Acute Brain Failure: Pathophysiology, Diagnosis, Management, and Sequelae of Delirium

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Acute Brain Failure

Pathophysiology, Diagnosis, Management, and Sequelae of Delirium

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KEYWORDS

• Delirium • Acute brain failure • Encephalopathy • Post-operative delirium
• ICU-psychosis • Neurotransmitter dysfunction • Network dysregulation
• Systems integration failure hypothesis

KEY POINTS

- Delirium is a neurobehavioral syndrome caused by the transient disruption of normal neuronal activity secondary to systemic disturbances.
- It is the most common neuropsychiatric syndrome found in the general hospital setting.
- In addition to causing distress to patients, families, and medical caregivers, the development of delirium 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.

EPIDEMIOLOGY OF DELIRIUM

Delirium is the most common neuropsychiatric syndrome found in the acute care setting, with a prevalence ranging from 10% in general medicine to 85% in advanced cancer and critical care (**Table 1**).[1–14] One study found that 89% of survivors of stupor or coma progressed to delirium.[15]

Risk Factors for Delirium

A systematic review among intensive care unit (ICU) patients revealed the following: age, dementia, hypertension, pre-ICU emergency surgery or trauma, Acute Physiology and Chronic Health Evaluation (APACHE) II score, mechanical ventilation, metabolic acidosis, delirium on the prior day, and coma as strong risk factors for delirium; whereas multiple organ failure was a moderate risk factor.[16,17] For every year after age 50, the chance of delirium increases by 10%.

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Table 1
A comparison of the incidence of psychiatric disorder in the general population and delirium among medically ill patients

Selected Medical Populations	Incidence of Delirium (%)
Medical Services	
At admission to inpatient medicine ward	10–31
New delirium: general medicine wards	3–29
HIV-AIDS	20–40
Poststroke	13–48
Medical: ICU	60–87
Sepsis	9–71
CCU	26
Surgical Services	
General surgical wards	11–46
Postoperative delirium	4.7–74
Post-CABG	13–32
Vascular surgery	22
Abdominal aneurysm repair	33
Orthopedic surgery	12–41
Postorthotopic liver transplant	45.2
Postcardiotomy	32–67
Critical Care Setting	
Coronary care units	26
Medical ICU	60–87
ARDS	70–73
Survivors of stupor or coma	Up to 89
Elderly	
In nursing homes	15–70
Delirium present at hospital admission	10.5–39
In-hospital delirium	15–31
Frail-elderly patients	Up to 60
Postsurgery	20–65
In Cancer Patients	
General prevalence	25–40
Hospitalized cancer patients	25–50
BMT	73
Terminally ill cancer patients	45–88

Abbreviations: AIDS, acquired immunodeficiency syndrome; ARDS, acute respiratory distress syndrome; BMT, bone marrow transplantation; CABG, coronary artery bypass grafting surgery; CCU, cardiac care unit; HIV, human immunodeficiency virus; ICU, intensive care unit.

The mnemonic END ACUTE BRAIN FAILURE encapsulates the many risk factors known to contribute to the development of delirium (Table 2).

Neuropathogenesis of Delirium

The various precipitants of delirium have been extensively reviewed elsewhere and are not fully discussed here (Fig. 1).[18] Whatever the proximate underlying cause, delirium is a neurobehavioral syndrome caused by an alteration in neurotransmitter synthesis, function,

Table 2
END ACUTE BRAIN FAILURE: predisposing and precipitating risk factors for delirium

Risk Factors	Examples
Electrolyte imbalance & dehydration	Electrolyte disturbances (eg, hyperammonemia, hypercalcemia, hypokalemia or hyperkalemia, hypomagnesemia, hyponatremia or hypernatremia)
Neurologic disorder & injury	All neurologic disorders: CNS malignancies, abscesses, CVA, intracranial bleed, meningitis, encephalitis, neoplasms, vasculitis, MS, epilepsy, Parkinson disease, NPH, TBI, DAI, paraneoplastic syndrome Of the various forms of sensory impairment, only visual impairment has been shown to contribute to delirium Visual impairment can increase the risk of delirium 3.5-fold
Deficiencies (nutritional)	Nutritional deficiencies (eg, malnutrition, low serum protein or albumin, low caloric intake, failure to thrive), malabsorption disorders (eg, celiac disease), and hypovitaminosis: specifically deficiencies in cobalamin (B12), folate (B9), niacin (B3, leading to pellagra), thiamine (B1, leading to beriberi & Wernicke disorder)
Age & gender	Age >65 y & gender male > female Old age is likely a contributor due to increased number of medical comorbidities: ↑ overall frailty, ↓ volume of ACH producing cells, ↓ cerebral oxidative metabolism, ↑ cognitive deficits, ↑ risk of dementia, ↑ age-related cerebral changes in stress-regulating neurotransmitter, intracellular signal transduction systems, chronic neurodegeneration with an increased production of inflammatory mediators, including cytokines and acute phase proteins
Cognition	Baseline cognitive deficits, even subtle ones, have been associated with an increased the risk of developing delirium The presence of dementia more than doubles the risk for postoperative delirium
U-Tox (intoxication & withdrawal)	Substance abuse: acute illicit substance intoxication (eg, cocaine, PCP, LSD, hallucinogens) and substance withdrawal, particularly abstinence syndromes from CNS-dep agents (eg, alcohol, benzodiazepines, muscle relaxants, opioids)
Trauma	Physical trauma & injury: heat stroke, hyperthermia, hypothermia, severe burns, surgical procedures
Endocrine disturbance	Endocrinopathies such as hyperadrenal or hypoadrenal corticoid, hyperglycemia or hypoglycemia, hyperthyroidism or hypothyroidism
Behavioral, psychiatric	Certain psychiatric diagnoses, including undue emotional distress, a history of alcohol and other substance abuse, and depression, schizophrenia, and bipolar disorder
Rx & other toxins	Several pharmacological agents have been identified as highly deliriogenic, including prescribed agents (eg, narcotics, GABA-ergic agents, steroids, sympathomimetics, dopamine agonists, immunosuppressant agents, some antiviral agents) & various OTC agents (eg, antihistaminic and anticholinergic substances), and polypharmacy Also consider the toxic effects of pharmacologic agents (eg, serotonin syndrome, neuroleptic malignant syndrome, anticholinergic states) and the deleterious effects of toxic levels of various therapeutic substances (eg, lithium, VPA, carbamazepine, immunosuppressant agents) Various toxins, including carbon dioxide & monoxide poisoning, solvents, heavy metals (eg, lead, manganese, mercury), insecticides, pesticides, poisons, biotoxins (animal poison), can also manifest with delirium

(*continued on next page*)

Table 2
(*continued*)

Risk Factors	Examples
Anemia, anoxia, hypoxia, & low perfusion states	Any state that may contribute to decreased oxygenation (eg, pulmonary or cardiac failure, hypotension, anemia, hypoperfusion, intraoperative complications, hypoxia, anoxia, carbon monoxide poisoning, shock)
Infections	Pneumonia, urinary tract infections, sepsis, encephalitis, meningitis, HIV/AIDS
Noxious stimuli (pain)	Data suggest that pain and medications used for the treatment of pain have been associated with the development of delirium Studies have demonstrated that the presence of postoperative pain is an independent predictor of delirium after surgery On the other hand, the use of opioid agents has been implicated in the development of delirium
Failure (organ)	End organ failure (eg, hepatic, cardiac, renal failure) may lead to a delirious state
APACHE score (severity of illness)	Evidence shows that the probability of transitioning to delirium increases dramatically for each additional point in the APACHE II severity of illness score
Isolation & immobility	Social isolation, decreased intellectual stimulation, physical immobility, and increased functional dependence (eg, requiring assistance for self-care and/or mobility)
Light, sleep, & circadian rhythm	Sleep deprivation, sleep disorders (eg, obstructive sleep apnea, narcolepsy), & disturbances in sleep-wake cycle
Uremia & other metabolic disorders	Acidosis, alkalosis, hyperammonemia, hypersensitivity reactions, glucose, acid-base disturbances
Restraints	The use of restraints, including endotracheal tubes (ventilator), soft and leather restraints, intravenous lines, bladder catheters, and intermittent pneumatic leg compression devices, casts, and traction devices all have been associated with an increased incidence of delirium
Emergence delirium	Emergence from medication-induced sedation, coma, or paralysis, which may be associated with CNS-dep withdrawal, opioid withdrawal, REM-rebound, sleep deprivation

Abbreviations: Ach, acetylcholine; APACHE, acute physiology and chronic health evaluation; CNS, central nervous system; CVA, cerebrovascular accident; DAI, diffuse axonal injury; GABA, gamma-Aminobutyric acid; LSD, Lysergic acid diethylamide; MS, multiple sclerosis; NPH, normal pressure hydrocephalus; OTC, over-the-counter; PCP, phencyclidine; REM, rapid eye movement; Rx, pharmacological agents; U-tox, urine toxicology test.

and/or availability, and a dysregulation of neuronal activity secondary to systemic disturbances that mediates the complex neurocognitive changes phenotypic manifestations.

Although many neurotransmitter systems have been implicated, the most commonly described changes associated with the development of delirium include deficiencies in acetylcholine (ACH) and/or melatonin (MEL) availability; excess in dopamine (DA), norepinephrine (NE), and/or glutamate (GLU) release; and variable alterations (eg, either a decreased or increased activity, depending on delirium presentation and cause) in 5-hydroxytryptamine or serotonin (5HT), histamine (His), and/or gamma-amino butyric acid (GABA) (**Table 3**).

A newly proposed theory, the Systems Integration Failure Hypothesis (SIFH), attempts to integrate and make sense of all previously described theories.[18] The SIFH

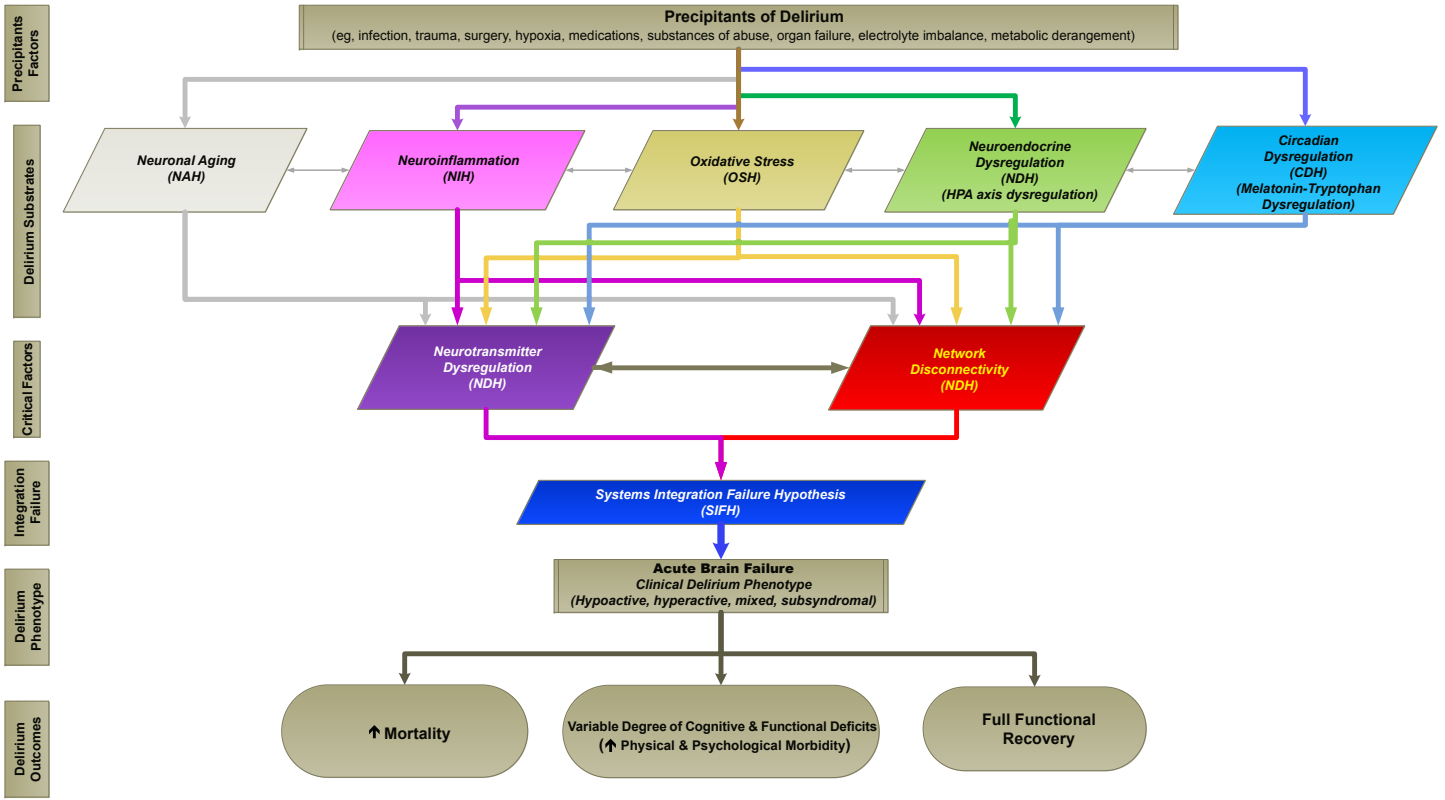

Fig. 1. Pathophysiology of delirium. (*Data from* Maldonado J. Delirium pathophysiology: current understanding of the neurobiology of acute brain failure. Int J Geriatr Psychiatry, in press.)

Table 3
Theorized neurochemical mechanisms associated with conditions leading to delirium

Delirium Source	ACH	DA	GLU	GABA	5HT	NE	Trp	MEL	Phe	His	Cytok	HPA Axis	Cort	NMDA activity	RBF Δ	Inflam	EEG
Anoxia or hypoxia	↓	↑	↑	↑	↓	↓	⇔	↓	↑	↑↓	⫫↑	⫫	↑	↑	⫫	↑	↓
Aging	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	⫫↑	⫫	↑	↓	⫫	↑	↓
TBI	↑	↑	↑	↑	↑	↑	↑	↓	↑	↓	↑⫫	↑	↑	↑	↑	↑⫫	↓
CVA	↓	↑	↑	↑	↑	↑	↑	↓	↑	↓	↑⫫	↑	↑	↑	⫫	↑⫫	↓
Hepatic encephalopathy	⇔	↓	↑	↑↑	↑	↓	↑	↓	↑	↑	↑⫫	⫫	↑	↑	⫫	↑	↓
Sleep deprivation	↓	↓	⫫	↑	↑	↑	↓	↓⫫	↑	↑	↑	⫫	↑	↑	↑	↑⫫	↓
Trauma, Sx, & Postoperative	↓	↑	↑	↑	↓	↑	↓	↓	↑	↑	↑	↑	↑	↑	⫫	↑	↓
ETOH & CNS-Dep withdrawal	↑	↑	↑	↓	↑	↑	↓	↓	↑	↑	↑	↑⫫	↑	↑	↓	↑	↑
Infection or sepsis	↓	↓	↑	↑	↓	↓	↓	↓	↓	↓	↑	↑⫫	↑	↑⫫	⫫	↑	↓
Dehydration & electrolyte imbalance	⇔	↑	↑	↑	↓	↑	?	↓	?	↑	↑	⫫	↑	↑	↓	⫫↑	⫫
Medical illness	↓	↑	↑	⫫	↓	↑	↓	↓	↑	↑	↑	↓	↑	↑	⫫	⫫	⫫

Abbreviations: (–), likely not to be a contributing factor; ⇔, no significant changes; (⫫), likely a contributor, exact mechanism is unclear; ↑, likely to be increased or activated; ↓, likely to be decreased; Cort, cortisol; Cytok, cytokine; EEG, electroencephalograph; ETOH, alcohol; GABA, gamma-aminobutyric acid; His, histamine; HPA axis, hypothalamic-pituitary-adrenocortical axis; Inflam, inflammation; NMDA, N-methyl-D-aspartic acid; Phe, phenylalanine; RBF, regional blood flow; Sx, surgery; Trp, tryptophan.

Data from Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. Am J Geriatr Psychiatry 2013;21:1190–222; and Maldonado J. Delirium pathophysiology: current understanding of the neurobiology of acute brain failure. Int J Geriatr Psychiatry, in press.

proposes that the specific combination of neurotransmitter dysfunction and the variability in integration and appropriate processing of sensory information and motor responses, as well as the degree of breakdown in network connectivity within the brain, directly contributes to the delirium phenotype observed (see Fig. 1).

Clinical Presentation of Delirium

Delirium is an organic mental syndrome characterized by disturbance in attention (ie, reduced ability to direct, focus, sustain, and shift attention) and awareness, with impaired orientation to the environment (criterion A); with additional disturbances in cognition (eg, memory deficit, disorientation), language, visuospatial ability, or perception (eg, hallucinations or delusions; criterion C).[19]

The author suggests there are 5 core domains of delirium: (1) cognitive deficits (characterized by perceptual distortions, impairment in memory, abstract thinking and comprehension, executive dysfunction, and disorientation), (2) attentional deficits (characterized by disturbances in consciousness and a reduced ability to direct, focus, sustain and shift attention), (3) circadian rhythm dysregulation (characterized by fragmentation of the sleep–wake cycle), (4) emotional dysregulation (characterized by perplexity, fear, anxiety, irritability and/or anger), and (5) psychomotor dysregulation (which confers the various phenotypic presentations) (Fig. 2).

Delirium Phenotypes

The clinical features of delirium include a prodromal phase, usually marked by restlessness, anxiety, irritability, and sleep disturbances, which usually develop over a period of hours to days.

There are 5 delirium phenotypes: (1) the subsyndromal type (often under-recognized because it usually is associated with only partial diagnostic criteria); (2) the hypoactive

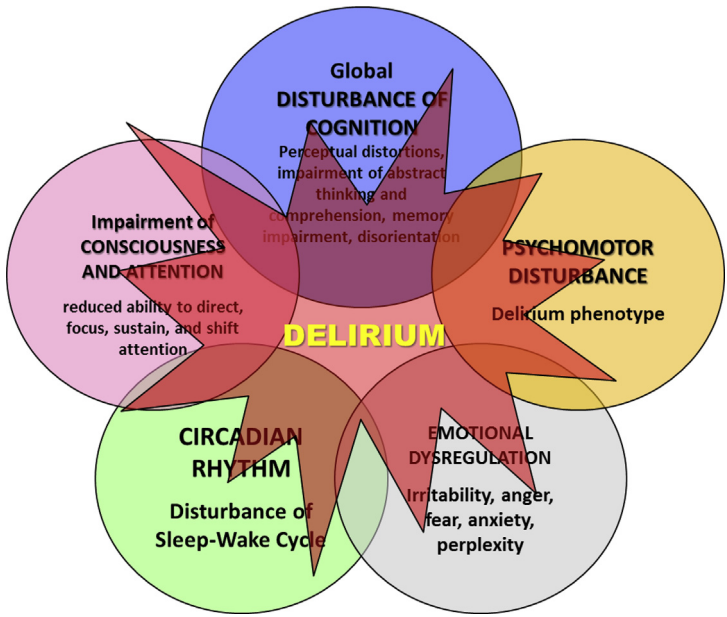

Fig. 2. Delirium core diagnostic characteristics.

delirium and its extreme, the catatonic subtype; (3) the hyperactive delirium and its extreme, the excited subtype; (4) and the mixed type, which often exhibits alternating characteristics of both hypoactive and hyperactive types, and likely gave rise to the classic description of delirium as waxing and waning in nature; and (5) the protracted or persistent type (Fig. 3). The progression or evolution of the syndrome can be best depicted in Fig. 4.

Subsyndromal delirium (SSD) represents an incomplete presentation of the diagnostic criteria, along with cognitive impairment. Available data suggest that medically ill patients with SSD experienced longer ICU length of stay and longer overall hospital stay, lower cognitive and functional outcomes, and increased postdischarge mortality.[20,21] In addition, patients with SSD have the same set of risk factors and experience similar outcomes as patients experiencing *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-defined delirium.[22] Conversely, patients with no delirium are more likely to be discharged home and less likely to need convalescence or long-term care than those with SSD.[23]

Though the DSM suggests delirium is an acute and transient syndrome, chronic forms may be seen in several scenarios, such as those with baseline cognitive impairment or experiencing delirium as sequelae to new intracranial processes, or the effects of acute substance intoxication or withdrawal.

Diagnosing Delirium

Despite its high prevalence, delirium remains unrecognized by most ICU clinicians in as many as 66% to 84% of patients,[24,25] likely due to difficulty at making an accurate diagnosis at the extreme of symptom presentation (Fig. 5). Vigilance and a high level of suspicion may be the most important tools for the timely diagnosis of delirium, particularly in patients at higher risk, such as those in the ICU.

The DSM-5 (Box 1)[19] and the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10)[26] (Box 2) are considered the diagnostic gold standards. There are many validated instruments to assist clinicians screen for the presence of delirium (Box 3), including an assessment for the re-emergence of pathologic primitive signs (Box 4). Newer surveillance and diagnostic tools include the Rapid Assessment Test for Delirium (4AT) (90% sensitive and 84% specific)[27] and the Stanford-Proxy Test for Delirium (S-PTD; 79% sensitivity and 90.8% specificity; using a cutoff score of 4).[28]

MANAGEMENT OF DELIRIUM

In general, the management of delirium includes the following steps: (1) knowledge and management of known delirium risk factors, (2) the implementation of prevention strategies (both pharmacologic and nonpharmacological) in an attempt to minimize the risk, (3) surveillance and accurate diagnosis of delirium (eg, hypoactive delirium vs depression, hyperactive delirium vs alcohol withdrawal or drug intoxication), (4) management of the behavioral and psychiatric manifestations and symptoms of delirium to prevent the patient from self-harm or harming of others, (5) identification of the etiologic causes of delirium, and (6) treatment of underlying medical problems. It is unclear whether (7) the pharmacologic manipulation to restore chemical balance and brain connectivity is of long-term usefulness and/or can mitigate the negative long-term effects of delirium.

A summary of the Stanford's Delirium Prevention and Management Model can be found in Box 5. The Stanford University ICU Delirium Management Protocol is shown in Fig. 6.

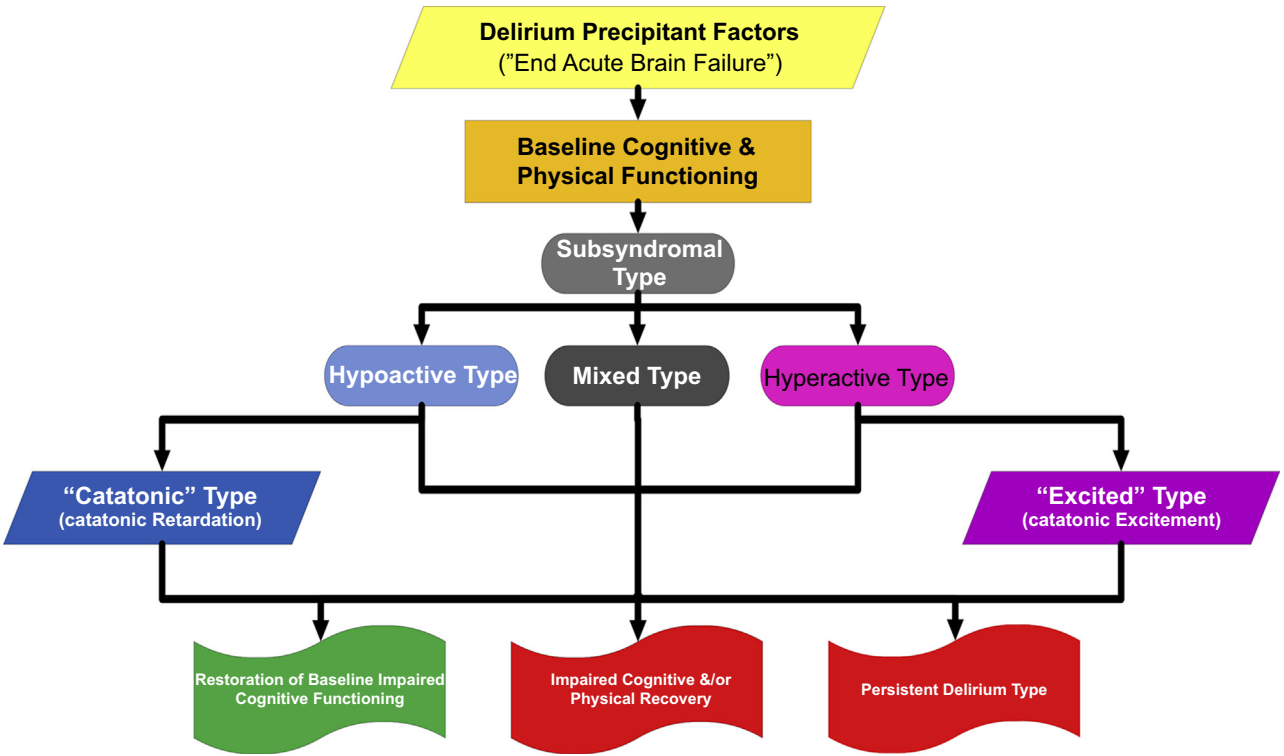

Fig. 3. Delirium phenotypes and clinical outcomes.

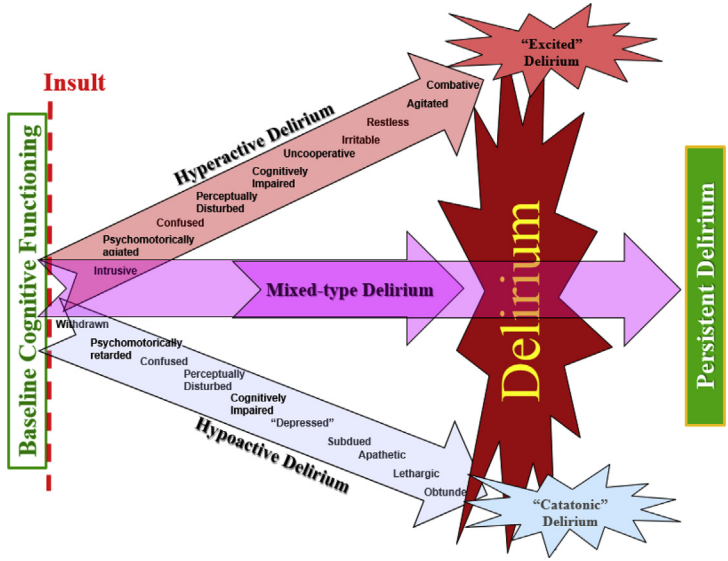

Fig. 4. Delirium phenotypes, symptom progression.

DELIRIUM PREVENTION STRATEGIES

Delirium has been listed as 1 of the 6 most common preventable conditions among hospitalized elderly patients.[58] Given the significant negative consequences of delirium, including worsening medical and cognitive outcomes, its prevention is of utmost importance.

Nonpharmacologic Management Strategies

The routine use of assessment scales or diagnostic interviews by properly trained personnel is paramount for the prevention and timely initiation of treatment. It is imperative to conduct a search for possible causes and conduct all appropriate diagnostic

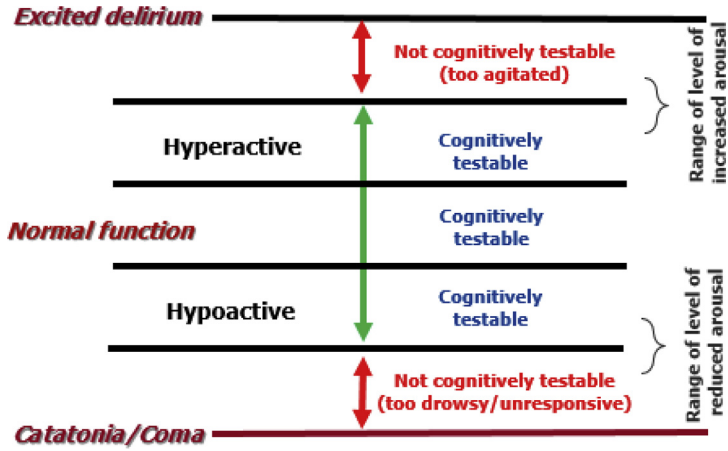

Fig. 5. Delirium phenotype diagnostic range.

Box 1
***Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, diagnostic criteria for delirium**

1. Disturbance in attention (ie, reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
2. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
3. An additional disturbance in cognition (eg, memory deficit, disorientation), language, visuospatial ability, or perception that is not better explained by a preexisting, established, or other evolving neurocognitive disorder.
4. The disturbances in Criteria 1 and 3 are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.
5. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the physiologic consequence of another medical condition, substance intoxication or withdrawal (ie, due to a drug of abuse or to a medication), or a toxin exposure, or is due to multiple causes.

Data from American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th edition. Washington, DC: American Psychiatric Association; 2013.

tests. Correct malnutrition, dehydration, and electrolyte abnormalities as quickly and safely as possible. Conduct an inventory of all pharmacologic agents and discontinue any medication known to cause delirium or have high anticholinergic potential. Prompt restoration of a circadian rhythm should be attempted, preferably by

Box 2
***International Statistical Classification of Diseases and Related Health Problems*, 10th edition, diagnostic criteria for delirium**

For a definite diagnosis, symptoms, mild or severe, should be present in each of the following areas:

1. Impairment of consciousness and attention (on a continuum from clouding to coma; reduced ability to direct, focus, sustain, and shift attention).
2. Global disturbance of cognition (perceptual distortions, illusions and hallucinations, most often visual; impairment of abstract thinking and comprehension, with or without transient delusions but typically with some degree of incoherence; impairment of immediate recall and of recent memory but with relatively intact remote memory; disorientation for time as well as, in more severe cases, for place and person).
3. Psychomotor disturbances (hypoactivity or hyperactivity and unpredictable shifts from 1 to the other, increased reaction time, increased or decreased flow of speech, enhanced startle reaction).
4. Disturbance of the sleep-wake cycle (insomnia or, in severe cases, total sleep loss or reversal of the sleep-wake cycle; daytime drowsiness; nocturnal worsening of symptoms; disturbing dreams or nightmares, which may continue as hallucinations after awakening).
5. Emotional disturbances, for example, depression, anxiety or fear, irritability, euphoria, apathy, or wondering perplexity.

Data from World Health Organization. The International Statistical Classification of Diseases and Related Health Problems (ICD-10): classification of mental and behavioural disorders. Geneva (Switzerland); World Health Organization: 1992.

Box 3
Objectives measures for the diagnosis of delirium (in order of development)

- DSM-II, gold standard[29]
  - Short Portable Mental Status Questionnaire (SPMSQ)[30]
- DSM-III gold standard[31]
  - Delirium Rating Scale (DRS)[32]
  - Confusion Assessment Method (CAM)[33]
  - Delirium Symptom Interview (DSI)[34]
- DSM-IV-TR, gold standard[35]
  - Delirium Assessment Scale (DAS)[36]
  - Cognitive Test for Delirium (CTD)[37]
  - Neelon and Champagne (NEECHAM) Confusion Scale[38]
  - Confusional State Evaluation (CSE)[39]
  - Memorial Delirium Assessment Scale (MDAS)[40]
  - Delirium Index (DI)[41]
  - Delirium Severity Scale (DSS)[42]
  - Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[10]
  - DRS, revised-98[43]
  - Delirium Detection Score (DDS)[44]
  - Delirium Detection Tool-Provisional (DDT-Pro) (Kean, Trzepacz and colleagues 2010)[205]
  - Brief Confusion Assessment Method (bCAM)[45]
  - 4AT[27]
- DSM-V (gold standard; APA 2014)
  - Stanford Proxy Test for Delirium (S-PTD)[28]

Tests for the Prediction of Delirium

- The Early Prediction (E-PRE-DELIRIC) model for delirium in ICU patients[46]
- Stanford's Algorithm for Predicting Delirium (SAPD)[47]

Brief Tests of Cognitive Functioning

- Mini-Mental State Examination (MMSE)[48]
- Modified Mini-Mental State Examination (3MS)[49]
- Trail-Making, A and B[50]

nonpharmacological means. Immobilizing lines and devices (eg, chest tubes, intravenous [IV] lines, bladder catheters) and physical restraints should be removed as early as possible. Correction of sensory deficits should be undertaken. Environmental isolation should be minimized, if possible. Family members and loved ones should be educated regarding the nature of delirium and how to assist in the patient's recovery, while encouraged to visit and provide a familiar and friendly environment, as well as provide appropriate orientation and stimulation.

A multicomponent approach, targeting identified, treatable, contributing factors may significantly decrease the risk of developing delirium, especially among populations at risk.[59,60] The awakening and breathing coordination, delirium prevention and management, and early physical mobility (ABCDE) bundle incorporates multidisciplinary measures to improve and/or preserve patients' function and neurocognitive status. Implementation of the ABCDE bundle was associated with a significant decrease in ICU delirium prevalence and the mean number of delirium days.[61]

The 2013 ICU pain, agitation, and delirium (PAD) guidelines were developed to provide a clear, evidence-based road map for clinicians to better manage PAD in critically ill patients. Strong evidence indicates that linking PAD management strategies with ventilator

Box 4
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 1 tap per second. A pathologic response is either absence of blink, no habituation, or a shower of blinks. Normal response is 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 knuckles between the patient's lips. A positive response is 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: the examiner tests 1 hand for sequential finger movements, and the fingers of the other hand wiggle or tap. Also, test for choreiform movements.
- Double simultaneous stimulation discrimination: test with the patients eyes closed. The examiner simultaneously brushes a finger against 1 of the patient's cheeks and another finger against 1 of the patient's hands, asking the patient where he or she has been touched.

weaning, early mobility, and sleep hygiene in ICU patients resulted in significant synergistic benefits to patient care and reductions in costs.[62] Similarly, among mechanically ventilated subjects (n = 187), implementation of the ABCDE bundle was associated with earlier extubation, reduction in delirium odds, and increased odds of mobilizing out of bed.[63] **Table 4** contains a comprehensive review of all published data on the use of nonpharmacological approaches to the management of delirium.

Environmental Manipulations

Implementation of an environmental noise and light reduction program has been effective in reducing sleep deprivation and delirium.[71] A prospective, quality improvement project of medical ICU (MICU) patients incorporated evidence-based nonpharmacologic bundled interventions along with nursing education, resulting in significant reductions in the percentage of time spent delirious while reducing the risk of future delirium development.[72]

Physical and Occupational Therapy

Occupational therapy has been an effective, nonpharmacological intervention in decreasing the duration and incidence of delirium among nonventilated, elderly ICU

Box 5
Algorithm for the prevention and management of delirium

I. Recognition of patients at risk
  A. A particular patient's odds of developing delirium are associated with the interaction between the following conditions:
    1. Knowledge of a patient's characteristic (eg, patient's age, sex, baseline cognitive status, previous experiencing of delirium when exposed to medical illness or treatment)
    2. Predisposing and precipitating medical risk factors (END ACUTE BRAIN FAILURE)
    3. Consider the use of the Stanford's Algorithm for Predicting Delirium (SAPD)[47]
    4. Modifiable and nonmodifiable risk factors for that particular patient or patient population

Modifiable Factors	Nonmodifiable Factors
• Various pharmacologic agents, especially GABA-ergic and opioid agents, and medications with anticholinergic effects • Prolonged and/or uninterrupted sedation • Immobility • Acute substance intoxication • Substance withdrawal states • Use of physical restraints • Water and electrolyte imbalances • Nutritional deficiencies • Metabolic disturbances and endocrinopathies (primarily deficiency or excess of cortisol) • Poor oxygenation states (eg, hypoperfusion, hypoxemia, anemia) • Disruption of the sleep-wake cycle • Uncontrolled pain • Emergence delirium	• Older age • Baseline cognitive impairment • Severity of underlying medical illness • Pre-existing mental disorders

    5. Exposure to specific medical conditions and surgical procedures
  B. Obtaining the patient's baseline level of cognitive functioning using information from accessory sources (eg, Informant questionnaire on cognitive decline in the elderly [IQCODE])

II. Implementation of prevention strategies
  A. A key focus should be placed on prevention strategies, particularly in at-risk populations
  B. Minimize the use of pharmacologic agents that may contribute or worsen delirium
    1. If possible, avoid all pharmacologic agents with high deliriogenic potential or anticholinergic load
    2. If possible, avoid using GABA-ergic agents to control agitation
      a. Exceptions: cases of central nervous system-depressant withdrawal (ie, alcohol, benzodiazepines, barbiturates) or when more appropriate agents have failed and sedations are needed, benzodiazepine-sparing protocol to prevent patient harm
      b. An alternative is the use of the benzodiazepine-sparing protocol developed at Stanford University[51]
      c. Avoid the use of opioid agents for management of agitation
  C. Improve sleep-wake cycle and restore normal circadian rhythm
    1. Use nonpharmacological methods to promote a more natural sleep-wake cycle; that is, light control (ie, lights on and curtains drawn during the day, off at night) and noise control (ie, provide ear plugs and sleep masks, turn off TVs, and minimize night staff chatter)
    2. Provide as much natural light as possible during the daytime
  D. Implement early mobilization techniques, to include all of the following components
    1. Daily awakening protocols (sedation holiday)
    2. Remove intravenous (IV) lines, bladder catheters, physical restraints, and any other immobilizing apparatuses as early as possible
    3. Begin aggressive physical therapy (PT) and occupational therapy (OT) as soon as it is medically safe to do

4. In bedridden patients, this may be limited to daily passive range of motion
5. Once medically stable, get the patient up and moving as early as possible
6. Provide patients with any required sensory aids (ie, eyeglasses, hearing aids)

E. Provide adequate intellectual and environmental stimulation as early as possible
F. Adequately assess and treat pain
   1. Yet, avoid the use of opioid agents for behavioral control of agitation
   2. Rotate opioid agents from morphine to hydromorphone or fentanyl
G. For patients in the ICU, especially those on ventilation or IV sedation, consider
   1. Sedating to a prescribed or target sedation level (eg, RASS range between −2 to +1)
   2. Using the sedative agent with lowest deliriogenic potential
      a. Dexmedetomidine use is associated with the lowest incidence of delirium
      b. Propofol use is a good second choice, followed by midazolam
H. Reassess pain levels daily and titrate opioid agents to the lowest effective required to maintain adequate analgesia
   1. Hydromorphone is preferred as baseline agent of choice for pain management
   2. Limit the use of fentanyl for rapid initiation of analgesia and as rescue agent
   3. Avoid the use of opioid agents for sedation or management of agitation or delirium
I. Provide daily sedation holidays, if possible, this includes
   1. Interrupt sedative infusions daily until the patient is awake
   2. Restart sedation, if needed, at the lowest effective dose
   3. Reassess target sedation level (eg, RASS).
J. Use nonpharmacologic delirium prevention protocols. Three studies have demonstrated significant reduction in the incidence of delirium:
   1. The Hospital Elder Life Program (HELP), which has demonstrated a reduction in the occurrence of delirium from 50% (in the usual care group) to 32% (in the intervention group), in a cohort of hip fracture repair subjects. In this study, the length of stay did not significantly differ between intervention and usual-care groups.
   2. A study was done on the use of preemptive delirium expert consultants and implementation of nonpharmacological protocols after femoral neck fracture repair with a reduction in the incidence of delirium from 75.3% (in control group) down to 54.9% (in the intervention group), with a concomitant reduction in length of stay and postoperative complications.[70]
   3. A study was done on the use of artificial light therapy as a way to prevent alterations in circadian rhythm (ie, 5000 lux, at a distance from the light source of 100 cm) was found to be superior to natural lighting environment (control group) in preventing delirium after esophageal cancer surgery (16% vs 40%).[70]
K. Consider one of the following pharmacologic prevention strategies:
   1. Better anesthetic choices
      a. Alpha-2 agonist agents: The use of dexmedetomidine, instead of conventional GABA-ergic agents (ie, propofol, midazolam) has been demonstrated to lead to a significant reduction in the incidence of delirium in postoperative patients (3% vs 50%) when compared with midazolam and propofol[52]
      b. A systematic review and meta-analysis revealed that sedation with dexmedetomidine was associated with less delirium compared with sedation produced by conventional GABA-ergic agents (ie, midazolam, propofol; pooled risk ratio 0.39, 95% CI 0.16–0.95).[53]
   2. Dopamine antagonist agents
      a. Several studies have demonstrated the benefits of typical and second-generation antipsychotics (SGAs) in delirium prevention:
         i. Two recent meta-analyses of studies using dopamine antagonist agents for delirium prophylaxis found that pooled relative risk of published studies suggested a 50% reduction in the relative risk of delirium among those receiving antipsychotic medication compared with placebo ($P<.01$).[54,55]
         ii. A third meta-analysis demonstrated that both typical and second generation antipsychotics decreased delirium occurrence when compared with placebos.[53]
         iii. The studies suggest that perioperative use of prophylactic dopamine antagonist agents (both typical and second generation antipsychotics), when compared with placebo (PBO), may effectively reduce the overall risk of postoperative delirium, thereby potentially reducing mortality, disease burden, length of hospital stay, and associated health care costs.

3. Melatonin or melatonin-agonists
   a. Melatonin (eg, 3 mg every 2000) or melatonin agonists (eg, ramelteon 8 mg every 2000) to help promote a more natural sleep and prevention of all types of delirium
   b. If that is ineffective, consider trazodone (eg, 25–100 mg every 2000) or mirtazapine (eg, 3.75–7.5 mg every 2000)
4. Acetylcholinesterase inhibitors
   a. Early studies suggested that the use of rivastigmine was associated with a significantly lower incidence of delirium compared with controls, among patients with dementia (ie, 45.5 vs 88.9% and 40 vs 62%, respectively)
   b. Donepezil has also been described as effective
5. Ketamine use
   a. At least 1 study found that the use of ketamine may decrease the incidence of emergence agitation and delirium in pediatric subjects undergoing dental repair under general anesthesia

III. Enhanced surveillance, screening and early detection
   A. The most important aspect in this stage is surveillance
      1. Knowledge about the condition and presenting symptoms
      2. A high level of suspicion for patients at risk
   B. Be vigilant for the development of delirium in high risk groups
      1. Use a standardized surveillance tool (eg, CAM, CAM-ICU, Intensive Care Delirium Screening Checklist (ICDSC), 4-AT, MDAS, S-PTD)
      2. Use psychiatric consultants (ie, DSM-5 or ICD-10 criteria)
      3. Be particularly aware of the presence of hypoactive delirium and its different manifestations
   C. Use psychiatric consultants to help with assessment and design of the treatment plan, if available
   D. Train medical personnel at all levels regarding the prevalence and symptoms of delirium and its subsyndromal presentations, and on the use of screening tools

IV. Management of delirium
   A. Nonpharmacological treatment of all forms of delirium
      1. Identify and treat underlying medical causes
         a. Treatment or correction of underlying medical problems and potential reversible factors
         b. The definitive treatment of delirium is the accurate identification and timely treatment of its underlying causes
         c. Malnutrition, dehydration, and electrolyte abnormalities, if present, should be corrected as quickly and safely as possible
      2. Conduct an inventory of all pharmacologic agents administered to the patient
         a. Any medication or agent known to cause delirium or to have high anticholinergic potential should be discontinued, if possible, or a suitable alternative instituted
      3. Implement early mobilization techniques should include all of the following components
         a. Daily awakening protocols or sedation holiday
         b. Remove IV lines, bladder catheters, physical restraints and any other immobilizing apparatuses as early as possible
         c. Aggressive PT and OT as soon as medically safe
            i. In bedridden patients, this may be limited to daily passive range of motion
            ii. Once medically stable, get the patient up and moving as early as possible
         d. Provide patient with any required sensory aids (ie, eyeglasses, hearing aids)
         e. Promote as normal a circadian light rhythm as possible
            i. Better if this can be achieved by environmental manipulations, such as light control (ie, lights on and curtains drawn during the day, off at night) and noise control (ie, provide ear plugs, turn off television, and minimize night staff chatter)
            ii. Provide as much natural light as possible during the daytime
         f. Provide adequate intellectual and environmental stimulation as early as possible
            i. Minimize environmental isolation
      4. If possible, avoid using GABA-ergic agents to control agitation
         a. Exception: cases of CNS-depressant withdrawal (ie, alcohol, benzodiazepines, and barbiturates) or when more appropriate agents have failed and sedations are needed to prevent patient's harm

   b. An alternative is the use of the benzodiazepine-sparing protocol developed at Stanford University[51]
5. Adequately assess and treat pain
   a. Yet, avoid the use of opioid agents for behavioral control of agitation
   b. Rotate opioid agents from morphine to hydromorphone or fentanyl
6. The British National Institute for Health and Clinical Excellence (NICE) provided a set of guidelines for the prevention of delirium in elderly at-risk patients, mostly based on the correction of modifiable of factors and the implementation of the multicomponent intervention package[56] (full version of these recommendations available at http://guidance.nice.org.uk/CG103/Guidance/pdf/English)

B. For pharmacologic treatment of delirium (all types), consider using
1. Dopamine antagonists to manage 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
   a. A systematic literature review of 28 delirium treatment studies with antipsychotic agents concluded (1) that around 75% of delirious patients who receive short-term treatment with low-dose antipsychotics experience clinical response, (2) that this response rates seem quite consistent across different patient groups and treatment settings, (3) that evidence does not indicate major differences in response rates between clinical subtypes of delirium, and (4) that there is no significant differences in efficacy for haloperidol versus atypical agent[57]
   b. The dose of dopamine antagonist use may depend on the type of delirium being treated
2. Acetylcholinesterase inhibitor (eg, rivastigmine, donepezil) for patients with a history of recurrent delirium or delirium superimposed on known cognitive deficits
   a. Initial data seem rather promising but more recent studies have been unable to replicate original findings, probably because of the time needed to observe clinically significant effects. At least 1 study suggested an increased mortality associated with the use of these agents
   b. Physostigmine, a reversible acetylcholinesterase inhibitor, has been suggested as first-line treatment for the management of the central anticholinergic syndrome and antimuscarinic delirium
3. Melatonin (eg, 6 mg every HS) or melatonin agonists (eg, ramelteon 8 mg every HS) to help promote a more natural sleep and management of all types of delirium
   a. If that is ineffective, consider trazodone (eg, 25–100 mg every HS) or mirtazapine (eg, 3.75–7.5 mg every HS)

C. Pharmacologic treatment of hyperactive delirium, consider the use of the following agents (in addition to IV-A)
1. Dopamine antagonist agents to address DA excess (eg, haloperidol, risperidone, quetiapine, aripiprazole)
   a. Moderate-dose haloperidol (eg, 5–30 mg/24 h, in divided doses) is still considered the treatment of choice if the patient's cardiac condition allows it and there are no significant electrolyte abnormalities.
   b. No study has demonstrated any other agent to be clinically superior, or safer than haloperidol
   c. When the use of haloperidol is contraindicated or not desirable, atypical antipsychotics should be considered
      i. Better evidence for risperidone (as a nonsedating agent, T1/2 = 20 hours), quetiapine (for a sedating agent; T1/2 = 7 hours)
      ii. There are limited data for olanzapine (concerns include: sedation, anticholinergic potential and long T1/2 > 50 h), aripiprazole as nonsedating agent especially for cases of hypoactive delirium (slow onset of action, T1/2 = 75 hours), lurasidone as a sedating agent (T1/2 = 18 hours), and paliperidone as a sedating agent (T1/2 = 23 hours)
      iii. Avoid clozapine and ziprasidone

   Before using antipsychotic agents
      i. Obtain 12-lead electrocardiogram (ECG) and measure QTc
      ii. Check electrolytes, correct potassium (K) and magnesium (Mg), if needed
      iii. Carefully review the patient's medication list and identify any other agents with the ability to prolong QTc

iv. If possible, avoid other medications known to increase QTc and/or inhibitors of CPY3A4
v. Discontinue dopamine antagonist agents use if QTc increases to greater than 25% of baseline or greater than 500 msec

2. Alpha-2 agonists (eg, dexmedetomidine, clonidine, guanfacine), for protection against the acute NE released secondary to hypoxia or ischemia, leads to further neuronal injury and the development of worsening of delirium
   a. Consider changing primary sedative agents from GABA-ergic agents (eg, propofol or midazolam) to an alpha-2 agent (eg, dexmedetomidine), starting at 0.4 mcg/kg/h, then, titrate dose every 20 minutes to targeted RASS goal
   b. In non-ICU patients, guanfacine is an excellent alternative (dose range from 0.5–3 mg/D in divided doses)
   c. Clonidine is also an alternative, especially to wean patients off dexmedetomidine but the main limiting factor is its hypotensive effect
3. Anticonvulsant and other agents with glutamate antagonism or calcium channel (Ca2+) modulation (eg, valproic acid [VPA], gabapentin, amantadine, memantine)
   a. VPA (either by mouth or IV) is increasingly used in the management of agitated delirious patients who either are not responsive or cannot tolerate conventional treatment, yet there are very little data regarding its effectiveness, which is limited to case series; the author recommends its use for the management of hyperactive or agitated delirium not responding the use of dopamine antagonist agents and adequate sedation, agitation occurring in the context of weaning sedation, or agitation associated with alcohol withdrawal
   b. Carbamazepine (available by mouth and IV) and gabapentin (available by mouth only) may be of equal use, although there are scant research data available. Clinical data suggest effectiveness in the management of alcohol withdrawal; no parenteral form is available
4. Consider the use of N-methyl-D-aspartic acid (NMDA)-receptor blocking agents, to minimize glutamate-induced neuronal injury (eg, amantadine, memantine), particularly in cases of traumatic brain injury (TBI) and cerebrovascular accident (CVA).
5. Serotonin antagonist (eg, ondansetron 8 mg IV, every 8 hours PRN). Note: this agent may prolong QTc, be cautious when combining with other agents known to prolong QTc, such as amiodarone, haloperidol

D. Pharmacologic treatment of hypoactive delirium, consider the use of the following agents (in addition to IV-A)
1. Evidence suggests that DA antagonists may still have a place given the excess DA theory. A systematic literature review of 28 delirium treatment studies with antipsychotic agents concluded (1) that around 75% of delirious patients who receive short-term treatment with low-dose antipsychotics experience clinical response, (2) that these response rates seem quite consistent across different patient groups and treatment settings, (3) that evidence does not indicate major differences in response rates between clinical subtypes of delirium (ie, hypoactive vs hyperactive), and (4) that there is no significant differences in efficacy for haloperidol versus atypical agents[57]
   a. If haloperidol is used, recommended doses are in the very-low range (ie, 0.25 to 1 mg/24 h); this is usually given as a single nighttime dose, just before sun down
   b. If an atypical is preferred, consider low doses of an agent with low sedation (ie, risperidone, <1 mg/24 h; aripiprazole, 2–10 mg/24 h)
2. 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)
3. Consider the use of NMDA-receptor blocking agents, to minimize glutamate-induced neuronal injury (eg, amantadine, memantine, bromocriptine) and help manage extreme psychomotor retardation, particularly in cases of TBI and CVA.

Abbreviations: CPY3A4, cytochrome P450–3A4; HS, *hora somni*, every bedtime; PRN, pro re nata, or as needed; QTc, Corrected QT Interval; RASS, Richmond Agitation-Sedation Scale; T1/2, drug half-life.

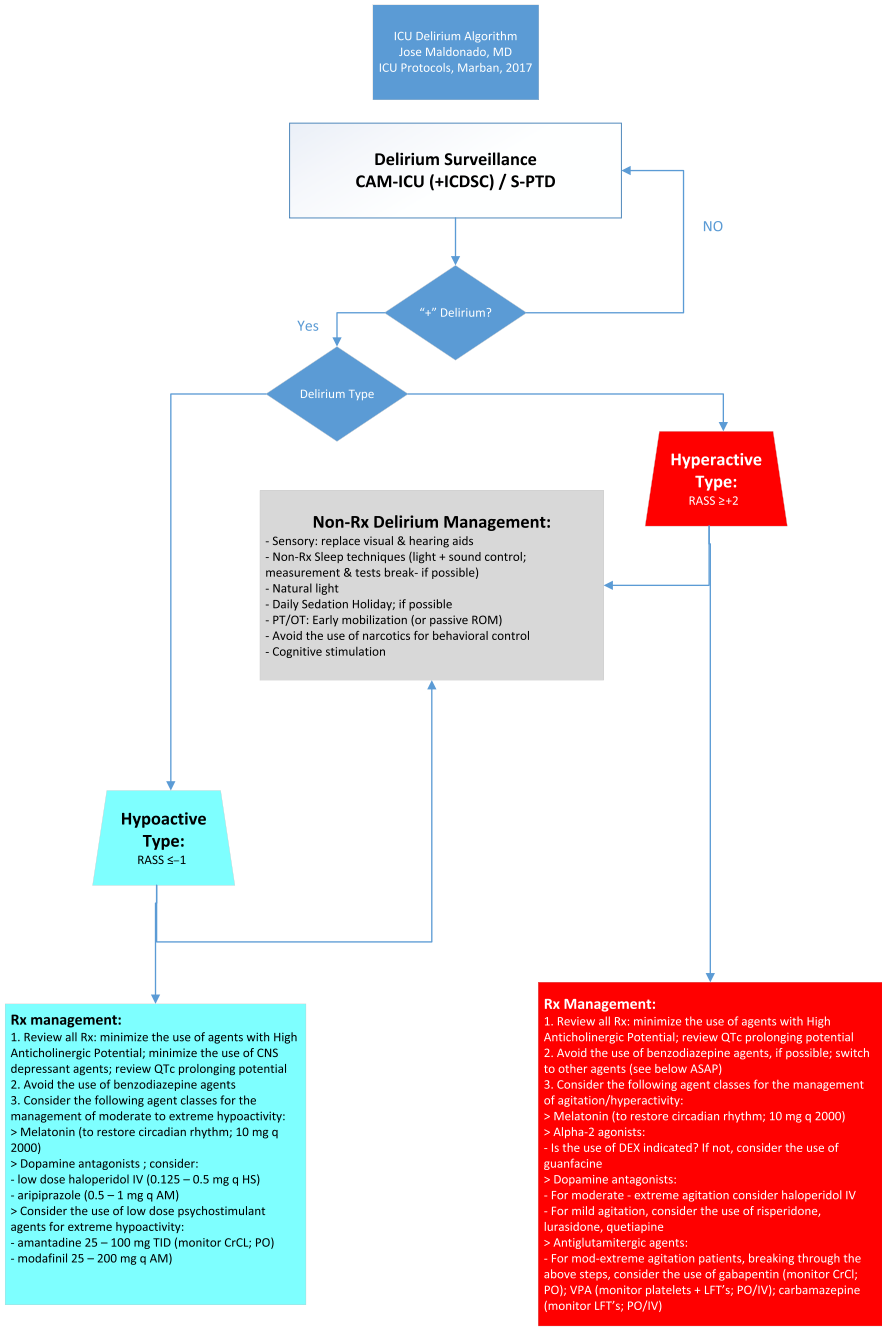

Fig. 6. Stanford University ICU delirium management protocol.

Table 4
Nonpharmacological prevention approaches

Study (n = 19)	Population	Intervention	Delirium Definition	Delirium Incidence (%)		
				Control	Intervention	*P*-Value
Schindler et al,[206] 1989 RCT, n = 33	CABG	NP: perioperative psychiatric intervention vs usual care	DSM-III	0 (0/17)	12.5 (2/16)	ns
Wanich et al,[207] 1992 NRCT, n = 235	Gen IM elderly subjects	NP: nursing intervention for elderly hospitalized subjects vs usual care	DSM-III	22 (22/100)	19 (26/135)	ns ($P = .61$)
Inouye et al,[64–69] 1999 NRCT, n = 852	Gen IM elderly subjects	NP: multicomponent intervention vs usual care	CAM	15 (64/426)	9.9 (42/426)	$P = .02$
Millisen et al,[208] 2001 NRCT, n = 120	Traumatic hip Fx Sx repair	NP: multicomponent vs usual care	CAM	23.3 (14/60)	20 (12/60)	$P = .82$
Marcantonio et al,[209] 2001 RCT, n = 126	Elderly subjects after hip Fx Sx	NP: multicomponent intervention vs usual care	CAM	50 (32/64)	32 (20/62)	$P = .04$
Tabet et al,[210] 2005 NRCT, n = 250	Gen IM elderly subjects	NP: staff education vs usual care	Single assessment psychiatrist	19.5 (25/128)	9.8 (12/122)	$P = .034$
Wong et al,[211] 2005 Pre-evaluation & postevaluation	Traumatic hip Fx Sx repair	NP: multicomponent vs usual care	CAM	35.7 (10/28)	12.7 (9/71)	$P = .012$

Vidan et al,[212] 2005 RCT, n = 319	Elderly subjects after hip Fx Sx	NP: multicomponent intervention vs usual care	CAM	45.2 (70/155)	61.7 (100/164)	$P = .003$ For ≥1 major complications
Lundström et al,[213] 2007 RCT, n = 199	Elderly subjects after hip Fx Sx	NP: multicomponent intervention vs usual care	OBSS	75.3 (73/97)	54.9 (56/102)	$P = .003$
Caplan et al,[214] 2007 Pre-evaluation & postevaluation, n = 37	Geriatric ward	NP: usual care vs volunteer-mediated intervention (Inouye style)	CAM	38.1 (8/21)	6.3 (1/16)	$P = .032$
Taguchi et al,[70] 2007 RCT, n = 11	Esophageal CA subjects	Normalization of natural circadian rhythm by of light therapy	NEECHAM scale	16	40	$P = .42$
Benedict et al,[215] 2009 NRCT, n = 65	Acute Care for Elders (ACE) units	NP: delirium prevention protocol vs usual care	Modified NEECHAM scale (3d average)	(3.24)	(3.76)	ns ($P = .368$)
Schweickert et al,[216] 2009 RCT, n = 104	MICU	Early exercise and mobilization (PT & OT) at daily sedation interruption vs sedation interruption	CAM-ICU	2 d	4 d	$P = .02$
Holroyd-Leduc et al,[217] 2010 NRCT, n = 134	Traumatic hip Fx Sx repair	NP: multicomponent delirium strategies	CAM	Preimplementation incidence 33 (23/70)	Postimplementation incidence 31 (20/64)	ns ($P = .84$)
Björkelund et al,[218] 2010 NRCT, n = 263	Elderly hip Fx Sx repair	NP: multicomponent delirium strategies	OBSS	34 (45/132)	22 (29/131)	$P = .096$

(*continued on next page*)

Table 4
(*continued*)

Study (n = 19)	Population	Intervention	Delirium Definition	Delirium Incidence (%)		
				Control	Intervention	*P*-Value
Colombo et al,[219] 2012 n = 314	All subjects admitted to mixed (med-surg) ICU over a year	NP: reorientation strategy + environmental, acoustic, and visual stimulation.	CAM-ICU	35.5 (60/170)	22 (31/144)	*P* = .020
Gagnon et al,[220] 2012 Randomized delirium prevention trial, n = 1516	Palliative care subjects, in 2 cancer centers	NP: multicomponent administered to subject and family education vs usual care	Confusion rating scale (CRS)	43.9 (370/842)	49.1 (330/674)	*P* = .045
Martinez et al,[221] 2012 n = 287	Older adults in gen medicine ward	Randomized to receive a multicomponent management protocol, delivered by family members (144 subjects) or standard management (143 subjects)	CAM	13.3 (19/143)	5.6 (8 kal/144)	*P* = .027

Abbreviations: CABG, coronary artery bypass grafting surgery; CAM, Confusion Assessment Method; CAM-ICU, Confusion Assessment Method for the ICU; IM, internal medicine; NEECHAM, NEECHAM Confusion Scale; NP, non-pharmacological; NRCT, non-randomized clinical trial; OBSS, Organic Brain Syndrome Scale; RCT, randomized clinical trial.

patients.[73] Even in patients unable to leave their beds, data suggest that range-of-motion exercises can prevent and shorten the duration of delirium among patients in the ICU who are 65 years and older.[74]

Light Therapy

Limited data suggest that therapeutic lighting might effectively reduce the incidence of delirium.[70]

PHARMACOLOGIC MANAGEMENT STRATEGIES

It cannot be overstated that the definitive treatment of delirium is the accurate identification and treatment of its underlying causes. Nevertheless, pharmacologic intervention often helps manage agitated or catatonic patients. A systematic review of ICU interventions concluded that pharmacologic interventions were associated with a reduction in delirium prevalence, length of stay, and duration of mechanical ventilation.[75]

Pharmacologic Prevention Options

Dopamine-antagonist agents

Antipsychotic agents have long been used for the treatment of delirium's behavioral manifestations. Space limitations prevent in-depth review of every published study. **Table 5** contains a comprehensive summary all published studies on the use of dopamine antagonist agents for the prevention of delirium.

In the ICU population, the use of low-dose risperidone was found to lower the incidence of postoperative delirium (POD).[76] Likewise, the use of low-dose olanzapine decreased the incidence of POD.[79] In a study of at-risk ICU subjects (n = 177) low-dose haloperidol was associated with lower delirium incidence, more delirium-free days, fewer ICU readmissions, and less frequent unplanned removal of tubes or lines compared with control group.[78]

Three meta-analyses concluded that perioperative use of prophylactic dopamine antagonist agents (both typical and second-generation antipsychotics [SGAs]), may effectively reduce the overall risk of POD, thereby potentially reducing mortality, disease burden, length of hospital stay, and associated health care costs.[53–55]

Alpha-2 agonists

The use of novel sedative agents may minimize delirium, in part by avoiding the use of more deliriogenic alternatives, such as GABA-ergic agents.[80] Studies have demonstrated that the choice of postoperative sedative may affect the incidence of delirium (P<.01): 3% for subjects on dexmedetomidine (DEX), 50% on propofol (PRO), or midazolam (MID) (**Fig. 7**, **Table 6**). Two subsequent double blind randomized placebo controlled trial (DBRPCT) confirmed DEX's delirium-sparing effects; achieving lower delirium incidence, a lower prevalence of coma, shorter intubation time, and more time within sedation goals.[81,82] Meta-analyses have found that the use of DEX is associated with significant reductions in the incidence of delirium, agitation and confusion.[53,83] **Table 7** contains a comprehensive summary all published studies on the use of alpha-2 adrenergic agonist agents for the prevention of delirium.

Glutamate antagonists and calcium channel modulators

Antiglutamatergic and calcium (Ca) channel blocking agents have been used in the prevention of delirium, including gabapentin, carbamazepine, and valproic acid (**Table 8**). Their deliriolytic effect is likely mediated via modulation of voltage-sensitive Ca2+ channels, N-methyl-D-aspartic acid (NMDA)-receptor antagonism, activation of spinal alpha-2 receptors, and attenuation of sodium (Na) dependent action potentials.

Table 5
Pharmacologic prevention of delirium: dopamine antagonist agents

Study (n = 10)	Population	Intervention	Delirium Definition	Delirium Incidence (%)		P-Value
				Control	Intervention	
Kaneko et al,[222] 1999 RPCT	Gastrointestinal surgery	Prophylaxis haloperidol vs PBO IV postoperatively for 5 d	DSM-III-R	32.5	10.5	*P*<.05
Kalisvaart et al,[223] 2005 DBRPCT, n = 430	Elderly hip-replacement Sx	PBO vs haloperidol 1.5 mg/d started preoperative, continued for up to 3 d postoperative	DSM-IV CAM DRS-R98	16.5 (36/216)	15.1 (32/212)	ns
Prakanrattana & Prapaitrakool,[76] 2007 DBRPCT, n = 126	Cardiac Sx under CPB	PBO vs sublingual risperidone immediately p-Sx	CAM	31.7 (20/63)	11.1 (7/63)	*P* = .009
Girard et al,[77] 2010* DBRPCT, n = 101	Med-surg ICU in mechanical ventilation	PBO vs haloperidol vs ziprasidone: days alive without delirium or coma, conducted in 6 tertiary medical centers.	CAM-ICU	12.5 (1.2–17.2) d	14.0 (6.0–18.0) d / 15.0 (9.1–18.0) d	*P* = .66*
Larsen et al,[79] 2010 DBRPCT, n = 495	Elderly elective total joint-replacement	PBO vs 5 mg of orally disintegrating olanzapine 1 dose presurgery & 1 dose postsurgery	DSM-III-R	40.2 (82/204)	14.3 (28/196)	*P*<.001

Wang et al,[224] 2012 RCT, n = 457	Elderly, noncardiac Sx	PBO vs HAL (0.5 mg bolus, followed by continuous infusion 0.1 mg/h × 12 h)	CAM	23.2	15.3	*P* = .031
Van den Boogaard et al,[78] 2013 Retrospective analysis, n = 177	ICU at risk for delirium	PBO vs HAL (1 mg/8 h) within 24 h of admission to ICU	CAM-ICU	75	65	*P* = .01
Hirota & Kishi,[54] 2013 Meta-analysis (RCTs), 6 studies, n = 1689	Various clinical settings	Meta-analysis of 6 studies (3 HAL, 1 olanzapine, 2 risperidone) using antipsychotic agent for delirium prophylaxis	Various tools	Sensitivity analysis showed that second-generation antipsychotics (SGAs) were superior to PBO (NNT = 4; *P*<.0001), whereas HAL failed to show superiority to PBO		*P*<.00001
Teslyar et al,[55] 2013 Meta-analysis (RCTs); 5 studies, n = 1491	Postoperative elderly subjects	Medication administered included haloperidol (3), risperidone (1), and olanzapine (1)	Various tools	The pooled relative risk of the 5 studies resulted in a 50% reduction in the relative risk of delirium among those receiving antipsychotic medication compared with placebo		*P*<.01
Neufeld et al,[225] 2016 Meta-analysis (RCTs); 19 studies, n = 140877	Prophylaxis (7) & treatment (12)	Various APA agents	Various tools	Antipsychotic use was not associated with change in delirium duration, severity, hospital or ICU length of stay, or mortality		(OR 0.56, 95% CI 0.23–1.34, I2 = 93%)

Abbreviations: APA, anti-psychotic agents; CAM, Confusion Assessment Method; DBPCT, double-blind, placebo clinical trial; DRS-R98, Delirium Rating Scale – revised 1998; DSM-III, Diagnostic and Statistical Manual of Mental Disorders, 3rd edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; NNT, number needed to treat; ns, sot significant; PBO, placebo; RPCT, randomized placebo clinical trial.

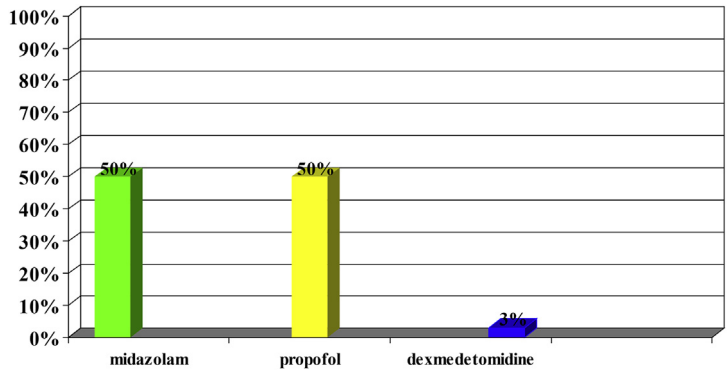

Fig. 7. DEX prophylaxis in postsurgical valve disease patients versus DEX, *P*<.01, adjusted for comparing multiple group means. (*Data from* Maldonado JR. Delirium in the acute care setting: characteristics, diagnosis and treatment. Crit Care Clin 2008;24(4):657–722.)

Ketamine

To date, there have been 2 studies using ketamine for delirium prevention.[85,86]

Melatonin and melatonin-agonists

The usefulness of melatonin and melatonin agonists in the prevention of POD has been documented.[87–90] Studies have found that subjects receiving melatonin experienced statistically significant lower incidence of medical delirium[91] and POD.[92] **Table 9** contains a comprehensive summary all published studies on the use of melatonin and agonist agents for the prevention of delirium.

Statins

The use of statins has been associated with associated with more delirium-free days and lower C-reactive protein (CRP), among critically ill patients,[95] and ICU patients with acute respiratory failure or shock.[96]

Acetylcholinesterase inhibitors

There have been at least 19 papers, mostly case reports, suggesting that acetylcholinesterase inhibitor agents may be effective in the prevention of delirium (**Table 10**).[97,98]

Pharmacologic Treatment Options

Among intubated delirious subjects, those treated with pharmacologic agents within 24 hours of the first positive delirium-screening test spent fewer days in physical restraints, less time receiving mechanical ventilation, and experienced shorter ICU and hospital length of stay (LOS) compared with controls (Michaud, Thomas and colleagues 2014).

Dopamine antagonists

The literature has long recognized IV neuroleptic agents as the recommended emergency treatment for agitated and mixed-type delirium.[64,100–104] **Table 11** contains a comprehensive summary all published studies on the use of dopamine antagonist agents for the treatment of delirium.

Safety concerns Despite the widespread use of IV-haloperidol and multiple reports describing its safety,[64,102,104,108–114] concerns about haloperidol's safety remain. These

Table 6
Selected postoperative outcome variables for cardiac patients with cardiopulmonary bypass by intervention group

	DEX (n = 30)	PRO (n = 30)	MID (n = 30)	Overall *P*-Value	Dex vs PRO	Dex vs MID
Delirium						
Incidence of Delirium (per protocol)	1/30 (3%)	15/30 (50%)	15/30 (50%)	<.001	<0.001	<0.001
Incidence of Delirium (ITT)	4/40 (10%)	16/36 (44%)	17/40 (44%)	<.001	0.001	0.002
Number of Days Delirious	2/216 (1%)	45/276 (16%)	75/259 (29%)	<.001	<0.001	<0.001
Average Length of Delirium[a] (d)	2.0 ± 0	3.0 ± 3.1	5.4 ± 6.6	.82	0.93	0.63
Time Variables						
ICU Length of Stay (d)	1.9 ± .9	3.0 ± 2.0	3.0 ± 3.0	.11	0.14	0.14
Hospital Length of Stay (d)	7.1 ± 1.9	8.2 ± 3.8	8.9 ± 4.7	.39	0.42	0.12
Intubation Time (h)	11.9 ± 4.5	11.1 ± 4.6	12.7 ± 8.5	.64	0.91	0.34
PRN Medications						
Fentanyl (mcg)	320 ± 355	364 ± 320	1088 ± 832	<.001	0.93	<0.001
Total Morphine Equivalents (mg)[b]	50.3 ± 38	51.6 ± 36	122.5 ± 84	<.001	0.99	<0.001
Antiemetic Use[c]	15/30 (50%)	17/30 (57%)	19/30 (63%)	.58	—	—
PRN Medications for the Management of Delirium[d]						
Lorazepam	1/30 (3%)	7/30 (23%)	6/30 (20%)	.07	0.06	0.11
Haloperidol	0/30	3/30 (10%)	2/30 (7%)	.23	0.07	0.15

Abbreviations: DEX, dexmedetomidine; ITT, intention-to treat; MID, midazolam; PRO, propofol.
[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 and/or promethazine HCl in postoperative days 1.
[d] Average amount over 3 days. None of these medications were given until a diagnosis of delirium was established.
Data from Maldonado JR. Delirium in the acute care setting: characteristics, diagnosis and treatment. Crit Care Clin 2008;24(4):657–722.

are mainly related to its effect on QTc prolongation, even though the risk of haloperidol inducing Torsade de pointes (TdP) is relatively low (0.27%).[115,116] Despite these concerns, multiple panels, task forces, expert panels, and various professional organizations (eg, American College of Critical Care Medicine, Society of Critical Care Medicine, American Psychiatric Association, National Institute for Health and Clinical Excellence) still recommend the use of IV haloperidol for the management of extreme agitation in the ICU.[117–122]

Antipsychotic alternatives to haloperidol

Due to stigma and fear of side effects, SGAs have been increasingly used for the management of psychiatric and behavioral symptoms among medically ill patients

Table 7
Pharmacologic management of delirium: centrally acting alpha-2-adrenergic receptors agonists

Study (n = 11)	Population	Intervention	Delirium Definition	Delirium Incidence (%) Control	Intervention		*P*-Value
Berggren et al,[226] 1987 RCT, n = 57	Femoral Neck Fx repair	Epidural vs halothane anesthesia	DSM-III	38 (11/29)	50 (14/28)		ns
Williams-Ruso et al,[227] 1992 RCT, n = 60	B knee replacement Sx	Continuous epidural bupivacaine + fentanyl vs continuous IV fentanyl	DSM-III	44 (11/25)	38 (10/26)		ns (P = .69)
Aizawa et al,[228] 2002 OL, n = 42	Gastrointestinal surgery	Usual care vs BZDP administration to promote sleep p-Sx	DSM-IV	35	5		P = .023
Maldonado et al,[80] 2003; Maldonado et al,[229] 2009 RCT, n = 118	Cardiac valve Sx	Postoperative anesthesia w MID vs PROP vs DEX	DSM-IV DRS-R98	50 (15/30)	50 (15/30)	3 (1/30)	P<.001
Pandharipande et al,[81] 2007 (MENDS) DBRPCT, n = 106	Med-surg ICU in mechanical ventilation	*DEX* vs lorazepam (2 tertiary care centers), days alive w/o delirium or coma	CAM-ICU	3.0 d	7.0 d		P = .01
Reade et al,[84] 2009 R, OL pilot trial; n = 20	Tx-agitated ICU subjects	IV haloperidol 0.5–2 mg/h vs DEX 0.2–0.7 μg/kg/h	Intensive Care Delirium Screening Checklist (ICDSC)	42 h	20 h		P = .016
				Above numbers represent time to extubation			

Hudetz et al,[85] 2009 DBRPCT, n = 58	Elective CABG or valve replacement/ repair w/ CPB	PBO vs IV ketamine (0.5 mg/kg) bolus during the induction of anesthesia	ICDSC	31 (9/29)	3 (1/29)	*P* = .01
Riker et al,[82] 2009 DBRPCT, n = 375	Med-surg ICU in mechanical ventilation	MID vs *DEX*; trial conducted in 68 centers in 5 countries	CAM-ICU	76.6 (93/122)	54 (32/244)	*P*<.001
Shehabi et al,[230] 2009 RCT, n = 306	Cardiac Sx	Morphine vs *DEX*	CAM-ICU	15	8.6	*P* = .088
Rubino et al,[231] 2010 DBRPCT, n = 30	Acute type-A aortic dissection repair	PBO vs clonidine IV on delirium neurologic outcome & respiratory function	Delirium Detection Score (DDS)	40 1.8 ± 0.8	33 0.6 ± 0.7	*P* = .705 *P* = .001
Jakob et al,[232] 2012; RDBCT; n = 498	Adult ICU subjects mechanical ventilation	PROP vs DEX	CAM-ICU	29% (71/247)	18% (45/251)	*P* = .008

Abbreviations: BIS, Bispectral Index; BZDP, benzodiazepine; CAM, Confusion Assessment Method; CAM-ICU, Confusion Assessment Method for the ICU; DBPCT, double-blind, placebo clinical trial; DEX, dexmedetomidine; DRS-R98, Delirium Rating Scale – revised 1998; DSM-III, Diagnostic and Statistical Manual of Mental Disorders, 3rd edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; MDAS, Memorial Delirium Assessment Scale; MENDS, Maximizing Efficacy of Targeted Sedation and Reducing Neurologic Dysfunction trial; OL, open label; PBO, placebo; POD, post-operative day; PROP, propofol; RCT, randomized clinical trial; Tx, treatment.

Table 8
Delirium management: glutamate and calcium channel modulators

Drug	T ½	Product Availability	Bioavailability (%)	Metabolism	Protein Binding (%)	Mechanism Action
Lamotrigine	25 h	po	~100	Hepatic	55	• Stabilizes neuronal membranes • Inhibits voltage-sensitive Na+ channels and/or Ca+ channels→ ↓ cortical GLU release • Ca+ channel blockers • Excitatory amino acid antagonists
Amantadine	17 ± 4 h	po	—	None Renal excretion	67	• NMDA-receptor antagonist • ↑ synthesis and release of dopamine
Memantine	60–80 h	po	100	Mostly unchanged renal excretion	45	• Noncompetitive NMDA-receptor antagonist • Blocks the effects of excessive levels of GLU • Some Ca+ channel blockade • 5HT antagonist
Gabapentin	5–7 h	po	60	None Renal excretion	<3	• Voltage-gated Ca+ channel blockade → ↓ cortical GLU release • NMDA antagonism • Activation of spinal alpha2-adrenergic receptors • Attenuation of Na+ dependent action potential
VPA	9–16 h	po or IV	90	Hepatic conjugation	90	• GABA transaminase inhibitor → ↑ GABA • Inhibits voltage-sensitive Na+ channels→ ↓ cortical GLU release • ↓ release of the epileptogenic amino acid gamma-hydroxybutyric acid (GHB)

(eg, agitation, psychosis, delirium). Data on SGAs are limited to small case reports (see **Table 11**).

Head-to-head data comparing SGAs against haloperidol and other typical antipsychotics in the treatment of delirium are lacking. A Cochrane database review found no significant differences in SGA ability to lower delirium scores or incidence of adverse effects, confirming that low-dose haloperidol was effective in decreasing the degree and duration of POD, when compared with placebo.[123]

Risperidone is the most thoroughly studied SGA for the management of delirium, found to be approximately 80% to 85% effective, followed by olanzapine at approximately 70% to 76% effective.[124] Limited data suggest that quetiapine may also be a safe and effective alternative to high-potency antipsychotics.

A systematic literature review of delirium treatment with antipsychotic agents (n = 28 studies) concluded that (1) approximately 75% of delirious subjects who receive short-term treatment with low-dose antipsychotics experience a clinical response, (2) the response rate seems quite consistent across different subject groups and treatment settings, (3) the evidence does not indicate major differences in response rates between the various clinical subtypes of delirium (ie, hypoactive vs hyperactive), and (4) there are no significant differences in efficacy for haloperidol versus atypical agents.[57]

Dopamine antagonist agents: treatment recommendations When antipsychotic agents are needed, it is wise to review the patient's medication list and identify any other agents with the ability to prolong QTc. If possible, avoid other medications known to increase QTc and/or inhibitors of CPY3A4. Before and during the use of antipsychotic agents, obtain a 12-lead ECG (for QTc) and correct any electrolyte abnormalities (especially potassium + and magnesium +). Guidelines recommend discontinuing antipsychotic use if the QTc increases greater than 25% of baseline or greater than 500 msec.

When treating hypoactive delirium, the author recommends doses in the very low daily range (ie, haloperidol and risperidone in the 0.25–1 mg per 24 hours). Available data suggest that excess dopamine may occur in all delirium types, even hypoactive type. It also suggests that antipsychotics may help prevent and treat all forms of deliria, including hypoactive type. Medication is usually given as a single nighttime dose, before sundown. Sedating agents (eg, quetiapine, olanzapine) should be avoided. Reports have confirmed the usefulness of aripiprazole, particularly in hypoactive delirium.[106,107,125]

Alpha-2 agonists

A randomized, open-label trial for the treatment of agitated delirium found that DEX significantly shortened median time to extubation, decreased ICU length of stay, and cut in half the time PRO was needed compared with IV haloperidol.[84] An open-label, prospective trial of POD in cardiovascular subjects (n = 60), found that DEX was associated with shorter delirium duration, increased rates of spontaneous breathing, shorter ICU LOS, and better achieved targeted richmond agitation-sedation scale (RASS) compared with haloperidol (HAL).[126]

A systematic review of ICU studies confirmed that the use of DEX lowered delirium prevalence.[16] When compared with PRO, DEX-sedation reduced delirium incidence, delayed onset, and shortened duration of POD.[80,127,128] Despite its high cost, DEX use is associated with a mean savings of $4370 per subject due to reductions in ICU LOS.[129]

A retrospective ICU study of agitated POD among liver transplantation subjects found that DEX significantly decreased the ICU LOS and lowered MID requirements compared with HAL.[130] A meta-analysis of randomized controlled trials (RCTs; 8 studies, n = 969 adults after cardiac surgery) found that DEX was associated with a

Table 9
Delirium management: melatonin prevention and treatment

Study (n = 8)	Population	Intervention	Delirium Definition	Results
Bourne et al,[90] 2008 N = 24, DBPCT	s/p tracheostomy to assist weaning from vent	Melatonin 10 mg po at 2000	BIS	Melatonin associated with a 1-h increase in nocturnal sleep (P = .09) and a decrease in BIS AUC indicating better sleep Melatonin use was associated with increased nocturnal sleep efficiency
Al-Aama et al,[91] 2010 N = 145	≥65 y/o admitted through the emergency department to a medical unit	Randomized to MEL 0.5 mg vs PBO q HS × 14 d or D/H	CAM	Melatonin was associated with a lower risk of delirium (12.0% vs 31.0%, P = .014)
Sultan,[92] 2010 N = 300	≥65 y/o scheduled for hip arthroplasty under spinal anesthesia	Randomized to PBO Melatonin 5 mg MID 7.5 mg Clonidine 100 μg	—	Melatonin showed a statistically significant decrease in POD to 9.43% POD: PBO, 32.7%; MEL, 9.4% (P = .003); MID, 44 & (P = .245); CLO, 37.3% (P = .629) Melatonin was successful in treating 58.06% of subjects suffered POD

de Jonghe et al,[233] 2010 Review	Meta-analysis	—	—	9 papers, including 4 RCTs (n-243), and 5 case series (n = 87) were reviewed 2 of the RCTs found a significant improvement on sundowning or agitated behavior All 5 case series found an improvement
de Jonghe et al,[234] 2011 N = 452	≥65 y/o admitted for surgical repair of hip fracture	Randomized to: PBO Melatonin 3 mg at 2100	CAM	Ongoing
Kimura et al,[93] 2011 N = 3 (case report)	Subjects >59, medically ill	Open label; ramelteon 8 mg q HS	DSM-IV-TR MDAS-Jap	All 3 cases demonstrated significant improvement in delirium scores as measured by MDAS, with steady improvement over 7 d, ramelteon 8 mg at HS
Furuya et al,[94] 2012 N = 5 (case report)	Elderly Hospitalized for delirium	Open label, ramelteon 8 mg	DSM-IV-TR	Successful treatment of 5 cases of delirium within 1 d, after ramelteon 8 mg at HS
Hatta et al,[89] 2014 8 mg q 2000	N = 67, gen medicine & ICU	Randomized, PC trial, prophylaxis	DSM-IV-TR	Ramelteon associated w lower risk of delirium (3% vs 32%; $P = .003$), w relative risk of 0.09 (95% CI 0.01–0.69)

Abbreviations: BIS, Bispectral Index; CAM, Confusion Assessment Method; DBPCT, double-blind, placebo clinical trial; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; MDAS, Memorial Delirium Assessment Scale; PBO, placebo; POD, post-operative day; RCT, randomized clinical trial; y/o, year-old.

Table 10
Acetylcholinesterase inhibitors in delirium prevention

Study (n = 7)	Population	Intervention	Delirium Definition	Delirium Incidence (%)		
				Control	Intervention	*P*-Value
Dautzenberg et al,[97] 2004 OL, retrospective review, n = 51	≥65 y/o hospitalized demented subjects	Subjects who used rivastigmine chronically with a randomly selected subgroup of all subjects not treated	Retrospective chart review of geriatric service consultations	88.9 (26/29)	45.5 (4/11)	*P*<.05
Moretti et al,[99] 2004 RCT, n = 230	≥65 y/o-o/p, w vascular dementia (24-mo follow-up)	Cardio aspirin vs rivastigmine po q D	CAM Behave-AD	62 (71/115)	40 (46/115)	*P*<.001
Liptzin et al,[235] 2005 DBRPCT, n = 80	Elderly elective total joint-replacement	PBO vs donepezil (14 d pre-Sx + 14 d post-Sx)	DSM-IV	17.1 (7/41)	20.5 (8/39)	Ns (*P* = .69)
Sampson et al,[236] 2007 DBRPCT, n = 33	Elderly elective hip replacement	PBO vs donepezil 5 mg immediately p-Sx + 3 d	DSI	35.7 (5/14)	9.5 (2/19)	*P* = .08
Oldenbeuving et al,[237] 2008 N = 26	Delirium p-CVA	Rivastigmine 3→12 mg/d; no PBO	DRS ≥12	In 16/17 (94%) delirium severity improved, mean decrease 14.8→8.5, mean duration 6.7 d, no side effects		
Gamberini et al,[238] 2009 DBRPCT, n = 120	Cardiac Sx under CPB	PBO vs po rivastigmine 1.5[a] preoperative, until POD#6	CAM	30 (17/57)	32 (18/56)	ns (*P* = .8)
van Eijk et al,[239] 2012 DBRPCT, n = 109	>18 y/o in ICU	2-arms, both receiving haloperidol, 1 on PBO other on rivastigmine	CAM-ICU	3d	5d	*P* = .06

Abbreviations: BEHAVE-AD, Behavioral Pathology in Alzheimer's Disease Rating Scale; CAM, Confusion Assessment Method; CAM-ICU, Confusion Assessment Method for the ICU; CPB, cardio-pulmonary bypass machine; DBRPCT, double-blind, randomized, placebo clinical trial; OL, open label; PBO, placebo; p-CVA, after cerebro-vascular accident; RCT, randomized clinical trial.

[a] Rivastigmine-treated subjects who experienced delirium had a shorter duration, lower use of benzodiazepine and neuroleptic for management of agitation, and improvement in all behavioral aspects measured by the BEHAVE-AD.

Table 11
Pharmacologic treatment of delirium: dopamine antagonist agents

Study (n = 32)	Population	Intervention	Delirium Definition	Results
Breitbart et al,[240] 1996 RCT, n = 30	AIDS, medical subjects	Haloperidol vs chlorpromazine vs lorazepam	DRS	Tx either HAL or CPM resulted in significant improvement in the symptoms of delirium, whereas no improvement was found in the LOR group Tx neuroleptic was associated with an extremely low prevalence of EPS, whereas all subjects receiving LOR developed treatment-limiting adverse effects
Sipahimalani et al,[241] 1998 OL, n = 22	Med-surg subjects	Haloperidol vs olanzapine	DRS	Improvement was similar in both groups (mean DRS + SD HAL = 11.1 $\pm$ 7.1; OLA = 10.3 $\pm$ 4.8; P = .760), with extrapyramidal symptoms found only in haloperidol subjects No side effects in olanzapine group
Schwartz et al,[242] 2000 Single-blind; n = 11	Med-surg subjects	Quetiapine vs haloperidol, retrospective chart review	DRS	Effectiveness of $\geq$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
Kim et al,[243] 2001 OL, n = 20	Med-surg subjects	Olanzapine po, variable dose	DRS	50% decrease in DRS scores (from pre of 20.0 $\pm$ 3.6, to post of 9.3 $\pm$ 4.6; P<.01) No side effects, including EPS
Breitbart et al,[105] 2002 OL, n = 79	Hospitalized cancer subjects	Olanzapine po, variable dose	MDAS	Olanzapine was effective in treating 76% of delirium subjects as evidenced by the MDAS, caused excessive sedation in 30% of subjects
Horikawa et al,[244] 2003 OL, n = 10	Med-surg subjects	Risperidone po	DSM-IV	At a low dose of 1.7 mg/d, on average, risperidone was effective in 80% of subjects and the effect appeared within a few days Most commonly cited adverse effects included sleepiness (30%) and mild drug-induced parkinsonism (10%)
Sasaki et al,[245] 2003 OL, n = 12	Med-surg subjects	Quetiapine po, flexible doses	DSM-IV	100% of subjects on quetiapine achieved resolution of delirium (mean on day 4.8 $\pm$ 3.5 d), no EPS reported
Kim et al,[246] 2003 OL, n = 12	Elderly medical in-subject	Quetiapine po, flexible doses	DSM-IV/DRS	100% of subjects on quetiapine achieved resolution of delirium by day 10 (mean on day 5.9 $\pm$ 2.2 d); no EPS reported Delirium Rating Scale scores along with scores of the MMSE and Clock Drawing Test continued to improve throughout the 3-mo study period

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Table 11
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Study (n = 32)	Population	Intervention	Delirium Definition	Results
Liu et al,[247] 2004 Retrospective record review, n = 77	Med-surg subjects with hyperactive delirium	Risperidone (average dose 1.17 ± 0.76 mg/d) vs haloperidol (average dose 4.25 ± 2.62 mg/d)	DSM-IV	Subjects treated with haloperidol were younger than subjects treated with risperidone (P<.05) The mean hyperactive syndrome scale score was higher in the haloperidol than that of the risperidone group No significant difference in the efficacy or frequency of response rate between haloperidol and risperidone (100% vs 95%; P = ns) Subjects on risperidone experienced less EPS (7% vs 69%)
Mittal et al,[248] 2004 OL, n = 10	Subjects admitted to med-surg unit	Risperidone, 0.5 mg po BID, flexible PRNs	DSM-IV/DRS	Rapid resolution of delirium while receiving low-dose Risperidone (mean dose 0.75 mg/d); no EPS reported
Parellada et al,[249] 2004 OL	Prospective, multicenter, observational 7-d study	Risperidone po	DSM-IV DRS PANSS-P MMSE	Risperidone was administered at the time of diagnosis, and treatment was maintained according to clinical response Found a significant improvement in DRS scores in 90.6% of treated subjects and significantly improved all symptoms measured by the scales from baseline to day 7 (P<.0; only 3% side effects
Pae et al,[250] 2004 OL, n = 22	Med-surg subjects	Quetiapine po	DRS-R98 CGI-s	DRS-R98 and CGI-s scores were significantly reduced by 57.3% and 55.1%, respectively Quetiapine was effective and safe
Han et al,[251] 2004 DBRCT, n = 28	Med-surg subjects	Haloperidol vs risperidone, 7d medication trial	CAM DRS MDAS	Both groups showed significant improvement in baseline DRS and MDAS scores with either haloperidol (75%) or risperidone (42%, P<.05) There was no significant difference in improvement of DRS (P = .35) or MDAS (P = .51) scores, comparing haloperidol with risperidone subjects
Hu et al,[252] 2004 RPCT, n = 175	Med-surg elderly subjects	Haloperidol vs olanzapine vs placebo, 7d medication trial	DRS CGI	Tx groups showed a decrease in DRS scores by 7th day compared with baseline (P<.01) Decrease in DRS scores of treated subjects at day 7 (OLA 72.2%; HAL 70.4%) differed significantly from DRS scores of PBO subjects (29.7%; P<.01) but not from each other (P>.05)

Skrobik et al,[253] 2004 OL-prospective RCT, n = 73	Critically ill med-surg subjects	Haloperidol (average 6.5 mg/d) vs olanzapine (average 4.5 mg/d)	Delirium Index (DI)	ICU DI Screening Checklist Scores were reduced in both groups compared with baseline ($P<.05$) but there was no significant difference in DIS scores between active Tx groups ($P = .9$) EPS were found in 13% of haloperidol subjects, 0% in olanzapine group
Toda et al,[254] 2005 n = 10	Elderly inpatient general medicine	Risperidone, OL, 0.5 mg oral sol; flexible titration, PRN	DSM-IV/DRS	Resolution reported in 7 subjects (mean dose 0.92 ± 0.47 mg/d) 1 nonresponder 2 side effects requiring Tx discontinuation
Lee et al,[255] 2005 RCT, n = 40	Med-surg subjects	Amisulpride vs quetiapine	DRS-R98 CGI	After treatment, DRS-R98 scores were significantly decreased from the baseline in both treatment groups ($P<.001$) without group difference Both atypical antipsychotics were generally well tolerated
Straker et al,[106] 2006 OL, n = 14	Medically ill subjects	Aripiprazole po was used in a flexible dosing range, from 5-15 mg/d	DSM-IV DRS-R98 CGI	50% of subjects had improved significantly by day 5, as indicated by a 50% reduction in DRS-R98 scores 86% of subjects had a 50% reduction in their DRS-R98 scores by end of treatment Mean CGI Severity scores at the beginning of treatment were 5.2, with a mean CGI improvement score after treatment of 2.1, indicating much improvement
Takeuchi et al,[256] 2007 OL, n = 38	Med-surg subjects	Perospirone, OL	DSM-IV/ DRS-R98	Perospirone was effective in 86.8% of subjects, within several days (5.1 ± 4.9 d) The initial dose was 6.5 ± 3.7 mg/d and maximum dose of perospirone was 10.0 ± 5.3 mg/d There were no serious adverse effects
Maneeton et al,[257] 2007 OL, n = 17	Medically ill subjects	Quetiapine, flexible dosing	CAM/DRS, CGI	88% subjects responded Mean (SDs) dose and duration (SD) of quetiapine treatment were 45.7 (28.7) mg/d and 6.5 (2.0) d, respectively The DRS and CGI-S scores of days 2–7 were significantly lower than those of day 0 ($P<.001$) for all comparisons Only 2 subjects were shown to have mild tremor
Reade et al,[84] 2009 OL-RCT	Med-surg ICU	Agitated delirium randomized to receive HAL 0.5–2 mg/h or DEX 0.2–0.7 μg/kg/h	ICDSC Time	DEX significantly shortened median time to extubation from 42.5 to 19.9 h ($P = .016$) Significantly decreased ICU length of stay, from 6.5 to 1.5 d ($P = .004$) Of subjects requiring ongoing sedation, it reduced the time PRO was required in half (79.5% vs 41.2%; $P = .05$)

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Table 11
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Study (n = 32)	Population	Intervention	Delirium Definition	Results
Devlin et al,[258] 2010 DBRPCT, n = 36	MICU	PBO vs quetiapine (50 mg BID) Multicenter-3	ICDSC	Tx with QUE was associated with: a shorter time to first resolution of delirium (P = .001), a reduced duration of delirium (P = .006), less agitation (P = .02), greater chance to be discharged home vs long-term care facility (P = .06), and lower requirement of as-needed haloperidol (P = .05)
Girard et al,[77] 2010 DBRPCT, n = 101	Mechanically ventilated medical and surgical ICU subjects	PBO vs HAL vs ziprasidone	CAM-ICU	Subjects in the haloperidol group spent a similar number days alive without delirium or coma (14.0 d, range 6.0–18.0) as did those on ziprasidone (15.0 d, range 9.1–18.0) and PBO groups (12.5 d, range 1.2–17.2); P = .66
Kim et al,[259] 2010 SB-RCT, n = 32	Elderly, med-surg subjects	Risperidone vs olanzapine	DSM-IV/ DRS-R98	Significant within-group improvements in the DRS-R98 scores over time were observed at every time point in both treatment groups The response rates did not differ significantly between the 2 groups (risperidone group, 64.7%; olanzapine group, 73.3%) and no difference in the safety profiles and side effects between groups
Tahir et al,[260] 2010 DBRCT, n = 42	Med-surg subjects	Quetiapine vs placebo	DSM-IV/ DRS-R98, CGI	Quetiapine has the potential to more quickly reduce the severity of noncognitive aspects of delirium Study was underpowered for treatment comparisons
Grover et al,[261] 2011 Prospective, single blind, n = 64	Med-surg subjects	Haloperidol (0.25–10 mg) vs olanzapine (1.25–20 mg) vs risperidone (0.25–4 mg), flexible dosing	DSM-IV or DRS-R98	Subjects in all 3 groups experienced a significant reduction in DRS-R98 severity scores and a significant improvement in MMSE scores over the period of 6 d, with no difference between the treatment groups Rate of side effects was also similar
Boettger & Breitbart,[107] 2011 OL, n = 21	Med-surg subjects at Cancer Center	Aripiprazole, flexible dosing	DSM-IV/MDAS	Subjects treated for delirium with aripiprazole (mean dose 18.3 mg, range of 5–30) experienced significant improvement and resolution of delirium MDAS scores declining from a mean of 18.0 at baseline (T1) to mean of 10.8 at T2 and a mean of 8.3 at T3 There was a 100% resolution of hypoactive delirium vs 58.3% of hyperactive delirium

Hakim et al,[262] 2012 PCRCT	Subjects aged 65 y or older who experienced SSD after on-pump cardiac surgery	Randomized using a computer-generated list to receive placebo (n = 50) or 0.5 mg risperidone (n = 51) every 12 h by mouth	ICDSC	7 (13.7%) subjects in the risperidone group experienced delirium vs 17 (34%) in the placebo group (P = .031) Competing-risks regression analysis showed that failure to treat SSD with risperidone was an independent risk factor for delirium (P = .002) 2 (3.9%) subjects in the risperidone group experienced extrapyramidal manifestations vs 1 (2%) in the placebo group (P = 1.0)
Kishi et al,[263] 2012 OL, n = 29	Adult delirious cancer subjects	Risperidone, mean dosage, 1.4 ± 1.3 mg/d	DRS-R98	Entry DRS-R98 score = 19.8 ± 6.8; 7-d follow-up score = 14.3 ± 7.8 DRS-R98 scores improved in 79.3% of subjects (P<.001) 38% achieved remission (ie, DRS-R98 ≤10)
Tagarakis et al,[264] 2012 n = 80	POD after on-pump heart surgery	Ondansetron iv (8 mg) vs HAL IV (5 mg); pts evaluated before and 10 min after Rx administration	Self-developed rating scale: 0–4	Statistically significant improvement in the test score rating after the administration of both ondansetron (from 3.1 to 1.2, improvement 61.29%, P<.01) and haloperidol (from 3.1 to 1.3, ± percentage improvement 58.064%, P<.01)
Yoon et al,[265] 2013 Observational study; n = 80	Subjects with delirium at a tertiary level hospital	Assigned to receive either haloperidol (N = 23), risperidone (N = 21), olanzapine (N = 18), or quetiapine (N = 18)	Korean version of the Delirium Rating Scale-Revised-98 (DRS-K)	Haloperidol, risperidone, olanzapine, and quetiapine were equally efficacious and safe in the treatment of delirium The treatment response rate was lower in subjects >75 y than in subjects <75 y, especially for olanzapine
Maneeton et al,[266] 2013 DBRCT, n = 52	Medically ill subjects with delirium	25–100 mg/d of quetiapine (n = 24) or 0.5–2.0 mg/d of haloperidol (n = 28)	DRS-R98 and total sleep time	Means (standard deviation) of the DRS-R98 severity scores were not significantly different between the quetiapine and haloperidol groups (−22.9 [6.9] vs −21.7 [6.7]; P = .59) Concluding that low-dose quetiapine and haloperidol may be equally effective and safe for controlling delirium symptoms

Abbreviations: AIDS, acquired immunodeficiency syndrome; CAM-ICU, Confusion Assessment Method for the ICU; CGI, clinical global impression scale; CGI-s, clinical global impression scale-severity; CPM, chlorpromazine; DI, delirium index; DRS-R98, Delirium Rating Scale – revised 1998; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EPS, extrapyramidal symptoms; HAL, haloperidol; ICDSC, Intensive Care Delirium Screening Checklist; LOR, lorazepam; MDAS, Memorial Delirium Assessment Scale; MMSE, mini mental status examination; OL, open label; OLA, olanzapine; PANSS-P, Positive and Negative Syndrome Scale; PBO, placebo; PCRCT, placebo-controlled, randomized clinical trial; PRN, as needed medication; RCT, randomized clinical trial.

lower risk of delirium, a shorter length of intubation but a higher incidence of bradycardia compared with PRO.[131]

Glutamate antagonists and calcium channel modulators

Multiple agents can be used in the management of hyperactive or excited delirium, including lamotrigine, gabapentin, carbamazepine, and VPA (see **Table 8**). There are no RCTs available. Two case series suggest VPA is effective in managing delirium and decreasing time to extubation, even in cases in which other medications have failed, with minimal side effects.[132,133] As with any patient receiving VPA, closely monitor liver function tests, bilirubin, platelet count, and amylase. As in the case of SGAs, there are case reports on VPA-induced delirium.

Acetylcholinesterase inhibitors

All published data are limited to small series or case reports (n = 19) for the treatment of delirium in older persons.[97,98] **Box 6** lists published case reports suggesting a positive effect of acetylcholinesterase inhibitors in the treatment of delirium.

Physostigmine is a fast, short-acting acetylcholinesterase inhibitor that increases synaptic acetylcholine concentrations and can overcome the postsynaptic muscarinic receptor-blockade produced by anticholinergic agents. It can reverse both central and peripheral anticholinergic receptors, and has been successfully used to treat emergence delirium in both adults[138,149] and pediatric patients.[150]

Physostigmine should be considered when a delirious patient exhibits signs of a central anticholinergic state (eg, confusion, sinus tachycardia, markedly dilated and fixed pupils, dry mouth, hypoactive bowel sounds, dry and flushed skin) and/or when it is known that the patient's altered mental status is due to the use of known

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

- Burt,[134] 2000
- Bruera et al,[135] 2003
- Dautzenberg et al,[97] 2004
- Fisher et al,[136] 2001
- Gleason,[137] 2003
- Hasse and Rundshagen,[138] 2007
- Hori et al,[139] 2003
- Kaufer et al,[140] 1998
- Kobayashi et al,[141] 2004
- Logan and Stewart,[142] 2007
- Moretti et al,[99] 2004
- Palmer,[143] 2004
- Rabinowitz,[144] 2002
- Weizberg et al,[145] 2006
- Wengel et al,[146,147] 1998
- Wengel et al,[148] 1999

anticholinergic substances, as in the case of medication overdose (whether accidental or intentional).[151–156] Other investigators have reported that, among subjects with suspected anticholinergic delirium, physostigmine controlled agitation and reversed delirium in 96% and 87% of cases, respectively,[157] with no significant side effects. An initial physostigmine dose of 1 to 2 mg (0.5 mg in children) given IV over 3 to 5 minutes is the recommended dose. If the response provides only an incomplete response, additional doses of 0.5 to 1.0 mg every 5 minutes may be given until delirium resolves or there are signs of cholinergic excess (eg, diaphoresis, salivation, vomiting, diarrhea). Absolute contraindications include a prolonged PR interval (>200 ms) or QRS complex (>100 ms and not related to bundle branch block) interval on ECG are for physostigmine use.

Serotonin antagonists

In a prospective study of ICU POD after coronary artery bypass graft surgery (n = 35), subjects were treated with a single dose (8 mg IV) of ondansetron with significant improvement in cognition and behavior, with no adverse events reported.[158]

Melatonin and melatonin agonists

Multiple case reports have documented the effectiveness of melatonin in treating severe POD unresponsive to conventional treatment (eg, antipsychotics or benzodiazepine agents),[87] demonstrating delirium resolution in 58% of subjects treated with melatonin.[92]

Similarly, there are 2 case reports of the successful use of ramelteon in the treatment of patients with delirium[93,94] (see **Table 9** for a summary of published case reports and studies on the use of melatonin for the treatment of delirium).

MANAGEMENT OF HYPOACTIVE DELIRIUM

Good, controlled studies on the management of hypoactive delirium 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. The use of activating agents (eg, modafinil and psychostimulants) may help mobilize hypoactive patients, particularly to address extreme psychomotor retardation and extreme somnolence.

Some NMDA-receptor blocking agents, such as amantadine and memantine, can be used in the management of hypoactive delirium, especially when associated with intracranial insults, such as traumatic brain injury (TBI) and cerebrovascular accident (see **Table 8**). Studies have demonstrated that memantine may be effective in reducing the damage induced by acute ischemia or reperfusion (Yigit and colleagues, 2011), whereas amantadine has been shown to enhance cognitive recovery and minimize delirium after severe TBI in humans.[159] Furthermore, data suggest that amantadine use was an effective and safe means of reducing frequency and severity of irritability and aggression[160] and may accelerate the pace of functional recovery during active treatment in individuals with TBI.[159] In fact, studies suggest that amantadine use produced marked improvement in measures of arousal and cognition.[161,162] Finally, there are case reports suggesting that amantadine may be useful in the management of post-TBI amotivational syndrome.[163]

DELIRIUM MANAGEMENT: WHAT DOES AND WHAT DOES NOT WORK

Studies suggest that the implementation of a delirium protocol with pharmacologic and nonpharmacological interventions had an impact on ICU patients experiencing acute delirium by significantly increasing delirium-free days and reducing the ICU

LOS.[164] A systematic review revealed a statistically significant reduction in the incidence of ICU delirium and a reduced ICU length of stay with appropriate sleep intervention.[88]

Data suggest that the use of delirium prevention bundle interventions (ie, sedation cessation, pain management, sensory stimulation, early mobilization, and sleep promotion) was effective in reducing the incidence of delirium in critically ill medical-surgical patients.[165]

The implementation of an ICU analgesia, sedation, and delirium protocol has been associated with more RASS and CAM-ICU assessments per day than the baseline cohort, a reduction in hourly benzodiazepine dose, and a decreased delirium duration, as well as reductions in the median duration of mechanical ventilation, ICU stay, and length of hospitalization.[166]

A study designed to explore the effect of sedative administration for the prevention of delirium among ICU mechanically ventilated patients demonstrated that the incidence of delirium was significantly lowered in the simulated circadian clock group.[167] In the simulated circadian clock group, the incidence of delirium in the DEX group was significantly lower than that of the PRO group. Similarly, the duration of mechanical ventilation in the DEX group was significantly shorter than that of PRO group and the length of ICU stay was significantly shorter in the DEX versus PRO group. This study found that the use of DEX could reduce the incidence of delirium and improve the prognosis of patients compared with other sedative agents.

The Dexmedetomidine to Lessen ICU Agitation (DahLIA) study demonstrated that DEX increased ventilator-free hours at 7 days, reduced time to extubation, and accelerated resolution of delirium compared with placebo.[168] Among elderly patients admitted to the ICU after noncardiac surgery, the prophylactic use of low-dose DEX significantly decreased the occurrence of delirium (9% vs 23% in PBO) during the first 7 days after surgery.[169] A literature review found that the use of DEX for the prevention or treatment of ICU delirium in the elderly was associated with a reduction in delirium and decreased morbidity and mortality compared with benzodiazepines.[170]

A qualitative study using focus groups of doctors and nurses caring for patients with delirium in the ICU found that these professionals regarded patients with delirium with uncertainty and thought these patients were often underdiagnosed and poorly managed.[171] Doctors displayed discrepancies regarding pharmacologic prescriptions and decision-making, with choice of medication been determined by experience. Nurses thought that, for many doctors, delirium was not considered a matter of urgency in the ICU. Nurses also reported difficulties when applying restraint, managing sleep disorders, and providing early mobilization. Overall, participants thought that the lack of a delirium protocol generates conflicts regarding what type of care management to apply, especially during the night shift.

Although the ABCDE bundled approach to ICU care has been widely publicized and promoted by various medical and nursing professional organizations, a survey of attendees of the Michigan Health and Hospital Association's Keystone ICU collaborative annual meeting (76% response rate) found that only 12% reported having implemented routine spontaneous awakening trials and delirium assessments, as well as early mobility. Of these, 36% reported not having early mobility as an active goal in their units (nonmovers) and 52% reported attempts at early mobility without routine sedation interruption and delirium screening implementation.[172] In adjusted models, those who implemented exercise with sedation-interruption and delirium screening, were 3.5 times more likely to achieve higher levels of exercise in ventilated patients than those who implemented exercise without both sedation interruption and delirium screening (95% CI 1.4–8.6).

THE IMPACT OF DELIRIUM

Morbidity and Mortality Related to Delirium

Between 2000 and 2009, the number of ICU beds in the United States increased 15%, mirroring population growth.[173] Every year, 3.5 to 4 million patients survive critical care illness,[174,175] although studies suggest that up to 87% of critically ill patients develop delirium.[10] Patients who develop delirium fare much worse than their nondelirious counterparts when controlling for all other factors. Among medically ill inpatients, the development of delirium was associated with increased mortality at discharge and at 12 months, increased length of hospital stay, and institutionalization.[176] A systematic review found that delirium is associated with an increased risk of death compared with controls (38.0% vs 27.5%).[177]

Among mechanically ventilated ICU subjects (n = 275), delirium was associated with higher 6-month mortality rates, spending 10 days additional in-hospital days, fewer median days alive and without mechanical ventilation, and a higher incidence of cognitive impairment at hospital discharge compared with those without delirium.[178] Among elderly ICU subjects, the number of delirium days was significantly associated with time to death within 1-year post-ICU admission, after controlling all factors.[179] Among critically ill subjects, the presence of delirium at 24 hours from admission is an independent risk factor for increased in-hospital mortality.[180]

A meta-analysis of critically ill subjects (16 studies; n = 6410), found that subjects with delirium experienced higher mortality rates, had longer LOS in both the ICU and the general hospital, spent more time on mechanical ventilation, experienced a significantly higher rate (6 times) of complications, and were more likely to be placed at a long-term care facility rather than return home.[181]

Among coronary care unit patients, the occurrence of delirium was associated with an increased risk of in-hospital mortality and 1-year mortality.[114] A systematic review and meta-analysis revealed that delirious subjects experienced significantly higher mortality during admission and longer durations of mechanical ventilation and lengths of stay, in both the ICU and in hospital.[182] Among intubated ICU patients, delirium at the initiation of the weaning process was associated with more respiratory and neurologic complications, and a reduced probability of successful extubation.[183]

Among ICU patients with bloodstream infections, delirious patients (60% incidence) experienced a higher mortality, a lower proportion of return to functional baseline, and higher proportion of unfavorable outcome.[184] A study on weaning from mechanical ventilation and delirium (n = 393), revealed that 40.7% of subjects were diagnosed with delirium on the day of the first Spontaneous Breathing Trial, which was associated with difficult extubation and prolonged weaning (Jeon and colleagues, 2016).

Cognitive Sequelae

Among ICU subjects (n = 79), those who developed delirium experienced higher rates of cognitive impairment, and there was a positive association between severity of delirium scores and cognitive impairment at the time of hospital discharge.[9] Maldonado and colleagues[7] found that only 14% of subjects who developed ICU-delirium had returned to their baseline level of cognitive functioning by the time of discharge from the hospital. Although other investigators have found an even lower rate of recovery (4%) before discharge from the hospital, an additional 20.8% achieved resolution of symptoms by the third month, and an additional 17.7% by the sixth month after hospital discharge.[21]

Some investigators have estimated that about 40% of patients who experience delirium develop some form of chronic brain syndrome.[185,186] In some cases, the functional decline persisted longer than 6 months after hospital discharge.[187] Later studies

found that cognitive deficits at hospital discharge were significantly associated with poor long-term cognitive functioning for up to 5 years after cardiac surgery.[188]

The occurrence of delirium among mechanically ventilated ICU patients was an independent predictor of worse scores on neuropsychological testing at follow-up, with cognitive impairment present in 79% and 71% of survivors at 3-month and 12-month follow-up, respectively, with 62% and 36% being severely impaired.[77] In addition, the investigators found that an increased delirium duration (from 1 to 5 days) was independently associated with a 7-point decline in cognitive battery mean scores at 12-month follow-up. Others have also found that longer duration of delirium was independently associated with worse global cognition and worse executive function at 3 and 12 months.[189]

A prospective 18-month follow-up study of ICU survivors (n = 1292) found that duration of delirium was significantly correlated to memory and naming impairments 18 months after discharge.[190] A study of critical care illness found that 81% and 72% of delirious patients experienced ongoing cognitive problems at 3 months and 12 months after release from the hospital, and that longer delirium duration was independently associated with increased odds of disability in activities of daily living and motor-sensory dysfunction in the following year.[191]

A systematic search found that patients who experienced delirium were at increased risk of dementia (62.5% vs 8.1%).[177] Even after adjusting for dementia severity, comorbidity, and demographic characteristics, patients who had developed delirium experienced greater cognitive deterioration in the year following hospitalization. With cognitive deterioration proceeding at twice the rate in the year after hospitalization compared with patients who did not develop delirium.[192]

The Vantaa 85+ study followed individuals 85 years and older (n = 553) for up to 10 years and found that delirium increased the risk of incident dementia and was associated with worsening dementia severity.[193] In fact, delirium was associated with the loss of 1.0 more Mini-Mental State Examination points per year (95% CI 0.11–1.89) compared with those with no history of delirium.

Studies have found a reciprocal relationship between cognitive deficits and dementia; that is, evidence suggests that the presence of baseline cognitive deficits, including dementia, lowers the threshold to develop delirium, whereas available data confirm that there is a significant acceleration in the slope of cognitive decline in patients with AD following an episode of delirium (Fong and colleagues, 2009).

Imaging studies have found a relationship between the occurrence of delirium and cerebral changes. Among ICU survivors with respiratory failure or shock, patients with longer delirium duration displayed greater evidence of brain atrophy as measured by a larger ventricle-to-brain ratio at the time of hospital discharge and at 3-month follow-up.[194] Similarly, longer delirium duration was also associated with smaller superior frontal lobe and hippocampal volumes at time of discharge ($P<.001$).

After ICU stay, fractional anisotropy was calculated using diffusion tensor imaging MRI. The imaging findings revealed that longer delirium duration (3 vs 0 days) was associated with lower fractional anisotropy in the genu ($P = .04$) and splenium ($P = .02$) of the corpus callosum, and in the anterior limb of the internal capsule ($P = .01$), at the time of hospital discharge and 3-month follow-up.[195] These associations persisted at 3 months for the genu ($P = .02$) and splenium of the corpus callosum ($P = .004$). Longitudinal follow-up revealed that white matter disruption was associated with worse cognitive scores up to 12 months later.

Behavioral Sequelae

An increasingly recognized consequence of delirium is the development of posttraumatic stress disorder (PTSD), likely associated with the dramatic and bizarre

delusional thinking and hallucinations experienced during a delirious state and facilitated by a lack of factual recall of their ICU stay.[105,196–199] Among ICU patients, standardized interviews found that 73% of patients had delusional memories of their ICU experience at 2 weeks and that patients with no factual memories had the highest anxiety levels and PTSD symptoms after ICU discharge.[198]

A systematic review of studies (n = 26) in general ICU settings with mixed-diagnosis subjects found that the range of PTSD prevalence was 8% to 27%.[200] It identified several clinical (eg, use of benzodiazepines, duration of sedation, and mechanical ventilation) and psychological risk (ie, stress and fear experienced acutely in ICU, and frightening memories of the admission) factors for the development of PTSD.

Fiscal Impact

The economic impact of delirium is substantial, rivaling the health care costs of falls and diabetes mellitus. A retrospective study of medical and surgical subjects (n = 254) in a step-down critical care unit found that subjects who developed delirium used 22% of the total inpatient days and represented greater total costs per case ($63,900 vs $30,800).[7] Multiple studies have demonstrated that delirious subjects experienced prolonged hospital stays (average 5–10 days longer).[7,14,24,178,201,202] A systematic search found that subjects who experienced in-hospital delirium were at increased risk of institutionalization (33.4% vs 10.7%)[177] and had a greater need for placement in nursing homes or rehabilitation facilities.[24,203]

The national burden of delirium on the health care system has been estimated to range from $38 billion to $152 billion each year.[204]

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 neuropsychiatric syndrome found in the general hospital setting. In addition to causing distress to patients, families, and medical caregivers, the development of delirium 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. What is clear from the evidence is that effective prevention and management strategies are needed in order better prevent delirium in the ICU and to decrease its economic burden and long-term physical, emotional, and cognitive effects. Given increasing evidence that delirium is not always reversible and the many sequelae associated with its development, physicians must do everything possible to prevents its occurrence or shorten its duration by recognizing its symptoms early, correcting underlying contributing causes, and using management strategies to improve functional outcomes.

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