The US Geriatric Psychiatry Approach to Delirium

6

Neil Evans and George T. Grossberg

6.1 Introduction

Delirium is a perturbation of the baseline cognitive equilibrium. It can have a wide variety of cognitive effects. It manifests in a decrease of attention, irritability, arousal, mood, amnesia, and disturbed cognition. Every time a patient is admitted to the hospital, they have an age-stratified risk of developing delirium. The hospital experience is jarring and can easily disrupt a patient's circadian rhythm and sense of normality and strains the patient's cognitive reserves. This is especially present in the ICU where often the patient's perception of days and nights merges. Length of hospital stay and days on a ventilator is strongly correlated with delirium. Greater than 50% of patients will have delirium during a prolonged ICU stay (Mattar et al. 2013). Consequences of delirium include doubling of the rate of cognitive decline of dementia. This results in earlier functional disability, increased healthcare costs, decreased quality of life, and an increase in mortality (Fong et al. 2017). Also, without resolution of the delirium, patients are 2.9 times more likely to die at 1 year compared to those who had their delirium resolved (Kiely et al. 2009). Currently, it has not been determined if there is a common underlying

N. Evans
Department of Internal Medicine, Saint Louis University School of Medicine,
St. Louis, MO, USA

G.T. Grossberg (✉)
Department of Psychiatry and Behavioral Neuroscience, Saint Louis University School of Medicine,
St. Louis, MO, USA

Division of Geriatric Medicine, Dementia, Healthy Aging, St. Louis University School of Medicine, St. Louis, MO, USA

Department of Anatomy and Neurobiology, St. Louis University School of Medicine,
St. Louis, MO, USA
e-mail: george.grossberg@health.slu.edu

A.T. Isik, G.T. Grossberg (eds.), *Delirium in Elderly Patients*,
https://doi.org/10.1007/978-3-319-65239-9_6

predisposition to dementia and delirium. Similarly, it is unclear whether dementia itself can be caused by the delirium.

6.2 Presentation

Delirium represents a disruption of the cognitive equilibrium. This disruption is a product of a cascade of cognitive and physiological events that ultimately progresses to dementia, frailty, functional decline, increased levels of care, morbidity, and mortality. Delirium is a state of confusion and a disturbance of consciousness. It has an altered cognitive equilibrium and a fluctuating course. There can be changes throughout the day, and the patient can have lucid periods, which may coincide with morning rounds, that hide the diagnosis and make input and reports from other caregivers crucial to the care of patients at risk for developing delirium.

The cardinal sign of delirium is the disturbance of attention. For example, the patient may be distractible to minor stimuli like the flow of foot traffic outside the room but relatively inattentive to conversation with direct caregivers or visitors. These patients have difficulty with competing thoughts; they are unable to maintain a normal stream of consciousness and lack directed thought processes. They are unable to focus on goal-directed behaviors and unable to order symbols or follow sequenced commands or perform sequenced activities like tying a shoe.

The recognition of delirium is frequently delayed because its most early signs are subtle (Young et al. 2010). This prodromal phase includes subtle thinking changes and sleep disturbance that may be more pronounced in the evening. These initial small changes may only be appreciated by a family member.

There is a spectrum of subtypes of delirium: hyperactive, hypoactive, and mixed. For example, some patients present with increased vigilance, others with psychomotor and autonomic overactivity with agitation, and yet others with tremulousness and visual hallucinations. The different presentations may have different pathophysiological combinations that disrupt the cognitive equilibrium (Fong et al. 2009).

Another more insidious presentation is that of hypoactive delirium. This type of delirium is pervasive and likely underdiagnosed (Fong et al. 2009). It may be the most difficult to diagnose because the symptoms may be vague or subtle or confused for depression with severe fatigue (Fong et al. 2009; Kalish et al. 2014). These patients present with confusion, somnolence, and decreased arousal. The frequency of hypoactive delirium increases with age and is the most common presentation of delirium in palliative care and hospice settings (Kalish et al. 2014).

6.3 Costs

Delirium is associated with profound healthcare system costs but also costs to the patient. In a 2014 analysis of post-hip fracture surgery patients, the incidence of postoperative delirium was 28.6%, and each day of delirium increased the hazard of dying at 6 months by 17% (Bellelli et al. 2014). In a study of patients who

underwent elective surgery with postoperative ICU admission, the 6-month mortality was 32% in patients with hypoactive delirium compared with 8.7% in the other types of delirium (Cavallazzi et al. 2012).

Attempts have been made to quantify the cost burden of delirium to the healthcare system. Healthcare costs for the average patient with delirium are roughly two and half times greater than for a patient without delirium given similar clinical characteristics during a given hospitalization. Per patient, delirium's total cost ranges from $16 to 64 k. Factoring in the prevalence of the disease, delirium costs 38–152 billion USD annually (Leslie et al. 2008). The type of delirium influences its costs, and hypoactive delirium is the costliest. More than a third of the delirious patients have the hypoactive delirium (Bellelli et al. 2016). Early diagnosis and treatment of delirium provides an opportunity for a substantial reduction in healthcare costs and improvements in quality of life.

The time course of the disease is related to its high healthcare cost; delirium was thought to be completely reversible, but sequelae are nearly ubiquitous. If delirium does develop, there is evidence that some older patients do not recover quickly nor at all, and the persistence of delirium is associated with adverse outcomes and need for ongoing high levels of care (Cole et al. 2009; McAvay et al. 2006). Hshieh et al. showed clinically meaningful impairment in postoperative patients who developed delirium for up to 18 months (Hshieh et al. 2017).

The reversibility of delirium depends on the pathophysiological cause. If the cause was medications, electrolyte disturbance, or infection, there is a higher likelihood of reversing an episode of delirium. However, patients are at higher risk of permanent cognitive disruption if their source of delirium was hypoxia or global metabolic encephalopathy. Delirium increases the odds of having dementia by eightfold. Delirium is associated with a loss of 0.4–1 point on mini-mental status exam each year subsequently (Davis et al. 2012, 2017). The rate of cognitive decline after delirium is more rapid with underlying dementia (Davis et al. 2017). Delirium may deplete the cognitive reserves and hasten the rate of cognitive decline.

6.4 Incidence

It is important to be vigilant for any cognitive disruption in all patients, but especially those who are at higher risk. Therefore, knowing the general delirium rates among different populations can help guide the allocation of resources for preventing delirium (see Table 6.1). In addition, several risk factors increase the likelihood of a patient having a disrupted cognitive equilibrium. These risks include dementia, age (>65 years), sex (male), frailty, loss of activities of daily living, malnutrition, the use of antipsychotics, feeding tubes, urinary catheters, living in a nursing home, acute pain, renal disease, hepatic disease, emotional distress, other comorbidities, and sleep deprivation (Fong et al. 2009; Leslie et al. 2008; Bellelli et al. 2016; Inouye et al. 2007; Han et al. 2009; Verloo et al. 2016). Also, those who have had a previous episode of delirium are at higher risk of developing delirium (Bush et al. 2014).

Table 6.1 Delirium rates among different populations

Patient population	Percentage of patients developing delirium
Adult in the community	1–2 (Fong et al. 2009)
General hospital patient	20 (Kostas et al. 2013; Ryan et al. 2013)
General neurology patient	29 (Bellelli et al. 2016)
Recent stroke	10–48 (Shi et al. 2012)
Age < 50 years old	5 (Ryan et al. 2013)
Age > 80	35 (Ryan et al. 2013)
Vascular dementia	32 (Hasegawa et al. 2013)
Alzheimer's disease	15 (Hasegawa et al. 2013)
Postcardiac surgery unit patients	26–52 (Brown 2014)
Intensive care unit	70–83 (Pisani et al. 2005)
Four weeks after the cancer treatment hematopoietic stem cell transplantation	50 (Fann et al. 2002)
Terminally ill cancer patients	85 (Breitbart and Alici 2008)

6.5 Pathophysiology

There are multiple proposed pathophysiologic mechanisms for delirium. Specifically, the following hypotheses have been suggested as leading to or coincident with delirium:

- Neurotransmitter alterations
- Neuroinflammatory
- Neuronal aging
- Oxidative stress
- Melatonin and sleep dysregulation

In each patient, cognitive equilibrium disruption may occur due to several processes that may simultaneously lead to dysregulated neuronal activity. Delirium is the ultimate outcome that is caused by dysregulation of neuronal activity secondary to systemic disturbances (Maldonado 2013).

In the 1940s, Engel and Romano showed that delirium was a disturbance of global cortical function. Their seminal work associated delirium with slowing of dominant posterior alpha rhythm and the presence of abnormal slow-wave activity on EEG (Romano and Engel 1944). Delirium-like behavior was observed in patients with alcohol and sedative drug withdrawal; however, these patients predominately demonstrated low-voltage, fast-wave activity (Engel and Romano 1959). Trzepacz in 1989 and 1994 cited subcortical contributions to delirium with brainstem auditory evoked potentials, somatosensory evoked potentials, and neuroimaging studies of the thalamus, basal ganglia, and the pontine reticular formation (Trzepacz et al. 1989; Trzepacz 1994).

6.6 Neurotransmitter Mechanisms

Acetylcholine is a well-studied neurotransmitter, and it is implicated in the delirium state. The lack of physiologically active acetylcholine (either by decreased absolute amount or ineffective receptors) has been correlated with the development of delirium. Several studies have used an objective test, the serum anticholinergic activity (SAA) to quantify anticholinergic effects. It has been shown that increased SAA positively correlated with the development of delirium (Mach et al. 1995; Campbell et al. 2009a; Golinger et al. 1987). Measurements of SAA, measured with binding assays with preparations of brain muscarinic receptors, correlate with the severity of delirium in postoperative and medical patients (Mach et al. 1995). In patients with hypoxia and thiamine deficiency, known risk factors for delirium, there is indirect evidence of associated decreased acetylcholine synthesis in the CNS (Mach et al. 1995; Osiezagha et al. 2013; Yogaratnam et al. 2013; Hshieh et al. 2008). It is important to note that while overall decreases in acetylcholine levels have been implicated in the pathophysiology of acetylcholine, increasing acetylcholine levels to baseline is not necessarily correlated with the amelioration of delirium (Hshieh et al. 2008).

Many medications taken by older adults have anticholinergic activity, even if the primary mechanism of drug is not anticholinergic (Chew et al. 2008). Therefore, it is important to consider medication effects in any adult at risk for delirium, as they can contribute to deterioration of the patient's cognitive equilibrium. Other neurotransmitters have also been implicated in the pathophysiology of delirium. Dopamine excess, disturbances in serotonin, and gamma-aminobutyric acid (GABA) are among the neurotransmitters studied in this context (Maclullich et al. 2008; Sapolsky 1996).

6.7 Neuroinflammatory and Oxidative Stress Hypotheses

The neuroinflammatory hypothesis, per Cerejeira et al., involves "acute peripheral inflammatory stimulation induces activation of brain parenchymal cells, expression of proinflammatory cytokines, and inflammatory mediators in the central nervous system" (Cerejeira et al. 2010). Cytokine release and other neuroinflammatory mediators decrease perfusion and oxygenation, leading to decreased cerebral oxidative metabolism. There is an increase in the blood-brain barrier (BBB) permeability leading to neuronal and synaptic dysfunction. The hypothesized BBB disruption and the presence of the inflammatory mediators from the systemic inflammation affect microglial cells and activate and modulate nearby cells, leading to the cognitive and behavioral symptoms of delirium (Maldonado 2013; Cerejeira et al. 2010; Butterworth 2013, 2015). There have been correlations of increased inflammatory mediators C-reactive protein, interleukin IL-1 and IL-6 tumor necrosis factors in delirious patients lending support to this hypothesis (Ritchie et al. 2014; Vasilevskis et al. 2012; George and Mukaetova-Ladinska 2007; Sheldon et al. 1993; de Rooij et al. 2007; Murray et al. 2012).

The activated immune system, as discussed above, can contribute to oxidative damage in the brain at the cellular level. Cellular aging, hypoperfusion, and infection all lead to the formation of reactive oxygen species (ROS) (Aliev et al. 2010; He et al. 2010; Gao et al. 2008). Aliev et al. have proposed this damages the blood-brain barrier through leukocyte adhesion to endothelial cells. The endothelial cells, which are the primary component of the blood-brain barrier, suffer impaired barrier function after leukocyte adhesion. This ultimately leads to increased permeability to ROS and thus oxidative stress in the brain (Aliev et al. 2010). The cycle continues as free radicals are implicated in systemic cellular damage and have been shown to further deteriorate the BBB, leading to increased endothelial permeability (Aliev et al. 2010; He et al. 2010; Hala 2007). The increased permeability allows increased fluid shifts into the brain with perivascular edema formation. At the cellular level, increased edema fluid can decrease perfusion and make oxygen diffusion more difficult. This ultimately leads to microcirculatory impairment and possible ischemic injury or dysfunction (Maldonado 2013). To support this theory further, deficiency in the antioxidant vitamin C is a known contributor to age-related cognitive decline and Alzheimer's disease (Harrison 2012). Pursuant to the previous discussion of neurotransmitter function in the pathogenesis of delirium, acetylcholine synthesis may be particularly sensitive hypoxic injury (Hshieh et al. 2008; Hirsch and Gibson 1984; Cinalli et al. 2013).

6.8 Neuronal Aging Hypothesis

The neuronal aging hypothesis derives from observations that there is an increased frequency of delirium in patients over 65 (Maldonado 2013; McNicoll et al. 2003). The probability of transitioning to a delirious state after administration of lorazepam increases by 2% per year after age 65 (Pandharipande et al. 2006). As we age, there is an increased vulnerability to stressors because of a lack of physiologic reserve (Troncale 1996). There are multifactorial reasons that include altered levels of neurotransmitters, blood flow to the brain decreases, and neuron loss (Kochunov et al. 2009; Kelly et al. 2006; Juraska and Lowry 2012; Chen et al. 2011). Neuronal aging helps to explain why younger patients frequently can tolerate greater stress conditions than elderly with a gradually decreasing physiologic reserve before the development of delirium (Maldonado 2013). Additionally, the presence of compromised cognitive abilities before a stressful event is associated with an increase in the incidence of delirium in medical and surgical patients (McNicoll et al. 2003; Franco et al. 2010; Litaker et al. 2001).

6.9 Melatonin and Sleep Dysregulation Hypothesis

Melatonin and sleep dysregulation hypothesis focuses on the disruption of the usual stages of sleep that occurs in hospitalized or stressed patients. Sleep deprivation itself has been associated with delirium, and this condition is quite prevalent in hospitalized patients (Flannery et al. 2016).

The 24-h circadian cycle is maintained by light exposure and other factors which affects melatonin secretion. Its disruption can lead to delirium (Fong et al. 2017; Bellelli et al. 2016; Hshieh et al. 2017; Davis et al. 2017; Verloo et al. 2016; Flannery et al. 2016; Fitzgerald et al. 2016; Taito et al. 2016a, b; Bellani et al. 2016; Chen et al. 2016; Dubb et al. 2016; Foster et al. 2016; Hodgson et al. 2016; Kuladee and Prachason 2016; Mo et al. 2016; Morris et al. 2016; Moss et al. 2016; Simel and Rennie 2016).

Melatonin has sleep-wake cycle regulatory effects and helps to reset the circadian rhythm if it is disturbed. Studies in the ICU environment have shown improved quality of sleep, and there are suggestions that prophylactic use may decrease the incidence of delirium (Fong et al. 2017; Bellelli et al. 2016; Hshieh et al. 2017; Davis et al. 2017; Verloo et al. 2016; Flannery et al. 2016; Fitzgerald et al. 2016; Taito et al. 2016a, b; Bellani et al. 2016; Chen et al. 2016; Dubb et al. 2016; Foster et al. 2016; Hodgson et al. 2016; Kuladee and Prachason 2016; Mo et al. 2016; Morris et al. 2016; Moss et al. 2016; Simel and Rennie 2016; Bourne et al. 2008; Sultan 2010; de Jonghe et al. 2014).

The multiple hypotheses of delirium complement and overlap with one another. There are multiple possible mechanisms that likely work in concert to produce the disruption of cognitive equilibrium and that clinicians see as the various manifestations of delirium (e.g., hyperactive, mixed, and hypoactive delirium) (Table 6.2).

6.10 Diagnosis

The diagnosis of delirium requires multidisciplinary vigilance and a low threshold for diagnosis. In a study by Inouye in 2001, on the sole basis of clinical judgement, nurses diagnosed 19% of patients with delirium (Inouye et al. 2001). To improve detection of delirium, it is important to know which patients are more susceptible to delirium.

In general, the most important risk factors for delirium are advanced age, preexisting cognitive impairment (e.g., major neurocognitive disorders such as Alzheimer's disease, vascular dementia), and multiple prescribed and over-the-counter medication usage (Bush et al. 2014; Hugo and Ganguli 2014).

The key to diagnosing early is identifying cognitive equilibrium changes. Certain patients have an increased probability of developing delirium (Table 6.1). For at-risk patients, multidisciplinary interaction is beneficial, including the patients' visitors, families, nurses, and physicians. Family members often have a better understanding of changes in cognitive equilibrium and may aid in the diagnosis (Inouye et al. 2001). Also helpful are afternoon and nighttime observations as the fluctuating mental status may worsen secondary to circadian processes.

Currently, DSM V (Table 6.3) criteria are used to diagnose delirium. The most accepted, validated, and rapid screening tool is the Confusion Assessment Method (CAM). The test looks for changes in mental status, distractibility, disorganized thinking, and the level of consciousness (e.g., hypervigilance versus somnolence).

Table 6.2 List of common drugs that can cause delirium

Prescription drugs	
Central acting agents	• Anticholinergics (oxybutynin) • Anticonvulsants (barbiturates) • Antiparkinsonian agents (benztropine, trihexyphenidyl, and selegiline) • Benzodiazepines (the medication and the withdrawal) • Hypnotics (trazodone)
Analgesics	• Opiates (especially meperidine) • Nonsteroidal anti-inflammatory drugs (case reports of COX-2 inhibitors) • Ketamine
Antihistamines	• First generation (diphenhydramine)
Gastrointestinal agents	• Antispasmodics • H_2 blockers
Antinauseants	• Scopolamine • Dimenhydrinate
Antibiotics	• Fluoroquinolones
Psychotropic medications	• Tricyclic antidepressants • Lithium
Cardiac medications	• Disopyramide • Digitalis • Antihypertensives (β-blockers, methyldopa, and diuretics)
Miscellaneous	• Skeletal muscle relaxants • High-dose steroids
Over-the-counter medications and complementary/alternative medications	• Tylenol PM, Motrin PM, Aleve PM (the PM component is diphenhydramine, a potent anticholinergic) • Antinauseants (dimenhydrinate, scopolamine) • Mandrake root, jimsonweed, *Atropa belladonna*, and henbane (contain scopolamine and anticholinergic compounds) • Medications combined with alcohol • Alcohol and its withdrawal

Adapted from: Alagiakrishnan and Wiens (2004)

Table 6.3 Condensed DSM V delirium criteria

An acute change from baseline in attention and orientation
With an additional cognitive disturbance (i.e., memory, language, perception, or vision)
That is not better explained by an established or evolving neurocognitive disorder

One of the difficulties with the CAM is the requirement of additional training before being able to perform it correctly. Another screening tool which has promise is the Global Attentiveness Rating (GAR). The test involves a 2-min or longer conversation with the patient performed by the clinician. At the conclusion, the

clinician answers the question: "How well did the patient maintain attention with you during the interview?" A score of ten is perfect engagement and zero is no communication.

The history of the present illness needs to be obtained from a reliable informant/caregiver. It is important to ascertain any recent and chronic illnesses, kidney or liver compromise, medication lists, herbs/supplements, over-the-counter medications, how and when they are taken, substance abuse whether drugs or ethanol, recent psychiatric history, and cognitive baseline (Fig. 6.1). These factors will help to understand the patient's baseline cognitive equilibrium.

6.11 Head-to-Toe Analysis

After the patient is identified as having delirium, the next step is to identify potentially reversible causes and/or contributors (Fig. 6.1). It begins with a thorough assessment of the history. This is followed by a whole-body assessment (Fig. 6.2). General physical examination is challenging in a confused and agitated patient but is important to pursue to the extent the patient allows. Vital signs with pulse rate, pulse oximetry, temperature, and BP with orthostatic changes (Fig. 6.1). The hydration status of skin and mucus membrane condition, as well as any possible infectious conditions, are important.

The neurologic exam may be challenging due to poor cooperation and inattention in a patient with delirium. Assessment focuses on assessing for changes from the patient's baseline cognitive equilibrium. This includes documenting the patient's level of consciousness and the extent of attentiveness. If possible, cranial nerve exam including visual fields and motor exam are important to rule out focal neurologic etiologies. Indicated diagnostic tests include urinalysis, complete blood count, chest x-ray, complete metabolic panel, thyroid hormone levels, and toxicology screen (Fig. 6.1).

History	Diagnostic Tests	As Needed
Medication List	Urinalysis	ABG
Over the Counter Medications	Urine Drug Screen	CT Scan
Herbs and Supplements	Glucose Levels	MRI
Drugs and Alcohol History	Hemoglobin Levels	Lumbar Puncture
Psychiatric History	Electrolytes (Ca, Na, Mg, PO_4)	Electroencephalogram
Current Medical History	Temperature	Vitamin B12 Levels
Recurrent Illnesses	Blood Pressure	
Trauma	Osmolality	
Sleep History	Thyroid Hormone Levels	
Bowel and Urinary History	Parathyroid Hormone Levels	
Hydration History	Pancreatic Enzymes	
Baseline Mental Status and Mobility	Liver and Kidney Function Tests	
	Pharmaceutical Drug Levels	
	X-ray for Pneumonia	

Fig. 6.1 Important information to obtain

Head to Toe Differential Diagnosis for Possible Causes of Delirium

Overall	TIA, cerebrovascular accident, subdural hematoma, post-ictal state, trauma, needle track marks, abuse, anemia, chronic pulmonary disease, sepsis, hypothermia, hyperthermia, leukemic blast cell crisis, thrombocytosis, alcohol abuse, malnutrition, sleep deprivation, bipolar, depression, delusions, hallucinations, withdrawal, and Wernicke's Encephalopathy.
HEENT	Head: Central nervous system infections, seizures, stroke. Eyes: Decreased visual acuity, acute angle closure glaucoma, retinal artery occlusion, vitreous hemorrhage. Ears: Deafness, presbycusis, ear infection, tinnitus. Nose: Sinus infection, influenza. Throat/Mouth: Cavities, retropharyngeal abscess.
Neck/ Hormonal	Thyroid toxicosis, hyperparathyroidism, adrenal insufficiency or overactivity, hyper or hypoglycemia.
Chest	Myocardial infarction, angina, coronary artery dissection, bronchitis, pneumonia, pleuritis, pulmonary embolism, asthma exacerbation, aspiration, and shingles.
Digestive Tract	Constipation, stool retention, bowel obstruction, peptic ulcer disease, pancreatitis, acute liver failure, cholecystitis, mesenteric ischemia, diverticulitis.
Genitourinary Tract	Urinary Retention, urinary tract infection, kidney stone, acute kidney injury, sexual transmitted diseases, hernia, bacterial vaginosis, pelvic prolapse, vulvar irritation, prostatitis, epididymitis.

Fig. 6.2 Head-to-toe differential diagnosis for possible causes of delirium

6.12 Differential

After a complete but directed history is obtained as described in Fig. 6.1, the causes described in Fig. 6.2 should also be considered, and it is also important to distinguish delirium from nonconvulsive status epilepticus, sundowning, worsening of dementia, and primary psychiatric illnesses. Nonconvulsive status epilepticus may be the most frequently missed diagnosis in the elderly presenting with altered mental status. It can present as a postictal confusion lasting without other signs suggesting status epilepticus, sudden stupor, confusion with hallucinations, and stroke-like symptoms that can disappear. It is a condition that does not have the classic ictal features. It is important if suspected to perform an EEG (Beyenburg et al. 2007). Dementia can have disorientation and difficulty with memory, but changes are frequently more progressive. Dementia with Lewy bodies may also have visual hallucinations like delirium (Scott and Barrett 2007). Sundowning frequently occurs in a patient with dementia, and its symptoms include increased confusion, restlessness, hallucinations, verbal outbursts, and wandering fluctuating loss of attention in a patient. It is important to get a clear cognitive baseline for patients with sundowning and patients with dementia (Evans and Grossberg 2016). Depression can present with reduced concentration symptoms similar to hypoactive delirium but will not fluctuate to the same extent. Assessing the patient at multiple times of the day or asking other caregivers can help rule it out. Mania can appear like delirium with agitation as it can present with attention difficulties, hallucinations, impulsivity, recklessness, and psychotic behavior. The hallucinations in mania will typically be auditory rather than visual and the speech will be pressured. It is important to get a family history and a psychiatric history to help rule it out (Hilty et al. 2006).

6.13 Treatment

The best treatment is prevention and the maintenance of vigilance for cognitive equilibrium changes. The early bedside application of the CAM criteria by all staff detects early perturbations in cognitive equilibrium. Close attention will reveal fluctuating mental status, inattention, altered level of consciousness, or disorganized thinking. All these observations may help with early identification of delirium. Combined preventive strategies appear to be effective in preventing delirium (Litaker et al. 2001; Clegg and Young 2011). First, one must identify and reverse the acute cause or causes to the extent that is possible. Early approach includes treating fluid and electrolyte imbalances, improving nutritional status, and treating infections. Modifying risk factors in the environment of the patient is a powerful way to help reduce and ameliorate delirium once it has developed; this includes maintaining supportive care with regular reorientation to person, place, time, and reasons for admission. Measures to reduce anxiety, reassuring family members, and surrounding the patient with familiar objects, visible clocks, and calendars with easily read characters also assist in the treatment of delirium. It is imperative to maintain adequate hydration and feeding and to avoid sleep deprivation by protecting normal sleep cycles. Also, correcting vision and hearing impairment is a priority as the loss of these senses can be very emotionally and cognitively disruptive.

Limiting unnecessary medications and withdrawal from benzodiazepines, barbiturates, selective serotonin reuptake inhibitors, alcohol, and other drugs is useful to remove any potential contributing substances to the delirium (Fong et al. 2009).

It is important to have a low threshold for treatment of pain. Pain medications should be provided on a scheduled basis as patients with delirium may have a difficult time reporting pain. Pain regimens should be centered around non-opioid agents, preferring acetaminophen and lidocaine patches if applicable. If there remain symptoms of pain, consider elevating analgesia with short-acting oral opioids with extreme caution as opioids can worsen delirium (Fong et al. 2006). Prophylactic bowel regimens may prevent and treat possible constipation and urinary retention issues (Manepalli et al. 1990). Monitoring of intake and output will assure that the patient has appropriate hydration and nutrition and will monitor for urinary or fecal retention as these are common causes of delirium (Gower et al. 2012). Ensure the patient is upright when eating to prevent aspiration. Thiamine deficiency is common in the elderly, and alcohol use disorder can be difficult to detect in this population; therefore, thiamine supplementation should be considered. With less evidence, other vitamins may also be considered for supplementation, folate and B12. Encourage a return to baseline activity levels by ambulating out of bed if possible and physical therapy-type activity (Taito et al. 2016b; Robinson and Eiseman 2008).

Disturbances in circadian rhythms have been reported as a potential contributor and effect of delirium. Improving circadian rhythms via good sleep hygiene, e.g., ensuring regular wake times and scheduled bedtimes, is important. It is important to refrain from interrupting these patients with midnight venipuncture, medications, and vital sign checks. There is also emerging evidence that melatonin given

prophylactically prevents elderly patients from becoming delirious when presenting to medical wards, though no difference was found when presenting to the surgical wards (Sultan 2010; de Jonghe et al. 2014). Melatonin also has been shown to improve agitated behaviors in delirium (Breitbart and Alici 2012; Al-Aama et al. 2011). One should minimize the use of chemical or physical restraints, as this can worsen or even precipitate delirium (Leslie et al. 2008; Inouye et al. 2007). In patients with agitation/aggressivity and/or psychosis in the context of delirium, short-term use of pharmacotherapy may be indicated.

Table 6.4 reviews various pharmacologic agents which may be useful to prevent harm to self/others or to give time to evaluate for potentially reversible etiologies. Haloperidol is considered the drug of choice for hospital-associated delirium by many healthcare professionals and professional guidelines (Flaherty et al. 2011; Schrijver et al. 2016).

The practice guideline for the treatment of patients with delirium states the first-line agent to treat the hyperactive symptoms of delirium is titrated haloperidol beginning with 0.5 mg (Trzepacz et al. 2010). If extrapyramidal side effects are seen early in the treatment with haloperidol, consider the possibility of Lewy body dementia or Parkinson's disease. If there is an allergy to haloperidol,

Table 6.4 Pharmacological therapy for delirium

Drug	Dose	Adverse effects	Comments
Antipsychotics			
Haloperidol	0.5–1 mg orally or intramuscularly; can repeat every 4 h (orally) or every 60 min (intramuscularly)	Extrapyramidal syndrome, prolonged QT interval, insomnia	Randomized, controlled trials demonstrate reduction in symptom severity and duration
Atypical antipsychotics			
Risperidone	0.5 mg twice daily	Extrapyramidal syndrome, prolonged QT interval, drowsiness Sedation, orthostasis	Randomized, controlled trials comparing efficacy against haloperidol showed comparable response rates
Olanzapine	2.5–5 mg daily		
Quetiapine	25 mg, 2–3 times daily		
Benzodiazepines			
Lorazepam	0.5–1 mg orally; can repeat every 4 h	Paradoxical excitation, respiratory depression, excessive sedation, confusion, long acting	Did not show improvement in condition; treatment limited by adverse effects. Benzodiazepines can worsen delirium and should be avoided
Cholinesterase inhibitors			
Donepezil	5 mg daily	Nausea, vomiting, diarrhea, bradycardia	No randomized, controlled studies have been conducted. Not recommended

Modified from Fong et al. (2009), Candy et al. (2012), and Breitbart et al. (1996)

atypical antipsychotics may also be considered (Schrijver et al. 2016; Trzepacz et al. 2010; Campbell et al. 2009b; Tampi et al. 2015). For further information, see Table 6.4.

Conclusion

In the hospital population, disruption to the fragile cognitive equilibrium can result in delirium. It is important to have vigilance with at-risk populations, including elderly, severely ill, and recently operated upon patients. Evaluation should include routine utilization of the CAM as a standard screening device. Preventive care, including prompt evaluation and treatment of precipitating conditions, withdrawal from alcohol and other drugs and medications, frequent reorientations, and good sleep practices, can prevent and may reduce the severity of subsequent delirium. Early diagnosis, evaluation, and treatment of precipitating conditions, combined with aggressive multimodal treatments, can result in a more favorable prognosis in patients with cognitive equilibrium changes and can improve the acute and long-term impact on the patient, family, and caregivers.

References

Al-Aama T, Brymer C, Gutmanis I, Woolmore-Goodwin SM, Esbaugh J, Dasgupta M (2011) Melatonin decreases delirium in elderly patients: a randomized, placebo-controlled trial. Int J Geriatr Psychiatry 26(7):687–694

Alagiakrishnan K, Wiens CA (2004) An approach to drug induced delirium in the elderly. Postgrad Med J 80(945):388–393

Aliev G, Palacios HH, Gasimov E, Obrenovich ME, Morales L, Leszek J et al (2010) Oxidative stress induced mitochondrial failure and vascular hypoperfusion as a key initiator for the development of alzheimer disease. Pharmaceuticals (Basel) 3(1):158–187

Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A et al (2016) Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 315(8):788–800

Bellelli G, Mazzola P, Morandi A, Bruni A, Carnevali L, Corsi M et al (2014) Duration of postoperative delirium is an independent predictor of 6-month mortality in older adults after hip fracture. J Am Geriatr Soc 62(7):1335–1340

Bellelli G, Morandi A, Di Santo SG, Mazzone A, Cherubini A, Mossello E et al (2016) "Delirium Day": a nationwide point prevalence study of delirium in older hospitalized patients using an easy standardized diagnostic tool. BMC Med 14(1):106

Beyenburg S, Elger CE, Reuber M (2007) Acute confusion or altered mental state: consider nonconvulsive status epilepticus. Gerontology 53(6):388–396

Bourne RS, Mills GH, Minelli C (2008) Melatonin therapy to improve nocturnal sleep in critically ill patients: encouraging results from a small randomised controlled trial. Crit Care 12(2):R52

Breitbart W, Alici Y (2008) Agitation and delirium at the end of life: "We couldn't manage him". JAMA 300(24):2898–2910, E1

Breitbart W, Alici Y (2012) Evidence-based treatment of delirium in patients with cancer. J Clin Oncol 30(11):1206–1214

Breitbart W, Marotta R, Platt MM, Weisman H, Derevenco M, Grau C et al (1996) A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry 153(2):231–237

Brown CH (2014) Delirium in the cardiac surgical ICU. Curr Opin Anaesthesiol 27(2):117–122

Bush SH, Kanji S, Pereira JL, Davis DH, Currow DC, Meagher DJ et al (2014) Treating an established episode of delirium in palliative care: expert opinion and review of the current evidence base with recommendations for future development. J Pain Symptom Manag 48(2):231–248

Butterworth RF (2013) The liver-brain axis in liver failure: neuroinflammation and encephalopathy. Nature reviews. Gastroenterol Hepatol 10(9):522–528

Butterworth RF (2015) Pathogenesis of hepatic encephalopathy and brain edema in acute liver failure. J Clin Exp Hepatol 5(Suppl 1):S96–S103

Campbell N, Boustani M, Limbil T, Ott C, Fox C, Maidment I et al (2009a) The cognitive impact of anticholinergics: a clinical review. Clin Interv Aging 4:225–233

Campbell N, Boustani MA, Ayub A, Fox GC, Munger SL, Ott C et al (2009b) Pharmacological management of delirium in hospitalized adults—a systematic evidence review. J Gen Intern Med 24(7):848–853

Candy B, Jackson KC, Jones L, Leurent B, Tookman A, King M (2012) Drug therapy for delirium in terminally ill adult patients. Cochrane Database Syst Rev 11:CD004770

Cavallazzi R, Saad M, Marik PE (2012) Delirium in the ICU: an overview. Ann Intensive Care 2(1):49

Cerejeira J, Firmino H, Vaz-Serra A, Mukaetova-Ladinska EB (2010) The neuroinflammatory hypothesis of delirium. Acta Neuropathol 119(6):737–754

Chen JJ, Rosas HD, Salat DH (2011) Age-associated reductions in cerebral blood flow are independent from regional atrophy. NeuroImage 55(2):468–478

Chen S, Shi L, Liang F, Xu L, Desislava D, Wu Q et al (2016) Exogenous melatonin for delirium prevention: a meta-analysis of randomized controlled trials. Mol Neurobiol 53(6):4046–4053

Chew ML, Mulsant BH, Pollock BG, Lehman ME, Greenspan A, Mahmoud RA et al (2008) Anticholinergic activity of 107 medications commonly used by older adults. J Am Geriatr Soc 56(7):1333–1341

Cinalli AR, Guarracino JF, Fernandez V, Roquel LI, Losavio AS (2013) Inosine induces presynaptic inhibition of acetylcholine release by activation of A3 adenosine receptors at the mouse neuromuscular junction. Br J Pharmacol 169(8):1810–1823

Clegg A, Young JB (2011) Which medications to avoid in people at risk of delirium: a systematic review. Age Ageing 40(1):23–29

Cole MG, Ciampi A, Belzile E, Zhong L (2009) Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. Age Ageing 38(1):19–26

Davis DH, Muniz Terrera G, Keage H, Rahkonen T, Oinas M, Matthews FE et al (2012) Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study. Brain 135(Pt 9):2809–2816

Davis DH, Muniz-Terrera G, Keage HA, Stephan BC, Fleming J, Ince PG et al (2017) Association of delirium with cognitive decline in late life: a neuropathologic study of 3 population-based cohort studies. JAMA Psychiat 74(3):244–251

Dubb R, Nydahl P, Hermes C, Schwabbauer N, Toonstra A, Parker AM et al (2016) Barriers and strategies for early mobilization of patients in intensive care units. Ann Am Thorac Soc 13(5):724–730

Engel GL, Romano J (1959) Delirium, a syndrome of cerebral insufficiency. J Chronic Dis 9(3):260–277

Evans NR, Grossberg GT (2016) Sundowning: phenomenology, pathophysiology, and treatment approaches. Psychiatry Advisor [Internet]. http://www.psychiatryadvisor.com/alzheimers-disease-and-dementia/sundowning-phenomenology-pathophysiology-and-treatment-approaches/article/524142/. Accessed 17 May 2017

Fann JR, Roth-Roemer S, Burington BE, Katon WJ, Syrjala KL (2002) Delirium in patients undergoing hematopoietic stem cell transplantation. Cancer 95(9):1971–1981

Fitzgerald J, O'Regan N, Adamis D, Timmons S, Dunne C, Trzepacz P, Meagher D (2016) Concordance between the delirium motor subtyping scale (DMSS) and the abbreviated version (DMSS-4) over longitudinal assessment in elderly medical inpatients. Int Psychogeriatr 28:845–851

Flaherty JH, Gonzales JP, Dong B (2011) Antipsychotics in the treatment of delirium in older hospitalized adults: a systematic review. J Am Geriatr Soc 59(Suppl 2):S269–S276
Flannery AH, Oyler DR, Weinhouse GL (2016) The impact of interventions to improve sleep on delirium in the ICU: a systematic review and research framework. Crit Care Med 44(12):2231–2240
Fong HK, Sands LP, Leung JM (2006) The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. Anesth Analg 102(4):1255–1266
Fong TG, Tulebaev SR, Inouye SK (2009) Delirium in elderly adults: diagnosis, prevention and treatment. Nat Rev Neurol 5(4):210–220
Fong TG, Inouye SK, Jones RN (2017) Delirium, dementia, and decline. JAMA Psychiat 74(3):212–213
Foster J, Burry LD, Thabane L, Choong K, Menon K, Duffett M et al (2016) Melatonin and melatonin agonists to prevent and treat delirium in critical illness: a systematic review protocol. Syst Rev 5(1):199
Franco JG, Valencia C, Bernal C, Ocampo MV, Trzepacz PT, Pablo J et al (2010) Relationship between cognitive status at admission and incident delirium in older medical inpatients. J Neuropsychiatry Clin Neurosci 22(3):329–337
Gao L, Laude K, Cai H (2008) Mitochondrial pathophysiology, reactive oxygen species, and cardiovascular diseases. Vet Clin North Am Small Anim Pract 38(1):137–155, vi
George J, Mukaetova-Ladinska EB (2007) Delirium and C-reactive protein. Age Ageing 36(2):115–116
Golinger RC, Peet T, Tune LE (1987) Association of elevated plasma anticholinergic activity with delirium in surgical patients. Am J Psychiatry 144(9):1218–1220
Gower LE, Gatewood MO, Kang CS (2012) Emergency department management of delirium in the elderly. West J Emerg Med 13(2):194–201
Hala M (2007) Pathophysiology of postoperative delirium: systemic inflammation as a response to surgical trauma causes diffuse microcirculatory impairment. Med Hypotheses 68(1): 194–196
Han JH, Morandi A, Ely EW, Callison C, Zhou C, Storrow AB et al (2009) Delirium in the nursing home patients seen in the emergency department. J Am Geriatr Soc 57(5):889–894
Harrison FE (2012) A critical review of vitamin C for the prevention of age-related cognitive decline and Alzheimer's disease. J Alzheimers Dis 29(4):711–726
Hasegawa N, Hashimoto M, Yuuki S, Honda K, Yatabe Y, Araki K et al (2013) Prevalence of delirium among outpatients with dementia. Int Psychogeriatr 25(11):1877–1883
He F, Yin F, Peng J, Deng X, Wu L, Zhang C (2010) Molecular mechanism for change in permeability in brain microvascular endothelial cells induced by LPS. Zhong Nan Da Xue Xue Bao Yi Xue Ban 35(11):1129–1137
Hilty DM, Leamon MH, Lim RF, Kelly RH, Hales RE (2006) A review of bipolar disorder in adults. Psychiatry (Edgmont) 3(9):43–55
Hirsch JA, Gibson GE (1984) Selective alteration of neurotransmitter release by low oxygen in vitro. Neurochem Res 9(8):1039–1049
Hodgson CL, Bailey M, Bellomo R, Berney S, Buhr H, Denehy L et al (2016) A binational multicenter pilot feasibility randomized controlled trial of early goal-directed mobilization in the ICU. Crit Care Med 44(6):1145–1152
Hshieh TT, Fong TG, Marcantonio ER, Inouye SK (2008) Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence. J Gerontol A Biol Sci Med Sci 63(7):764–772
Hshieh TT, Saczynski J, Gou RY, Marcantonio E, Jones RN, Schmitt E et al (2017) Trajectory of functional recovery after postoperative delirium in elective surgery. Ann Surg 265(4):647–653
Hugo J, Ganguli M (2014) Dementia and cognitive impairment: epidemiology, diagnosis, and treatment. Clin Geriatr Med 30(3):421–442
Inouye SK, Foreman MD, Mion LC, Katz KH, Cooney LM Jr (2001) Nurses' recognition of delirium and its symptoms: comparison of nurse and researcher ratings. Arch Intern Med 161(20):2467–2473

Inouye SK, Zhang Y, Jones RN, Kiely DK, Yang F, Marcantonio ER (2007) Risk factors for delirium at discharge: development and validation of a predictive model. Arch Intern Med 167(13):1406–1413

de Jonghe A, van Munster BC, Goslings JC, Kloen P, van Rees C, Wolvius R et al (2014) Effect of melatonin on incidence of delirium among patients with hip fracture: a multicentre, double-blind randomized controlled trial. CMAJ 186(14):E547–E556

Juraska JM, Lowry NC (2012) Neuroanatomical changes associated with cognitive aging. Curr Top Behav Neurosci 10:137–162

Kalish VB, Gillham JE, Unwin BK (2014) Delirium in older persons: evaluation and management. Am Fam Physician 90(3):150–158

Kelly KM, Nadon NL, Morrison JH, Thibault O, Barnes CA, Blalock EM (2006) The neurobiology of aging. Epilepsy Res 68(Suppl 1):S5–20

Kiely DK, Marcantonio ER, Inouye SK, Shaffer ML, Bergmann MA, Yang FM et al (2009) Persistent delirium predicts greater mortality. J Am Geriatr Soc 57(1):55–61

Kochunov P, Ramage AE, Lancaster JL, Robin DA, Narayana S, Coyle T et al (2009) Loss of cerebral white matter structural integrity tracks the gray matter metabolic decline in normal aging. NeuroImage 45(1):17–28

Kostas TR, Zimmerman KM, Rudolph JL (2013) Improving delirium care: prevention, monitoring, and assessment. Neurohospitalist 3(4):194–202

Kuladee S, Prachason T (2016) Development and validation of the Thai version of the 4 'A's test for delirium screening in hospitalized elderly patients with acute medical illnesses. Neuropsychiatr Dis Treat 12:437–443

Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK (2008) One-year health care costs associated with delirium in the elderly population. Arch Intern Med 168(1):27–32

Litaker D, Locala J, Franco K, Bronson DL, Tannous Z (2001) Preoperative risk factors for postoperative delirium. Gen Hosp Psychiatry 23(2):84–89

Mach JR Jr, Dysken MW, Kuskowski M, Richelson E, Holden L, Jilk KM (1995) Serum anticholinergic activity in hospitalized older persons with delirium: a preliminary study. J Am Geriatr Soc 43(5):491–495

Maclullich AM, Ferguson KJ, Miller T, de Rooij SE, Cunningham C (2008) Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. J Psychosom Res 65(3):229–238

Maldonado JR (2013) Neuropathogenesis of delirium: review of current etiologic theories and common pathways. Am J Geriatr Psychiatry 21(12):1190–1222

Manepalli J, Grossberg GT, Mueller C (1990) Prevalence of delirium and urinary tract infection in a psychogeriatric unit. J Geriatr Psychiatry Neurol 3(4):198–202

Mattar I, Chan MF, Childs C (2013) Risk factors for acute delirium in critically ill adult patients: a systematic review. ISRN Crit Care 2013:1–10

McAvay GJ, Van Ness PH, Bogardus ST Jr, Zhang Y, Leslie DL, Leo-Summers LS et al (2006) Older adults discharged from the hospital with delirium: 1-year outcomes. J Am Geriatr Soc 54(8):1245–1250

McNicoll L, Pisani MA, Zhang Y, Ely EW, Siegel MD, Inouye SK (2003) Delirium in the intensive care unit: occurrence and clinical course in older patients. J Am Geriatr Soc 51(5): 591–598

Mo Y, Scheer CE, Abdallah GT (2016) Emerging role of melatonin and melatonin receptor agonists in sleep and delirium in intensive care unit patients. J Intensive Care Med 31(7): 451–455

Morris PE, Berry MJ, Files DC, Thompson JC, Hauser J, Flores L et al (2016) Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure: a randomized clinical trial. JAMA 315(24):2694–2702

Moss M, Nordon-Craft A, Malone D, Van Pelt D, Frankel SK, Warner ML et al (2016) A randomized trial of an intensive physical therapy program for patients with acute respiratory failure. Am J Respir Crit Care Med 193(10):1101–1110

Murray C, Sanderson DJ, Barkus C, Deacon RM, Rawlins JN, Bannerman DM et al (2012) Systemic inflammation induces acute working memory deficits in the primed brain: relevance for delirium. Neurobiol Aging 33(3):603–616, e3

Osiezagha K, Ali S, Freeman C, Barker NC, Jabeen S, Maitra S et al (2013) Thiamine deficiency and delirium. Innov Clin Neurosci 10(4):26–32

Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS et al (2006) Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 104(1):21–26

Pisani MA, Redlich CA, McNicoll L, Ely EW, Friedkin RJ, Inouye SK (2005) Short-term outcomes in older intensive care unit patients with dementia. Crit Care Med 33(6): 1371–1376

Ritchie CW, Newman TH, Leurent B, Sampson EL (2014) The association between C-reactive protein and delirium in 710 acute elderly hospital admissions. Int Psychogeriatr 26(5): 717–724

Robinson TN, Eiseman B (2008) Postoperative delirium in the elderly: diagnosis and management. Clin Interv Aging 3(2):351–355

Romano J, Engel GL (1944) Electroencephalographic data. Arch Neurol Psychiatr 51(356)

de Rooij SE, van Munster BC, Korevaar JC, Levi M (2007) Cytokines and acute phase response in delirium. J Psychosom Res 62(5):521–525

Ryan DJ, O'Regan NA, Caoimh RO, Clare J, O'Connor M, Leonard M et al (2013) Delirium in an adult acute hospital population: predictors, prevalence and detection. BMJ Open 3(1)

Sapolsky RM (1996) Stress, glucocorticoids, and damage to the nervous system: the current state of confusion. Stress (Amsterdam, Netherlands) 1(1):1–19

Schrijver EJ, de Graaf K, de Vries OJ, Maier AB, Nanayakkara PW (2016) Efficacy and safety of haloperidol for in-hospital delirium prevention and treatment: a systematic review of current evidence. Eur J Intern Med 27:14–23

Scott KR, Barrett AM (2007) Dementia syndromes: evaluation and treatment. Expert Rev Neurother 7(4):407–422

Sheldon J, Riches P, Gooding R, Soni N, Hobbs JR (1993) C-reactive protein and its cytokine mediators in intensive-care patients. Clin Chem 39(1):147–150

Shi Q, Presutti R, Selchen D, Saposnik G (2012) Delirium in acute stroke: a systematic review and meta-analysis. Stroke 43(3):645–649

Simel DL, Rennie D (2016) Delirium. In: The rational clinical examination: evidence-based clinical diagnosis. McGraw-Hill Education, New York, NY

Sultan SS (2010) Assessment of role of perioperative melatonin in prevention and treatment of postoperative delirium after hip arthroplasty under spinal anesthesia in the elderly. Saudi J Anaesth 4(3):169–173

Taito S, Ota K, Shime N (2016a) Is earlier and more intensive physical therapy program better? Am J Respir Crit Care Med 194(8):1032

Taito S, Shime N, Ota K, Yasuda H (2016b) Early mobilization of mechanically ventilated patients in the intensive care unit. J Intensive Care 4(1):50

Tampi RR, Tampi DJ, Barua S et al (2015) Management of delirium in the elderly patients: a review of evidence. J Drug Abuse 1:1

Troncale JA (1996) The aging process. Physiologic changes and pharmacologic implications. Postgrad Med 99(5):111–114, 20–2

Trzepacz PT (1994) The neuropathogenesis of delirium. A need to focus our research. Psychosomatics 35(4):374–391

Trzepacz PT, Sclabassi RJ, Van Thiel DH (1989) Delirium: a subcortical phenomenon? J Neuropsychiatry Clin Neurosci 1(3):283–290

Trzepacz PT, Breitbart W, Franklin J, Levenson J, Richard Martini D, Wang P (2010) Treatment of patients with delirium. In: Practice Guideline for the treatment of patients with delirium. Trzepacz PT, cheir. American Psychiatric Association, APA Press. 2010

Vasilevskis EE, Han JH, Hughes CG, Ely EW (2012) Epidemiology and risk factors for delirium across hospital settings. Best Pract Res Clin Anaesthesiol 26(3):277–287

Verloo H, Goulet C, Morin D, von Gunten A (2016) Association between frailty and delirium in older adult patients discharged from hospital. Clin Interv Aging 11:55–63

Yogaratnam J, Jacob R, Naik S, Magadi H, Sim K (2013) Prolonged delirium secondary to hypoxic-ischemic encephalopathy following cardiac arrest. Clin Psychopharmacol Neurosci 11(1):39–42

Young J, Murthy L, Westby M, Akunne A, O'Mahony R, Guideline Development G (2010) Diagnosis, prevention, and management of delirium: summary of NICE guidance. BMJ 341:c3704