Delirium in the Elderly

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Learning Objectives

1. Explain theories of the pathogenesis of delirium.
2. Assess patient risk factors for delirium.
3. Analyze patient drug regimens to determine the likelihood that delirium or delirium-like symptoms are drug related.
4. Adjust a patient's drugs to prevent delirium.
5. Prepare a patient care plan that includes patient-specific pharmacologic and nonpharmacologic methods to prevent delirium.
6. Compare and contrast differences in screening tools to detect delirium.
7. Apply the best available evidence to manage delirium.

Introduction

Delirium can have devastating outcomes that burden patients, family members, and the health care system. Delirium has been associated with increased health care costs, long-term cognition deficits, and increased mortality. However, there is often a delay in recognition of delirium symptoms. This chapter will describe outcomes that have been associated with delirium, discuss strategies to prevent and detect delirium, and outline the benefits and risks of treatment options.

Delirium has been described by many terms in the literature, including *an acute confusional state, septic encephalopathy, acute brain failure*, and *intensive care unit* (ICU) *psychosis*. The Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) defines *delirium* as a disturbance of consciousness and cognition that develops quickly (hours to days) and fluctuates with time. In addition to fluctuating cognition, it is characterized by inattention and either disorganized thinking or an altered level of consciousness. Delirium differs from *dementia* because delirium has a sudden onset, fluctuates, and is characterized by inattention and disorganized thoughts and speech. Dementia has an insidious onset, does not fluctuate, and is not normally characterized by inattention or speech disturbances. Delirium is usually (but not always) reversible, whereas dementia is not.

Delirium is categorized further on the basis of psychomotor symptoms. Hyperactive delirium refers to the restless or agitated patient. In contrast, a patient with hypoactive delirium will be lethargic and apathetic. The patient with a mixed delirium will have periods of both hyperactivity and hypoactivity. Older age is a significant independent predictor for hypoactive delirium. Hypoactive delirium is often missed and is associated with a poorer prognosis than hyperactive delirium.

Prevalence

Delirium is common, occurring in as many as 56% of hospitalized patients. Delirium occurs in 20% to 79% of hospitalized older patients. It is also common in ICU patients, occurring in 20% to 50% of non-mechanically ventilated ICU patients and in 60% to 80% of mechanically ventilated ICU patients. Postoperative delirium and end-of-life delirium are also common.

Outcomes

Patients who have had delirium are more likely to have longer hospital stays (an average of 5–10 additional

days) and are more likely to be discharged to a nursing facility than to home (16% vs. 3%). Patients with delirium are more likely to be reintubated if they are in an ICU. Each day spent in delirium in the ICU is associated with a 20% increased risk of prolonged hospitalization and a 10% increased risk of death.

Negative financial outcomes accompany these negative clinical outcomes. More than $100 billion was spent in the United States because of delirium in 2005. Delirium cases have higher ICU costs (median $22,346 vs. $13,332 for non-delirium cases) and hospital costs (median $41,836 vs. $27,106 for non-delirium cases).

Studies have also shown that patients with delirium are more likely to die while in the hospital or within 1 year of hospital discharge. In-hospital mortality rates for patients with delirium range from 22% to 76%, similar to mortality rates for acute myocardial infarction or sepsis. Patients older than 70 years who experienced delirium during hospitalization have a 62% increased risk of death at 1 year. Intensive care unit mechanically ventilated patients with delirium have a significantly higher 6-month mortality rate than ICU mechanically ventilated patients without delirium (34% vs. 15%). Patients admitted to a postacute care unit with persistent delirium are significantly more likely to die in 1 year than those who do not have persistent delirium.

Long-term studies have found that a significantly higher percentage of patients who experienced delirium will eventually be given a diagnosis of dementia. Although no clear cause-and-effect relationship between delirium and subsequent dementia exists, a delirium episode may increase the progression of an unrecognized early dementia.

Some investigators have questioned whether these negative outcomes are because of delirium or whether, instead, delirium is a marker for more serious illness that leads to worse outcomes. A meta-analysis assessed the association between delirium and mortality, institutionalization, and dementia in elderly patients. All qualified studies were required to adequately adjust outcomes by statistical analysis for age, sex, comorbid illness, illness severity, and baseline dementia. A significant relationship between delirium diagnosis and need for institutionalization, dementia diagnosis, and mortality was found, suggesting that in elderly patients, a relationship between delirium and increased risk of death, institutionalization, and dementia exists that is independent of age, sex, comorbid illness, illness severity, and baseline dementia.

Pathogenesis

The pathology of delirium is not fully understood; it may result from acute illness (Figure 1-1). A disturbance in the production, release, or inactivation of neurotransmitters controlling cognitive function (γ-aminobutyric acid [GABA], glutamate, acetylcholine, serotonin, norepinephrine, dopamine, and tryptophan) has been proposed to occur at the same time as delirium.

An excess of dopamine and a depletion of acetylcholine occurs in patients with delirium. A study showed that high serum anticholinergic activity has a 100% predictive value for delirium (defined as a positive Confusion Assessment Method [CAM] score). The CAM is a widely used, validated tool to recognize delirium. When dividing the values for serum anticholinergic activity into five quintiles ranging from very low to very high serum anticholinergic activity, each increase in quintile is associated with a 2.38 times increased risk of delirium.

There are other related pathogenic theories for delirium. One theory postulates that a decrease in oxygenation of the brain (possibly caused by decreased neurotransmitter concentrations) leads to delirium symptoms. An inflammatory hypothesis suggests that variable stresses cause an increase in cytokines that then affect the neurotransmitters. Disturbances in cellular signaling are also suggested as a possible cause. Neuroimaging studies show that extensive cerebral hypoperfusion occurs in patients with delirium. A recent theory proposes that disturbances in tryptophan metabolim lead to delirium. Patients with dementia are known to be at increased risk of delirium, and a recent study reported a longer duration of delirium in patients with the apolipoprotein E4 phenotype, suggesting that patients with underlying dementia are unable to recover from delirium as quickly as others.

Risk Factors for Delirium

Risk factors for delirium include those the patient arrives with (predisposing) and those that are iatrogenic (precipitating) (Table 1-1, Table 1-2). Patients with many risk factors will be vulnerable to a low-level precipitating insult, whereas those without risk factors may only become delirious after a high-level insult.
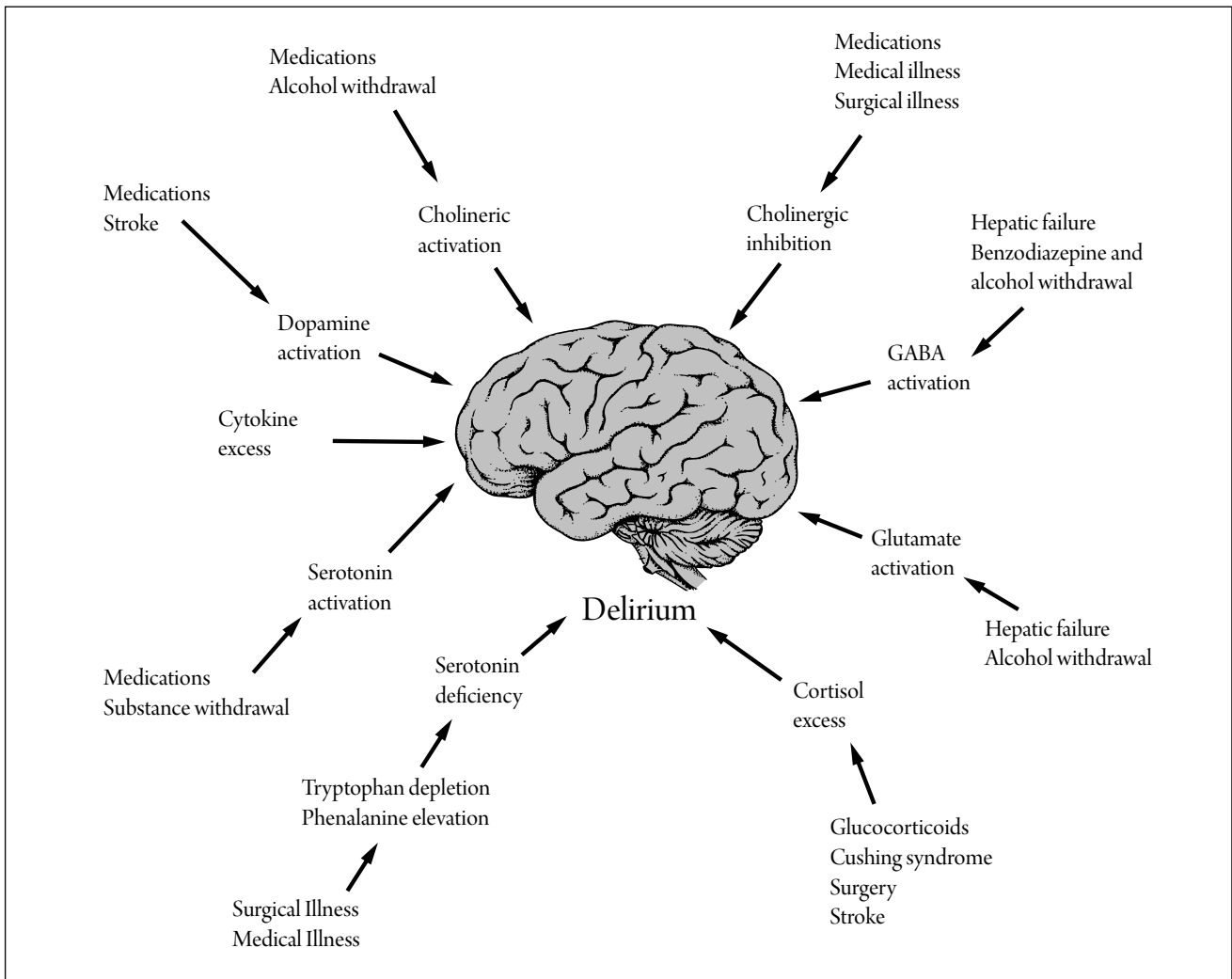
Figure 1-1. Neurotransmitters and biomarkers of delirium.

Reprinted with permission from: Flacker JM, Lipsitz LA. Neural mechanisms of delirium: current hypotheses and evolving concepts. J Gerontol Biol Sci Med Sci 1999;54A:B243.

Alcoholism and smoking have been noted as risk factors for delirium, likely because of withdrawal symptoms. Because currently recommended treatments for delirium will not reverse these withdrawal symptoms, they must be recognized and treated appropriately.

Although drugs can play a significant role in the etiology of delirium, randomized controlled trials identifying drugs that increase the risk are rare. Much of this information is derived from observational studies. Box 1-1 contains a summary of common drugs for which evidence of an association with delirium exists.

Drugs with Anticholinergic Activity

Anticholinergics directly augment the documented decrease in cholinergic activity that occurs in delirious patients. In a prospective cohort study of 426 hospitalized patients older than 70 years, diphenhydramine (an agent with known anticholinergic effects) was associated with an increased risk of delirium. Many drugs have anticholinergic effects, which are thought to be additive. A prospective observational trial of 278 patients older than 65 years found that a score based on cumulative anticholinergic load (calculated by adding a ranking of anticholinergic effect of each drug) was correlated with delirium severity. Early investigators evaluated anticholinergic activity by using the same concentration of each drug, regardless of the concentration that had therapeutic effects. Therefore, some drugs may have been tested at concentrations that are never achieved with normal dosing. A recent investigation looked at six therapeutic concentrations to identify anticholinergic activity by a radioimmune assay. This method provides a more practical reference of agents high in anticholinergic activity.

Table 1-1. Delirium: Predisposing Risk Factors

Risk Factors	AOR* (95% CI)	OR (95% CI)
Age ≥ 85 years[a]		2.4 (1.6–3.6)
> 1 activity of daily living impairment[a]		3.1 (2–4.7)
Baseline activities of daily living independence[b]		0.78 (0.69–0.89)
Vision impairment[a]		3.6 (2.5–5.4)
Dementia diagnosis[a,b,c,d]	6.3 (2.9–13.8)	5.1 (3.3–7.7) 1.2 (1.1–1.3) 2.14 (1.1–4.0)
Cognitive impairment[e]	2.9 (1.4–6.1)	
Mini-Mental State Examination score < 24[a]		4.1 (2.7–6.1)
Severe disease as rated by nurse or APACHE II score > 15[a]		1.6 (1.1–2.4)
Blood urea nitrogen-to-creatinine ratio ≥ 18[a]		1.7 (1.2–2.5)
Elevated creatinine[c]	2.1 (1.1–4)	
Elevated blood urea nitrogen[f]		4.6 (1.4–15.6)
Hypocalcemia[f]		30.9 (5.8–163.2)
Hyponatremia[f]		8.2 (2.5–26.4)
Hypoalbuminemia[g]		5.9 (1.2-28.7)
Elevated hepatic enzymes[f]		6.3 (1.2–32.2)
Hyperamylasemia[f]		43.3 (4.2–442)
Hyperbilirubinemia[f]		8.7 (2–37.7)
Low arterial pH[c]	2.1 (1.1–3.9)	
Metabolic acidosis[f]		4,5 (1.1–17.7)
< 20 kg/m² body mass index[e]	2.9 (1.3–6.7)	

[a]Inouye SK, et al. Arch Intern Med 2007;167:1406–13.
[b]Vidan MT, et al. J Am Geriatr Soc 2009;58:2029–36.
[c]Pisana MA, et al. Arch Intern Med 2007;167:1629–34.
[d]Pisana MA,et al. Crit Care Med 2009;37:177–83.
[e]Juliebo V, et al. J Am Geriatr Soc 2009;57:1354–61.
[f]Aldemir M, et al. Crit Care 2001;5:265–70.
[g]Lin SM, et al. J Crit Care 2008;23:372–9.
*Adjusted for confounding factors.
AOR = adjusted odds ratio; APACHE II = Acute Physiology and Chronic Health Evaluation II; ARR = adjusted relative risk; CI = confidence interval; OR = odds ratio.

Benzodiazepines

Benzodiazepines and propofol affect GABA receptors. The GABA neurotransmitter impairs slow-wave sleep. Slow-wave sleep impairment has been proposed to contribute to delirium. Patients who receive benzodiazepines before ICU admission are almost 3 times more likely to develop delirium. In a study examining risk factors for delirium in mechanically ventilated patients, lorazepam use and dosage were significantly associated with delirium. Midazolam was also found to be an independent risk factor for delirium in the ICU. A prospective trial evaluated delirium in 118 postcardiac surgery patients randomly assigned to midazolam, propofol, or dexmedetomidine. Fifty percent of the patients in the propofol and midazolam groups became delirious versus only 8% in the dexmedetomidine group.

Benzodiazepines also increase the duration of delirium in ICU patients older than 60 years.

Benzodiazepine use outside the ICU is also associated with increased delirium risk. In a delirium study of patients with acquired immune deficiency syndrome (AIDS), the lorazepam arm was discontinued early because of worsening delirium symptoms. In addition, benzodiazepine use is associated with postsurgery delirium.

Opioids

Opioids are associated with an increased risk of delirium, especially at high doses. Meperidine is the most troublesome because it is metabolized to normeperidine, which may accumulate in patients with kidney dysfunction and induce delirium. Meperidine use has

Table 1-2. Delirium: Precipitating Risk Factors

Risk Factors	RR (95% CI)	OR (95% CI)
Physical restraints[a,b]	3.5 (2–6.3)	5.7 (3.6–8.9)
Bladder catheter[a,b]	3.1 (1.7–5.5)	2.1 (1.4–3.1)
Any iatrogenic event[a]		2.5 (1.6–3.9)
> 4 iatrogenic events[a]		2.4 (1.5–3.9)
New diagnosis of illness[a]		1.2 (1.1–1.3)
Out of bed < 1 time/day[b]	2.3 (1.2–4.1)	
Anticonvulsants[b]	3.6 (1.3–9.8)	
Antiemetics[b]	2.3 (1.1–5.1)	
Benzodiazepine before admission to ICU[c]		3.4 (1.6–7)
Midazolam[d]		2.75 (1.4–5.3)
Lorazepam (no risk)[d]		0.45 (0.16–1.27)
Lorazepam[e]		1.2 (1.1–1.4)
Morphine (negative risk factor)[d]		0.36 (0.16–0.82)
≥ 2 psychoactive agents[b]	4.5 (2.1–9.9)	
> 3 drugs added[b]	4.0 (2.1–7.3)	
In emergency department for > 12 hours[b]	2.1 (1.1–3.7)	
Malnutrition[b]	3.9 (2–7.5)	
Respiratory insufficiency[b]	2.7 (1.2–5.8)	
Infection[g]		18.0 (3.5–90.6)
Sepsis[f]		3.6 (1.03–12.9)
Fever[g]		14.3 (4.1–49.3)
Hypotension[g]		19.8 (5.3–74.3)
Anemia[g]		5.4 (1.6–17.8)

[a]Inouye SK, et al. Arch Intern Med 2007;167:1406–13.
[b]Inouye SK, et al. JAMA 1996;275:852–7.
[c]Pisana MA, et al. Arch Intern Med 2007;167:1629–34.
[d]Pandharipande P, et al. J Trauma 2008;65:34–41.
[e]Pandharipande P, et al. Anesthesiology 2006;104:21–6.
[f]Lin SM, et al. J Crit Care 2008;23:372–9.
[g]Aldemir M, et al. Crit Care 2001;5:265–70.
CI = confidence interval; ICU = intensive care unit; OR = odds ratio; RR= relative risk.

been associated with delirium in several studies. Pentazocine has more central nervous system effects than other equianalgesic drugs and should be avoided in patients at risk of delirium.

Attention to dosing is essential in opioid-naïve patients, and even more so in opioid-naïve elderly patients. Rapid escalation of any long-acting opioid may precipitate delirium. Fentanyl patches should be used cautiously and only in opioid-tolerant patients. In a study to identify risk factors for delirium in the ICU, morphine was a strong predictor. Opioids were also associated with increased delirium duration in ICU patients older than 60 years. Not all studies have shown a positive relationship between opioid use and delirium. For example, morphine use has been associated with a significantly decreased risk of delirium in ICU trauma patients.

It is important to monitor pain in patients at risk of delirium because inadequate pain control can precipitate delirium. In contrast, the agitation associated with hyperactive delirium may be mistaken for inadequate pain control and lead to escalated doses of opioids, which in turn worsen delirium. In these cases, a vigilant trial of lower opioid doses may improve not only delirium but also pain ratings.

Other Central Nervous System Drugs

Any drug that has central nervous system effects may precipitate delirium in a vulnerable patient. Anticonvulsants and antiemetics are associated with an increased risk of delirium. Drug regimens that contain more than two psychoactive agents also are associated with an increased risk of delirium, as are glucocorticoids.

Box 1-1. Common Drugs Associated with Delirium

Agents with Significant Anticholinergic Effects
Amitriptyline
Belladonna alkaloids
Chlorpromazine
Cyproheptadine
Cyclobenzaprine
Dicyclomine
Diphenhydramine
Doxepin
Flavoxate
Hyoscyamine
Hydroxyzine
Imipramine
Meclizine
Orphenadrine
Prochlorperazine
Promethazine
Thioridazine
Trimethobenzamide

Benzodiazepines
Alprazolam
Chlordiazepoxide
Clonazepam
Clorazepate
Diazepam
Flurazepam
Lorazepam
Oxazepam
Temazepam

Muscle Relaxants
Carisoprodol
Chlorzoxazone
Cyclobenzaprine
Metaxalone
Methocarbamol
Orphenadrine
Tizanidine

Opioids
Fentanyl patches in opioid naïve
Hydromorphone doses greater than 0.5 mg
    intravenously every 3 hours or 2 mg orally every 4
    hours in opioid naïve
Morphine in doses greater than 4 mg intravenously
    every 3 hours or 10 mg orally every 4 hours in opioid
    naïve (5 mg orally every 4 hours in frail elderly)
Oxycodone in doses greater than 5 mg every 4 hours in
    opioid-naïve patients (2.5 mg orally every 4 hours in
    frail elderly)
Meperidine
Pentazocine

Other
Corticosteroids
Metoclopramide in doses > 5 mg before meals and at
    bedtime in patients with moderate to severe renal
    impairment

Careful monitoring for delirium at initiation or during up-titration of these drugs is recommended.

Prevention

About 40% of delirium cases are preventable. In the past decade, progress has been made in increasing awareness of the potential negative outcomes of delirium and documenting reliable methods to detect and prevent it. Prevention of delirium now focuses on eliminating or reversing as many risk factors as possible. Although guidelines originating in the United States have not been published, three sets of consensus guidelines have been published in other countries. The Australian delirium guidelines, the Swiss guidelines, and the National Institute for Health and Clinical Excellence (NICE) delirium guidelines recommend risk factor reduction by trained health care providers.

Role of the Pharmacist in Prevention

Pharmacist intervention is important in reducing many delirium risk factors (Box 1-2). Pharmacists have an important role in the recognition and prevention of alcohol, nicotine, and drug withdrawal. A thorough evaluation of home drugs is essential to prevent abruptly discontinuing those with withdrawal potential. Interviewing the patient and family and accessing state electronic resources for controlled substances are helpful methods to obtain accurate histories. Common agents causing withdrawal symptoms that may be mistaken for delirium are benzodiazepines, muscle relaxants, and high doses of selective serotonin reuptake inhibitors or serotonin/norepinephrine reuptake inhibitors. Proactively reinitiating these drugs at the previous dose or at an appropriate dose for first-step weaning is essential.

Pharmacists may also promote the avoidance of drugs that are associated with delirium. In addition, appropriate dosing of opioids and other agents with central nervous system effects should be ensured. As hospitals develop systems to screen for the risk of delirium development, notification systems that include the pharmacist will help promote the avoidance of high-risk agents. Electronic screenings and notifications can facilitate this process.

Pharmacists are also in a position to prevent other risk factors. Appropriate selection and dosing of analgesics to achieve acceptable pain control can decrease pain-induced delirium. Pharmacists have the knowledge base to anticipate and recommend interventions for drug-induced electrolyte disorders and hypotension. The early selection of appropriate antibiotics will decrease the impact of infectious processes. Appropriate treatment of hyperglycemia may prevent delirium symptoms caused by poor glycemic control.

Box 1-2. Evaluating for Drug-Related Causes of Delirium

1. **Evaluate for drug withdrawal:**
   (a) Compare before-admission agents with current agents. Look for drugs that might precipitate withdrawal with abrupt discontinuation (e.g., benzodiazepines, barbiturates, muscle relaxants).
   (b) Check that the patient is taking an appropriate dose (investigate actual as-needed use before admission).
2. **Evaluate anticholinergic drug use:**
   (a) Eliminate agent if possible.
3. **Evaluate pain regimen:**
   (a) Efficacy of current regimen (pain can also cause delirium)
   (b) Appropriateness of drug choice on the basis of age and kidney function
   (c) Efficacy of dose on the basis of drug history
4. **Evaluate for any other agents with central nervous system effects:**
   (a) Evaluate appropriateness of dose.
   (b) If recently initiated or dose changed, consider an alternative.
5. **Evaluate for other drug-related causes of delirium:**
   (a) Appropriateness of glucose control regimen
   (b) Whether electrolyte supplement is needed or requires adjustment
   (c) Appropriateness of antibiotic regimen

Box 1-3. Interventions to Prevent or Decrease Delirium Duration

What to Do:
Use an interdisciplinary team
Provide educational sessions explaining characteristics, recognition, and risk factors for delirium for health care providers
Provide delirium education to family members
Reorient patient, and encourage family involvement
Use eyeglasses, hearing aids, and interpreters
Use music, massage, and relaxation techniques
Use sitters
Maintain the patient's mobility and self-care ability
Start physical and occupational therapy early in mechanically ventilated patients
Normalize sleep-wake cycle, aim for uninterrupted period of sleep at night, have patient sleep in quiet room with low-level lighting, space drugs and blood draws away from sleep time, and offer noncaffeinated warm drink at bedtime
Promote nutrition and hydration
Treat pain
Treat urinary retention
Treat fecal impaction
Use dexmedetomidine for sedation instead of lorazepam or midazolam

What to Avoid:
Physical restraints
Foley catheters
Intravenous lines
Psychoactive and sedative agents (or reduce dose to wean)
Drugs with anticholinergic effects
Daytime napping

Information from Schweickert WD, et al. Lancet 2009;373:1874–82; Pandharipande PP, et al. JAMA 2007;298:2644–53; Riker RR, et al. A randomized trial. JAMA 2009;301:489–99; Inouye SK, et al. J Am Geriatr Soc 2000;48:1697–706; Marcantonio ER, et al. J Am Geriatr Soc 2001;49:516–22; Naughton B, et al. J Am Geriatr Soc 2005;53:18–23; Vidan MT, et al. J Am Geriatr Soc 2009;58:2029–36; and Marcantonio ER, et al. J Am Geriatr Soc 2010;58:1019–26.

Delirium Prevention Interventions

Protocols to decrease risk factors have successfully reduced delirium in acute care settings. In the Yale Delirium Prevention trial, 852 non-ICU patients older than 70 years were assigned to usual care or to a delirium prevention intervention. The intervention group had a significantly lower risk of developing delirium (15% vs. 9.9%). A randomized controlled trial compared a prevention intervention by a geriatric consult service with usual care; delirium was found to be significantly reduced in patients admitted for emergency hip fracture repair (50% vs. 32%). An intervention that changed processes of care in cognitively impaired hospitalized patients older than 75 years produced a significant decrease in delirium (40.9% vs. 19.1%). Finally, a prospective controlled trial compared the use of preventive interventions on a geriatric unit with usual care on general medical units; delirium incidence was significantly lower on the intervention unit (11.7% vs. 18.5%). Despite these successful results, a recent survey of 147 hospitals indicated that only 21% of the 95 respondents assessed patients for delirium risk factors.

In contrast to these positive results, implementation of a nurse-led delirium program in postacute care facilities was unsuccessful in decreasing the persistence of delirium. Although a significant increase in the identification of delirium occurred in the intervention group, nurses did not consistently notify physicians or nurse practitioners so that abatement measures could be enacted. This study illustrates that inadequate interdisciplinary teamwork is a barrier to implementing delirium treatment protocols.

A variety of interventions, all targeting delirium risk factors, have been used in these prevention trials (Box 1-3). The Hospital Elder Life Program (HELP) is a commercially available program that helps institutions with the administrative and clinical activities necessary to incorporate prevention interventions into approved protocols. The program recommends a small, well-trained core of clinical staff that coordinates the policy changes and education needed to institute interventions. Well-trained volunteers help provide the nonpharmacologic interventions that are core to this program. A recent study of a HELP program in place for 7 years in a community teaching hospital reported lower prevalence of delirium and shorter length of stay. A financial return of $7.3 million was calculated on the basis of fewer delirium cases, decreased length of stay, and increased availability of hospital beds.

A recent randomized double-blind controlled trial in 145 patients older than 65 years tested a single intervention to decrease delirium. Administering 0.5 mg of melatonin each evening was associated with a significantly lower risk of delirium. Further studies are needed to ensure that the benefits of this agent outweigh the risks in a large population.

Although results of system-wide protocols in ICU patients have not yet been published, individual interventions in this setting have shown promise. In one trial, 104 ICU patients received sedation interruptions and physical therapy/occupational therapy that progressed from range of motion to pre-walking exercises. Walking was attempted by patients who had been functional (Barthel Index score of 70 or greater) before admission. The intervention group had a markedly shorter duration of delirium, and more patients in the intervention group returned to an independent functional status at discharge.

Several principles are recommended to avoid delirium in ICU patients. An analgesia first (or A1) approach to sedation should be used. Pain assessment and, if appropriate, administration of an opioid are recommended before increasing sedatives. Validated sedation scores are essential, and titration to light sedation is recommended. Interrupting sedation at least daily also decreases the risk of delirium.

The use of dexmedetomidine as a sedative agent has been associated with a lower incidence of delirium in manufacturer-sponsored studies. Dexmedetomidine is an α_2-adrenergic receptor agonist that causes sedation and provides analgesic activity. It is currently approved for initial sedation only, with a maximal duration of 24 hours at a maximal dose of 0.7 mcg/kg/hour. Trials for continuous sedation have used dexmedetomidine at doses as high as 1.5 mcg/kg/hour for durations of up to 120 hours.

In a trial that randomly assigned postcardiac surgery patients to dexmedetomidine, propofol, or midazolam, the dexmedetomidine group had an 8% incidence of delirium, whereas the propofol and midazolam groups both had an incidence of 50%. The SEDCOM (Safety and Efficacy of Dexmedetomidine Compared with Midazolam) trial is another manufacturer-sponsored randomized controlled trial of 366 ICU patients requiring sedation. There was no significant difference in the primary end point of time spent in the target sedation range; however, the dexmedetomidine group required significantly more open-label midazolam boluses. Although the prevalence of delirium was similar before the sedation protocol was initiated, the prevalence of delirium was significantly lower (22.6% difference) in the dexmedetomidine group than in the midazolam group after initiation of the sedation protocol. Delirium-free days and ventilator-free days were significantly lower in the dexmedetomidine group. Considerably more patients in the dexmedetomidine group experienced bradycardia (heart rate less than 40 beats/minute), whereas significantly more patients in the midazolam group experienced tachycardia and hypertension.

Another manufacturer-sponsored trial used a double-blind, randomized controlled design to compare dexmedetomidine with lorazepam in 103 ICU patients. The dexmedetomidine group had a significant decrease in the combined end point of delirium-free and coma-free days. The dexmedetomidine group had a significantly higher incidence of bradycardia, a significantly higher use of fentanyl, and a large but nonsignificant median increase of $22,500 in hospital costs in the 90 patients for whom cost data were available. A small randomized controlled trial compared haloperidol with dexmedetomidine in 20 intubated ICU patients. Haloperidol was given as a 0.5- to 2-mg/hour infusion with an optional load of 2.5 mg, whereas dexmedetomidine was given at a dose of 0.2–0.7 mcg/kg/hour with an optional loading dose of 0.1 mcg/kg over 20 minutes. Significant decreases in median time to extubation and ICU stay were noted in the dexmedetomidine group, but no difference in time to achieve negative delirium scores was noted. The design of this study may have biased the results toward dexmedetomidine for the primary outcome of extubation. Haloperidol has a long half-life, yet it was given as a continuous infusion, allowing accumulation and thereby increasing the risk of prolonged sedation.

In summary, dexmedetomidine may be an important alternative to high-risk drugs used for ICU sedation. Further independent studies are needed as well as cost-benefit analyses to determine whether improved outcomes justify the expense of a change to dexmedetomidine in sedation protocols.

Detection of Delirium

Although prevention protocols reduce the incidence of delirium, they do not eliminate it. When delirium occurs, early recognition of symptoms may lead to a more rapid identification of its cause and a more rapid recovery.

A tool to monitor for delirium in clinical practice is a critical part of developing a delirium protocol. Without tools to identify delirium, many hypoactive delirium cases would be missed. In addition, many hyperactive delirium cases may be recognized only after the harm has occurred. The 2002 sedation guidelines from the Society of Critical Care Medicine recommend routine monitoring for delirium in patients receiving mechanical ventilation. All recent guidelines support a structured process to screen for and diagnose delirium.

Many validated tools exist for monitoring delirium (Table 1-3, Table 1-4). In patients not in ICUs, the CAM, Delirium Symptom Interview, Memorial Delirium Assessment Scale (MDAS), Nursing Delirium Screening Scale (Nu-DESC), Delirium Rating Scale (DRS), Delirium Observation Screening Scale (DOSS), and the Global Attentiveness Rating (GAR) are validated.

In addition to acceptable sensitivity and specificity, ease of use is important because nurses need to incorporate these tools into their daily routines. The CAM, DOSS, GAR, and Nu-DESC can be completed in 5 minutes or less. The CAM is the validated tool most widely used in non-ICU patients and is recommended by the NICE guidelines. The Nu-DESC is a another descriptive tool that may be easily incorporated into workflow with minimal training.

Tools for monitoring delirium in the ICU patient include the Confusion Assessment Method for the ICU (CAM-ICU), a modified form of the CAM that is also recommended by the NICE guidelines. The CAM-ICU has a high sensitivity and specificity and is a widely used and validated tool; however, it requires nurse training before use. Training materials and videos are available at *www.ICUdelirium.org*. Like the CAM, the CAM-ICU evaluates the basic components of the definition of delirium in an organized fashion. A standardized method to assess sedation is essential for appropriate use of the CAM-ICU. The Intensive Care Delirium Screening Checklist (ICDSC) is another validated tool for use in the ICU patient. This scale assesses the patient for the previous shift or 24 hours instead of at a particular time and is quicker to administer.

Table 1-3. Sensitivity and Specificity for Selected Delirium Screening Tools for Use in Medical/Surgical Areas

Screening Tool	Sensitivity (%)	Specificity (%)	Comparison
CAM[a]			
First site	100	95	Expert rater using DSM-IV criteria
Second site	94	90	Expert rater using DSM-IV criteria
Nursing Delirium Screening Scale[b]	85.7	86.8	CAM
MDAS[b]	95.2	89.5	CAM
CRS[b]	76.2	81.6	CAM

[a]Inouye SK, et al. Ann Intern Med 1990;113:941–8.
[b]Gaudreau JD, et al. J Pain Symptom Manage 2005;29:368–75.
CAM = Confusion Assessment Method; CRS = Confusion Rating Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders IV; MDAS = Memorial Delirium Assessment Scale.

Table 1-4. Sensitivity and Specificity for Selected Delirium Screening Tools for Use in Intensive Care Area

Screening Tool	Sensitivity (%)	Specificity (%)	Comparison
Intensivists[a]	28	100	CAM-ICU
Intensivists and fellows[b]	63	100	Expert rater using DSM-IV criteria
ICU residents[b]	14	93	Expert rater using DSM-IV criteria
CAM-ICU[b,c]	64	88	Expert rater using DSM-IV criteria
	100	98	Expert rater using DSM-IV criteria
ICDSC[b]	43	95	Expert rater using DSM-IV criteria

[a]Spronk PE. Intensive Care Med 2009;35:1276–80.
[b]Van Eljk MM, et al. Crit Care Med 2009;37:1881–5.
[c]Ely EW. JAMA 2001;286:2703–10.
CAM-ICU = Confusion Assessment Method for the IDU; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders IV; ICDSC = Intensive Care Delirium Screening Checklist; ICU = intensive care unit.

Treatment of Delirium

Underlying Causes

When delirium is suspected, the first priority is to determine its etiology (see Figure 1-1). A variety of acute disease states may precipitate delirium. These include conditions that cause hypoxia (e.g., acute myocardial infarction, respiratory failure), infection, stroke, and metabolic disorders.

Drugs or the lack of appropriate drugs may also lead to delirium. Pharmacists play an important role in identifying drug-related causes of delirium. Agents associated with delirium should be scrutinized, and alternatives chosen when possible. Newly initiated benzodiazepines should be discontinued, but long-term users should be screened for benzodiazepine withdrawal. Thorough drug reconciliation should be done to evaluate other agents that may cause withdrawal. Pain regimens should be evaluated to ensure appropriate pain control and opioid dosing on the basis of previous exposure. The appropriateness of antibiotic regimens and blood glucose control should also be evaluated, and electrolyte disturbances should be corrected. Any new agent with central nervous system effects should be scrutinized and discontinued or changed if possible.

Together with attempting to reverse all apparent underlying causes of delirium, nonpharmacologic management of delirium should always be tried before initiating medication therapy. Recommended nonpharmacologic measures are identical to the measures used to prevent delirium (see Box 1-3). Watching a loved one in a delirious state can be very distressing. It is important to explain the importance of nonpharmacologic measures to family members and enlist their support in providing these measures. Information booklets that explain delirium interventions in lay language can help reinforce this education.

Box 1-4. Starting Doses of Antipsychotics for the Treatment of Delirium in Elderly Patients

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Haloperidol 0.5–1 mg intramuscularly; observe after 30–60 minutes and repeat if needed

Haloperidol 0.5–1 mg orally two times/day and 0.5–1 mg orally every 4 hours as needed

Risperidone 0.5 mg two times/day

Olanzapine 2.5–5 mg/day

Quetiapine 25 mg two times/day[a]

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[a]Author recommends more conservative dosing of 12.5 mg every 12 hours in frail elderly patients.
Information from Inouye S. Delirium in older persons. N Engl J Med 2006;354:1157–65.

Pharmacotherapy

There are no drugs with U.S. Food and Drug Administration (FDA)-approved labeling for treatment of delirium. Little evidence-based information is available to guide the pharmacotherapy of delirium. Although the Australian, Swiss, and NICE delirium guidelines all address prevention and treatment, pharmacologic treatment recommendations are not Grade A and lack support by randomized controlled trials.

Haloperidol

Haloperidol has become the standard agent for the treatment of delirium despite the lack of FDA-approved labeling for this indication. It has minimal anticholinergic effects, making it a preferred antipsychotic for delirium treatment. The Australian, Swiss, and NICE delirium guidelines and the Society of Critical Care Medicine sedation guidelines recommend haloperidol as first-line treatment of delirium. The evidence base to guide haloperidol dosing to treat delirium is weak. Haloperidol has a long and variable half-life with a terminal half-life of up to 7 days. It has a large volume of distribution (18 L/kg plus or minus 7 L/kg). Drug effects for delirium are needed quickly, and haloperidol characteristics are consistent with agents that require loading doses. The Society of Critical Care Medicine guidelines and expert opinion recommend repeated doses of haloperidol in the ICU patient until an effect is seen (Figure 1-2).

Haloperidol dosing for delirium in the non-ICU patient is not specified in most reference materials. Although dosing for younger patients remains undefined, experts have suggested dosing regimens for elderly patients. The suggested loading dose is 0.5–1 mg intramuscularly. The dose should be repeated every 30 minutes until the patient becomes calm but not sedate. Most patients respond to a total dose of less than 3 mg. If doses greater than 5 mg are needed, it is recommended to investigate drug or alcohol withdrawal or an underlying psychiatric disorder as possible causes. Oral loading doses have not been defined, but based on the time to peak concentration, 0.5–1 mg may be given every 2 hours until the patient is calm but not sedate. Doses greater than 5 mg by any route are associated with an increased risk of QTc prolongation.

The effectiveness of the haloperidol loading dose should be monitored, along with adverse effects such as excess sedation and extrapyramidal effects,. Subsequent dosing should be based on the patient response, starting with 0.5 mg orally or intramuscularly every 6 hours as needed and adding scheduled doses if repeated as-needed doses are given.

Although widely used, FDA-approved labeling does not include intravenous haloperidol administration for any use. There is a higher risk of QTc prolongation if haloperidol is administered intravenously.
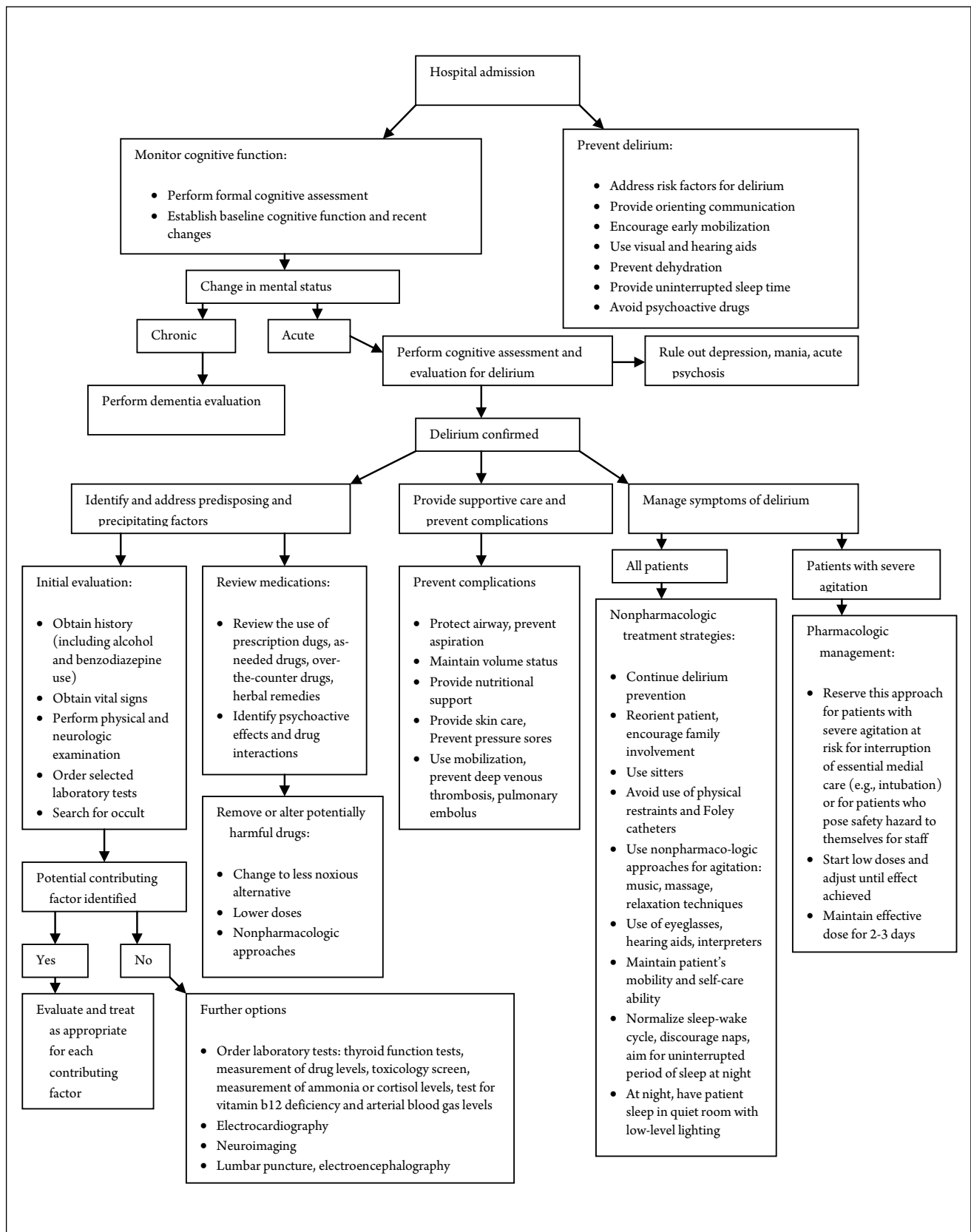
Hospital admission

Monitor cognitive function:
- Perform formal cognitive assessment
- Establish baseline cognitive function and recent changes

Prevent delirium:
- Address risk factors for delirium
- Provide orienting communication
- Encourage early mobilization
- Use visual and hearing aids
- Prevent dehydration
- Provide uninterrupted sleep time
- Avoid psychoactive drugs

Change in mental status

Chronic → Perform dementia evaluation

Acute → Perform cognitive assessment and evaluation for delirium → Rule out depression, mania, acute psychosis

Delirium confirmed

- Identify and address predisposing and precipitating factors
- Provide supportive care and prevent complications
- Manage symptoms of delirium

Initial evaluation:
- Obtain history (including alcohol and benzodiazepine use)
- Obtain vital signs
- Perform physical and neurologic examination
- Order selected laboratory tests
- Search for occult

Potential contributing factor identified

Yes → Evaluate and treat as appropriate for each contributing factor

No → Further options

Review medications:
- Review the use of prescription dugs, as-needed drugs, over-the-counter drugs, herbal remedies
- Identify psychoactive effects and drug interactions

Remove or alter potentially harmful drugs:
- Change to less noxious alternative
- Lower doses
- Nonpharmacologic approaches

Further options
- Order laboratory tests: thyroid function tests, measurement of drug levels, toxicology screen, measurement of ammonia or cortisol levels, test for vitamin b12 deficiency and arterial blood gas levels
- Electrocardiography
- Neuroimaging
- Lumbar puncture, electroencephalography

Prevent complications
- Protect airway, prevent aspiration
- Maintain volume status
- Provide nutritional support
- Provide skin care, Prevent pressure sores
- Use mobilization, prevent deep venous thrombosis, pulmonary embolus

All patients

Nonpharmacologic treatment strategies:
- Continue delirium prevention
- Reorient patient, encourage family involvement
- Use sitters
- Avoid use of physical restraints and Foley catheters
- Use nonpharmaco-logic approaches for agitation: music, massage, relaxation techniques
- Use of eyeglasses, hearing aids, interpreters
- Maintain patient's mobility and self-care ability
- Normalize sleep-wake cycle, discourage naps, aim for uninterrupted period of sleep at night
- At night, have patient sleep in quiet room with low-level lighting

Patients with severe agitation

Pharmacologic management:
- Reserve this approach for patients with severe agitation at risk for interruption of essential medial care (e.g., intubation) or for patients who pose safety hazard to themselves for staff
- Start low doses and adjust until effect achieved
- Maintain effective dose for 2-3 days

Figure 1-2. Delirium algorithm for the non-mechanically ventilated patient.

Reprinted with permission from: Inouye S. Delirium in older persons. N Engl J Med 2006;354:1157–65.

Electrocardiographic monitoring for QTc prolongation is recommended if intravenous administration is required.

Use of haloperidol after discharge is not recommended because of its significant extrapyramidal effects and its propensity to increase mortality in patients with dementia. Once a patient's delirium is controlled, the patient should be weaned off the scheduled doses. If symptoms reappear and behavior control is required, an atypical agent with low metabolic effects (e.g., risperidone, quetiapine) is preferred to haloperidol. A discussion with the patient and/or family on the benefits and risks of long-term antipsychotic agents, especially in elderly patients, and the obtainment of informed consent are recommended.

Haloperidol interacts with several common drugs. It is a moderate cytochrome P450 (CYP) 2D6 inhibitor; therefore, it may decrease the effect of codeine and tramadol by preventing the metabolism of these analgesics to their active metabolite. Haloperidol is also a CYP 2D6 substrate; therefore, bupropion, fluoxetine, paroxetine, duloxetine, sertraline, and other CYP 2D6 inhibitors may increase haloperidol concentrations. Ciprofloxacin may increase haloperidol effects by its CYP 1A2 inhibition. Verapamil, diltiazem, and other CYP 3A4 inhibitors may also increase haloperidol concentrations. Although recommendations for dosage adjustments are unavailable, it is important to consider these interactions when recommending maintenance dosing of haloperidol.

Atypical Antipsychotics

Several studies have evaluated atypical antipsychotics for delirium. A randomized controlled trial of ICU patients did not find a significant difference in response or adverse effects when olanzapine was compared with haloperidol. A randomized trial comparing delirium scores for 7 days after treatment with risperidone or olanzapine in older patients did not show a significant difference. A recent Cochrane review of three randomized studies of 629 patients found no significant differences in delirium scores or adverse effects when low-dose haloperidol (less than 3 mg/day) was compared with olanzapine or risperidone. A systematic review that included only randomized controlled clinical trials in patients older than 18 years treating only nonpsychotic and nonalcoholic delirium identified four studies meeting these criteria from January 1966 to October 2008. No significant difference in efficacy or adverse effects was found between haloperidol and atypical antipsychotics.

Quetiapine is attractive as a delirium treatment because of its antihistaminic mechanism of action, which may induce short-term drowsiness; its short elimination half-life (about 6 hours), which allows titration of doses; its lower incidence of QTc prolongation compared with haloperidol; and its low incidence of extrapyramidal adverse effects. Investigators evaluated the combined use of quetiapine and haloperidol in managing delirium in critically ill patients in a randomized, double-blind, placebo-controlled trial. Thirty-six adult patients (mean age 63 years) in the ICU with a positive delirium score were randomized to receive quetiapine 50 mg every 12 hours or placebo. Because uncontrolled agitation can cause serious harm in ICU patients, all patients were also allowed to receive haloperidol 1–10 mg intravenously to control symptoms associated with agitation. The quetiapine dosage was titrated daily in increments of 50 mg every 12 hours to a maximum of 200 mg every 12 hours if patients received at least one dose of the as-needed haloperidol. The primary outcome was the time in hours from the first dose of study drug until resolution of delirium (defined as an ICDSC score of 3 or less). Secondary outcomes included total hours in delirium, total hours spent deeply sedated or agitated, episodes of patient-initiated device removal, use of haloperidol, number of days of therapy, use of sedatives, maximal study drug dose, length of mechanical ventilation, duration of ICU and hospital stay, hospital mortality, and disposition at discharge. The time to first resolution of delirium, hours spent in delirium, duration of study drug use, and hours of agitation were significantly decreased in the quetiapine group. Other outcomes did not differ significantly between the two groups. Dosing of quetiapine and breakthrough as-needed haloperidol was aggressive in this study when considering the mean age of the study population. This aggressive dosing and the small study group may account for the lack of significant differences in important outcomes. Only a small portion of total patients screened (36 of 258 patients) met the requirements for inclusion in the study, thereby limiting its applicability to a general ICU population.

Expert recommendations for the initial dosing of quetiapine are 25 mg every 12 hours (Box 1-4); however, 12.5 mg every 12 hours is often appropriate in elderly frail patients. Concentrations of quetiapine also may be increased by CYP 3A4 inhibitors including diltiazem and verapamil.

In another randomized, placebo-controlled trial, ziprasidone, haloperidol, and placebo were compared in 101 adult mechanically ventilated patients enrolled in the Modifying the Incidence of Delirium (MIND) trial. No difference in the number of days spent in delirium or coma between the three groups was identified. The lack of difference may have been caused by supplemental antipsychotic doses that were permitted in all three groups, transforming the placebo group into a treatment group also.

Delirium Algorithms

Delirium prevention and treatment algorithms based on expert opinion have been published for non-ICU
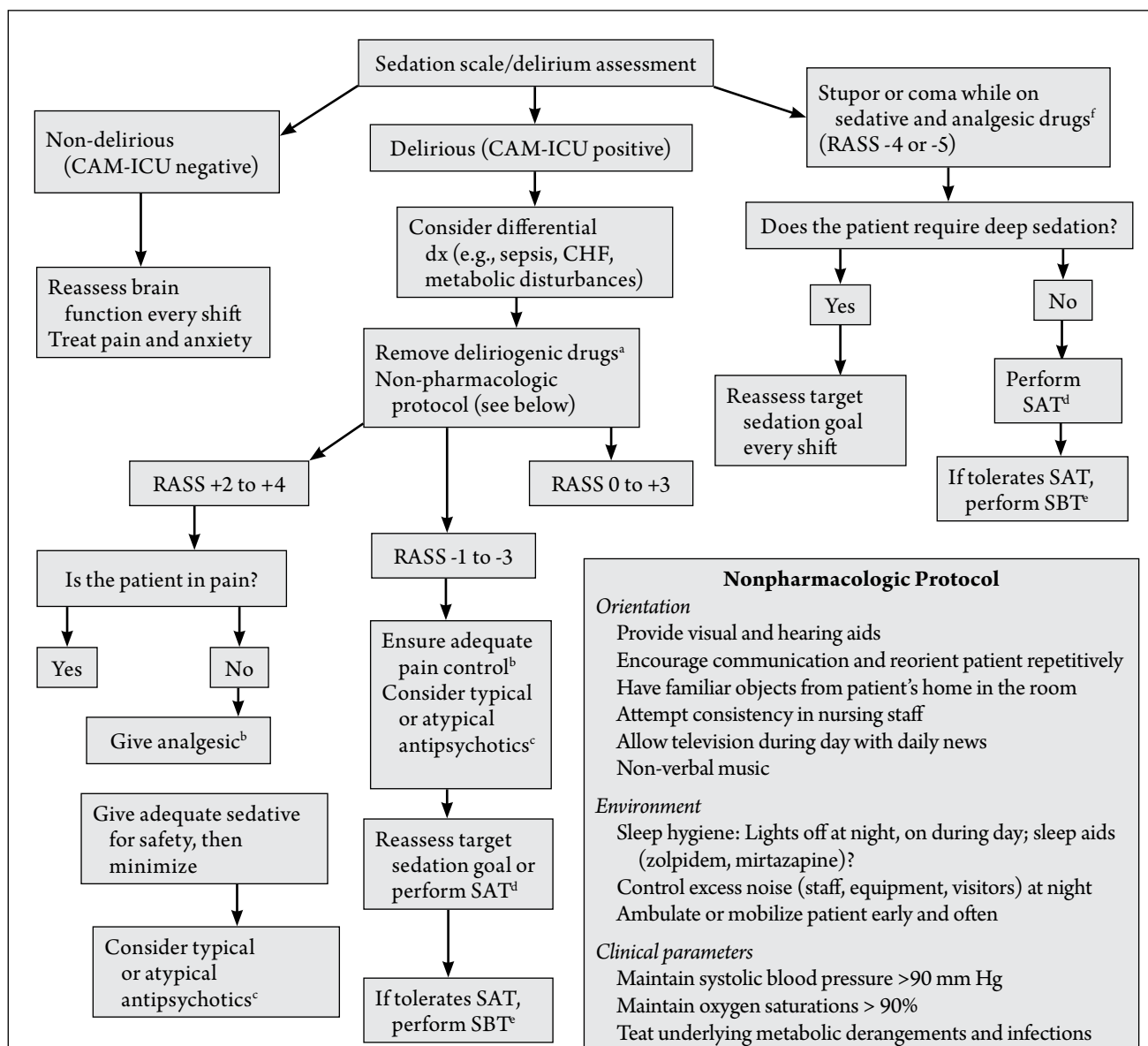
Sedation scale/delirium assessment

Non-delirious (CAM-ICU negative)
→ Reassess brain function every shift. Treat pain and anxiety

Delirious (CAM-ICU positive)
→ Consider differential dx (e.g., sepsis, CHF, metabolic disturbances)
→ Remove deliriogenic drugs[a] Non-pharmacologic protocol (see below)

RASS +2 to +4
→ Is the patient in pain?
- Yes
- No → Give analgesic[b]
→ Give adequate sedative for safety, then minimize
→ Consider typical or atypical antipsychotics[c]

RASS 0 to +3

RASS -1 to -3
→ Ensure adequate pain control[b] Consider typical or atypical antipsychotics[c]
→ Reassess target sedation goal or perform SAT[d]
→ If tolerates SAT, perform SBT[e]

Stupor or coma while on sedative and analgesic drugs[f] (RASS -4 or -5)
→ Does the patient require deep sedation?
- Yes → Reassess target sedation goal every shift
- No → Perform SAT[d] → If tolerates SAT, perform SBT[e]

Nonpharmacologic Protocol

Orientation
- Provide visual and hearing aids
- Encourage communication and reorient patient repetitively
- Have familiar objects from patient's home in the room
- Attempt consistency in nursing staff
- Allow television during day with daily news
- Non-verbal music

Environment
- Sleep hygiene: Lights off at night, on during day; sleep aids (zolpidem, mirtazapine)?
- Control excess noise (staff, equipment, visitors) at night
- Ambulate or mobilize patient early and often

Clinical parameters
- Maintain systolic blood pressure >90 mm Hg
- Maintain oxygen saturations > 90%
- Teat underlying metabolic derangements and infections

Figure 1-3. Algorithm for delirium in the intensive care unit patient.

[a]Consider stopping or substituting for deliriogenic medications such as benzodiazepines, anticholinergic medications (metochlorpromide, H2 blockers, promethazine, diphenhydramine), steroids.

[b]Analgesia – adequate pain control may decrease delirium. Consider intermittent narcotics if feasible. Assess with objective tool.

[c]Typical or atypical antipsychotics – while tapering or discontinuing sedatives, consider haloperidol 2–5 mg IV initially (0.5–2 mg in elderly) and then q6 hours. Guideline for maximal haloperiodol dose is 20 mg/day due to ~60% D_2-receptor saturation. May also consider using any of the atypicals (e.g., olanzapine, quetiapine, risperidone, ziprasidone, ariproprazole). Discontinue if high fever, QTc prolongation, or drug-induced rigidity.

[d]Spontaneous Awakening Trial (SAT – stop sedation or decrease infusion (especially benzodiazepines) to awaken patient as tolerated.

[e]Spontaneous Breathing Trial (SBT) – CPAP trial if on 50% and 8 PEEP and Sats 90%.

[f]Sedatives and analgesics may include benzodiazepines, propofol, dexmedetomidine, fentanyl, or morphine.

RASS = Richmond Agitation-Sedation Scale.

Reprinted with permission from: icudelirium.org [homepage on the Internet] Nashville, TN. Available at *icudelirium.org/docs/Delirium_Protocol_2001_30_07.pdf*. Accessed May 19, 2010.

patients (see Figure 1-2) and for ICU patients (Figure 1-3). The ICU algorithm uses the Richmond Agitation-Sedation Scale scores and the CAM-ICU to access the need for delirium treatment as well as to gather recommendations for optimizing sedation.

Adverse Effects of Antipsychotics in Patients with Delirium

Antipsychotics are not benign. Even the short-term antipsychotic use that is typical when treating delirium may cause QTc-interval prolongation with rare resultant torsades de pointes. Extrapyramidal effects may also occur. Because patients with dementia are at high risk of delirium, the FDA warning regarding use of these drugs in patients with dementia is also a consideration.

Cardiac Effects

The FDA has included a boxed warning for haloperidol because of increased risk of QTc prolongation with resultant torsades de pointes; QTc prolongation is more likely in patients who received intravenous or high-dose haloperidol. If the intramuscular or oral route is not possible, there is some evidence that the subcutaneous route is acceptable. Electrocardiographic monitoring is recommended if intravenous haloperidol is necessary. Monitoring for other conditions that prolong QTc intervals (e.g., hypokalemia, hypomagnesemia, hypocalcemia, concomitant drugs associated with QTc prolongation, drug interactions that decrease elimination of QTc prolongers) is also prudent. It is recommended that haloperidol be discontinued in patients with QTc intervals that exceed 500 milliseconds or QTc intervals that increase by more than 25%.

Although haloperidol has the highest risk of torsades de pointes (see the Arizona Center for Education and Research on Therapeutics Web site at *www.azcert.org/index.cfm)*, the atypical antipsychotics also may have risk. Quetiapine, risperidone, and ziprasidone are listed in the possible risk group; this indicates that some reports have associated these drugs with torsades de pointes risk or QTc prolongation but substantial evidence of risk is lacking. Olanzapine is listed with the conditional drug risk group, indicating that some reports have shown a weak association with torsades de pointes or QTc prolongation, but it is unlikely to be a risk at normal doses in patients without other risk factors.

Extrapyramidal Effects

Haloperidol blocks the nigrostriatal dopamine tract more strongly than other antipsychotics, so it is most likely to cause extrapyramidal symptoms and worsen Parkinson disease. The Cochrane review examining antipsychotics for delirium found that high-dose haloperidol (greater than 4.5 mg/day) was associated with an increase in extrapyramidal effects. Patients with Parkinson disease often have accompanying dementia, causing an increased risk of delirium. If an antipsychotic is needed in a patient with Parkinson disease, quetiapine or clozapine (with the required hematologic monitoring) is recommended. From a practical standpoint, quetiapine is the drug of choice for patients with delirium who require short-term antipsychotic therapy.

Antipsychotic-Related Mortality Use

Increases in mortality have been documented in older patients receiving either atypical or typical antipsychotics for behavioral symptoms associated with dementia. The FDA issued a boxed warning for all antipsychotics to notify prescribers of this risk. It is unknown whether these risks are also present when used for short-term treatment of delirium. Antipsychotics should be reserved for elderly patients who are at risk of threatening their own safety or the safety of others or when behavior interferes with essential therapy.

Benzodiazepines

Benzodiazepines have historically also been used to treat delirium. This has become controversial in light of the previously mentioned studies that show an association between benzodiazepine use and increased delirium risk. A 2009 Cochrane review that examined the use of benzodiazepines in non–alcohol-related delirium concluded that no adequately controlled trials support this use. All three sets of guidelines recommend antipsychotics as the drugs of choice in those who require pharmacotherapy for non-alcoholic or non-benzodiazepine withdrawal delirium.

Cholinergics

Cholinergic activity is decreased in delirium. Compounds that increase cholinergic activity have been proposed as a treatment for delirium. However, results from small studies that evaluated acetylcholinesterase inhibitors have not been promising. A recent study investigating the use of rivastigmine in ICU patients with delirium was terminated early because of increased mortality in the intervention group.

ROLE OF THE PHARMACIST

Drugs often contribute to delirium, and the pharmacotherapy of delirium is not well defined. Pharmacists can play a key role in the prevention of delirium and the promotion of safe and effective treatment. Identification of key members of several disciplines (e.g., medicine, nursing, pharmacy, physical therapy, volunteer services, administration) to form an interdisciplinary team is one of the first steps in developing a delirium improvement project. This team will address the system-wide changes in procedures that are necessary to optimally prevent and treat this serious complication of hospitalization.

The Australian guidelines have incorporated this inter-disciplinary approach into their recommendations.

Conclusion

Delirium is a serious complication in hospitalized patients. To decrease delirium, increased education and protocol-driven changes are effective. The pharmacist can play a key role on the intervention team, particularly in the development of methods to prevent the use of high-risk drugs, the reduction of risk factors, and the development of best evidence treatment protocols.

Annotated Bibliography

1. Witlox J, Eurelings LSM, de Jonghe JFM, Kalisvaart KJ, Eikelenboon P, van Gool WA. Delirium in elderly patients and the risk of post discharge mortality, institutionalization and dementia: a meta-analysis. JAMA 2010;304:443–51.

    This meta-analysis attempts to answer whether delirium is a contributor to poor outcomes in older patients or whether it represents a marker of underlying disease. The primary outcome assessed the association between delirium and mortality, institutionalization, and dementia in elderly patients while controlling for age, sex, comorbid illness or illness severity, and baseline dementia. The delirium group had significantly higher mortality (hazard ratio [HR] 1.95; 95% confidence interval [CI], 1.51–2.52), risk of institutionalization (odds ratio [OR] 2.41; 95% CI, 1.77–3.29), and risk of dementia (OR 12.52; 95% CI, 1.86–84.21). The results suggest a relationship between delirium and increased risk of death, institutionalization, and dementia that is independent of age, sex, comorbid illness, illness severity, or baseline dementia.

2. Inouye S, Jones RN, Kiely DK, Yang F, Marcantonio SM. Risk factors for delirium at discharge. Arch Intern Med 2007;167:1406–13.

    This investigation identified risk factors at discharge for persistent delirium and then developed and validated a predictive model based on these findings. Twenty-one risk factors were tested for their relationship with delirium at discharge. Vision impairment, dementia diagnosis, and restraint use were significantly associated with delirium at discharge. Activities of daily living impairment and high comorbidity did not reach significance for delirium at discharge, but they (among others) showed significance for the development of delirium in the hospital and were added to the model. A risk stratification model was formulated, creating low-, intermediate-, and high-risk groups. Delirium rates at discharge significantly increased from the low- to high-risk groups. The likelihood of death or nursing home placement significantly increased from 23% to 77% when low- and high-risk populations were compared in the developmental cohort and significantly increased from 15% to 64% in the validation cohort. This model

may be useful to identify patients who will most benefit from delirium prevention strategies.

3. Pandharipande P, Cotton BA, Shintani A, Thompson J, Pun BT, Morris JA Jr, et al. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. J Trauma 2008;65:35–41.

    This prospective observational study sought to determine the delirium prevalence in a population of surgical and medical patients and to determine modifiable risk factors. The investigators found a delirium prevalence of 70% in this group. Midazolam was significantly associated with delirium, and morphine had a significant negative association with delirium. Anesthetics, histamine-2 blockers, lorazepam, and fentanyl showed no significant association with delirium in this study.

4. Pisani MA, Murphy TE, Araujo KLB, Slattum P, Van Ness PH, Inouye SK. Benzodiazepine and opioid use and duration of intensive care unit delirium in an older population. Crit Care Med 2009;37:177–83.

    This study examined the impact of opioids and benzodiazepines on the duration of delirium by means of a prospective observational study of 304 ICU patients. A significant association between the dual outcome of benzodiazepine and opioid use and duration of delirium was found, in addition to a significant association between haloperidol and duration of delirium. This study had several important flaws. First, although study design allowed the open use of other drugs, the methods indicated that only two opioids and two benzodiazepines were tallied. Propofol use and use of antipsychotics other than haloperidol were not reported. Another very serious flaw is that delirium was only objectively assessed Monday through Friday, introducing error to the primary outcome measure. The reporting of benzodiazepine use only as a dual outcome without providing the single outcome statistics is also a concern. Finally, the haloperidol risk was reported without a correction for other risk factors for delirium.

5. Vidan MT, Sanchez E, Alonso M, Montero B, Ortiz J, Serra JA. An intervention integrated into daily clinical practice reduces the incidence of delirium during hospitalization in elderly patients. J Am Geriatr Soc 2009;58:2029–36.

    This is a prospective clinical trial comparing the effects of a delirium prevention protocol enacted for 170 patients on a geriatric unit versus usual care for 372 patients on two internal medicine units. The primary outcome was the incidence of delirium during hospitalization. The intervention included education sessions explaining characteristics, recognition, and risk factors for delirium; written portable educational resources; and procedures promoting maintenance of patient orientation, sensorial perception, sleep, mobilization, hydration, and nutrition. In addition, avoidance or reduction in the dose of psychoactive and sedative agents and withdrawal of drugs with anticholinergic effects were enacted. The diagnoses of

new delirium (11.7% vs. 18.5%; p=0.04) and functional decline (45.5% vs. 56.3%; p=0.03) were significantly decreased in the intervention group. There were no statistical differences among groups in the intensity of delirium or the duration of a delirium episode.

6. Tropea J, Slee J, Brand CA, Gray L, Snell T. Clinical practice guidelines for the management of delirium in older people in Australia. Australas J Ageing 2008;27:150–6.

This is a summary of the clinical practice guidelines for the management of delirium in older people that was commissioned on behalf of the Australian Health Ministers' Advisory Council. Recommendations for the detection and diagnosis of delirium include a structured process to screen for and diagnose delirium. For the prevention of delirium, risk factor reduction is recommended with appropriate training of health care providers to implement this prevention strategy. Prevention strategies also include a recommendation for consultation by a geriatrician to assess and observe older surgery patients (especially orthopedic surgery patients). Management of delirium recommendations includes investigation and treatment of delirium causes, use of a multidisciplinary team, nonpharmacologic methods to manage delirium, guidance in the use and dosing of antipsychotic agents, discharge planning and follow-up for those who have experienced delirium, and continuing staff education through educational programs and guidelines.

7. Michaud L, Bula C, Berney A, Camus V, Voellinger R, Stiefel F, et al. Delirium: guidelines for general hospitals. J Psychosom Res 2007;62:371–83.

This Swiss group of delirium experts reviewed the literature to formulate guidelines related to risk factors associated with delirium, interventions to prevent delirium, and treatment of delirium. A 14-member expert panel reviewed and rated the guideline statements. Predisposing and precipitating risk factors, prevention recommendations, and pharmacologic treatment methods were identified and graded based on the level of evidence. None of the pharmacologic treatments reviewed was assigned a Grade A recommendation. (Grade A recommendations are based on randomized controlled trials or systemic reviews of randomized controlled trials or a high consensus if based on nonrandomized controlled trials or prospective cohort trials.)

8. Young J, Murthy L, Westby M, Akunne A, O'Mahoney R. Diagnosis, prevention and management of delirium: summary of NICE guidance. BMJ 2010;341:c3704.

These guidelines recommend assessing patients who present to a hospital or long-term care facility with risk factors for delirium (e.g., age, current or previous cognitive dysfunction, current hip fracture, serious illness). It is recommended that patients at risk have consistent care providers; limited room transfers; and an assessment for cognition, dehydration, constipation, hypoxia, immobility, infection, several drugs, pain, poor nutrition, sensory impairment, and sleep disturbances.

Assessments for changes or fluctuations in behavior are recommended on admission for those at risk and daily for others. Administration of the CAM or ICU-CAM by trained providers are then suggested for those patients who screen positive. If delirium occurs and patients are distressed or considered a risk to themselves or others and have not responded to nonpharmacologic measures, short-term haloperidol or olanzapine is recommended.

9. Pun BT, Ely EW. The importance of diagnosing and managing ICU delirium. Chest 2007;132:624–36.

This key review article presents the incidence of delirium and outcomes related to delirium. The authors note that delirium is common in ICU patients and that ICU delirium is associated with a 3-fold higher reintubation rate, a greater than 10-day prolonged length of stay, a higher ICU mortality, a higher in-hospital mortality, and a higher 6-month mortality even after controlling for confounding factors. Delirium cases are noted to have higher ICU costs and hospital costs than non-delirium cases. The authors also provide a review of the literature documenting an association between the diagnosis of delirium and a subsequent diagnosis of dementia. A description of two screening tests commonly used for delirium in the ICU setting is provided, with a detailed description of the CAM-ICU. Predisposing and precipitating risk factors for delirium are also reviewed. Finally, the authors review treatment options and provide a treatment algorithm.

10. van Eljk MM, Marum RJ, Klijn IAM, Wit N, Kesecioglu J, Slooter AJC. Comparison of delirium assessment tools in a mixed intensive care unit. Crit Care Med 2009;37:1881–5.

The authors of this study compared the detection of delirium by the CAM-ICU, ICDSC, physician clinical impression, and a rating based on experts using DSM-IV criteria in 125 ICU patients. They found that the CAM-ICU had a sensitivity of 64% and specificity of 88%. The ICDSC had a sensitivity of 43% and specificity of 95%. Intensivists and fellows diagnosing delirium found a sensitivity of 63% and specificity of 100%, whereas ICU residents had a sensitivity of 14% and specificity of 93%. Based on this study, ICU physicians and fellows detected delirium in a percentage of patients similar to the CAM-ICU. The ICDSC was inferior in detecting delirium, and ICU residents had a lower rating still, detecting only 14% of the delirium cases.

11. Girard TD, Pandharipande PP, Carson SS, Schmidt GA, Wright PE, Canonico AE, et al. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. Crit Care Med 2010;38:428–37.

This randomized, placebo-controlled trial of 101 mechanically ventilated ICU patients examined the relationship between haloperidol and ziprasidone use and days without delirium or coma compared with placebo. The CAM-ICU and Richmond

Agitation-Sedation Scale scores were assessed every 12 hours. Antipsychotic drug doses were adjusted on the basis of these scores. Neither haloperidol nor ziprasidone significantly decreased the number of delirium- or coma-free days or the delirium duration compared with the placebo group. An important limitation of this investigation was that supplemental antipsychotic doses were unregulated and were administered to one-third of all patients. Fifteen of the 36 patients in the placebo group received antipsychotic doses, and seven of these patients did so on more than a single day. This lack of a true placebo group may partly account for the lack of differences seen between these groups.

12. Chew ML, Mulsant B, Pollock BG, Lehman ME, Greenspan A, Mahmoud RA, et al. Anticholinergic activity of 107 medications commonly used by older adults. J Am Geriatr Soc 2008;56:1333–41.

    Anticholinergic activity of compounds has previously been tested in vitro using a standard 10^{-8} M concentration of the drug. These tests may have limited clinical validity for agents in which a 10^{-8} M concentration is not within the therapeutic range. This study was performed to measure the in vitro anticholinergic activity of common drugs used by older adults at six therapeutic concentrations. The highest anticholinergic activity for various therapeutic concentrations was noted. A chart classifying anticholinergic activity into five categories ranging from no anticholinergic activity to more than 15 pmol/mL of atropine equivalents is provided. Twenty of the 107 compounds are included in a chart, which reports anticholinergic activity by specific concentration. This method of rating anticholinergic effect improves on previous methods used to determine these effects and allows the choice of low anticholinergic options in patients at risk of delirium.

13. Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium? Value of bedside instruments. JAMA 2010;304:779–86.

    This review aimed to systematically evaluate the accuracy of bedside instruments used to diagnose the presence of delirium in non-ICU patients. Twenty-five studies met the inclusion criteria. A description of a variety of delirium screening tools was provided. The CAM, DOSS, GAR, or Nu-DESC was reported to be completed in 5 minutes or less. The MDAS, DRS, and Delirium Rating Scale-Revised-98 were reported to require more than 5 minutes to complete. A review of published sensitivity and specificity scores was also provided. The authors concluded that the CAM was the preferred method to screen for delirium.

14. Rubin FH, Neal K, Fenlon K, Hassan S, Inouye SK. Sustainability and scalability of the Hospital Elder Life Program at a community hospital. J Am Geriatr Soc 2011;59:359–65.

    This article aimed to describe the adaptations and outcomes made in a HELP program during a 7-year period at a community teaching hospital. Noteworthy adaptations include the substitution of a hand massage for a back massage for improved sleep and the enhanced training in feeding and mobility protocols that were provided to some volunteers. To document outcomes, a proxy measure of delirium was developed. This proxy measure was validated by geriatricians and nurse practitioners against formal delirium assessments. The delirium prevalence decreased from 41% (obtained by the proxy calculation) in 2001 before the HELP program started to 18% (obtained by a CAM score obtained by the Elder Life Nurse Specialist) in 2008 after its implementation on six nursing units. Incident delirium (delirium of new onset while in the hospital) remained constant in this program from 2004 to 2008. Although higher satisfaction scores were reported, specifics were not listed in the article. Length of stay was 2.8 days shorter for patients with delirium who received the HELP program at baseline versus those with delirium who did not receive the HELP program at baseline. Patients who had the HELP program at baseline but who did not become delirious also had a 0.8-day shorter length of stay than those who did not have the HELP program at baseline. A financial return of $7.3 million was calculated on the basis of cost avoidance because of decreased delirium cases, decreased length of stay, and increased availability of hospital beds.

    An important, but difficult to avoid, shortcoming of this report is the use of a proxy calculation to determine baseline delirium. Another surprising outcome of this report is that the rate of incident delirium (delirium occurring after admission) did not decrease, but the rate of prevalent delirium (delirium present on admission) did decrease from 2004 to 2008 as more nursing units started the HELP program. Finally, although the statistics on the decreased length of stay are impressive, it is not clearly stated in the article that the financial return calculations are balanced against the cost of the program. (It is stated that the program includes 7.5 full-time equivalents of paid HELP staff and more than 100 volunteers to service 7000 patients per year on six nursing units.)

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Self-Assessment Questions

1. A 72-year-old man is admitted to the hospital because of abdominal pain. His history includes an ischemic stroke, hypertension, depression, anxiety, and insomnia. His drugs before admission include clopidogrel 75 mg daily, metoprolol 50 mg every 12 hours, citalopram 20 mg daily, and lorazepam 1 mg three times/day. His family and refill records indicate he is adherent to his drugs. He currently receives ondansetron 4 mg intravenously every 8 hours and hydralazine 10 mg intravenously every 6 hours as needed for systolic blood pressure greater than 160 mm Hg. His current laboratory values are normal. On day 2 of his admission, his Confusion Assessment Method (CAM) score becomes positive. The nurse notes he is agitated and states he tried to hit her when she went into his hospital room to give him a hydralazine dose. Nonpharmacologic treatments are initiated. **Which one of the following is most appropriate to also initiate for this patient?**

   A. Haloperidol.
   B. Donepezil.
   C. Lorazepam.
   D. Quetiapine.

2. A 78-year-old woman with a history of chronic obstructive pulmonary disease, Parkinson disease, and hypertension is admitted to the hospital for community-acquired pneumonia. Her home regimen includes tiotropium 18 mcg, the contents of 1 capsule inhaled daily, albuterol 90 mcg/puff 1–2 puffs every 4 hours as needed, carbidopa 25 mg/levodopa 100 mg four times/day, lisinopril 20 mg/day, and hydrochlorothiazide 12.5 mg/day. She is currently taking all of her home drugs plus ceftriaxone 1 g intravenously every 24 hours and azithromycin 500 mg intravenously every 24 hours. On the third day of her admission, she becomes agitated and combative. She tries to pull out her intravenous line. Nonpharmacologic methods to control her agitation are unsuccessful. The decision is made to pharmacologically treat her delirium. **Which one of the following regimens is most appropriate for this patient?**

   A. Haloperidol 0.5 mg intramuscularly every 30 minutes until response up to 5 mg; then 0.5 mg intramuscularly every 6 hours as needed.
   B. Haloperidol 0.5–1 mg orally every 6 hours as needed.
   C. Risperidone 0.5 mg every 12 hours and 0.5 mg every 6 hours as needed.

   D. Quetiapine 12.5 mg every 12 hours and 12.5 mg every 12 hours as needed.

3. You are part of a hospital committee that is developing a delirium protocol for the intensive care unit (ICU). The committee believes the tool should be validated and widely used and prefers that it be included as a recommendation in the recent National Institute for Health and Clinical Excellence (NICE) guidelines addressing delirium. **Which one of the following tools would be most appropriate to recommend?**

   A. Intensive Care Delirium Screening Checklist (ICDSC).
   B. Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).
   C. Memorial Delirium Assessment Scale (MDAS).
   D. Delirium Symptom Interview (DSI).

4. When reviewing articles evaluating delirium screening tools, you find a study that found assessments by ICU medical/surgical residents to have 14% sensitivity and 93% specificity for detecting delirium in ICU patients compared with an expert rater using Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria. **Which one of the following statements best describes the patients identified by ICU medical/surgical residents in this study?**

   A. 93% of patients who were delirious and 14% of patients who were not delirious.
   B. 14% of patients who were delirious and 93% of patients who were not delirious.
   C. 7% of patients who were delirious and 86% of patients who were not delirious.
   D. 86% of patients who were delirious and 7% of patients who were not delirious.

5. A patient is admitted to the hospital with pneumonia. He has a history of congestive heart failure, hypertension, and dementia. When he became delirious in the hospital, he was given a haloperidol loading dose, and he required haloperidol 0.5 mg two times/day to control his symptoms. Attempts to wean him off haloperidol have been unsuccessful. A discussion with the family reveals that he is often agitated at home, and the family has been considering nursing home placement. The risks versus benefits of continued medications to control his agitation are discussed, and the family agrees that

they would like for him to continue taking a drug for this use. The geriatrician asks for your opinion on drug choice. **Which one of the following regimens is most appropriate for this patient?**

A. Continue haloperidol 0.5 mg two times/day.
B. Change to risperidone 0.5 mg two times/day.
C. Change to alprazolam 0.25 mg two times/day as needed.
D. Change haloperidol dose to 0.5 mg each morning.

6. You are part of a hospital committee that is developing a delirium protocol for a general medical unit. The team is most concerned with not missing any patients who have delirium. They are willing to accept that some patients who do not actually need the protocol will be included. The table below lists sensitivity and specificity for selected delirium screening tools in a medical/surgical area. **Whichone of the following screening tools would be most appropriate to recommend based only on this information?**

Screening Tool	Sensitivity (%)	Specificity (%)	Comparison
CAM[a]			
First site	100	95	Expert rater using
Second site	94	90	DSM-IV criteria
Nu-DESC[b]	85.7	86.8	CAM
MDAS[b]	95.2	89.5	CAM
CRS[b]	76.2	81.6	CAM

[a]Inouye SK, et al. Ann Intern Med 1990;113:941–8.
[b]Gaudreau JD, et al. 2005;29:368–75.
CAM = Confusion Assessment Method; CRS = Confusion Rating Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders IV; MDAS = Memorial Delirium Assessment Scale; Nu-DESC = Nursing Delirium Screening Scale.

A. CAM or MDAS.
B. CAM or Nursing Delirium Screening Scale (Nu-DESC).
C. Confusion Rating Scale (CRS) or Nu-DESC.
D. MDAS or CRS.

Questions 7–9 pertain to the following case.
S.M., a 76-year-old woman who lives with her daughter, is admitted to a general medical unit for functional decline and failure to thrive. Her medical history includes an ischemic stroke, dementia, hypertension, and a myocardial infarction. Her home drugs include clopidogrel 75 mg daily, donepezil 10 mg daily, and metoprolol 25 mg every 12 hours. She is currently taking just her home drug regimen with the addition of sulfamethoxazole/trimethoprim 800/160 mg orally every 12 hours and acetaminophen 650 mg orally every 6 hours

as needed. She has no allergies. Her laboratory tests are within normal limits, except for a urinalysis that is positive for leukocytes, nitrites, and bacteria. Her estimated creatinine clearance is 40 mL/minute. She has flank pain rated as 5/10. S.M.'s screening test for delirium is positive. Her daughter states that although S.M. is normally forgetful, she has become very confused and drowsy during the past few days. Her current behaviors include a decrease in cognition with some fluctuation, inattention, and very slow responses to all questions.

7. The nurse reported that S.M.'s delirium screen was positive using the CAM with the following results: positive for acute onset and fluctuation, positive for inattention, negative for disorganized thinking, and positive for an altered level of consciousness (lethargic.) **Which one of the following best describes the most likely outcome for S.M.?**

A. Poorer than a patient scoring positive for delirium with an altered level of consciousness that is hyperalert.
B. Better than a patient scoring positive for delirium with an altered level of consciousness that is hyperalert.
C. Poorer than a patient scoring positive for delirium with an altered level of consciousness that fluctuates between lethargic and hyperalert.
D. Better than a patient scoring positive for delirium with an altered level of consciousness that fluctuates between lethargic and hyperalert.

8. S.M. receives antibiotic therapy for her urinary tract infection, acetaminophen as-needed for her pain, and nonpharmacologic therapies for delirium are instituted. **Which one of the following is most appropriate for S.M.?**

A. No additional treatment.
B. Risperidone 0.5 mg orally twice daily.
C. Haloperidol 0.5 mg intramuscularly every 30 minutes; may repeat as needed up to 5 mg.
D. Haloperidol 0.5 mg orally two times/day plus 0.5 mg two times/day as needed.

9. The next morning, S.M.'s urine culture grows *Escherichia coli* resistant to the chosen antibiotic. She states that her back hurts and rates her pain as 7/10. The nurse wants an order for an analgesic. You note that S.M. received a 650-mg dose of her as-needed acetaminophen yesterday morning when she arrived. Her pain scores indicate she has been in pain since late yesterday afternoon. **Which one of the following is most appropriate for S.M.?**

A. Hydromorphone 2 mg intravenously every 3 hours as needed.
B. Morphine 8 mg intravenously every 3 hours as needed.
C. Ibuprofen 400 mg every 6 hours.
D. Acetaminophen 650 mg orally every 6 hours.

Questions 10–12 pertain to the following case.
J.J. is an 85-year-old man who had been doing well at home until about a week ago when he started coughing and sneezing. He was admitted to the hospital with pneumonia. He has a history of a myocardial infarction, atrial fibrillation, and chronic obstructive pulmonary disease. His current drugs include warfarin 3 mg daily, metoprolol 25 mg every 12 hours, dofetilide 250 mg every 12 hours, tiotropium 18 mcg, the contents of 1 capsule inhaled daily, and albuterol 1 puff every 6 hours as needed. On admission, he was initiated on azithromycin 500 mg intravenously daily. On his second evening in the hospital, he was having difficulty sleeping, so an order for diphenhydramine 25 mg at bedtime as needed for insomnia was written. J.J. received one dose. The next day, his delirium assessment became positive. The nurse states that he is now agitated at times but that she has been able to easily redirect his behavior so far.

10. **In addition to discontinuing diphenhydramine, and starting nonpharmacologic therapies, which one of the following is most appropriate for J.J.?**

A. No additional therapies.
B. Haloperidol 0.5 mg intravenously every 30 minutes as needed for up to 10 doses.
C. Temazepam 15 mg at bedtime, which may be repeated one time for sleep.
D. Quetiapine 12.5 mg every 12 hours with an additional dose of 12.5 mg every night as needed.

11. **Which one of the following is most likely contributing to J.J.'s delirium?**

A. Metoprolol.
B. Azithromycin.
C. Pneumonia.
D. Atrial fibrillation.

12. Later in the day, J.J.'s symptoms progress. He is not cooperating with the nurse and refuses blood draws. He tries to hit the nursing aide when his blood pressure is taken. The nurse camouflages his intravenous line, but he still picks at it. **Which one of the following is most appropriate for J.J.?**

A. Quetiapine 12.5 mg orally every 12 hours and 12.5 mg every 12 hours as needed.

B. Haloperidol intravenously 0.5 mg every 30 minutes until patient is calm, up to a maximal dose of 5 mg; then 0.5 mg orally every 6 hours as needed.
C. Morphine 10 mg intravenously every 3 hours as needed for pain.
D. Mirtazapine 7.5 mg orally daily at bedtime.

Questions 13–16 pertain to the following case.
B.R. is a 70-year-old woman who presents to the emergency department with acute respiratory distress. She requires intubation and will be transferred to the ICU. Her home drugs, as verified with dispensing records and her family, are tiotropium 18 mcg, the contents of 1 capsule inhaled daily, and albuterol 90 mcg/puff 1 or 2 puffs every 4 hours as needed.

13. **Which one of the following best describes the chances of B.R. becoming delirious while admitted to the ICU?**

A. Less than 10%.
B. 10% to 30%.
C. 31% to 50%.
D. More than 50%.

14. **Which one of the following measures would best decrease B.R.'s chances of becoming delirious?**

A. Use of opioid if appropriate before increase in sedative when agitation occurs; physical therapy consult.
B. Use of lorazepam if appropriate before increase in opioid when agitation occurs; physical therapy consult.
C. Daily awakenings from sedation; use of lorazepam when sedative is necessary.
D. Daily awakenings from sedation; use of propofol when sedative is necessary.

15. **Should B.R. become delirious, which one of the following outcomes is most likely?**

A. Her risk of death will be about the same as if she had an acute myocardial infarction.
B. Her ICU costs will likely decrease, but her total hospital costs will increase.
C. Her delirium will reverse quickly after she is weaned off the ventilator.
D. Her delirium symptoms will improve when given lorazepam 0.5 mg intravenously every 4 hours as needed for agitation.

16. B.R.'s physician is concerned that she will develop delirium and prefers dexmedetomidine for her sedation. B.R.'s vital signs include heart rate 125 beats/minute and blood pressure 155/75 mm Hg.

She is afebrile. Her last pain score was 9/10. **Which one of the following is of most concern in choosing this agent for B.R.?**

A. Dosing for greater than 24 hours has not been studied.
B. The opioid antagonist activity may aggravate pain.
C. Higher cost has not been justified in non-manufacturer sponsored trials.
D. The agent's cardiac effects may worsen tachycardia.

17. The ICU manager at your hospital does not agree with instituting procedures to prevent delirium. He does not believe that the increased workload for nurses will result in improved outcomes. He believes delirium is just a marker for patients who have serious illness, and that poor outcomes seen with delirium are caused by the underlying illness. You reference a recent meta-analysis that studied the association between delirium, mortality, and institutionalization while controlling for age, sex, comorbid illness, and baseline dementia. This meta-analysis reported that delirium patients had a hazard ratio for mortality of 1.95 (95% confidence interval [CI] = 1.51–2.52) and an odds ratio for risk of institutionalization of 12.52 (95% CI = 1.86–84.21) **Which one of the following best describes the results of this meta-analysis?**

A. There is a decreased mortality risk in patients with delirium compared with those without delirium when data are corrected for age, sex, comorbid illness, and baseline dementia.
B. There is no difference in mortality in patients with delirium compared with those without delirium when data are corrected for age, sex, comorbid illness, and baseline dementia.
C. There is an increased risk of institutionalization in patients with delirium, even when data are corrected for age, sex, comorbid illness, and baseline dementia.
D. There is no difference in the risk of institionalization in patients with delirium when data are corrected for illness severity and baseline dementia.

Questions 18 and 19 pertain to the following case.
P.K. is an 88-year-old man who comes to the emergency department with weakness and abdominal pain. He is admitted to critical care with a diagnosis of starvation ketosis. P.K. lives alone and is thought to have not been eating or taking his drugs. His home regimen consists of omeprazole 20 mg daily, metoprolol 25 mg every 12 hours, hydrochlorothiazide 25 mg daily, and celecoxib 200 mg daily. P.K. has no known drug allergies;

however, he has a history of gastroesophageal reflux disease, hypertension, and arthritis. His screening for delirium is negative. He is stabilized quickly in the ICU and transferred to a medical floor on day 2 of his admission with only intravenous 5% dextrose in normal saline running at 70 mL/hour. His nurse charts that he is oriented, pleasant, and cooperative, but forgetful. His delirium screen remains negative on day 2. His laboratory tests normalize except for a low-density lipoprotein cholesterol concentration of 140 mg/dL. His estimated creatinine clearance is 34 mL/minute. His blood pressure is 160/90 mm Hg, and his hydrochlorothiazide is reinitiated. He is also initiated on simvastatin 20 mg daily and aspirin 81 mg daily. On the evening of day 2, P.K. experiences abdominal pain. Belladonna alkaloids and phenobarbital 1 or 2 tablets every 6 hours as needed are ordered. He receives 4 tablets through the evening. The next morning, he is alert to self only and does not reorient. His delirium screen is positive. He tries to hit the nurse with his cane. His morning laboratory values are normal. His blood pressure is 140/80 mm Hg.

18. **Which one of the following most likely contributed to P.K.'s delirium symptoms?**

A. Abrupt discontinuance of celecoxib.
B. Initiation of hydrochlorothiazide.
C. Initiation of belladonna opioids and phenobarbital.
D. Initiation of phenobarbital concurrently with simvastatin use.

19. P.K. becomes more agitated, and his blood pressure increases to 170/98 mm Hg. He refuses care and has been threatening care providers. His physician wants to treat P.K.'s delirium symptoms. **Which one of the following is most appropriate for P.K.?**

A. Haloperidol 0.5 mg intramuscularly every 30 minutes until patient is calm (up to 5 mg); then 0.5 mg every 6 hours as needed.
B. Lorazepam 0.5 mg every 6 hours as needed for anxiety.
C. Lorazepam 2 mg intravenously once; then 1 mg orally every 6 hours as needed.
D. Haloperidol 0.5 mg orally every 6 hours as needed.

20. A 73-year-old woman comes to the emergency department after a motor vehicle crash. She sustained a hip fracture that will require surgical repair. She has a history of diabetes, hypertension, and depression. Home medication include glipizide 5 mg two times/day, metformin 500 mg two times/day, lisinopril 20 mg daily, aspirin 81 mg daily, and paroxetine 40 mg daily. She currently takes nothing

orally, but she takes heparin 5000 units subcutaneously every 8 hours, insulin glargine 10 units/day at bedtime, sliding-scale insulin before meals and at bedtime, enalaprilat 1.25 mg intravenously every 6 hours, morphine 4 mg intravenously every 6 hours as needed for pain, and cefazolin 1 g intravenously every 8 hours. The patient becomes delirious on her third day of admission. You are asked to evaluate whether the cause of her delirium is drug related. Reviewing her chart, you find that she has dizziness and abdominal upset. Her pain score has been zero, and her electrolyte panel and complete blood cell count are within normal limits. Her serum glucose concentrations have been between 80 mg/dL and 120 mg/dL. **Which one of the following is the most likely cause of this patient's delirium?**

A. Her morphine dose.
B. Her insulin dose.
C. Her cefazolin dose.
D. Paroxetine withdrawal.