Delirium in the Acute Care Setting:
Characteristics, Diagnosis and Treatment

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Delirium is an acute or subacute organic mental syndrome characterized by disturbance of consciousness, global cognitive impairment, disorientation, the development of perceptual disturbance, attention deficits, decreased or increased psychomotor activity (depending on the type of delirium), disordered sleep-wake cycle, and fluctuation in presentation (eg, waxing and waning). The term “delirium,” from the Latin roots de (meaning “away from”) and lira (meaning “furrow in a field”) and ium (Latin for singular), literally means “a going off the ploughed track, a madness.” The term “delirium” is reported to have been coined by the lay Roman writer Celsus (1AD) and described in his compendium De Medicina [1,2]. Clear descriptions of the syndrome are contained in Hippocrates’s writings, who called the syndrome by the term phrenitis [3]. In 1813, the British physician Thomas Sutton introduced the term delirium tremens to designate delirium caused by the withdrawal from central nervous system (CNS) depressant agents, but which is almost exclusively applied in modern times to delirium resulting from alcohol withdrawal [4].

In the acute care setting, many names are used to describe the acute mental status changes associated with delirium. Commonly used terms include “intensive care unit (ICU) psychosis” or “sundowning.” The first describes the fact that mental status changes are often seen in the ICU, the second is a descriptor of a pattern by which subjects tend to experience confusion more frequently during periods of decreased or inappropriate stimulation, such as at night or “sun down.” The psychiatric literature uses other terms that usually describe common characteristics or features of the syndrome, such as “acute confusional state” (ie, acute, confusion) and “acute brain failure” to describe the gravity of the situation. Yet, neurologists and internists prefer the term “encephalopathy,” which literally means “disease of

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the brain.” The term encephalopathy is meant to convey a brain malfunction in the face of systemic metabolic derangements (eg, metabolic encephalopathy), cardiopulmonary or vascular problems (eg, hypoxic or hypertensive encephalopathy), renal disease (eg, uremic encephalopathy), liver disease (eg, hepatic encephalopathy), or endocrine disease (eg, Hashimoto’s encephalopathy); or to be a consequence of toxic factors (eg, toxic encephalopathy or Wernicke’s encephalopathy) or problems with oxygenation (eg, hypoxic encephalopathy). Unfortunately, the use of these various terms, even if accurate, may add to the confusion and difficulties of identifying and treating the syndrome of delirium.

**Epidemiology of delirium**

Delirium is the most common psychiatric syndrome found in the general hospital setting. Its prevalence surpasses most commonly known and identified psychiatric syndromes and varies depending on the medical setting. Table 1 compares the incidence of delirium in different medical settings and various psychiatric disorders [5]. The incidence of delirium among medically ill patients ranges from 10% in the general medicine ward to 85% in advanced cancer [6–11]. This wide range is associated with the organ system and disease process under consideration. For example, in the adult general medicine population the incidence of delirium ranges from 10% to 24%: as reported by Speed and colleagues 10.9% [12], Maldonado and colleagues 14% [13], Ritchie and colleagues 14.6% [14], and Gonzalez and colleagues 24% [15]. As expected, the incidence goes up with increased severity of illness, rising to 13% to 48% in after-stroke victims [16], 20% to 40% among HIV/AIDS patients [17,18], 60% in frail-elderly patients [19], 60% to 80% among patients in the medical ICU [20], and as high as 80% to 90% in terminally ill cancer patients [21]. One study found that 89% of survivors of stupor or coma progressed to delirium [22].

A European multinational study \((n = 3,608)\) by Valdés and colleagues [23] found a delirium prevalence rate of 9.1% in the general hospital population. A Spanish study by Gonzalez and colleagues [15] confirmed findings in the United States and similarly suggested that the average hospital stay is prolonged from 12 days to 17.5 days when delirium is present. Similarly, a study conducted in Western Australia found a 10.9% prevalence rate of delirium among patients admitted to two general medicine wards \((n = 1,209)\) [12].

Similarly, in the general surgical population the incidence of delirium is about 37% to 46% [24], and postoperative delirium has been described to occur in 10% to 60% of patients [25]. Again, the range in incidence of postoperative delirium depends on the type of surgery and the population studied: 25% to 32% among patients undergoing coronary artery bypass grafting (CABG); 50% to 67% among patients undergoing cardiotomy (eg, cardiac valve replacement) [26–29]; about 20% of elderly patients after
surgery for gynecologic malignancies [30]; 33% of patients undergoing abdominal aneurysm repair [31]; 12.5% in patients undergoing spine surgery [32]; 41% after bilateral knee replacement [33]; and 25% of elderly patients undergoing elective hip or knee replacement, compared with 65% after femoral neck fracture repair [34–36]. Acute mental status changes, neuropsychiatric dysfunction, and neurocognitive deficits are common after cardiac surgery [37]. Delirium and other forms of acute organic mental syndrome occurred in 32% to 80% of patients undergoing cardiac surgery [29,38,39].

The incidence of delirium is well documented in the acutely medically ill patient. A study by Ely and colleagues [20] involving patients admitted to the medical intensive care unit (MICU), 50% of which were receiving mechanical ventilation, found that 81.3% of MICU patients developed delirium during the course of their ICU stay. The mean onset of delirium was 2.6 days (standard deviation or SD ± 1.7), and the mean duration was 3.4 days (SD ± 1.9). The duration of delirium was associated with length of stay in the ICU ($r = 0.65$, $P = .0001$) and total length of hospital

<table>
<thead>
<tr>
<th>Incidence of psychiatric disorders</th>
<th>% of general adult us population [5]</th>
<th>Incidence of delirium in selected medical populations</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depression</td>
<td>6.7</td>
<td>General medicine wards</td>
<td>10–18</td>
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<tr>
<td>Dysthymic disorder</td>
<td>1.5</td>
<td>HIV/AIDS</td>
<td>30–40</td>
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<tr>
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<td>2.6</td>
<td>Medical-ICU</td>
<td>60–80</td>
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<tr>
<td>All mood disorders</td>
<td>9.5</td>
<td>General surgical wards (range)</td>
<td>37–46 (10–60)</td>
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<td></td>
<td></td>
<td>After stroke</td>
<td>13–48</td>
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<tr>
<td>Panic disorder</td>
<td>2.7</td>
<td>After CABG</td>
<td>25–32</td>
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<td>OCD</td>
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<td>After cardiotomy</td>
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<td>3.5</td>
<td>Elderly</td>
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<td>Out-patient minor (cataract) surgery</td>
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<td>Social phobia</td>
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<td>At time of hospitalization</td>
<td>10–15</td>
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<tr>
<td>Agoraphobia</td>
<td>8.7</td>
<td>In nursing homes</td>
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<td>All anxiety disorders</td>
<td>18.1</td>
<td>After hip replacement</td>
<td>21–63</td>
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<tr>
<td>Schizophrenia</td>
<td>1.1</td>
<td>In cancer patients</td>
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<td>Anorexia nervosa</td>
<td>0.5–3.7</td>
<td>General prevalence</td>
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<tr>
<td>Bulimia</td>
<td>2–5</td>
<td>Hospitalized cancer patients</td>
<td>25–50</td>
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<tr>
<td>Alzheimer’s Disease</td>
<td>10%</td>
<td>Bone marrow transplant</td>
<td>73</td>
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<td></td>
<td>&gt; 80 years old = 50%</td>
<td>Advanced cancer</td>
<td>Up to 85</td>
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</table>

**Table 1**

A comparison of the incidence of psychiatric disorder in the general population and delirium among medically ill patients.

*Abbreviations: CABG, coronary artery bypass graft surgery; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder.*

stay (LOS) \( r = 0.68, \ P = .0001 \). Multivariate analysis demonstrated that delirium was the strongest predictor of LOS in the hospital \( (P = .006) \), even after adjusting for severity of illness, age, gender, race, and days of benzodiazepine and narcotic drug administration.

Maldonado and colleagues [13] found an 18% incidence of delirium in an acute ICU (eg, combined medical and surgical patients) based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. As in previous studies, the average delirious patient age was over 65 years old and mostly male (60%). The presence of delirium significantly extended the overall length of stay (ie, 15 days in delirious patients, compared with 11 days in nondelirious counterparts).

Finally, delirium has been found to be the most common clinical neuropsychiatric condition in specialized palliative care units. It has been reported to occur in 26% to 44% of cancer patients admitted to hospital or hospice. As the disease progresses, over 80% of all advanced cancer patients eventually experience delirium in their final days [21,40].

**Etiology of delirium**

The syndrome of delirium is better thought of as having a multifactorial etiology, as is often the case in most medically ill patients. Patients in the ICU are usually critically ill, which makes them more susceptible to developing delirium. There are many risk factors known to contribute to the development of delirium.

**Delirium clinical risk factors**

- Age (greater than 75 years old)
- Baseline cognitive functioning:
  - 25% delirious are demented
  - 40% demented in hospital develop delirium
- Male gender
- Sensory impairment
- Use of intravenous lines, bladder catheters, and physical restraints
- Severe illness
  - Infections (particularly urinary tract infections and pneumonias, in older persons)
  - Hip fracture
  - Hyperthermia
  - Hypothermia
  - Hypotension and hypoperfusion
  - Hypoxia or anoxia
  - Malnutrition and nutritional deficiencies (eg, thiamine deficiency leading to Wernicke’s encephalopathy)
Metabolic disorders
Acute metabolic encephalopathies (eg, cardiac, hepatic and renal failure)
Acute vascular problems (eg, myocardial infarction, pulmonary embolism)
Endocrinopathies (eg, hyper- and hypothyroidism)
Water and electrolyte abnormalities
Hypo- or hyperglycemia
Hypo- or hypernatremia
Hypo- or hyperkalemia
Dehydration
Elevation in serum cortisol levels
CNS pathology (ie, stroke, intracranial hemorrhages, normal pressure hydrocephalus)
Trauma (eg, severe physical trauma or surgery)

Exogenous substances
Medication side effects:
Polypharmacy (more than three medications)
Psychoactive medications
Serotonergic agents
Anticholinergic agents
Over-the-counter substances
Substance abuse and withdrawal
Alcoholism
CNS-depressant substances (both prescribed and illegal)
CNS-depressant withdrawal (eg, delirium tremens)
CNS-stimulant substances (both prescribed and illegal)
Hallucinogens
Over-the-counter substances
Heavy metal poisoning
Toxins (ie, toxic psychosis)

Sleep deprivation
Over-sedation
Pain, poorly controlled

Two of the known risk factors for delirium include the patient’s age and the presence of a baseline cognitive disorder (eg, dementia, stroke). Studies have suggested that increasing age was an independent predictor of transitioning to delirium. A study of mechanically ventilated adults \( n = 275 \) suggests that there is an incremental risk for transitioning into delirium for patients older than 65 years (odds ratio or OR of transitioning to delirium for age was 1.02 [1.00–1.03; \( P = .04 \)]. In fact, the results suggest that for each additional year after age 65, the probability of transitioning to delirium increased by 2% (multivariable \( P \) values < 0.05) (Fig. 1) [41]. Similarly, a study of elderly patients undergoing hip surgery, found that mini-mental
state examination (MMSE) scores were identified as an independent predictor of postoperative delirium [42].

Milstein and colleagues [43] reported on the development of delirium among the elderly patient undergoing relatively simple outpatient surgery. They studied elderly patients (n = 296) undergoing cataract surgery and found a 4.4% incidence of postoperative delirium. As others have suggested, those developing delirium were older (82.1 versus 73.06 years; P < .001) and received higher benzodiazepine doses as pre-medication for surgery (69% versus 39.9%; P < .002).

In a prospective study evaluating neuropsychologic performance in older patients (ie, > 70 years), subjects (n = 100) who were free of dementia and admitted for elective orthopedic surgery underwent a series of neuropsychiatric testing pre- and postoperatively [44]. Findings suggest that subtle preoperative attention deficits were closely associated with postoperative delirium. Patients who developed postsurgical delirium had significantly slower mean reaction times (P ≤ .011) and greater variability of reaction time (P = .017) preoperatively. A four- to fivefold increased risk of delirium was observed for people one standard deviation above the sample means on these variables.

A study by Wahlund and Bjorlin [45] found that approximately 70% of elderly patients admitted to a specialized delirium ward had a pre-existing cognitive disorder, either dementia or mild cognitive impairment. Bergmann and Eastham [46] studied elderly patients (n = 100) admitted to an acute medical unit in a general hospital for the presence of psychiatric morbidity. They found that 7% suffer from dementia, while 16% suffered from acute
delirious states. Demented patients or patients suffering from other conditions associated with deficient brain function (ie, traumatic brain injury, drug and alcohol abuse and withdrawal) have a lower threshold for developing delirium and do so with greater frequency. Similarly, a study of elderly subjects undergoing hip or knee replacement \( (n = 572) \) demonstrated that the presence of dementia increased the occurrence of delirium [36]. Twenty four percent of subjects had preoperative dementia. Postoperatively, all (100%) of demented subjects developed delirium, compared with 31.8% in the nondemented population.

Poor oxygenation (ie, hypoperfusion and hypoxemia) has long been associated with the development of delirium, both because of medical problems as well as postoperatively. Severe illness processes, combined with both decreased oxygen supply and increased oxygen demand may lead to the same common end problem, namely decreased oxygen availability to brain tissue [47–50]. Inadequate oxidative metabolism may be one of the underlying causes of the basic metabolic problems initiating the cascade that leads to the development of delirium, namely: inability to maintain ionic gradients causing cortical spreading depression (ie, spreading of a self-propagating wave of cellular depolarization in the cerebral cortex) [51–56]; abnormal neurotransmitter synthesis, metabolism and release [57–65]; and a failure to effectively eliminate neurotoxic by-products [58,59,63].

A study of postthoracotomy patients demonstrated that 21% of the patients developed clinically significant postoperative delirium [66]. In this sample, delirium occurred in all patients who had inadequate oxygenation. The treatment of choice was supplementary oxygen, with a near perfect treatment success. Others have similarly linked delirium to the presence of poor oxygenation associated with untreated obstructive sleep apnea [67] and to the presence of occult hypoxia after total hip arthroplasty [68].

Of note, animal studies have suggested that subjects with baseline organic cerebral disorders, such as cerebrovascular disease, may be particularly sensitive to hypoxic injury. Miyamoto and colleagues [69] submitted laboratory animals to hypocapnia during surgical anesthesia, causing tissue damage in the caudoputamen. This model may suggest that a similar mechanism may be responsible for long-lasting postoperative delirium in patients with stroke or dementia.

Sleep is another factor that seems to play a significant role in developing delirium in the ICU. Sleep deprivation has long been linked to the development of delirium [70] and psychosis [71]. Studies have found that the average amount of sleep in ICU patients is limited to 1 hour and 51 minutes per 24-hour period [72]. Many factors may affect sleep in the ICU, including frequent therapeutic interventions, the nature of diagnostic procedures, pain, fear, and the noisy environment. Similarly, oversedation has been found to be an independent predictor of prolonged mechanical ventilation. In a prospective, controlled study \( (n = 128) \) of adults undergoing mechanical ventilation, subjects were randomized to either continuous sedation or daily
awakenings [73]. They found that the median duration of mechanical ventilation was 4.9 days in the intervention group (ie, daily awakening), as compared with 7.3 days in the control group ($P = .004$), and the median LOS in the intensive care unit was 6.4 days as compared with 9.9 days, respectively ($P = .02$).

A great number of medications have been associated with an increased risk of delirium (Box 1). The highest incidence medication-induced delirium has been observed in patients taking more than three medications [74], medications with high psychoactive activity [75], and when drugs have high anticholinergic potential [76].

Medications with significant psychoactive effects have long been identified as a frequent cause of delirium. Several studies have linked the use of psychoactive agents to the etiology of 15% to 75% of delirium cases [19,21,77–81]. More specifically, opioids, corticosteroids, and benzodiazepines have been identified as major contributors to delirium in several studies (Fig. 2) [75]. Other medications, such as nonsteroidal anti-inflammatory agents, and chemotherapeutic agents, were also identified as causes of delirium.

There is significant evidence to suggest that there is a direct association between a medication’s anticholinergic potential and their incidence of causing delirium [74,76,82–86]. Some drugs (eg, diphenhydramine, atropine) are easier to identify as having a high anticholinergic load. On the other hand, others are not so obvious. Several studies have demonstrated a direct relationship between a drug’s anticholinergic potential (as measured by serum anticholinergic activity) and the development of delirium [76,85,87–90]. Tune has conducted several studies looking at the cumulative effect of drugs with subtle anticholinergic potential and their serum anticholinergic activity (Box 2, Table 2) [76,83,84,86,90,91].

Blazer and colleagues [92] conducted a study of the potential for anticholinergic toxicity among long-term care residents. Their study included residents aged 65 years and older ($n = 5,902$) who continuously resided in a nursing home for 1 year and determined drug administration and drug quantity. The survey revealed that 60% of residents received drugs with significant anticholinergic properties and nearly 10% of the residents received three or more medications with high anticholinergic load. Finally, Han and colleagues [93] followed medical inpatients ($n = 278$) and measured their exposure to anticholinergic medications. They found that exposure to anticholinergic agents was an independent risk factor for the development of delirium, and specifically associated with a subsequent increase in delirium symptom severity.

As suggested by many others, many gamma amino-butyric acid (GABA)-ergic medications have been implicated in the development of delirium [20,94–97]. It is now beginning to be understood that agents commonly used for achieving postoperative sedation may in fact contribute to delirium by (a) interfering with physiologic sleep patterns and (b) causing a centrally mediated acetylcholine deficient state (ie, interruption of central cholinergic
Box 1. Drugs believed to induce delirium

5-FU
Acetophenazine
Acyclovir
Aldesleukin
Alprazolam
Amandatine
Amidoarone
Amitriptyline
Amphetamine (in overdose)
Amphotericine B
Ampicillin
Anticonvulsants
Antihistamines
Antiparkinsonian Rx
Asparginase
Aspirin
Atropine
Azathioprine
Azithromycin
Barbiturates
Benzodiazepines (and “paradoxical disinhibition”)
Benzquinamide
Beta-blockers
Betamethasone (and psychosis)
Bupropion
Cabergoline
Captopril
Cefalothin
Cefoxitin
Celecoxib
Cephalosporins
Chloramphenicol
Chlordiazepoxide
Chlorpromazine (and psychosis)
Chlorthalidone
Choline salicylate
Cimetidine
Ciprofloxacin
Clindamycin
Clioquinol
Clomipramine
Clozapine

(continued on next page)
Box 1 (continued)
Cocaine
Codeine
Corticosteroids
Cortisone (and psychosis)
Cotrimozazole
Cyclobenzaprine
Cycloserine
Cyclosporine
Desipramine
Dexamethasone (and psychosis)
Diazepam
Digoxin (and psychosis)
Diltiazem
Dimenhydrinate
Diphenhydramine
Dipyridamole
Disulfiram (and mania and psychosis)
Dopamine
Doxepin
Droperidol
Ergotamine
Ethanol
Famotidine
Fentanyl
Fludarabine
Flurazepam
Furosemide
Gentamicin
Glutethimide
Halothane
Hydralazine
Hydrocortisone (and psychosis)
Hydrochlorothiazide
Hydroxyzine
Interleukin-2
Imipramine
Interferon
Isoflurane (and psychosis)
Isosorbide monitrate
Itraconazole
Ketamine (and psychosis)
Ketoprofen
Levodopa/carbidopa (and psychosis)
Lidocaine
Lithium (and organic brain syndrome)
Lorazepam (and “paradoxical disinhibition”)
Magnesium salicylate (and psychosis, headache, dizziness, drowsiness, confusion)
Monoamine oxidase inhibitors
Medazepam (and withdrawal syndromes)
Mefloquine
Memantine
Methohexital
Methyldopa
Methylprednisolone (and psychosis)
Methotrexate
Metrizamide
Midazolam
Mirtazapine
Nicotine (and withdrawal syndromes)
Nifedipine
Nitrazepam (and withdrawal syndromes)
Nitroprusside (and psychosis)
Nortriptyline
Opiates (and withdrawal syndromes)
Oxazepam
Oxycodone
Pancuronium
Paraldehyde
Paramethasone (and psychosis)
Paroxetine
Perazine
Perphenazine
Perphenazine/amitriptyline
Phenelzine
Phenobarbital (and withdrawal syndromes)
Phenytoin (and psychosis)
Piperacillin
Prednisolone (and psychosis)
Prednisone (and psychosis)
Promazine (and psychosis)
Propofol (and central a-chol synd)
Protriptyline (and central a-chol synd)
Quinidine
Rantidine
(continued on next page)
muscarinic transmission at the level of the basal forebrain and hippocampus) [95–97]. A study of blood and urine melatonin levels revealed an abolition of the circadian rhythm of melatonin release in deeply sedated ICU patients [98]. This suggests that sedative agents may contribute to the development of delirium by more than one mechanism (ie, disruption of sleep patterns; central acetylcholine inhibition; disruption of melatonin circadian rhythm). Therefore, it appears that commonly used sedative (eg, propofol, midazolam) may promote the development of delirium.

The irony is that these are the same medications physicians often use to manage agitated or delirious patients. This practice, even if immediately effective in tranquilizing a patient may, in the long run, aggravate and perpetuate the syndrome of delirium. One of the first studies to demonstrate the

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**Box 1 (continued)**

- Rasagiline
- Risperidone (and anxiety, depression, apathy)
- Rofecoxib (and psychosis)
- Scopolamine
- Sodium salicylate
- Sodium Thiosalicylate
- Sympathomimetics
- Tacrine
- Tamoxifen
- Tricyclic antidepressants
- Teceleukin (and psychosis, paranoia, fatigue, apathy, drowsiness, sleep disturbances)
- Thophylline
- Thiothixene
- Tiaprofenic acid
- Tobramycin
- Trazodone
- Triamcinolone (and psychosis)
- Triamterene
- Trimethobenzamide (central a-chol synd)
- Triprolidine (and restlessness, insomnia, euphoria, nervousness, irritability, palpitations, nightmares, or seizures)
- Vancomycin
- Vincristine
- Warfarin
- Zolpidem
- Zotepine (and anxiety, agitation)

*Data from Electronic Physicians Desk Reference, 2007.*
relationship between benzodiazepine use and delirium was conducted by Marcantonio and colleagues [94]. They found that development of delirium was significantly associated with postoperative exposure to benzodiazepines (OR, 3.0; 95% confidence interval or CI, 1.3–6.8). These findings have been confirmed by Pandharipande and colleagues [41], who studied adult ventilated patients \( (n = 275) \) in the ICU for the development of delirium. They found that lorazepam was an independent risk factor for daily transition to delirium (OR, 1.2; 95% CI, 1.1–1.4; \( P = .003 \)) (Fig. 3). These findings confirm many others who have previously suggested benzodiazepines to be culprits in the development of delirium and other cognitive impairment in medically ill patients [20,94,99,100]. Being aware of what types of medications a patient is taking and eliminating unnecessary medications can help reduce the potential for anticholinergic side effects.

As in the case with sleep, both pain and medications used for the treatment of pain have been associated with the development of delirium. Vaurio and colleagues [25] demonstrated that presence of postoperative pain is an independent predictor of delirium after surgery. Furthermore, they found a direct relationship between levels of preoperative pain and the risk for the development of postoperative delirium. On the other hand, the use of opioid agents has been implicated in the development of delirium [101–103]. Opioids are blamed for nearly 60% of the cases of delirium in patients with advanced cancer [40]. A study of cancer patients \( (n = 114) \) showed a significant associations between opioids and delirium, after controlling for other medications used [104]. Several studies have reported that patients
Box 2. Commonly used medicines that have anticholinergic effects

**Antihistamines**
- Diphenhydramine
- Hydroxyzine

**Cardiovascular**
- Captopril
- Chlorthalidone
- Digoxin
- Diltiazem
- Dipyridamole
- Furosemide
- Hydrochlorothiazide
- Hydralazine
- Isosorbide mononitrate
- MethylDopa
- Nifedipine
- Triamterene
- Warfarin

**Central nervous system**
- Alprazolam
- Amitriptyline
- Chlordiazepoxide
- Codeine
- Desipramine
- Diazepam
- Doxepin
- Flurazepam
- Imipramine
- Oxazepam
- Oxycodone
- Phenelzine
- Phenobarbital

**Corticosteroids**
- Corticosterone
- Dexamethasone
- Hydrocortisone
- Prednisolone
who used oral opioid analgesics as their sole means of postoperative pain control were at decreased risk of developing delirium in comparison with those who used opioid analgesics via intravenous (IV) patient-controlled analgesia technique (OR, 0.4; 95% CI, 0.2–0.7) [25,103].

There is some data that suggests that some opioid agents may have greater deliriogenic potential than others. For example, several reports suggest that meperidine has a greater deliriogenic potential than other opioids [94,101,105]. Other studies have suggested that an opioid rotation from morphine to fentanyl has been associated with improved pain management and lower delirium rating scores [106]. Similarly, at least one case report suggests that the use of acetylcholinesterase inhibitors successfully reversed opioid-induced hypoactive delirium [107]. This may implicate an anticholinergic mechanism of opioid induced delirium.

Besides their potential anticholinergic effect or their disruption of sleep patterns, medications may cause delirium by disrupting thalamic gating

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
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<tbody>
<tr>
<td>Atropine</td>
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<td>Ranitidine</td>
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<td>Immunosuppression</td>
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<td>Cyclosporine</td>
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<td>Infection</td>
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<td>Muscle relaxants</td>
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<td>Respiratory system</td>
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</tbody>
</table>

function (ie, the thalamus ability to act as a filter, allowing only relevant information to travel to the cortex). The cholinergic and the dopaminergic systems interact not only with each other but with glutamatergic and GABA pathways. Besides the cerebral cortex, critical anatomic substrates of psychotic pathophysiology would comprise the striatum, the substantia nigra/ventral tegmental area, and the thalamus. The thalamus can be understood as acting as a filter, usually allowing only relevant information to travel to the cortex. On the other hand, drugs of abuse (eg, phencyclidine, Ecstasy), as well as psychoactive medications frequently prescribed to hospitalized patients (eg, benzodiazepines, opioids, sympathomimetics, steroids) could compromise the thalamic gating function, leading to sensory overload and hyperarousal. Gaudreau and Gagnon [108] have propose that drug-induced delirium would result from such transient thalamic dysfunction caused by exposure to medications that interfere with central glutamatergic, GABAergic, dopaminergic, and cholinergic pathways at critical sites of action.

Table 2
Anticholinergic drug levels in 25 medications ranked by the frequency of their prescription for elderly patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>Anticholinergic drug level (ng/mL of atropine equivalents)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Furosemide</td>
<td>0.22</td>
</tr>
<tr>
<td>2. Digoxin</td>
<td>0.25</td>
</tr>
<tr>
<td>3. Dyazide</td>
<td>0.08</td>
</tr>
<tr>
<td>4. Lanoxin</td>
<td>0.25</td>
</tr>
<tr>
<td>5. Hydrochlorothiazide</td>
<td>0.00</td>
</tr>
<tr>
<td>6. Propranolol</td>
<td>0.00</td>
</tr>
<tr>
<td>7. Salicylic acid</td>
<td>0.00</td>
</tr>
<tr>
<td>8. Dipyridamole</td>
<td>0.11</td>
</tr>
<tr>
<td>9. Theophylline anhydrous</td>
<td>0.44</td>
</tr>
<tr>
<td>10. Nitroglycerin</td>
<td>0.00</td>
</tr>
<tr>
<td>11. Insulin</td>
<td>0.00</td>
</tr>
<tr>
<td>12. Warfarin</td>
<td>0.12</td>
</tr>
<tr>
<td>13. Prednisolone</td>
<td>0.55</td>
</tr>
<tr>
<td>14. Alpha-methyldopa</td>
<td>0.00</td>
</tr>
<tr>
<td>15. Nifedipine</td>
<td>0.22</td>
</tr>
<tr>
<td>16. Isosorbide dinitrate</td>
<td>0.15</td>
</tr>
<tr>
<td>17. Ibuprofen</td>
<td>0.00</td>
</tr>
<tr>
<td>18. Codeine</td>
<td>0.11</td>
</tr>
<tr>
<td>19. Cimetidine</td>
<td>0.86</td>
</tr>
<tr>
<td>20. Diltiazem hydrochloride</td>
<td>0.00</td>
</tr>
<tr>
<td>21. Captopril</td>
<td>0.02</td>
</tr>
<tr>
<td>22. Atenolol</td>
<td>0.00</td>
</tr>
<tr>
<td>23. Metoprolol</td>
<td>0.00</td>
</tr>
<tr>
<td>24. Timolol</td>
<td>0.00</td>
</tr>
<tr>
<td>25. Ranitidine</td>
<td>0.22</td>
</tr>
</tbody>
</table>

a At a 10–8 M concentration.
b = Threshold for delirium = 0.80ng/mL.

There are several surgical procedures known to increase the risk of developing delirium, presumably because of the complexity of the surgical procedure, the extensive use and type of intraoperative anesthetic agents, and potential postoperative complications [109]. For example, in cases of cardiac surgery the following factors have been associated with the increased risk for delirium: the use of cardio-pulmonary by-pass (CPB) (eg, hypoperfusion, embolic load), management strategies (eg, pH stat versus alpha stat, on-pump versus off-pump) or to the type of procedure (eg, intracardiac versus extracardiac) [39,110–112]. In the case of orthopedic procedures, fat embolism, blood loss, older age, and the type of anesthetic agent used have all been associated with a greater risk of delirium [105,113,114].

Certain psychiatric diagnoses, including a history of alcohol and other substance abuse (6.9%), as well as schizophrenia and bipolar disorder (up to 14.6%) have also been associated with a higher incidence of delirium [14,115].

Finally, the severity of the patient’s underlying medical problems has a significant role in the development and progression of delirium. Pandharipande and colleagues [41] found that increased severity of illness, as measured by the modified Acute Physiology and Chronic Health Evaluation (APACHE) II (ie, removing the Glasgow Coma Scale) is associated with a greater probability of transitioning to delirium. Furthermore, it indicated that the incremental risk becomes larger until reaching a plateau APACHE score of 18 (Fig. 4). The adjusted odds ratio of transitioning to delirium for APACHE II score was 1.06 (1.02–1.11; P = .004). This odd ratio suggests that for each additional APACHE II score, the probability of transitioning to delirium increased by 6%. Similarly, in a study of elderly patients
undergoing hip surgery, APACHE II scores were identified as an independent predictor of delirium [42].

Mortality and morbidity of delirium

According to the latest statistics (2006) from the Society of Critical Care Medicine, there are 5,980 ICUs in the United States, caring for approximately 55,000 patients per day [116]. The incidence of delirium in the ICU has been reported to be as high as 81.3% [20]. Several studies have found that patients who developed delirium fare much worse than their nondelirious counterparts when controlling for all other factors. One study [19] found that the mortality rate was higher among delirious patients, as high as 8% (compared with 1% in nondelirious patients). In another study, ICU-patients who developed delirium had higher 6-month mortality rates (34% versus 15%, \( P = .03 \)) (Fig. 5) [117]. Similarly, another study found that the 90-day mortality was as high as 11% among delirious patients, compared with only 3% among nondelirious elderly patients [118].

Not only is delirium associated with an increased mortality, but the rate of morbidity is also increased. Multiple studies have demonstrated that delirious patients have prolonged hospital stays (ie, average 5–10 days longer), compared with patients suffering from the same medical problem who do not develop delirium as a complication [13,19,20,117]. Similarly, a study of psychiatric inpatients demonstrated that the hospital stays of patients with delirium were 62.1% longer than those of patients without delirium [14].
There are concerns regarding the long-term effects of delirium. It has been estimated that about 40% of delirium cases develop some form of chronic brain syndrome [118]. Some have suggested that the functional decline observed during the acute delirious state may persist 6 months or longer after discharge from the hospital [119]. In fact, Maldonado and colleagues [13] found that only about 14% of those patients who developed delirium returned to their baseline level of cognitive functioning by the time of discharge from the hospital. Levkoff and colleagues [120] found an even lower rate of recovery. In their sample, only 4% of delirious patients experienced full resolution of all symptoms of delirium before discharge from the hospital. After following this sample longitudinally, they found that an additional 20.8% achieved resolution of symptoms by the third month after hospital discharge; and an additional 17.7% by the sixth month after discharge from the hospital. Furthermore, a study by Newman and colleagues [121] reported that cognitive deficits at discharge were significantly associated with poor long-term cognitive functioning for up to 5 years after cardiac surgery. This may explain why patients who develop delirium while in the hospital have a greater need for placement in nursing homes or rehabilitation facilities instead of returning home (16% versus 3%) [19,122]. Others have also suggested that elderly patients who develop delirium “are never the same” even after they recover from the acute event [118,120,123].

Fann and colleagues [124] looked at the impact of delirium on cognition in myeloablative hematopoietic stem-cell transplantation (HSCT) patients \((n = 90)\). All patients completed a comprehensive battery of neuropsychiatric testing before receiving their HSCT and were subsequently followed for 30 and 80 days after transplantation. After adjusting for confounding factors, patients who experienced delirium after HSCT had significantly worse executive functioning \((\beta = -1.1; \ P < .02)\), and worse attention and
processing speed postoperatively (beta = −4.7 and −5.4, respectively) compared with those who did not experience delirium.

In addition to a patient’s increased morbidity and mortality, increased risk of delivery of care to medical and nursing staff, and causing distress to the patient, the family, and medical caregivers, the development of postoperative delirium has been associated with greater care costs, poor functional and cognitive recovery, and prolonged hospital stays [117,125,126]. An increasingly recognized phenomena is the development of posttraumatic stress disorder (PTSD) secondary to the dramatic and bizarre delusional and hallucinatory experiences that occur during a delirious state. The theory behind this phenomenon is that the strong emotional tone of the frightening delusions may have contributed to the development of PTSD, particularly in individuals with no factual recall of their ICU stay [78,127–130].

The economic impact of delirium is substantial, rivaling the health care costs of falls and diabetes mellitus. Maldonado and colleagues [13] conducted a retrospective chart review of all patients who experienced delirium on a step-down critical care unit. The sample of medical and surgical patients (n = 254) included all subjects admitted to the unit over a predetermined, 60-day period. Delirious patients were initially identified from a nursing log of patients who manifested symptoms of delirium. Medical records were extensively reviewed to validate whether delirium occurred, and registered the duration of symptoms and the treatment regimen applied in each case. Supporting data included two or more of the following: administration of antipsychotic agents or a benzodiazepine for the management of agitation or psychosis, use of a sitter or physical restraints for the management of confusion or agitation, and results of cognitive function assessment methods (eg, MMSE, Delirium Rating Scale or DRS). Overall, 14% of patients developed delirium during their ICU stay. Collectively, all patients had a total of 1,471 inpatient days. Delirious patients were reported to be symptomatic for a total of 318 days. Thus, even though they were only 14% of the entire critical care unit population, they used 22% of the total inpatient days. Men were over-represented among all admissions to the unit (61%); however, the proportion of men manifesting delirium was statistically identical to that of the nondelirious patient group (chi square = 0.757, P = .38). The average number of days from symptomatic onset to resolution was 10.8 days for untreated patients and 6.3 days for treated patients. As a group, delirious patients were older (71.3 versus 63.6 years), remained hospitalized longer (16.4 versus 6.6 days), and represented greater total costs per case ($63,900 versus $30,800).

Similarly, Leslie and colleagues [131] studied hospitalized elderly patients and looked at the difference in health care costs for those developing delirium. Regression models were used to determine costs associated with delirium after adjusting for patient sociodemographic and clinical characteristics. In their sample (n = 841), 13% of patients developed delirium during the index hospitalization. Patients with delirium had significantly higher
unadjusted health care costs and survived fewer days. After adjusting for pertinent demographic and clinical characteristics, average costs per day survived among patients with delirium were more than 2.5 times the costs among patients without delirium. Total cost estimates attributable to delirium ranged from $16,303 to $64,421 per patient. Another study demonstrated that in patients who developed delirium in the ICU, the health care costs were 31% higher than for patients with similar medical problems but without delirium ($41,836 versus $27,106) [126]. The national burden of delirium on the health care system has been estimated to range from $38 billion to $152 billion each year [131].

Diagnosing delirium

Despite its high prevalence, delirium remains unrecognized by most ICU clinicians in as many as 66% to 84% of patients experiencing this complication [19,132]. Several studies have demonstrated that hospital staff in general and physicians in particular are not good at identifying delirium. Often, mental status changes associated with delirium are misattributed to dementia, depression, or just an expected occurrence in the critically ill patient. A study by Farrell and Ganzini [133] found that about 41.8% of subjects referred to the psychiatry consultation service for depression were in fact delirious, highlighting how easy it is to misdiagnose this condition. Similarly, Kishi and colleagues [134] looked at the rate of missed diagnosis of delirium by general medicine and surgical services. Again, they found these services missed the diagnosis of delirium in 46% of requested psychiatric consultations (ie, they called psychiatric consultations for reasons other than delirium, but delirium was the cause for the behavior for which the consult was requested). The factors associated with their failure to identify delirium accurately were first, the presence of a past psychiatric diagnosis, which the primary team used to explain delirium symptoms; and second, the presence of pain.

Eissa and colleagues [111] followed patients (n = 48) after cardiac surgery for signs of postoperative confusion. Subjects were assessed by a nonstructured physician interview, and by the short portable mental status questionnaire (SPMSQ). The “ward interviews” involved informal dialogue between the patients and medical staff during routine ward visits. There was no structured format to the questions asked by the physician, although standard clinical management includes assessment of the subject’s orientation to time, place, person, and dialogue. Ultimately, the presence or absence of confusion was based solely on the medical staff’s subjective decisions. The nonstructured physician interview detected confusion in only 2% of the subjects, whereas the SPMSQ diagnosed confusion in 31% of them. The nonstructured ward interviews failed to detect confusion in 14 of the 15 subjects (93%) detected by the SPMSQ and also provided no standardized means by which to classify the degree of confusion. This study highlights
the need to actively assess for the presence of delirium in medically ill patients. These findings are similar to those of Rolfson and colleagues [135], who followed 71 patients after cardiac surgery to detect the incidence of delirium using the Confusion Assessment Method (CAM) [136], the MMSE [137], the clock drawing technique [138,139], and DSM-III-R (revised) criteria [140]. They found that delirium was present in 32.4% of subjects.

The lack of recognition may be worsened by medical personnel’s unawareness of the patient’s pre-existing cognitive deficits. In a study of elderly patients (ie, older than 65) (n = 165) admitted to the ICU, researchers assessed patients and interviewed their families for evidence of pre-existing cognitive deficits. They found that the prevalence of pre-existing cognitive impairment was 38%. Yet ICU attending physicians were unaware of the existence of these in 53% of the cases. The number was similar (59%) for resident physicians [141]. As previously discussed, the presence of cognitive deficits predicts a greater occurrence of delirium; thus, it is important for physicians to know the substrate they are working with and institute techniques that would minimize delirium in populations at risk.

Overall, the most important aspects of accurate diagnosis are vigilance and a high level of suspicion, particularly in patients at higher risk. The diagnostic gold standard for delirium is the Diagnostic and Statistical Manual for Mental Disorders, Fourth edition, text revised (TR) (Box 3) [142].

There are a number of clinically available instruments (Box 4) developed to assist nonpsychiatric personnel in screening for the presence of delirium. These instruments were designed to help nonpsychiatrists (eg, nurses,
All these scales (eg, CAM [136], CAM-ICU [145], DRS [144], and DRS-98 [146]) have been derived from, and validated against expert psychiatric opinions and the DSM diagnostic criteria. Unfortunately, these tools have a high false-positive rate (as high as 10%), thus the team that developed the instrument recommends that all patients identified as delirious by screening instruments "have a complete clinical evaluation to confirm the diagnosis" [136,147]. The most critical part of the assessment, given the characteristic waxing and waning of this syndrome, is to add the interview of the family members, nursing and medical staff, and a thorough review of the chart for behaviors exhibited during the preceding 24 hours to the clinical examination. The DRS was administered by the study’s research assistant and used only as a confirmatory measure.

Another potential clue of the presence of delirium may come from a thorough neuropsychiatric examination. In the author’s experience, patients with delirium tend to exhibit a re-emergence of primitive signs (Box 5). This appears to be more consistent in cases of hypoactive delirium. The

### Box 4. Objectives measures for the diagnosis of delirium

<table>
<thead>
<tr>
<th>Objective measure</th>
<th>Source/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM-IV-TR (Gold Standard; APA 1994)</td>
<td>[142]</td>
</tr>
<tr>
<td>Cognitive Test for Delirium (CTD) (Hart, et al 1996)</td>
<td>[271]</td>
</tr>
<tr>
<td>Confusion Assessment Method (CAM) (Inouye, et al)</td>
<td>[136]</td>
</tr>
<tr>
<td>Confusion Assessment Method for the Intensive Care unit (CAM-ICU) (Ely, et al)</td>
<td>[145]</td>
</tr>
<tr>
<td>Confusional State Evaluation (CSE) (Robertsson, et al 1997)</td>
<td>[272]</td>
</tr>
<tr>
<td>Delirium Assessment Scale (DAS) (O’Keeffe 1994)</td>
<td>[273]</td>
</tr>
<tr>
<td>Delirium Detection Score (DDS) (Otter, et al 2005)</td>
<td>[274]</td>
</tr>
<tr>
<td>Delirium Index (DI) (McCusker, et al 1998)</td>
<td>[275]</td>
</tr>
<tr>
<td>Delirium Rating Scale (DRS) (Trzepacz, et al 1988)</td>
<td>[144]</td>
</tr>
<tr>
<td>Delirium Rating Scale-revised-98 (DRS) (Trzepacz, et al 2001)</td>
<td>[146]</td>
</tr>
<tr>
<td>Delirium Severity Scale (DSS) (Bettin, et al 1997)</td>
<td>[276]</td>
</tr>
<tr>
<td>Delirium Symptom Interview (DSI) (Albert, et al 1992)</td>
<td>[277]</td>
</tr>
<tr>
<td>Memorial Delirium Assessment Scale (MDAS) (Breitbart, et al)</td>
<td>[211]</td>
</tr>
<tr>
<td>Short portable mental status questionnaire (SPMSQ)</td>
<td>[278]</td>
</tr>
<tr>
<td>Brief tests of cognitive functioning</td>
<td></td>
</tr>
<tr>
<td>Mini-Mental State Examination (MMSE) (Folstein, et al)</td>
<td>[137]</td>
</tr>
<tr>
<td>Modified Mini-Mental State Examination (3MS) (Bland, et al 2001)</td>
<td>[279]</td>
</tr>
<tr>
<td>Trail-Making, A and B (O’Donnell 1983)</td>
<td>[280]</td>
</tr>
</tbody>
</table>
## Box 5. Primitive reflexes

These are clinical features that indicate brain dysfunction but that cannot be precisely localized or lateralized. When present, these signs suggest cortical disease, especially frontal cortex, resulting in disinhibition of usually extinguished or suppressed primitive reflexes. Their clinical significance is uncertain and is difficult to correlate with psychiatric illnesses and other behavior disorders, including delirium.

**Glabellar reflex:** with the examiner’s fingers outside of patient’s visual field, tap the glabellar region at a rate of one tap per second. A pathologic response is either absence of blink, no habituation, or a shower of blinks. Normal response equals blinking to the first few taps with rapid habituation.

**Rooting reflex:** tested by stroking the corner of the patient’s lips and drawing away. Pursing of the lips and movement of the lips or head toward the stroking is a positive response.

**Snout reflex:** elicited by tapping the patient’s upper lip with finger or percussion hammer causing the lips to purse and the mouth to pout.

**Suck reflex:** tested by placing your knuckles between the patient’s lips. A positive response would be puckering of the lips.

**Grasp reflex:** elicited by stroking the patient’s palm toward fingers or crosswise while the patient is distracted, causing the patient’s hand to grasps the examiner’s fingers.

**Palmomental reflex:** test by scratching the base of the patient’s thumb (noxious stimulus of thenar eminence). A positive response occurs when the ipsilateral lower lip and jaw move slightly downward, and does not extinguish with repeated stimulation.

**Babinski sign:** downward (flexor response) movement of the great toe in response to plantar stimulation.

**Adventitious motor overflow:** seen as the examiner tests one hand for sequential finger movements, and the fingers of the other hand wiggle or tap. Also, if there are choreiform movements.

**Double simultaneous stimulation discrimination:** tested with the patient’s eyes closed. The examiner simultaneously brushes a finger against one of the patient’s cheeks and another finger against one of the patient’s hands, asking the patient where he has been touched.
relationship between poor cognitive status and primitive reflexes has been described in patients suffering from HIV-related cognitive disorders [148] and in cases of dementia [149]. There is at least one study describing the presence of primitive reflexes in postcardiotomy patients suffering from postoperative neuropsychiatric complications [150]. Further studies are needed to determine whether an assessment for the presence of primitive reflexes may add to the diagnostic accuracy for delirium, or at least assist in the characterization of delirium type, or whether it has any prognostic value.

Some have advocated the use of the electroencephalogram (EEG) as a way to identify and diagnose delirium. Engel and colleagues [151] were the first to describe the relationship between delirium and the diffuse slowing and progressive disorganization of rhythm seen in the EEG. The most common EEG findings in delirium include slowing of peak and average frequencies, and decreased alpha activity but increased theta and delta waves. Studies suggest that EEG changes correlate with the degree of cognitive deficit, but there does not appear to be a relationship between EEG patterns and delirium motoric type [152–160]. The clinical usefulness of EEG in the diagnosis of delirium may be limited by its limited specificity (given there are a number of conditions and medications that may affect the EEG) and the practicality of conducting the test (particularly in the case of agitated and combative patients). Still, the EEG may provide useful in differentiating delirium from other psychiatric and neurologic conditions, such as catatonic states, seizure activity, somatoform disorders, and malingering.

The most critical part of the assessment, given the characteristic waxing and waning of this syndrome, is to obtain as much information and from as many sources as possible (eg, interview of family members, nursing and other medical staff), coupled with a thorough review of the chart for behaviors exhibited during the preceding 24 hours to the clinical examination.

**Delirium subtypes**

Liptzin and Levkoff [147] were the first to characterize the different types of delirium based on behavioral characteristics (Table 3). Others have confirmed the presence of these motoric subtypes. According to these studies, there are at least three types of delirium based on their clinical manifestations: hyperactive, hypoactive, and mixed (Fig. 6) [161,162]. The most common type is the mixed form (46%), followed by the hyperactive (30%) and the hypoactive (24%). To most physicians, the most clear and recognizable form is the hyperactive type. Most clinicians agree that a confused, disoriented patient who does not have a pre-existing psychiatric diagnosis, who suddenly becomes agitated, combative, or assaultive, is probably suffering from the hyperactive or “agitated type” of delirium. The term “mixed type” is used to describe the classic “waxing and waning” pattern, commonly seen in medically ill patients who appear agitated and combative at times, with alternating episodes of somnolence and hypoactivity.
The most difficult type of delirium to identify is the hypoactive type. Classically, these patients present with symptoms that are commonly associated with depression [147]. These include unawareness of the environment, lethargy, apathy, decreased level of alertness, psychomotor retardation, decreased speech production, and episodes of unresponsiveness or staring. Patients with hypoactive delirium often endorse depressive symptoms, such as low mood (60%), worthlessness (68%), and frequent thoughts of death (52%) [133]. Studies have demonstrated that a large percentage of these patients are inappropriately diagnosed and treated as depressed [133]. The author’s own experience at Stanford University Hospital parallels that of others [133,134]. Maldonado and colleagues [13] found that 42% of

<table>
<thead>
<tr>
<th>Hyperactive (three or more)</th>
<th>Hypoactive (four or more)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypervigilance</td>
<td>Unawareness</td>
</tr>
<tr>
<td>Restlessness</td>
<td>Lethargy</td>
</tr>
<tr>
<td>Fast/loud speech</td>
<td>Decreased alertness</td>
</tr>
<tr>
<td>Anger/irritability</td>
<td>Staring</td>
</tr>
<tr>
<td>Combativeness</td>
<td>Sparse/slow speech</td>
</tr>
<tr>
<td>Impatience</td>
<td>Apathy</td>
</tr>
<tr>
<td>Uncooperative</td>
<td>Decreased motor activity</td>
</tr>
<tr>
<td>Laughing</td>
<td></td>
</tr>
<tr>
<td>Swearing/singing</td>
<td></td>
</tr>
<tr>
<td>Euphoria</td>
<td></td>
</tr>
<tr>
<td>Wandering</td>
<td></td>
</tr>
<tr>
<td>Easy startling</td>
<td></td>
</tr>
<tr>
<td>Distractibility</td>
<td></td>
</tr>
<tr>
<td>Nightmares</td>
<td></td>
</tr>
<tr>
<td>Persistent thoughts</td>
<td></td>
</tr>
</tbody>
</table>


The most difficult type of delirium to identify is the hypoactive type. Classically, these patients present with symptoms that are commonly associated with depression [147]. These include unawareness of the environment, lethargy, apathy, decreased level of alertness, psychomotor retardation, decreased speech production, and episodes of unresponsiveness or staring. Patients with hypoactive delirium often endorse depressive symptoms, such as low mood (60%), worthlessness (68%), and frequent thoughts of death (52%) [133]. Studies have demonstrated that a large percentage of these patients are inappropriately diagnosed and treated as depressed [133]. The author’s own experience at Stanford University Hospital parallels that of others [133,134]. Maldonado and colleagues [13] found that 42% of

the time when the psychiatry consultation service was called to treat a patient for “depression,” the patient’s correct diagnosis was hypoactive delirium. The same study found that nearly 80% of these patients had been inappropriately prescribed antidepressant medications.

Management of delirium

Clinicians have three potential approaches when it comes to the management of delirium: (1) managing delirium (ie, symptomatically managing behavioral dyscontrol, such as agitation and psychosis); (2) treatment of delirium (ie, directly addressing either the underlying causes and the neurochemical cascade triggered by the underlying cause itself); or (3) prevention of delirium (ie, use of techniques or methods, either pharmacologic or behavioral, with the purpose of avoiding the development of delirium). This section covers the first; the following section addresses the third. The second section is covered in the article by Dr. Maldonado, elsewhere in this issue.

The adequate treatment of delirium includes the following steps: (1) accurate diagnosis of the condition (eg, hypoactive delirium versus depression), (2) management of the behavioral and psychiatric manifestations and symptoms to prevent the patient from self-harm or harming of others, (3) identification of the etiologic causes of delirium, and (4) treatment of underlying medical problems. Adequate medical management begins with timely diagnosis and early intervention, as shown in the following algorithm for the prevention and management of delirium.

Algorithm for the prevention and management of delirium

I. Be vigilant for the possibility of delirium.
   A. Obtain baseline level of cognitive functioning information from accessory sources.
   B. Screen for the development of delirium in high risk groups, either by the use of psychiatric consultants or objective scales (eg, DRS-98; CAM).
   C. Use psychiatric consultants to help with assessment and design of the treatment plan, if available.

II. Identify and treat underlying medical causes.

III. Non-Pharmacological Treatment Strategies:
   A. Correct malnutrition, dehydration and electrolyte abnormalities should be corrected as quickly and safely as possible.
   B. Remove immobilizing lines and devices (ie, IV lines, chest tubes, bladder catheters and physical restraints) as early as possible.
   C. Correct sensory deficits (ie, eyeglasses, hearing aids).
   D. Promote as normal a circadian light rhythm as possible. Better if this can be achieved by environmental manipulations, such as light
control (ie, lights on & curtains drawn during the day; off at night) and noise control (ie, provide ear plugs, turn off TVs, minimize night staff chatter), rather than by the use of medications.

E. Provide adequate intellectual and environmental stimulation as early as possible.

F. Minimize environmental isolation.

IV. Pharmacological Treatment Strategies:

A. Conduct an inventory of all pharmacological agents been administered to the patient. Any medication or agent known to cause delirium (see Table C) or to have high anticholinergic potential (see Table G) should be discontinued, if possible, or a suitable alternative instituted.

B. Avoid using GABAergic agents to control agitation, if possible. Exceptions: cases of CNS-depressant withdrawal (ie, alcohol, benzodiazepines, barbiturates) or when more appropriate agents have failed and sedations is needed to prevent patient’s harm.

C. Adequately assess and treat pain.

D. Avoid the use of opioids for behavioral control of agitation.

E. For the pharmacological management of delirium (all types) consider using:

   i. Acetylcholinesterase inhibitor (eg, rivastigmine, donepezil, physostigmine, rivastigmine) for correction of central anticholinergic syndrome.

   ii. Serotonin antagonist (eg, ondansetron) to control toxic elevations of 5-HT usually associated with hypoactive delirium, although some studies have suggested its use may be indicated in all types of delirium.

   iii. Rotate opioids from morphine and meperidine to fentanyl or hydromorphone.

   iv. Melatonin or melatonin agonists (eg, ramelteon) to promote a more natural sleep.

   v. Dopamine agonists to manage the theorized abnormally elevated levels of dopamine, and provide restoration of putative hippocampal functions (eg, short-term memory) and reversal of other regional brain disturbances (eg, agitation, psychosis, primitive reflexes), as well as to protect neurons against hypoxic stress and injury. The dose of dopamine antagonist use may depend on the type of delirium been treated.

   vi. Alpha-2 agonists (eg, dexmedetomidine, clonidine), for protection against the acute NE released secondary to hypoxia or ischemia, leads to further neuronal injury and the development of worsening of delirium.

   vii. NMDA-receptor blocking agents, to minimize glutamine induced neuronal injury (eg, amantadine, memantine).
F. In case of hyperactive delirium:
   i. Use low to moderate dose haloperidol (eg, < 20mg/24hr), if the patient’s cardiac condition allows it and there are no significant electrolyte abnormalities.
      a. Before using haloperidol: obtain 12-lead ECG; measure QTc & electrolytes. Correct K+ & Mg+, if needed.
      b. If possible avoid other medications known to increase QTc and/or inhibitors of CPY3A4.
      c. Discontinue its use if QTc increases to > 25% of baseline or > 500msec.
   ii. When the use of haloperidol is contraindicated or not desirable, atypical antipsychotics should be considered:
      b. Limited data for: olanzepine, aripiprazole, perospirone.
      c. Avoid: clozapine, ziprasidone.

G. In case of hypoactive delirium:
   i. Evidence suggests that DA antagonists may still have a place given the excess DA theory.
      a. If haloperidol is used, recommended doses are in the very low range (ie, 0.25 to 1mg / 24hr).
      b. If an atypical is preferred, consider an agent with low sedation (ie, risperidone); unless a sedative agent is needed to restore sleep-wake cycle not responding to E-iv (see above).
   ii. In cases of extreme psychomotor retardation or catatonic features, in the absence of agitation or psychosis, consider the use of psychostimulant agents (eg, methylphenidate, dextroamphetamine, modafinil) or conventional dopamine agonists (eg, bromo-cripette, amantadine, memantine).

Nonpharmacologic treatment strategies

Given the findings reported by Inouye and colleagues [74,163], a multi-component approach is recommended; targeting identified, treatable contributing factors must be undertaken early. As mentioned above, given the high rate of under and missed diagnosed cases, vigilance and a high level of suspicion is essential, particularly in high-risk patients. The routine use of assessment scales or diagnostic interviews by properly trained personnel is key both in prevention and timely treatment. Early involvement of the Psychosomatic Medicine team (Psychiatry) or a Geropsychiatric service has been shown to be extremely valuable, both in prevention and early intervention. An active search for possible etiologies of delirium must first attempt to rule out the common causes of the syndrome (see list titled “Delirium clinical risk factors” above). This must include a review of all medications and identification and possible discontinuation of agents with
high deliriogenic potential (see Box 1). Appropriate diagnostic tests and assays should be ordered and reviewed in a timely fashion, and all abnormal findings addressed accordingly.

Immobilizing lines and devices (eg, chest tubes, IV lines, bladder catheters) should be removed as early as possible. Similarly, physical restraints should be avoided and eliminated as soon as it is safe to do so. Early correction of sensory deficits should be undertaken. That is, eyeglasses and hearing aids should be replaced or fitted (if not using them before the hospitalization) as soon as possible. This will allow patients to familiarize themselves with the environment and reorient themselves early on. It will also minimize the occurrence of misperceptions or misinterpretation of environmental cues and stimuli. Environmental isolation should be minimized if possible. Family members and loved ones should be encouraged to visit and provide a familiar and friendly environment, as well as provide appropriate orientation and stimulation to patients, especially those with baseline cognitive deficits.

Dehydration and electrolyte abnormalities should be corrected as quickly and safely as possible. Malnutrition should be corrected, unless there are good reasons not to (eg, terminal dementia).

Early correction of sleep disturbance, preferably by nonpharmacologic means, should occur, although the use of nonbenzodiazepine agents, such as melatonin or melatonin agonists (ie, ramelteon) or sedating antidepressant agents (eg, trazodone or mirtazapine) should be considered. On the other hand, clinicians must consider factors, such as drug–drug interaction and medication half-lives when prescribing. For example, mirtazapine and trazodone may indeed promote night sleep, but their effects may last well into the next day, interfering with cognition, attention, and concentration. Sedative agents with high anticholinergic load, such as antihistaminic agents (eg, diphenhydramine, hydroxyzine) or tricyclic antidepressants (eg, amitriptyline) should be avoided, as they will aggravate delirium even if immediately effective in promoting sleep. Similarly, benzodiazepines should also be avoided if at all possible.

Finally, conduct an inventory of all pharmacologic agents being administered to the patient. Any medication or agent known to cause delirium (see Box 1) or to have high anticholinergic potential (see Box 2) should be discontinued, if possible, or a suitable alternative instituted.

Pharmacologic treatment strategies

It cannot be overstated that the definitive treatment of delirium is the accurate identification and treatment of its underlying causes. Nevertheless, pharmacologic intervention with various psychoactive agents is often needed to help manage agitated patients. Following the Hippocratic principle of “first, do no harm,” clinicians should first avoid the use of GABAergic agents, if at all possible. As described above, all such agents (ie, benzodiazepines, propofol) may cause or aggravate delirium and its behavioral manifestations [20,41,94]. The use of benzodiazepines in the
management of delirium should be limited to: (a) patients experiencing delirium related to the withdrawal from a CNS-depressant agent (ie, alcohol, barbiturates, benzodiazepines); or (b) when other more appropriate agents (see below) have failed and the level of agitation and need for behavioral control outweighs the potential detrimental effects of benzodiazepines. Similarly, clinicians should do everything possible to avoid the use of opioid agents to tranquilize agitated patients, as opioids have been implicated in the development of delirium in many patient populations [25,40,101–106]. On the other hand, opioids should be administered when there is evidence that pain may be a contributor to the patient’s agitation.

The literature has long recognized that intravenous neuroleptic agents are the recommended emergency treatment for agitated and mixed type delirium [164–169]. The intravenous administration of haloperidol has always been thought of as superior to oral administration because the IV route has more reliable absorption, even in cases of systemic organ failure. Intravenous haloperidol use has the added advantage of requiring no patient’s cooperation, thus facilitating its use even in uncooperative and agitated patients. Studies suggest that the IV use of high-potency neuroleptic agents is associated with minimal effects on blood pressure, respiration, and heart rate [167,170–175].

Further research suggests a decreased incidence of extrapyramidal symptoms (EPS) when the intravenous route versus the oral route is used [176]. This study consisted of a retrospective chart review of all patients admitted to a large university hospital receiving haloperidol in any form over a 90-day period. A total of 238 subjects receiving haloperidol were identified during the index period, using data obtained through the digital pharmacy distribution system (Pyxis). Only patients with a known pre-existing movement disorder (eg, Parkinson disease) were excluded. In this sample, 51% of the subjects were women and the mean age was 62 years for women and 55 years for men. The most common reasons for which haloperidol was prescribed included delirium (69%), psychosis (11%), nausea or vomiting (9%), affective disorder (6%), and dementia (5%). Haloperidol doses ranged from 0.5 mg to 90 mg per day for subjects receiving intravenous administration, and from 0.5 mg to 20 mg per day for those receiving oral administration. Results show that patients receiving IV-haloperidol experienced much lower EPS than patients receiving the oral form (7.2% versus 22.6%; \( P < .01 \)). In this sample, the most common forms of EPS observed included medication-induced Parkinsonism (50%), akathisia (32%), and acute dystonic reactions (14%). The investigators found no cases of significant respiratory depression or Torsade de Pointes (TdP) deemed to have been caused by haloperidol use. These findings are similar to those previously reported, also suggesting a lower incidence of EPS when haloperidol is administered intravenously [168].

Maldonado and Dhami [177] conducted a prospective study, involving all patients \( n = 225 \) admitted to the critical care unit during a 6-month period.
Subjects were monitored throughout their hospital stay to assess the effectiveness of a protocol-based management of delirium among critical care patients. Subjects were followed daily by the study research assistant, using objective methods to assess delirium (ie, the MMSE [137] and the DRS [144]). There were slightly more surgical cases (n = 129), than medical cases (n = 96). A total of 18% of the subjects were identified as being delirious by DRS-criteria during the index period. Consultations to the Psychosomatic Medicine Service (PMS) were called in only 42% of the cases. On average, the surgical team consulted psychiatry 2.8 days after the onset of manifestation of delirium, whereas medicine services called after 4.2 days. Pharmacologic management varied significantly between the two groups (ie, standard of care versus study protocol). Medical and surgical services managed their delirious patients with varying combinations of medications, including opioids, benzodiazepines (ie, primarily midazolam or lorazepam), propofol, and various neuroleptic agents, usually on an as-needed basis. On the other hand, the treatment used by the PMS consisted of the routine use of IV haloperidol given throughout the day, on a regular schedule every 0400-, 1000-, 1600-, and 2200-hours. Lorazepam was used in cases of agitated delirium not responding to haloperidol alone, in cases of primary CNS-depressant agent withdrawal (ie, alcohol, benzodiazepines), or at night only to help promote sleep. The treatment regime doses were adjusted every 24 hours and titrated to effect. The dosing difference maintained a haloperidol-to-lorazepam ratio of at least two-to-one (the H2A protocol) to avoid the possibility of disinhibition by the benzodiazepines. That is, when used, the lorazepam dose was always less than half the haloperidol dose in milligrams. Nevertheless, because of the possibility that benzodiazepines themselves may contribute to delirium, the lowest effective dose was always used. Whenever possible, no benzodiazepines were used.

The results demonstrated that the PMS-management approach (ie, scheduled IV haloperidol use) was superior to the “standard approach” (ie, as-needed use of sedatives and antipsychotics) at treating delirium [177]. The length of stay (15 versus 11 days) (Fig. 7A), total duration of delirium (13 versus 6 days) (Fig. 7B), and percentage time being delirious (86% versus 58%) (Fig. 7C) were all shorter on patients treated by the PMS protocol. In addition, a significant improvement in cognitive functioning was observed in patients treated with the PMS-protocol. Finally, complete resolution of delirium (as measured by a MMSE greater than 26 and a DRS less than 10) at the time of discharge home was greater for patients treated with the PMS-protocol than (90% in the psychiatry group versus 14% in the medical/surgical group) (Fig. 7D). As many previous studies have indicated, these results suggest that a rational and controlled approach to the early identification and treatment of delirium in critical care patients results in a more accurate and prompt diagnosis, shorter hospital stays, a reduction in the use of restraints, faster recovery, and a substantially greater resolution of symptoms of delirium at the time of hospital discharge. Even though the
number of patients treated by “standard or conventional” approach achieving a complete resolution of their symptoms of delirium appears dismal, these findings may represent more of the rule than the exception.

Levkoff and colleagues [120] followed all older patients ($n = 325$) admitted to the medical and surgical services of a teaching hospital. During the index period, 10.5% of all patients fulfilled DSM-III [178] criteria for delirium on admission and an additional 31.1% developed delirium during the index hospitalization. Similar to previous studies, development of delirium was associated with prolonged hospital stay and an increased risk of institutional placement among community-dwelling older persons. In their sample, only 4% of delirious patients in their study experienced full resolution of delirium symptoms before discharge from the hospital. On longitudinal follow-up, an additional 20.8% had resolution of all symptoms by 3 months, and an additional 17.7% had resolution of all symptoms by 6 months after discharge from the hospital.

Despite the widespread use of IV haloperidol and multiple reports in the literature describing its safety [166,167,169–172,174,175,179], even when used at fairly high doses, some reports suggesting a range of

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**Fig. 7.** Effects of the early identification and treatment of delirium according to protocol. (A) total length of stay; (B) average total delirious days; (C) percentage of delirious days. Final bar graph represents complete resolution; (D) percentage of complete resolution of delirium on discharge home by treatment groups. Red = treatment as usual by medical/surgical teams; Blue = psychological protocol treatment. (From Maldonado JR, Dhami N. “Recognition and Management of Delirium in the Medical and Surgical Intensive Care Wards.” Poster presentation. 17th World Congress on Psychosomatic Medicine, Waikoloa, Hawaii. August 27, 2003; with permission; Data from Maldonado JR, Dhami N. Recognition and management of delirium in the medical and surgical intensive care wards. Journal of Psychosomatic Research 2003;55(2):150.)
500 mg–1,000 mg per day [172], fears about its use remain. The main concern when used in the acute care setting is related to it potential effect in prolonging QTc. There have been reports regarding the occurrence of QTc prolongation and even the development of TdP associated with haloperidol use. Nevertheless, the literature suggests that the risk is relatively low (0.27%) [180]. One of the problems in determining the exact contribution of IV haloperidol on TdP is that most patients for whom IV haloperidol is prescribed are very medically ill, usually in a critical care environment, and receiving multiple medications, many of which themselves could cause QTc prolongation and lead to TdP (Table 4) [181]. Justo and colleagues [182] conducted a review of published cases (n = 70) of TdP induced by psychotropic agents (PAs). They concluded that the most commonly identified risk factor for this patient population included female gender (50 of 70, 71.4%); advanced heart disease (24 of 70, 34.2%); hypokalemia; high doses of the offending agent (19 of 70, 27.1%); concomitant use of more than one PA, or another agent that might prolong the QT interval (21 of 70, 30%), and a history of long-QT syndrome (13 of 70, 18.5%) (Fig. 8). For

Table 4
Twenty drugs most commonly associated with Torsades de Pointes (TdP) according to adverse drug reactions (ADR) reported to world health organization, 1983–1999

<table>
<thead>
<tr>
<th>Drug</th>
<th>TdP N\textsuperscript{a}</th>
<th>Fatal N\textsuperscript{b}</th>
<th>Total N\textsuperscript{c}</th>
<th>TdP/total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotalol</td>
<td>130</td>
<td>1</td>
<td>2,758</td>
<td>4.71</td>
</tr>
<tr>
<td>Cisapride</td>
<td>97</td>
<td>6</td>
<td>6,489</td>
<td>1.49</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>47</td>
<td>1</td>
<td>13,725</td>
<td>0.34</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>44</td>
<td>2</td>
<td>24,776</td>
<td>0.18</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>43</td>
<td>1</td>
<td>173</td>
<td>24.86</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>41</td>
<td>1</td>
<td>10,047</td>
<td>0.41</td>
</tr>
<tr>
<td>Quinidine</td>
<td>33</td>
<td>2</td>
<td>7,353</td>
<td>0.45</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>33</td>
<td>0</td>
<td>17,448</td>
<td>0.19</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>21</td>
<td>6</td>
<td>15,431</td>
<td>0.14</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20</td>
<td>1</td>
<td>70,929</td>
<td>0.03</td>
</tr>
<tr>
<td>Digoxin</td>
<td>19</td>
<td>0</td>
<td>18,925</td>
<td>0.10</td>
</tr>
<tr>
<td>Procainainide</td>
<td>19</td>
<td>0</td>
<td>5,867</td>
<td>0.32</td>
</tr>
<tr>
<td>Terodilne</td>
<td>19</td>
<td>0</td>
<td>2,248</td>
<td>0.85</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>17</td>
<td>0</td>
<td>5,613</td>
<td>0.30</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>16</td>
<td>1</td>
<td>3,378</td>
<td>0.47</td>
</tr>
<tr>
<td>Bepridil</td>
<td>15</td>
<td>0</td>
<td>384</td>
<td>3.91</td>
</tr>
<tr>
<td>Furosemide</td>
<td>15</td>
<td>0</td>
<td>15,119</td>
<td>0.10</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>12</td>
<td>0</td>
<td>6,565</td>
<td>0.18</td>
</tr>
<tr>
<td>Flecainide</td>
<td>11</td>
<td>2</td>
<td>3,747</td>
<td>0.29</td>
</tr>
<tr>
<td>Loratadine</td>
<td>11</td>
<td>1</td>
<td>5,452</td>
<td>0.20</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Total number of ADR reports that named TdP for this drug.
\textsuperscript{b} Number of ADR reports that named TdP with fatal outcome.
\textsuperscript{c} Total number of ADR reports for this drug.

A comprehensive review of medications that cause QTc prolongation and TdP, see Yap and Camm (Table 5) [183].

A MEDLINE and manual search of the literature published between 1966 and 1996 was conducted looking for cases of conduction disturbances associated with the use of butyrophenone antipsychotics [184]. They found only 18 patients described and concluded that, “it seems reasonable to suggest that the incidence of adverse cardiovascular effects due to droperidol and haloperidol is small.” The investigators made several recommendations regarding the use of haloperidol in the critically ill patient. Before initiating therapy with haloperidol, a baseline QTc interval and serum magnesium and potassium concentrations should be measured. Electrolytes should be corrected, if necessary, before initiation of treatment. If the baseline QTc interval is greater than or equal to 440 msec, and patients are receiving other drugs that may prolong the QTc interval or in the presence of significant electrolyte disturbances, a butyrophenone antipsychotic should be used with caution. Once treatment has been initiated, all critically ill patients receiving haloperidol should undergo regular electrocardiograph monitoring and QTc interval measurement. Special attention should be given to those receiving doses greater than 50 mg every 24 hours. Based on the currently available literature, any critically ill patient receiving droperidol or

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Fig. 8. Prevalence of risk factors for Torsade de Pointes among patients with TdP induced by psychotropic drugs. (From Justo D, Prohorov V, Heller K, et al. Torsade de Pointes induced by psychotropic drugs and the prevalence of its risk factors. Acta Psychiatr Scand 2005;111(3):171–6; with permission.)
Table 5
Drugs that can prolong QT interval and Torsades de Pointes (this list is not comprehensive)

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmic drugs</td>
<td>Type 1A (TdP reported in all)</td>
</tr>
<tr>
<td></td>
<td>Quinidine (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Procainamide (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Disopyramide (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Ajmaline (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Type 1C (increase QT by prolonging QRS interval)</td>
</tr>
<tr>
<td></td>
<td>Encainide</td>
</tr>
<tr>
<td></td>
<td>Flecaïnide</td>
</tr>
<tr>
<td></td>
<td>Type 3 (TdP reported in all)</td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
</tr>
<tr>
<td></td>
<td>Sotalol</td>
</tr>
<tr>
<td></td>
<td>d-Sotalol</td>
</tr>
<tr>
<td></td>
<td>Bretylium</td>
</tr>
<tr>
<td></td>
<td>Ibutilide</td>
</tr>
<tr>
<td></td>
<td>Dofetilide</td>
</tr>
<tr>
<td></td>
<td>Amakalant</td>
</tr>
<tr>
<td></td>
<td>Semantilide</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Prenylamine (TdP reported, withdrawn)</td>
</tr>
<tr>
<td></td>
<td>Bepridil (TdP reported, withdrawn)</td>
</tr>
<tr>
<td></td>
<td>Terodiline (TdP reported, withdrawn)</td>
</tr>
<tr>
<td>Psychiatric drugs</td>
<td>Thoridazine (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Chlorpromazine (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Haloperidol (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Droperidol (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Amitriptyline</td>
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<tr>
<td></td>
<td>Nortriptyline</td>
</tr>
<tr>
<td></td>
<td>Imipramine (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Desipramine (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Clomipramine</td>
</tr>
<tr>
<td></td>
<td>Maprotiline (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Doxepin (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Lithium (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Chloral hydrate</td>
</tr>
<tr>
<td></td>
<td>Sertindole (TdP reported, withdrawn in the UK)</td>
</tr>
<tr>
<td></td>
<td>Pimozide (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Ziprasidone</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Terfenadine (TdP reported, withdrawn in the United States)</td>
</tr>
<tr>
<td></td>
<td>Astemizole (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Diphenhydramine (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Hydroxyzine</td>
</tr>
<tr>
<td></td>
<td>Ebastine</td>
</tr>
<tr>
<td></td>
<td>Loratadine</td>
</tr>
<tr>
<td></td>
<td>Mizolastine</td>
</tr>
<tr>
<td>Antimicrobial and antimalarial</td>
<td>Erythromycin (TdP reported)</td>
</tr>
<tr>
<td>drugs</td>
<td>Clarithromycin (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole</td>
</tr>
<tr>
<td></td>
<td>Pentamidine (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Quinine</td>
</tr>
<tr>
<td></td>
<td>Chloroquine (TdP reported)</td>
</tr>
<tr>
<td></td>
<td>Halofantrine (TdP reported)</td>
</tr>
</tbody>
</table>
haloperidol therapy, whose QTc interval lengthens by greater than or equal to 25% over baseline, should undergo dose reduction or should be switched to a different agent.

Despite these concerns, in 1995 a task force of more than 40 experts in disciplines related to the use of analgesic and sedative agents in the ICU was convened from the membership of the American College of Critical Care Medicine and the Society of Critical Care Medicine (SCCM) [185]. This consensus of experts provided six recommendations with supporting data for intravenous analgesia and sedation in the ICU setting:

Morphine sulfate is the preferred analgesic agent for critically ill patients.
Fentanyl is the preferred analgesic agent for critically ill patients with hemodynamic instability, for patients manifesting symptoms of histamine release with morphine, or morphine allergy.
Hydromorphone can serve as an acceptable alternative to morphine.
Midazolam or propofol are the preferred agents only for the short-term (< 24 hours) treatment of anxiety in the critically ill adult.
Lorazepam is the preferred agent for the prolonged treatment of anxiety in the critically ill adult.
Haloperidol is the preferred agent for the treatment of delirium in the critically ill adult.

Similarly, the use of IV haloperidol as the agent of choice for critically ill patients was reinforced by the SCCM’s most recent guidelines, published in 2002 [186]. Since then, a “best evidence topic in cardiac surgery” was written according to a structured protocol, addressing the issue of haloperidol safety for critically ill patients. Their search included 294 articles and concluded that haloperidol should be considered the first-line drug for agitated patients after cardiac surgery [187].
Of note, in September 2007, the Food and Drug Administration (FDA) issued a “black-box” warning for the “off-label” clinical practice of using IV haloperidol [188]. It is important to remember that haloperidol has never been approved by the FDA for IV use.

**Alternatives to haloperidol**

Because of the stigma and potential side effects associated with typical antipsychotics, atypical agents (also known as second-generation antipsychotics, or SGA) have been used at increasing rates over the last few years for management of psychiatric symptoms (eg, agitation, psychosis, delirium) in medically ill patients. Large studies, particularly head-to-head comparison between SGA and more conventional agents (ie, haloperidol) are lacking. At least one study suggested that SGA may have a greater incidence of adverse effects than typical agents, excluding EPS [189]. Leucht and colleagues [190] conducted a meta-analysis of all randomized, controlled trials in which new generation antipsychotics (ie, SGA) had been compared with conventional drugs. The study included studies that met quality criteria A or B in the *Cochrane Collaboration Handbook*, and assessed quality with the Jadad scale. The investigators included in their analysis 31 studies with a total of 2,320 participants. The findings concluded that of the new generation drugs, only clozapine was associated with significantly fewer EPS (risk difference or RD = −0.15, 95% CI, −0.26 to −0.4, \( P = .008 \)) and higher efficacy than low-potency conventional drugs. The reduced frequency of EPS seen with olanzapine was of borderline significance (RD = −0.15, CI, −0.31 to −0.01, \( P = .07 \)). Similarly, they identified only one inconclusive trial of quetiapine and risperidone, and no investigations of ziprasidone and sertindole. They concluded that as a group, new generation drugs were moderately more efficacious than low-potency antipsychotics, largely irrespective of the comparator doses used; and that optimum doses of low-potency conventional antipsychotics might not induce more EPS than new generation drugs.

Other problems to consider when choosing an alternative agent include the fact that SGA may be associated with weight gain, dyslipidemia, high blood pressure, and ultimately with cardiovascular disease, diabetes, and metabolic syndrome [191]. As when considering the use of typical agents (ie, haloperidol), clinicians must consider these factors and weigh potential risks and benefits before prescribing these agents to a critically ill patient. Finally, there is also evidence that some atypical agents may aggravate or cause delirium (eg, clozapine, olanzepine), probably because of their anticholinergic potential [189]. Data on most atypical agents are limited to small case reports.

Horikawa and colleagues [192] conducted a prospective open trial on risperidone for the treatment of delirium among medically ill patients (\( n = 10 \)). They reported an overall effectiveness of 80%, using doses of risperidone between 0.5 mg to 2 mg per day. Side effects included sedation in 30%.
and EPS in 10% of subjects. Mittal and colleagues [193] reported similar results \((n = 10)\) with risperidone, using a mean daily dose of 0.75 mg. The largest, open-label risperidone study was reported by Parellada and colleagues [194], who followed subjects hospitalized for a medical condition \((n = 64)\). Once the diagnosis of delirium was established (based on the DRS) treatment with risperidone was initiated. The investigators reported improvements on all studied measures (ie, Clinical Global Impressions or CGI scale, DRS, and MMSE) after 7 days of treatment. There was a very low incidence of overall adverse effects (3.1%) and no EPS reported. On the other hand, there are at least four publications reporting risperidone-induced delirium [195–198].

There are six publications reporting on the use of quetiapine for the treatment of delirium. Torres and colleagues [199] reported improvements on MMSE and DRS-R-98 in two subjects. Similarly, Al-Samarrai and colleagues [200] reported on another two delirious subjects responding to quetiapine. Sasaki and colleagues [201] reported on a prospective, open-label study \((n = 12)\) of delirious subjects treated with a mean daily dose of quetiapine of 45 mg plus or minus 31 mg per day. They found a mean duration of symptoms of 4.8 plus or minus 3.5 days and improvements on MMSE, and reported no significant side effects. Similarly, Kim and colleagues [202] reported on another 12 subjects treated with a mean daily dose of quetiapine of 94 mg plus or minus 23 mg per day. The mean duration of symptoms was 5.9 plus or minus 2.2 days, as well as improvements on the clock drawing test and MMSE. Pae and colleagues [203] treated 22 subjects with a mean daily dose of quetiapine of 127.1 mg plus or minus 72.2 mg per day. In this group, the mean duration of symptoms was 8.5 plus or minus 4.5 days, as well as improvements on DRS-R-98 and CGI. Again, no significant side effects were reported. Maneeton and colleagues [204] studied the effectiveness of quetiapine in the management of delirium \((n = 22)\) in an open-label study. The means (SDs) dose and duration (SD) of quetiapine treatment were 45.7 (28.7) mg per day and 6.5 (2.0) days, respectively. Results show that the DRS and CGI-S scores of days two to seven were significantly lower than those of day 0 \((P < .001)\) for all comparisons. The incidence of side effects was minimal. Finally, Balit and colleagues [205] and Sim and colleagues [206] reported on a case each in which quetiapine was the suspected cause of delirium.

There are several publications reporting the use of olanzapine for the treatment of delirium. Kim and colleagues [207] reported on an open trial \((n = 20)\) on the use of olanzapine for the treatment of delirium caused by multiple medico-surgical conditions. The average olanzapine dose was 5.9 mg plus or minus 1.5 mg per day and the average duration of treatment was 6.6 plus or minus 1.7 days. Their data showed improvement in the DRS at relatively low doses \((5.9 \text{ mg} \pm 1.5 \text{ mg per day})\) and no evidence of significant side effects. Passik and Cooper [208] and Halil and colleagues [209] reported a single case report each in which olanzapine was successfully used in the treatment of delirium associated to a medical problem. Breitbart
and colleagues [210] conducted an open, prospective trial of olanzapine for the treatment of delirium in hospitalized cancer patients \( n = 79 \). In this sample, olanzapine was effective in treating 76% of delirium patients as evidenced by the Memorial Delirium Assessment Scale (MDAS) [211], but recorded problems with excessive sedation in 30% of patients. They also described several factors significantly associated with poorer response to olanzapine treatment for delirium, including age greater than 70 years, history of dementia, central nervous system spread of cancer and hypoxia as delirium etiologies, hypoactive delirium, and delirium of “severe” intensity (as measured by an MDAS greater than 23). Robinson and colleagues [212], Steil [213], Morita and colleagues [214], Samuels and Fang [215], Prommer [216], Arora and Praharaj [217], and Lim and colleagues [218] all reported on cases associated with olanzapine-induced delirium at therapeutic doses. Delirium has been reported as a side effect in 54% of the cases when large doses of olanzapine have been ingested in an overdose. Patients with olanzapine-induced delirium had an increased length of hospital stay and ICU admission rate (50%), and 70% of them required physical or chemical restraint [219].

Aripiprazole has been described as an effective treatment of delirium in two case reports [220]. Straker and colleagues [221] reported on an open-label series of subjects \( n = 14 \) treated with aripiprazole for management of delirium used in a flexible dosing range, from 5 mg per day to 15 mg per day, titrated over a 7-day period, with dose increases on day 3 and day 7, as clinically indicated. DRS-R-98 scores declined from 25.1 (±5.2) on initial evaluation to 9.4 (4.9) at treatment end-point. Fifty percent of the subjects (7 out of 14) had improved significantly (ie, ≥ 50% reduction in DRS-R-98 scores) by day 5, while 12 of the 14 subjects had a reduction in their DRS-R-98 scores greater than or equal to 50% by treatment end-point.

To date, there are two single case reports on the use of ziprasidone for the management of delirium [222,223]. There is at least one open-label study \( n = 38 \) on the use of perospirone, a recently developed atypical antipsychotic with potent serotonin 5-HT2 and dopamine D2 antagonist activity. Perospirone was effective in 86.8% of patients (based on DRS-98 assessments) and the effect appeared within several days (5.1 ± 4.9 days). The initial dose was 6.5 mg plus or minus 3.7 mg per day and maximum dose of perospirone was 10.0 mg plus or minus 5.3 mg per day. Reported side effects included fatigue (15.2%), sleepiness (6.1%), akathisia (3.0%), and hypotension (3.0%) [224].

There is little published data regarding controlled studies of atypical antipsychotics for the treatment of delirium. Sipahimalani and Masand [225] conducted a single-blind study using olanzapine versus haloperidol. Eleven subjects with delirium were treated, using a mean daily dose of olanzapine of 8.2 mg plus or minus 3.4 mg versus haloperidol 5.1 mg plus or minus 3.5 mg per day. Peak response (ie, the number of days the patient received the neuroleptic before achieving maximum improvement) was similar in both groups (mean ± SD: 6.8 ± 3.5 days for olanzapine and
7.2 ± 4.9 days for haloperidol, *P* = .8279). Mean plus or minus SD pretreatment DRS scores were comparable in the olanzapine (17.9 ± 4.4) and the haloperidol (20.1 ± 5.2) groups (*P* = .2968). Mean plus or minus SD after-treatment DRS scores were 10.3 plus or minus 4.8 for the olanzapine group and 11.1 plus or minus 7.1 for the haloperidol group (*P* = .7601). The mean improvement was 7.6 for the olanzapine group and 10 for the haloperidol group. Five of the olanzapine subjects and six of the haloperidol subjects showed a greater than 50% reduction in their DRS scores.

Schwartz and Masand [226] performed a single-blind study of quetiapine versus haloperidol in delirious subjects (*n* = 11). The quetiapine average daily dose was 200 mg per day. The investigators reported an effectiveness of greater than or equal to 50% in reducing DRS scores. When compared with haloperidol, there was no difference in onset of symptom resolution, duration of treatment, and overall clinical improvement. Skrobik and colleagues [227] conducted an open-label, prospective randomized trial, comparing the use of enteral olanzapine (dosed at 5 mg per day) or haloperidol (dosed at 2.5 mg–5 mg every 8 hours) in the treatment of delirium in a critical care setting. Delirium Index decreased over time in both groups, as did the administered dose of benzodiazepines. Clinical improvement was similar in both treatment arms. The dose of rescue haloperidol, opiates, sedatives other than benzodiazepines, Ramsay scores, vital signs, and liver function tests were no different between groups. Thus, no significant clinically effective difference was appreciated between groups. Liu and colleagues [228] conducted a single-blind risperidone versus haloperidol study. They treated 41 subjects with a mean daily dose of risperidone of 1.2 mg plus or minus 0.75 mg per day. The investigators found no significant difference in the efficacy or frequency of response rate between haloperidol and risperidone on any of the measures (ie, DRS, MDAS).

The only published double-blind, randomized study looked at 28 subjects with delirium who were randomly assigned to receive a flexible-dose regimen of haloperidol or risperidone over a 7-day treatment period [229]. The severity of delirium was assessed by using the MDAS and the DRS. The study investigators found no significant difference in the efficacy, frequency, or rate of response between haloperidol and risperidone on any of the measures. Similarly, there were no clinically significant side effect differences among study groups.

A Cochrane Database review study looking at the use antipsychotics for the treatment of delirium was conducted and included haloperidol and all atypical antipsychotics for which data has been published [230]. Only three studies met the design criteria. These compared haloperidol with risperidone, olanzapine, and placebo in the management of delirium and the incidence of adverse drug reactions. The authors concluded that the decreases in delirium scores were not significantly different comparing the effect of low dose haloperidol (< 3.0 mg per day) with the atypical antipsychotics olanzapine and risperidone (OR 0.63; 95% CI, 10.29–1.38; *P* = .25), and that low-dose haloperidol did not have a higher incidence of adverse effects.
than the atypical antipsychotics. Finally, low-dose haloperidol may be effective in decreasing the degree and duration of delirium in postoperative patients, compared with placebo.

Ozbolt and colleagues [231] conducted a search of the published literature on atypical antipsychotic agents for the treatment of delirium using MEDLINE and PubMed for articles (including review articles, randomized controlled trials, clinical trials, or meta-analyses) written in English. They found that risperidone was the most thoroughly studied atypical antipsychotic for the management of delirium. In most studies, risperidone was found to be approximately 80% to 85% effective in treating the behavioral disturbances of delirium at doses of 0.5 mg to 4 mg per day. The search indicates that olanzapine was approximately 70% to 76% effective in treating the behavioral manifestations of delirium at doses of 2.5 mg to 11.6 mg per day. There were very few studies conducted using quetiapine, although available data suggests that it also appears to be a safe and effective alternative to high-potency antipsychotics. In the limited number of trials comparing atypical antipsychotics to haloperidol, haloperidol consistently produced a higher rate (an additional 10% to 13%) of extrapyramidal side effects.

Antipsychotics are widely used to manage behavioral disorders, including delirium, in patients with dementia. Recently, serious concerns have been raised about the stroke and mortality risk of atypical antipsychotics when administered to patients with dementia. Schneider and colleagues [232] reviewed 15 clinical trials, including 16 contrasts of atypical antipsychotic drugs with placebo (aripiprazole \( n = 3 \), olanzapine \( n = 5 \), quetiapine \( n = 3 \), risperidone \( n = 5 \)) and a total of 3,353 subjects randomized to study drug versus 1,757 randomized to placebo. The investigators found that death occurred more often among patients randomized to drugs (118 or 3.5% versus 40 or 2.3%; the OR by meta-analysis was 1.54; 95% CI, 1.06–2.23; \( P = .02 \); RD 0.01; 95% CI, 0.004–0.02; \( P = .01 \)). The results suggested that atypical antipsychotic drugs may be associated with a small increased risk for death compared with placebo.

Yet, an even more recent study by Raivio and colleagues [233] examined the use of antipsychotic agents to manage behavioral disorders in patients \( n = 254 \) with dementia. In this sample, nearly half (48.4%) of the patients were administered antipsychotic medication. A total of 37.4% received conventional neuroleptics \( n = 95 \), while only 11.0% received atypical antipsychotics \( n = 28 \). The mean number of hospital admissions was higher among the non-users than among the users of conventional or atypical antipsychotics. Among the users of atypical antipsychotics (eg, risperidone, olanzapine), 32.1% died within 2 years, compared with 45.3% in the conventional neuroleptics group, and 49.6% in the non-neuroleptic user group. In the Cox proportional hazard model, a high number of medications and the use of physical restraint predicted higher mortality at 2 years. On the other hand, the use of atypical antipsychotics showed lower risk of mortality, if any. The investigators concluded that neither the use of atypical
antipsychotics, nor the use of conventional neuroleptics increased mortality or hospital admissions.

One study pooled QTc interval data from acutely agitated patients across four double-blind trials and showed that when all of the intramuscular olanzapine data were considered, QTc interval changes were small, variable, and generally symmetric at around 0, suggesting that these values were reflective of normal and random intra-individual variability [234]. A series of case reports by Balit and colleagues [205] implicated that quetiapine poisoning was associated with an increase in the mean QTc interval. The FDA has published data on the effect of atypical antipsychotics on QTc interval (Table 6). Yet, no new generation antipsychotic drug has been associated with Torsade de Pointes. All of them have been associated with QTc interval prolongation. In order of degree, QTc interval prolongation is greatest with ziprasidone and least with olanzapine [235].

Finally, one must consider the fact that newer antipsychotic agents (SGA) have a wider range of pharmacologic affinity (ie, affects a greater number of neurotransmitters and receptors) than older agents. Although SGA may have lower EPS side effects, they have other undesirable side effects, such as high sedation and anticholinergic activity (Fig. 9). The sedative effect may be considered desirable in the case of agitated agents, although given the agents relatively long half-lives this may later affect attention and cognition and be detrimental in cases of hypoactive delirium. On the other hand, anticholinergic side effects are never desirable when it comes to delirium and this may be a consideration when making treatment choices.

Nonantipsychotic agents

Addressing the theory that proposes delirium is caused by a central cholinergic deficiency state, some researchers and clinicians have experimented with the use acetylcholinesterase inhibitor agents. Most of the published data consists of small series of case reports associated with the use of rivastigmine in the treatment of delirium in older persons [236,237]. There have been at least 19 articles, mostly case reports, suggesting that

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Table 6

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean increase in QTc (ms)</th>
<th>% of subjects with &gt; 60 ms increase in QTc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thioridazine</td>
<td>35.8</td>
<td>29</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>20.6</td>
<td>21</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>14.5</td>
<td>11</td>
</tr>
<tr>
<td>Risperidone</td>
<td>10.0</td>
<td>4</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>6.4</td>
<td>4</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>4.7</td>
<td>4</td>
</tr>
</tbody>
</table>

acetylcholinesterase inhibitor agents (eg, donepezil, galantamine, physostigmine, rivastigmine) may be effective in the treatment of delirium (Box 6).

Some have theorized that an impaired serotonin metabolism may play a role in the development of delirium. At least one report suggests that the antiemetic agent ondansetron (ie, a selective serotonin 5-HT₃-type receptor antagonist) may be effective in the treatment of delirium. Bayindir and colleagues [238] conducted a prospective study of patients (n = 35) who developed delirium in the intensive care unit after coronary artery bypass graft surgery. The investigators developed a behavioral scoring scale, with

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**Box 6. Case reports suggesting a positive effect of acetylcholinesterase inhibitors in the treatment of delirium**

Burt 2000 [281]
Bruera, et al 2003 [282]
Dautzenberg, et al 2004 [236]
Fisher, et al 2001 [283]
Gleason 2003 [284]
Hasse and Rundshagen 2007 [285]
Hori, et al 2003 [286]
Kobayashi, et al 2004 [82]
Logan and Stewart 2007 [288]
Moretti, et al 2007 [266]
Palmer 2004 [289]
Rabinowitz 2002 [290]
Weizberg, et al 2006 [291]
Wengel, et al 1999 [293]
normal scored as 0, and severe verbal and physical agitation was scored as 4. After a subject was determined to be delirious, patients received a single IV dose of ondansetron (ie, 8 mg), and were re-evaluated 10 minutes later. Before the treatment, 7 subjects had a score of 2 (20%); 10 subjects had a score of 3 (28.6%); and 18 subjects had a score of 4 (51.4%). After the treatment, 28 subjects (80%) dropped their score to 0; 6 subjects (17.1%) dropped to a score of 1, and 1 subject (2.9%) remained at a score of 4. The mean score dropped from 3.20 plus or minus 1.01 to 0.29 plus or minus 0.75 after treatment. No adverse side effects were reported.

What about the treatment of hypoactive delirium?

This is a difficult aspect to discuss, as there is no available literature to guide us. As discussed above, most of these cases are unrecognized or misdiagnosed as depression. In either case, lack of recognition and treatment leads to the same poor outcomes previously described. Therefore, vigilance and screening, particularly in high-risk populations is imperative. Early intervention by specialized clinicians (eg, Psychosomatic Medicine Service or Geropsychiatric Service) has been shown to improve outcomes. Overall, several clinical principles apply: (1) prevention is key (see next section); (2) all other factors described above under nonpharmacologic approaches apply; (3) if pharmacologic agents are to be used, consider the least sedating available agents, such as haloperidol (for typical) or risperidone (for atypical). Furthermore, take into consideration the anticholinergic potential of the antipsychotic agent use (see Fig. 9). There may be reasons to consider use of nonantipsychotic agents (as described in the section above) to accelerate the rate of recovery and prevent further deterioration of cognitive status, but good controlled studies are lacking. Similarly, given the mechanism of delirium development, there may be a rationale for the use of very low doses of nonsedating antipsychotic agents (see the article by Maldonado titled, A Comprehensive Multifactorial Understanding of the Neurobiology of Delirium and an Evidence-based Approach to Prevention & Treatment, elsewhere in this issue). Similarly, the use of activating agents (eg, modafinil and psychostimulants) may help mobilize hypoactive patients, particularly to address extreme psychomotor retardation and extreme somnolence once all potential contributing pharmacologic agents (eg, sedatives, opioids) have been removed.

Prevention of delirium

As described above, there are many risks factors for the development of delirium. Controlling for some of these may better assist on delirium prevention. The majority of patients in the ICU, particularly those who are mechanically ventilated, receive some form of sedation to reduce anxiety, encourage sleep, and to increase tolerance to the critical care environment,
including multiple lines, pain management, endotracheal tubes, and ventilators. Sedative and analgesic drugs are among the most commonly prescribed medications in the ICU [239]. As discussed above (see etiology section), sedative agents (mostly GABAAergic) and opioids may contribute to the development of delirium by one of five mechanisms: (1) interfering with physiologic sleep patterns; (2) interfering with central cholinergic function; (3) increasing compensatory up-regulation of N-methyl D-aspartate and kainite receptors and Ca2+ channels; (4) disrupting the circadian rhythm of melatonin release; and (5) disrupting thalamic gating function. To try to prevent delirium altogether, Maldonado and colleagues [240] were the first to report on the use of novel agents as alternative sedation in order minimize delirium by avoid the use of benzodiazepines and related agents (eg, midazolam, propofol) during the postoperative state. Postcardiotomy patients were selected, given the high incidence of delirium in postcardiotomy patients (around 57%) nationwide [26].

In the final analysis, Maldonado and colleagues [241] studied patients (n = 118) undergoing cardiac surgery (ie, repair or replacement) with CPB. Intraoperative anesthesia for the surgical procedures was standardized for all subjects. All procedures were performed via median sternotomy in conjunction with CPB and induction of moderate hypothermia. After successful weaning from CPB, subjects were started on one of three randomly assigned, postoperative sedation regimens: dexmedetomidine, propofol, or midazolam. Upon arrival at the ICU, a standardized protocol for postoperative care was implemented for all subjects. Study results show there were no significant preoperative or intraoperative differences between treatment groups (eg, age, sex, American Society of Anesthesiologists classes, bypass time, clamp time, or lowest temperature achieved). The only real difference in management between groups was the type of postoperative sedation. Final results demonstrated an incidence of delirium of 3% (1 out of 30) for subjects on dexmedetomidine, 50% (15 out of 30) for propofol, and 50% (15 out of 30) for midazolam (P < .01) (Fig. 10). The absolute risk reduction in the incidence of delirium associated with using dexmedetomidine was 47% (95% CI, 28%–66%) corresponding to an NNT (number needed to treat) of 2.1 subjects (95% CI, 1.5–3.6). As in other studies, subjects who developed postoperative delirium experienced significantly longer intensive care stays (4.1 versus 1.9 days, P < .001) and longer total hospitalization (10.0 versus 7.1 days, P < .001) compared with subjects without delirium. The average age of subjects who developed delirium was significantly older than those who did not (64.9 ± 15.9 versus 52.9 ± 16.1 years, P < .001) (Table 7).

Even though previous reports have suggested that the cognitive decline observed after cardiac surgery could be attributed to the use of the CPB pump [110,242,243], Van Dijk and colleagues [244] found no difference in cognitive outcomes in cardiac patients operated with the aid of CPB and without (off-pump), suggesting that factors other than CPB may be responsible for cognitive decline after cardiac surgery. Maldonado and
colleagues [241] study results support this theory, and suggest that postoperative sedation, not the CPB, is an independent negative factor for mental status changes (ie, delirium) in cardiac surgery patients.

The investigators proposed at least two sets of theories used to explain the fact that patients in the dexmedetomidine group experienced a lower incidence of postoperative delirium [241]. The first theory suggests that dexmedetomidine has intrinsic “delirium-sparing effects.” Several specific characteristics of the drug may account for this effect. First, studies have suggested that the likelihood of delirium is increased with the number of neurotransmitter pathways disrupted [245–247]. Dexmedetomidine asserts its sedative effects by blocking a single neurotransmitter, norepinephrine, via \( \alpha_2 \)-adrenoceptor binding. The second characteristic is its effect in presynaptic noradrenergic transmission. Changes in the noradrenergic system have been described as potential causative factors in delirium, with increased levels of plasma free-MHPG (3-methoxy-4-hydrophenylglycol) concentration observed in some delirious states [246,248]. Third, dexmedetomidine produces sedation without respiratory depression [249]. Studies have demonstrated that hypoxia and anoxia in the central nervous system are critical events leading to the biomolecular derangements in delirium [245,250], while others [66] have reported lower postoperative oxygen saturation in postthoracotomy patients who developed delirium, compared with patients who did not develop delirium with the resolution of mental status changes after oxygen supplementation. Fourth, dexmedetomidine lacks clinically significant anticholinergic effects and, in fact, has some mild cholinergic activation [251]. A strong association has been documented between medications with anticholinergic potential and the development of delirium [86,88,90]. Fifth, several studies have suggested that postoperative sedation with dexmedetomidine has been associated with lower opioid requirements, an average of...
Table 7
Selected postoperative outcome variables for cardiac patients with cardiopulmonary bypass by intervention group

<table>
<thead>
<tr>
<th></th>
<th>Dexmedetomidine (n = 30)</th>
<th>Propofol (n = 30)</th>
<th>Midazolam (n = 30)</th>
<th>overall p-value</th>
<th>Dex versus propofol</th>
<th>Dex versus midazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of delirium (per protocol)</td>
<td>1/30 (3%)</td>
<td>15/30 (50%)</td>
<td>15/30 (50%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incidence of delirium (ITT)</td>
<td>4/40 (10%)</td>
<td>16/36 (44%)</td>
<td>17/40 (44%)</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>Number of days delirious</td>
<td>2/216 (1%)</td>
<td>45/276 (16%)</td>
<td>75/259 (29%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average length of delirium (days)</td>
<td>2.0 ± 0</td>
<td>3.0 ± 3.1</td>
<td>5.4 ± 6.6</td>
<td>0.82</td>
<td>0.93</td>
<td>0.63</td>
</tr>
<tr>
<td>Time variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU length of stay (days)</td>
<td>1.9 ± .9</td>
<td>3.0 ± 2.0</td>
<td>3.0 ± 3.0</td>
<td>0.11</td>
<td>0.14</td>
<td>0.14</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>7.1 ± 1.9</td>
<td>8.2 ± 3.8</td>
<td>8.9 ± 4.7</td>
<td>0.39</td>
<td>0.42</td>
<td>0.12</td>
</tr>
<tr>
<td>Intubation time (hours)</td>
<td>11.9 ± 4.5</td>
<td>11.1 ± 4.6</td>
<td>12.7 ± 8.5</td>
<td>0.64</td>
<td>0.91</td>
<td>0.34</td>
</tr>
<tr>
<td>As needed medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl (mcg)</td>
<td>320 ± 355</td>
<td>364 ± 320</td>
<td>1,088 ± 832</td>
<td>&lt;0.001</td>
<td>0.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total morphine equivalents (mg)</td>
<td>50.3 ± 38</td>
<td>51.6 ± 36</td>
<td>122.5 ± 84</td>
<td>&lt;0.001</td>
<td>0.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antiemetic use</td>
<td>15/30 (50%)</td>
<td>17/30 (57%)</td>
<td>19/30 (63%)</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>As needed medications for the management of delirium</td>
<td>1/30 (3%)</td>
<td>7/30 (23%)</td>
<td>6/30 (20%)</td>
<td>0.07</td>
<td>0.06</td>
<td>0.11</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0/30</td>
<td>3/30 (10%)</td>
<td>2/30 (7%)</td>
<td>0.23</td>
<td>0.07</td>
<td>0.15</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0/30</td>
<td>3/30 (10%)</td>
<td>2/30 (7%)</td>
<td>0.23</td>
<td>0.07</td>
<td>0.15</td>
</tr>
</tbody>
</table>

a Of patients who developed delirium.
b Sum of average morphine equivalents (fentanyl, oxycodone, and hydrocodone) received in postoperative days 1 to 3.
c Number of patients who received dolasetron mesylate or promethazine HCl in postoperative day 1.
d Average amount over 3 days. None of these medications were given until a diagnosis of delirium was established.

Data from Maldonado J, Wysong A, van der Starre PJA, et al. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. Accepted for publication, Psychosomatics 2008, in press; with permission.
40% lower [252,253]. This is significant, as studies have demonstrated a direct relationship between opiate use and development of delirium [254,255]. Sixth, dexmedetomidine is believed to promote a more physiologic sleep-wake cycle in the ICU setting [249,256]. This is important, as sleep deprivation and disruption have been implicated in the onset and perpetuation of delirium [166]. Finally, dexmedetomidine has been shown to have neuroprotective effects [257] in animal models of ischemia [258] and in human beings undergoing cardiac surgery [259].

The second theory suggests that the reason subjects had significantly less delirium in the dexmedetomidine group was not because of its use per se, but because those subjects were not exposed to other sedative agents with much greater delirium potential. As suggested by many others, GABAergic agents (ie, propofol, midazolam) have been implicated in the development of delirium. In fact, GABAergic medications and narcotics are among the factors associated with the onset and worsening of delirium [20,41,95,96], by interfering with physiologic sleep patterns and causing a centrally mediated acetylcholine deficient state, via interruption of central cholinergic muscarinic transmission at the level of the basal forebrain and hippocampus [95,97,245]. These may be mechanisms by which midazolam or propofol may contribute to higher rates of delirium [41,96]. Midazolam and propofol were specifically chosen as comparators, given these agents are customarily used in routine medical practice throughout critical and intensive care settings, and are both commonly used for postoperative sedation after cardiac surgery.

**Antipsychotic agents for prevention of delirium**

Antipsychotic agents have long been used for the treatment of the behavioral symptoms of delirium. Some suspect that they could be used to prevent delirium as well. At least one randomized, controlled trial addressed the issue of prophylactic haloperidol. In at-risk patients aged greater than 70 years, oral haloperidol 0.5 mg twice a day was administered from up to 72 hours preoperatively until the third postoperative day. The study found that prophylactic haloperidol use did not alter the incidence of postoperative delirium (15.1%) compared with placebo (16.5%; relative risk or RR 0.91; 95% CI, 0.59–1.44) [260].

On the other hand, in another study, elderly patients (n = 430) undergoing hip surgery were given 1.5-mg haloperidol per day or placebo, started preoperatively and continued for up to 3 days postoperatively [261]. Neuropsychiatric evaluations demonstrated that the overall incidence of postoperative delirium was 15.8%, but that subjects in the haloperidol group had a slightly lower incidence compared with placebo (15.1% versus 16.5%) (RR 0.91, 95% CI, 0.6–1.3); the mean highest DRS-R-98 score plus or minus SD was 14.4 plus or minus 3.4 and 18.4 plus or minus 4.3, respectively (mean difference 4.0, 95% CI, 2.0–5.8; P < .001); delirium duration was 5.4 versus 11.8 days, respectively (mean difference 6.4 days, 95% CI,
4.0–8.0; \( P < .001 \)); and the mean number of days in the hospital was 17.1 plus or minus 11.1 and 22.6 plus or minus 16.7, respectively (mean difference 5.5 days, 95% CI, 1.4–2.3; \( P < .001 \)). No haloperidol-related side effects were noted. Thus, the study suggests that although prophylactic treatment with low-dose haloperidol had no efficacy in reducing the incidence of postoperative delirium, it did have a positive effect on the severity and duration of delirium and shortened the length of hospital stay.

Prakanrattana and Prapaitrakool [262] conducted a randomized, double-blinded, placebo controlled trial (\( n = 126 \)) of patients undergoing cardiac surgery with CPB. Subjects were randomly assigned to receive either 1-mg risperidone or placebo sublingually when they regained consciousness (ie, immediately after surgery). They found that the incidence of postoperative delirium in the risperidone group was lower than the placebo group (11.1% versus 31.7% respectively, \( P = .009 \), RR 0.35, 95% CI, 0.16–0.77). A recently presented abstract reported a significant decreased in the incidence of postoperative delirium following orthopedic joint replacement surgery (\( n = 400 \)). The study compared olanzepine (5-mg Zydis formulation, administered just preoperatively, and 5 mg administered immediately after surgery upon awakening) to placebo. Researchers found the incidence of delirium in the intervention group was 15%, compared with 41% in the placebo-controlled group (\( P < .0001 \)) [263].

Acetylcholinesterase inhibitors in delirium prevention

Despite the logical premise behind the prophylactic use of acetylcholinesterase inhibitor agents, two studies have failed to demonstrate efficacy in the prevention of postoperative delirium. The first study was a randomized, double-blind, placebo-controlled trial involving elderly patients undergoing elective total joint replacement surgery (\( n = 80 \)) [264]. Each participant was evaluated before surgery and then received donepezil or placebo for 14 days before surgery and 14 days afterward. Delirium, diagnosed by DSM-IV criteria, was found in 18.8% of subjects, but there were no significant differences between the donepezil and placebo groups. Subsyndromal delirium was found in 68.8% of subjects, but again, there was no difference between groups.

A second study also failed to demonstrate efficacy of donepezil in preventing postoperative delirium after elective total hip replacement surgery in older people without pre-existing dementia (\( n = 33 \)) [265]. The investigators randomized (double-blind, placebo controlled) subjects to receive either placebo or donepezil (5 mg) immediately postoperatively and every 24 hours thereafter for the first 3 postoperative days, with no serious adverse events reported. The overall incidence of postoperative delirium was 21.2% in all subjects, but there was no significant difference between the groups. The unadjusted risk ratio (donepezil versus placebo) for delirium was 0.29 (95% CI, 0.06, 1.30). The mean length of hospital stay was 9.9 days for
the donepezil group versus 12.1 days in the placebo group; difference in means equals −2.2 days (95% CI, −0.39, 4.78).

There have been some positive trials involving other agents. A study of dementia patients \((n = 366)\) demonstrated that the chronic rivastigmine (a slowly reversible inhibitor of acetylcholinesterase and butyrylcholinesterase) group had a much lower incidence of delirium (45.5%), compared with the control group (88.9%) \((P < .05)\) [236]. Another study has also demonstrated a decrease in the occurrence and duration of delirium in elderly patients \((n = 246)\) suffering from vascular dementia [266]. Subjects were divided into two homogenous groups (matched for age and education levels): Group A received 3-mg to 6-mg rivastigmine per day, while Group B received 100-mg cardioaspirin per day. Both groups presented episodes of delirium, which occurred during a concomitant medical illness. During the follow-up period, the incidence of delirium was 40% in Group A versus 62% in group B \((P < .001)\). Moreover, the mean duration of the delirium was shorter in Group A (mean duration 4 ± 1.71 days) compared with Group B (7.86 ± 2.73 days; \(P < .01)\).

Other pharmacologic agents as prevention strategies

A randomized, double-blind study involving children \((n = 85)\) undergoing dental repair studied the effectiveness of ketamine (versus placebo) for the prevention of delirium in sevoflurane-induced anesthesia using the Pediatric Anesthesia Emergence Delirium scale. The study demonstrated a substantially lower incidence of emergence agitation in the ketamine group (16.6%) compared with the placebo group (34.2%). There was no difference in time to meet recovery room discharge criteria between the two groups [267].

Nonpharmacologic prevention strategies

Still, not all proposed prophylactic methods are pharmacologic. Inouye and colleagues [166] conducted a landmark study of hospitalized patients \((n = 852)\) and assessed for manifestations of delirium in response to the correction of environmental factors commonly associated with increased risk for delirium. The intervention consisted of simple techniques applied by the hospital staff, including reorientation, appropriate cognitive stimulation three times a day, the implementation of a nonpharmacologic sleep protocol to help normalize a patient’s sleep-wake cycle, early mobilization after surgery or extubation, timely removal of catheters and restraints, correction of sensory deficiencies (ie, eyeglasses and hearing aids), and early correction of dehydration and electrolyte abnormalities. As a result to these environmental manipulations, they observed an astonishing 40% reduction in odds for delirium (Fig. 11).

Another study looked at the effectiveness of proactive geriatric consultation compared with usual care (ie, control group) in reducing delirium in
a group of patients 65 and older \((n = 126)\) admitted emergently for surgical repair of hip fracture [114]. There were no statistical differences between intervention and control groups regarding baseline measures and characteristics. The results suggest a reduction in the occurrence of delirium in the intervention group (32%) compared with usual care (50%) \((P = .04)\), representing a relative risk of 0.64 (95% CI, 0.37–0.98) for the consultation group. One case of delirium was prevented for every 5.6 subjects in the geriatrics consultation group. There was an even greater reduction in cases of “severe delirium,” occurring in 12% of intervention subjects and 29% of usual-care subjects, with a relative risk of 0.40 (95% CI, 0.18–0.89). Despite this reduction in delirium, length of stay did not significantly differ between intervention and usual-care groups (median \(7/\text{C6} 2\) days in both groups), likely because protocols and pathways predeter-
mined length of stay.

Lundström and colleagues [268] randomly assigned elderly patients \((n = 190)\) after femoral neck fracture repair to postoperative care in a specialized geriatric ward (ie, intervention group) or a conventional orthopedic ward. The intervention consisted of staff education focusing on the assessment, prevention, and treatment of delirium and associated complications. As a result of the intervention, the number of days of postoperative delirium was fewer \((5.0 \pm 7.1\) days versus 10.2 \(\pm 13.3\) days, \(P = .009)\) compared with controls. A lower proportion of intervention subjects were delirious postoperatively than controls \((54.9\% \text{ versus } 75.3\%, P = .003)\). Similarly, subjects in the intervention group suffered from fewer complications (eg, decubitus ulcers, urinary tract infections, nutritional complications, sleeping problems, and falls). Overall, the total postoperative hospitalization was shorter in the intervention ward \((28.0 \pm 17.9\) days versus 38.0 \(\pm 40.6\) days, \(P = .028)\), suggesting that prevention methods can have a significant impact on

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Fig. 11. A multicomponent intervention to prevent delirium in hospitalized older patients. (From Inouye SK, Bogardus ST, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med. 1999;340(9):674; with permission. Copyright © 1999, Massachusetts Medical Society.)
postoperative delirium, resulting in fewer days of delirium, lower incidence of medical complications, and shorter length of hospitalization.

Others have studied the use of light therapy as a method of maintaining or restoring the natural circadian rhythm [269]. The investigators followed patients \(n = 11\) after esophageal cancer and after removal of the endotracheal tube. Subjects were either exposed to therapeutic lighting (ie, 5,000 lx at a distance from the light source of 100 cm; study group), or placed in a natural lighting environment (control group) after extubation. The study found that the incidence of delirium was 16% in the study group compared with 40% in the control group suggesting that alterations in circadian rhythm may serve as a possible contributor to the development of delirium. It also suggests that light therapy may serve as potential prophylaxis or treatment option.

Finally, a Cochrane database review study was conducted (searching the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group and searches in MEDLINE, EMBASE, CINAHL and PsycINFO for delirium prevention trials; searched on October 28, 2005) to assess the effectiveness of interventions for preventing delirium in hospitalized patients [270]. The final analysis included only six randomized, controlled trials. The researchers found there was heterogeneity in methods, participants, and outcomes examined. The investigators concluded that at the time of their search there was little evidence from delirium prevention studies to guide clinical practice. In summary, there was no trial evidence available on the effectiveness of pharmacologic strategies. Based on a single study, the investigators suggest that prophylactic low-dose haloperidol may reduce severity and duration of delirium episodes and shorten length of hospital admission in hip surgery, but that further studies of delirium prevention are needed. A study on the proactive use of geropsychiatric consultations showed favorable results in reducing the severity and duration of postoperative hip surgery.

**Summary**

Delirium is a neurobehavioral syndrome caused by the transient disruption of normal neuronal activity secondary to systemic disturbances. It is also the most common psychiatric syndrome found in the general hospital setting, its prevalence surpassing most commonly known psychiatric syndromes. In addition to causing distress to patients, families, and medical caregivers, the development of delirium in general, and postoperative delirium in particular, has been associated with increased morbidity and mortality, increased cost of care, increased hospital-acquired complications, poor functional and cognitive recovery, decreased quality of life, prolonged hospital stays, and increased placement in specialized intermediate and long term care facilities. Given increasing evidence that delirium is not always reversible and the many sequelae associated with its development, physicians must do everything possible to prevent its occurrence or shorten its
duration by recognizing its symptoms early, correcting underlying contributing causes, and using treatment strategies proven to help recover functional status.

References


[123] 'Never been the same since.' Delirium in older people might have permanent effects on the brain. Harv Health Lett 2007;32(6):4.


