The pathophysiology of delirium remains poorly understood. Electroencephalographic studies have demonstrated diffuse slowing of cortical background activity, which does not correlate with underlying causes.[28] Neuropsychological and neuroimaging studies reveal generalized disruption in higher cortical function, with dysfunction in the prefrontal cortex, subcortical structures, thalamus, basal ganglia, frontal and temporoparietal cortex, fusiform cortex, and lingual gyri, particularly on the nondominant side.[29,30] The leading hypotheses for the pathogenesis of delirium focus on the roles of neurotransmission, inflammation, and chronic stress.

Extensive evidence supports the role of cholinergic deficiency. Administration of anticholinergic drugs can induce delirium in humans and animals, and serum anticholinergic activity is increased in patients with delirium. Physostigmine reverses delirium associated with anticholinergic drugs, and cholinesterase inhibitors appear to have some benefit even in cases of delirium that are not induced by drugs.[15,29,31]

Dopaminergic excess also appears to contribute to delirium, possibly owing to its regulatory influence on the release of acetylcholine.[29] Dopaminergic drugs (e.g., levodopa and bupropion) are recognized precipitants of delirium, and dopamine antagonists (e.g., antipsychotic agents) effectively treat delirium symptoms. Perturbations of other neurotransmitters, such as norepinephrine, serotonin, γ-aminobutyric acid, glutamate, and melatonin, may also have a role in the pathophysiology of delirium, but the evidence is less well developed.[1,29,32] These neurotransmitters may exert their influence through interactions with the cholinergic and dopaminergic pathways.

Cytokines, including interleukin-1, interleukin-2, interleukin-6, tumor necrosis factor α (TNF-α), and interferon, may contribute to delirium[1,29,33] by increasing the permeability of the blood–brain barrier and altering neurotransmission. Finally, chronic stress brought on by illness or trauma activates the sympathetic nervous system and hypothalamic–pituitary–adrenocortical axis, resulting in increased cytokine levels and chronic hypercortisolism.[34] Chronic hypercortisolism has deleterious effects on hippocampal serotonin (5-hydroxytryptamine [5-HT]) 5-HT_{1A} receptors, which may contribute to delirium.[29,35,36] Given the clinical heterogeneity and multifactorial nature of delirium, it is likely that multiple pathogenic mechanisms contribute to the development of delirium.

APPROACH TO EVALUATION

A flowchart for the prevention and management of delirium from the time of admission of an older patient is shown in Figure 1. This approach, based on current clinical guidelines and expert opinion,[9,20] must be guided by the individual patient's medical history, findings on physical and neurologic examination, and clinical setting. Although the provision of detailed procedures is beyond the scope of this report, we will highlight common pitfalls to avoid. When a patient with confusion is admitted, determining the acuity of the change in mental status is the essential first step. Neglecting this step is the leading reason for missing the diagnosis of delirium. If no history can be obtained, then the patient should be assumed to be delirious until proved otherwise. Every older hospitalized patient should undergo brief but formal cognitive testing with the use of instruments such as the Mini–Mental State Examination and the Confusion Assessment Method, since subtle de-

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Table 1. Clinical Features of Delirium.*

Acute onset
Occurs abruptly, usually over a period of hours or days
Reliable informant often needed to ascertain the time course of onset
Fluctuating course
Symptoms tend to come and go or increase and decrease in severity over a 24-hour period
Characteristic lucid intervals
Inattention
Difficulty focusing, sustaining, and shifting attention
Difficulty maintaining conversation or following commands
Disorganized thinking
Manifested by disorganized or incoherent speech
Rambling or irrelevant conversation or an unclear or illogical flow of ideas
Altered level of consciousness
Clouding of consciousness, with reduced clarity of awareness of the environment
Cognitive deficits
Typically global or multiple deficits in cognition, including disorientation, memory deficits, and language impairment
Perceptual disturbances
Illusions or hallucinations in about 30 percent of patients
Psychomotor disturbances
Psychomotor variants of delirium
Hyperactive
Marked by agitation and vigilance
Hypoactive
Marked by lethargy, with a markedly decreased level of motor activity
Mixed
Altered sleep–wake cycle
Characteristic sleep-cycle disturbances
Typically daytime drowsiness, nighttime insomnia, fragmented sleep, or complete sleep-cycle reversal
Emotional disturbances
Common
Manifested by intermittent and labile symptoms of fear, paranoia, anxiety, depression, irritability, apathy, anger, or euphoria

* Additional details are provided in Table 2 in the Supplementary Appendix.

lirium is often missed. Older patients should be aroused during rounds and evaluated daily for the hypoactive form of delirium, which is often overlooked.

When clinicians search for the underlying cause of delirium, they need to be aware of the possibility of occult or atypical presentations of many diseases in the elderly, including myocardial infarction, infection, and respiratory failure, because delirium is often the sole manifestation of serious underlying disease. All preadmission and current medications should be reviewed; even long-standing medications can contribute to delirium and should be reevaluated. If changes in long-term medications are appropriate after the indications and risk–benefit ratios have been carefully weighed, the hospital represents the ideal venue for making these changes. A medical history must be meticulously obtained to detect occult alcohol or benzodiazepine use, which can contribute to delirium.

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Table 2. Predisposing Factors for Delirium.

Demographic characteristics
Age of 65 years or older
Male sex
Cognitive status
Dementia
Cognitive impairment
History of delirium
Depression
Functional status
Functional dependence
Immobility
Low level of activity
History of falls
Sensory impairment
Visual impairment
Hearing impairment
Decreased oral intake
Dehydration
Malnutrition
Drugs
Treatment with multiple psychoactive drugs
Treatment with many drugs
Alcohol abuse
Coexisting medical conditions
Severe illness
Multiple coexisting conditions
Chronic renal or hepatic disease
History of stroke
Neurologic disease
Metabolic derangements
Fracture or trauma
Terminal illness
Infection with human immunodeficiency virus

Electroencephalography has a limited role in the diagnosis of delirium, because of its false negative rate of 17 percent and false positive rate of 22 percent[12]; it is most useful for detecting occult seizures and differentiating delirium from psychiatric disorders. Neuroimaging studies have a low clinical yield (the number of positive results divided by the total number of studies performed) in the evaluation of delirium and should be reserved for patients with new focal neurologic signs, those with a history or signs of head trauma, those with fever and acute changes in mental status in whom encephalitis is suspected, or those with no other identifiable cause of the delirium.[12] However, neuroimaging should be considered when the history cannot be obtained or the neurologic examination cannot be completed (e.g., when the patient is combative) so as not to miss uncommon conditions that are life-threatening but treatable, such as subarachnoid hemorrhage and encephalitis.

PREVENTION AND MANAGEMENT

Preventing delirium is the most effective strategy for reducing its frequency and complications. Successful preventive strategies include multicomponent approaches to reduce risk factors. Because delirium has many causes, multicomponent approaches represent the most effective and clinically relevant ones. The Yale Delirium Prevention Trial[8] demonstrated the effectiveness of intervention protocols targeted toward six risk factors: orientation and therapeutic activities for cognitive impairment, early mobilization to avert immobilization, nonpharmacologic approaches to minimize the use of psychoactive drugs, interventions to prevent sleep deprivation, communication methods and adaptive equipment (particularly eyeglasses and hearing aids) for vision and hearing impairment, and early intervention for volume depletion. A randomized clinical trial involving patients who had had hip fractures demonstrated the effectiveness of a multicomponent strategy for geriatric consultation targeted toward 10 domains[38]: oxygen delivery to the brain, fluid and electrolyte balance, pain management, reduction in the use of psychoactive drugs, bowel and bladder function, nutrition, early mobilization, prevention of postoperative complications, appropriate environmental stimuli, and treatment of symptoms of delirium.

Once delirium occurs, the key steps in management are to address all evident causes, provide supportive care and prevent complications, and treat behavioral symptoms. Because delirium can be a medical emergency, the first aim of management is to address predisposing and precipitating factors promptly (Fig. 1). Supportive care should include protecting the patient's airway, maintaining hydration and nutrition, positioning and mobilizing the patient to prevent pressure sores and deep venous thrombosis, avoiding the

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use of physical restraints, and supporting the patient's daily care needs. Nonpharmacologic approaches to managing symptoms of delirium should be instituted in every patient. These approaches include creating a calm, comfortable environment with the use of orienting influences, such as calendars, clocks, and familiar objects from home; regular reorienting communication with staff members; involving family members in supportive care; limiting room and staff changes; coordinating schedules for administering drugs, obtaining vital signs, and performing procedures to allow the patient an uninterrupted period for sleep at night with low levels of noise and lighting; and encouraging normal sleep–wake cycles by opening blinds and encouraging wakefulness and mobility during the daytime. Since delirium may take weeks or months to resolve, patients must be cared for in supervised settings. Close clinical follow-up after discharge is needed, especially because of the poor long-term prognosis associated with delirium.

Pharmacologic management should be reserved for patients whose symptoms of delirium would threaten their own safety or the safety of other persons or would result in the interruption of essential therapy, such as mechanical ventilation or central venous catheters. Pharmacologic treatment strategies are outlined in Table 4.

Table 3. Precipitating Factors or Insults That Can Contribute to Delirium.

Drugs
Sedative hypnotics
Narcotics
Anticholinergic drugs
Treatment with multiple drugs
Alcohol or drug withdrawal
Primary neurologic diseases
Stroke, particularly nondominant hemispheric
Intracranial bleeding
Meningitis or encephalitis
Intercurrent illnesses
Infections
Iatrogenic complications
Severe acute illness
Hypoxia
Shock
Fever or hypothermia
Anemia
Dehydration
Poor nutritional status
Low serum albumin level
Metabolic derangements (e.g., electrolyte, glucose, acid–base)
Surgery
Orthopedic surgery
Cardiac surgery
Prolonged cardiopulmonary bypass
Noncardiac surgery
Environmental
Admission to an intensive care unit
Use of physical restraints
Use of bladder catheter
Use of multiple procedures
Pain
Emotional stress
Prolonged sleep deprivation

RELATIONSHIP BETWEEN DELIRIUM AND DEMENTIA

Delirium and dementia are highly interrelated, yet the nature of their interrelationship remains poorly examined. Although a cause-and-effect relation has not been established between delirium and dementia, investigation of their intersection may yield important insights that will advance our understanding of both conditions (see Table 3 in the Supplementary Appendix). Dementia is the leading risk factor for delirium, and fully two thirds of cases of delirium occur in patients with dementia.[1,39] Thus, the underlying vulnerability of the brain in patients with dementia may predispose them to the development of delirium as a result of insults related to acute medical illnesses, medications, or environmental perturbations. Recent studies suggest that delirium persists much longer than previously believed,[4,40-44] with symptoms in many patients lasting months or years. The existence of the well-described entities of persistent delirium[4,40-44] and reversible dementia[45] blurs the boundaries between these conditions. Moreover, studies have shown that delirium and dementia are both associated with decreased cerebral metabolism, cholinergic deficiency, and inflammation,[46] reflecting their overlapping clinical, metabolic, and cellular mechanisms. In fact, delirium and dementia may represent points along

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a continuum of cognitive disorders, rather than two entirely separate conditions.[39]

Does delirium contribute to dementia? Although it is not likely that the delirium itself causes the pathologic changes of dementia, there is no question that delirium contributes to worsening functional status, loss of independence, and poorer outcomes among patients with dementia. The long-standing traditional view is that delirium and dementia are two separate conditions; however, emerging evidence has highlighted their overlap. First, epidemiologic studies have documented long-term cognitive decline in patients with delirium, after controlling for relevant covariates.[47] Second, several causes of delirium may not be completely reversible, particularly those resulting in neuronal injury and permanent cognitive sequelae, such as prolonged hypoxia or hypoglycemia.[39] Third, neuroimaging studies demonstrate regions of hypoperfusion in patients with delirium.[48] Thus, delirium may herald the onset of dementia in many instances. Fourth, dementia with Lewy bodies, which includes fluctuating cognition and visual hallucinations as core signs, illustrates the overlap of delirium and dementia.

Delirium can alter the course of an underlying dementia, with dramatic worsening of the trajectory of cognitive decline, resulting in more rapid progression of functional losses and worse long-term outcomes. This phenomenon has been well recognized clinically in elderly patients with dementia: clinicians and family members have noted that the patients "never returned to baseline" after an episode of delirium. In follow-up studies, patients in whom delirium develops have worse outcomes than those with dementia alone,[49] including worsened cognitive function and increased rates of hospitalization, institutionalization, and death.[49-52]

Delirium may serve as an important model for research by offering a unique approach to advance our general understanding of cognitive disorders and dementias (see Table 3 in the Supplementary Appendix). The development of delirium in certain persons may help to identify those who are vulnerable to cognitive decline through genetic predisposition or through the presence of early dementia or mild cognitive impairment that may otherwise remain unidentified. Moreover, a better understanding of the pathogenesis of delirium may help elucidate factors that lead directly to neuronal injury and, thus, to permanent cognitive sequelae. Studies investigating the pathogenesis of delirium with the use of neuropsychological testing, neuroimaging methods, electrophysiological methods, laboratory markers, genetic studies, and neuropathological approaches are greatly needed. Investigation of delirium provides an important opportunity to clarify the link between brain pathophysiology and behavioral manifestations, which might hold broader implications for other cognitive and psychiatric disorders. New prospects for therapy include strategies to increase acetylcholine activity in the brain (e.g., through the use of procholinergic agents and avoidance of highly anticholinergic drugs), the use of selective dopamine antagonists that affect D_1, D_2, D_3, and D_4 receptors differently, and the use of drugs to enhance cerebrovascular flow (e.g., antiinflammatory or antiplatelet agents). Finally, targeting delirium with new therapeutic approaches may offer opportunities for early intervention, preservation of cognitive-reserve capacity, and prevention of permanent cognitive damage, which may potentially delay or abate the ultimate development of dementia.

Figure 1 (facing page). Prevention and Management of Delirium in the Older Hospitalized Patient.

Thyroid-function tests include measurement of the thyroxine level, thyroid index, and thyrotropin level. More information about pharmacologic treatment can be found in Table 4.

DELIRIUM AS AN INDICATOR OF THE QUALITY OF HEALTH CARE

Delirium represents one of the most common preventable adverse events among older persons during hospitalization[53,54] and meets Williamson's criteria for an indicator of the quality of health care[55]: the condition is common, frequently iatrogenic, and integrally linked to processes of care. Although many cases of delirium may be unavoidable, clinical trials[8,38] provide compelling evidence that at least 30 to 40 percent of cases may be preventable. Many aspects of hospital care contribute to the development of delirium, including adverse effects of medications, complications of invasive procedures, immobilization, malnutrition, dehydration, the use of bladder catheters, and sleep deprivation.[9] Delirium is currently included as a marker of the quality of care and patient safety by the National Quality Measures Clearinghouse of the Agency for Healthcare Research and Qual-

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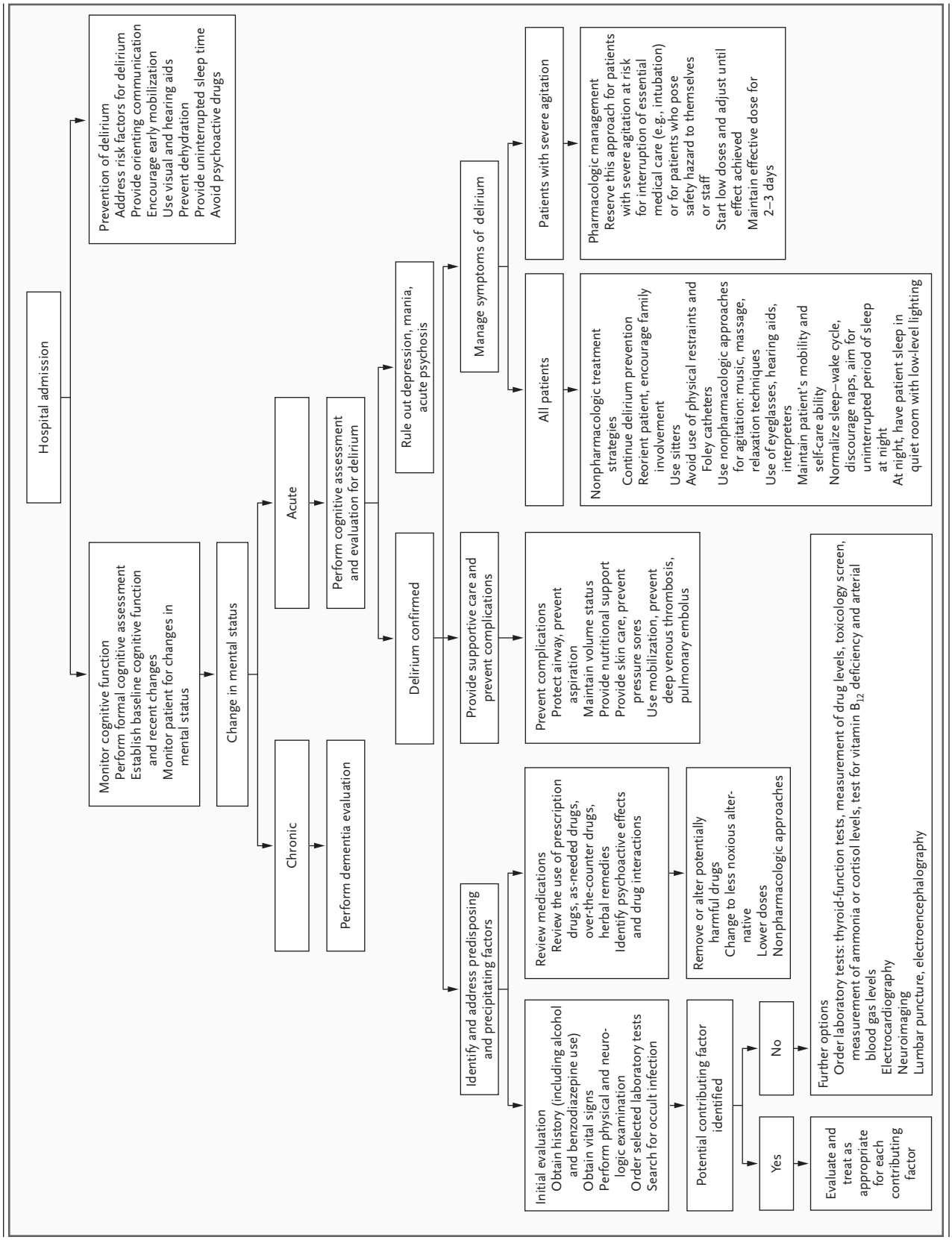

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Table 4. Pharmacologic Treatment of Delirium.

Class and Drug	Dose	Adverse Effects	Comments
Antipsychotic			
Haloperidol	0.5–1.0 mg twice daily orally, with additional doses every 4 hr as needed (peak effect, 4–6 hr) 0.5–1.0 mg intramuscularly; observe after 30–60 min and repeat if needed (peak effect, 20–40 min)	Extrapyramidal symptoms, especially if dose is >3 mg per day Prolonged corrected QT interval on electrocardiogram Avoid in patients with withdrawal syndrome, hepatic insufficiency, neuroleptic malignant syndrome	Usually agent of choice Effectiveness demonstrated in randomized, controlled trials[20,37] Avoid intravenous use because of short duration of action
Atypical antipsychotic			
Risperidone	0.5 mg twice daily	Extrapyramidal effects equivalent to or slightly less than those with haloperidol Prolonged corrected QT interval on electrocardiogram	Tested only in small uncontrolled studies Associated with increased mortality rate among older patients with dementia
Olanzapine	2.5–5.0 mg once daily		
Quetiapine	2.5–5.0 mg once daily		
Benzodiazepine			
Lorazepam	0.5–1.0 mg orally, with additional doses every 4 hr as needed*	Paradoxical excitation, respiratory depression, oversedation	Second-line agent Associated with prolongation and worsening of delirium symptoms demonstrated in clinical trial[37] Reserve for use in patients undergoing sedative and alcohol withdrawal, those with Parkinson's disease, and those with neuroleptic malignant syndrome
Antidepressant			
Trazodone	25–150 mg orally at bedtime	Oversedation	Tested only in uncontrolled studies

* Intravenous use of lorazepam should be reserved for emergencies.

ity (as explained at www.qualitymeasures.ahrq.gov/). After adjusting for case mix, higher delirium rates would be expected to correlate with lower quality of hospital care. The Assessing Care of Vulnerable Elders Project has ranked delirium among the top three conditions for which the quality of care needs to be improved.[56] Total national costs related to preventable adverse events are estimated to be between $17 billion and $29 billion per year,[57] and delirium may account for at least a quarter of these costs.[53,54,57,58] The changes required to reduce the incidence of delirium on a national scale would require shifts in local and national policies and system-wide changes to provide high-quality care for older persons.[9]

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