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Delirium in the Elderly: A Comprehensive Review

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Abstract

Delirium is a common neuropsychiatric syndrome in the elderly characterized by concurrent impairments in cognition and behaviors. The etiologies for delirium are often multifactorial and are due to underlying medical illnesses and/or due to medication effect. The diagnosis of delirium is often missed in elderly patients and this condition may be mislabeled as depression or dementia. Untreated, delirium can have devastating consequences in the elderly with high rates of morbidity and mortality. Available evidence indicates that early detection, reduction of risk factors, and better management of this condition can decrease its morbidity rates. In this review, we discuss the etiology, neurobiology, diagnosis, prevention, and treatments for this potentially lethal condition in the elderly.

Keywords

delirium, elderly, neurobiology, treatments

Introduction

Delirium as a disorder was first noted in literature as long as 2500 years ago.[1] In 500 BC, Hippocrates used the words *phrenitis* and *lethargus* to describe the hyperactive and hypoactive forms of delirium.[1] The word delirium is derived from the Latin word *delirare* meaning "crazy or to rave."[2] The term delirium was first used in medical literature by Celcus, a Roman writer, to describe mental disorders associated with fever or head trauma.[1]

Over the last century, many diverse terms have been used to describe delirium, including "acute confusional state," "acute brain syndrome," "acute cerebral insufficiency," and "toxic–metabolic encephalopathy."[3,4] Currently, the term delirium is used to describe a transient, reversible neurospychiatric syndrome that is of acute onset, with a fluctuating course which often occurs in the setting of a medical condition.[5,6]

The *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision; *DSM-IV-TR*) describes delirium as a condition characterized by a disturbance of consciousness (ie, reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.[6] Delirium also involves a change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.[6] These disturbances usually tend to develop over a short period of time (usually hours to days) and they tend to fluctuate during the course of the day. Evidence from history, physical examination, or laboratory findings usually indicates that the disturbance is caused by the direct physiological consequences of a general medical condition.[6]

Epidemiology

The prevalence of delirium depends on the population that is being studied.[7] Higher rates are noted in medical and surgical settings.[2] The rates of delirium in the community are low with the overall prevalence varying from 0.4% to 2%.[2,7] The rates in general hospital admissions increases to 11% to 42%.[8] The incidence of delirium during a hospital stay ranges from 6% to 56%.[7] Postoperative delirium occurs in 15% to 62% of elderly patients.[2,7] In intensive care units (ICU), the incidence of delirium among elderly patients range from 70% to 87%.[2,7] Elderly patients with dementia and those undergoing

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cardiothoracic, emergency orthopedic procedures, vascular surgery, or cataract removal are at higher risk for developing delirium.[2,7] It is estimated that at least one fifth of the 12.5 million patients over 65 years who are hospitalized each year in the United States experience complications during the hospitalization because of delirium.[7]

Predisposing and Precipitating Factors

Although not fully understood, it appears that delirium develops due to a complex interplay between various predisposing and precipitating factors.[2,7] The predisposing factors are those that place elderly patients at higher risk (vulnerability) for developing delirium. Increasing age and a pre-existing cognitive deficit are thought to be the 2 most common predisposing factors for delirium.[2] Delirium may often unmask an underlying cognitive deficit.[2] A study by Inouye demonstrated that a simple predictive model based on 4 predisposing factors—vision impairment, severe illness, cognitive impairment, and BUN/creatinine ratio—can identify at admission older persons at greatest risk for delirium.[9] The proportion of patients developing delirium increased progressively with the number of risk factors present at admission.[9]

Precipitating factors are those that trigger the pathophysiological mechanisms (acute insults) resulting in delirium.[7,9] Inouye and Charpentier identified 5 independent precipitating factors for delirium in the elderly: use of physical restraints adjusted relative risk (RR) 4.4, 95% CI, 2.5-7.9, malnutrition RR, 4.0, 95% CI, 2.2-7.4, more than 3 medications added RR, 2.9, 95% CI, 1.6-5.4, use of bladder catheter RR, 2.4, 95% CI, 1.2-4.7, and any iatrogenic event RR, 1.9, 95% CI, 1.1-3.2.[10] The delirium rates increased progressively from low-risk to high-risk groups in all directions (double-gradient phenomenon). The contributions of baseline precipitating factors were documented to be independent and statistically significant.[10]

Neurobiology

It appears that the known etiologic factors for the development of delirium may act by similar mechanisms, namely causing changes to neuronal membrane function which in turn leads to a number of neurotransmitter aberrations.[2,11] The final common pathway most likely involves a variety of neurotransmitters such as acetylcholine and dopamine and traverse the cortical and subcortical central nervous system pathways. Any process interfering with neurotransmitter function or with the supply or use of substrates can cause delirium.[2,11] In this section, we describe some of the known neurobiological changes associated with delirium.

Neurochemistry

The current evidence indicates that the cholinergic system is involved in the development of delirium.[12] Drugs with anticholinergic properties can induce the development of delirium.[13,14] Patients who have higher anticholinergic burden based on drug-related exposure often have more severe cases of delirium.[15,16] Mechanisms that can result in cholinergic deficiency and contribute to delirium include impaired acetylcholine synthesis, cholinergic synaptic mechanisms, ischemia and global stressors, and neurotransmitter imbalance.[12] Although there is good evidence supporting the cholinergic deficiency hypothesis, there are also weaknesses to this theory. The data for the use of cholinesterase inhibitors for treating delirium is limited.[17] Cholinergic dysfunction also does not completely explain as to why delirium and Alzheimer's disease although pathophysiologically related present differently with relation to attention and memory deficits.[12]

The acetylcholine hypothesis is not separable from the dopamine hypothesis because these 2 neurotransmitters interact closely with each other in the brain, often reciprocally.[13,18] Elevated levels of dopamine can cause delirium as seen in treatment with dopaminergic medications, cocaine abuse, and electroconvulsive therapy (ECT).[11] Dopamine-blocking medications are used to treat delirium as they may temporarily rebalance the ratio of acetylcholine and dopaminergic activity until the underlying causes of delirium is treated.[13] Studies show that dopamine agonists can create slower electroencephalogram (EEG) patterns in spite of motor hyperactivity which is seen in hyperactive delirium. Increases in dopamine availability may lead to increased psychomotor activity, hyperalertness, agitation, irritability, restlessness, combativeness, distractibility, and psychosis, often associated with hyperactive or mixed-type delirium.[11]

Other neurotransmitters like glutamate, -aminobutyric acid, 5-hydroxytryptamine (5-HT), and norepinephrine have also been implicated in the development of delirium although their roles are less well studied than those for acetylcholine and dopamine.[19]

Neural Injury, Inflammation, and Stress Response

Delirium may result from direct injury to the neurons.[7] These injuries can be caused by a variety of metabolic or ischemic insults to the brain.[11] Hypoxia, hypoglycemia and other metabolic derangements can result in impaired synthesis and release of neurotransmitters causing alterations in neural transmission thus leading to delirium.[7]

Delirium also represents a central nervous system manifestation of a systemic disease state that has damaged the blood-brain barrier.[20] Change in the blood-brain barrier integrity allows the brain to become more susceptible to the effects of systemic inflammation.[21] Emerging data indicates that trauma, infection, and surgical procedures lead to increased levels of proinflammatory cytokines, which can induce delirium in high-risk individuals by direct neurotoxic effects and also affecting neurotransmission by altering the level of acetylcholine, dopamine, norepinephrine, and serotonin in the brain.[22,23]

Research indicates that precipitants of delirium can usefully be divided into 2 conceptually distinct classes: direct brain

insults and aberrant stress responses.[24] Direct brain insult indicates dysfunction or damage to the brain resulting from conditions like hypoxia or metabolic disturbances.[24] The aberrant stress responses include the harmful effect of acute stress responses.[24] Evidence suggests that these adaptive processes have the potential to become deleterious when they are exaggerated, sustained, or when they affect a brain already compromised by disease states.[24] Risk factors for delirium including severe illness, surgery, and trauma can induce immune activation and a physical stress response comprising increased activity of the limbic-hypothalamic-pituitary-adrenocortical (LHPA) axis and changes in the permeability of the blood-brain barrier.[21,24] Available evidence indicates that elevated levels of cortisol can precipitate and maintain delirium.[24] Studies indicate that in patients with delirium, cortisol levels are not only elevated in the serum but also in the cerebrospinal fluid.[25,26]

Neurostructural Changes

In an excellent systematic review of studies of neuroimaging in delirium, the investigators noted that most studies of structural abnormalities found that patients with delirium had more brain atrophy and increased white matter lesions, although confounding by age and/or cognitive ability could not be excluded. Basal ganglia lesions were commonly reported as being associated with delirium, but in the absence of analysis of other brain regions, it is not certain whether this is a specific finding. Two functional studies suggest that delirium might be associated with perfusion abnormalities, but further work is required to determine whether these are global or whether specific regions are implicated.[27] They concluded that the findings in these studies are broadly consistent, there being associations between delirium and cortical atrophy, and between ventricular enlargement and increased white matter lesions. Associations between neuroimaging data and delirium do not necessarily imply that these changes are causal in the etiology of delirium; they may simply indicate a more generally vulnerable brain.[27]

Genetics

Although the studies on the genetics of delirium in elderly patients are scarce, recent studies indicate that the genetic make-up of an individual may increase the risk of becoming delirious.[28] Most of these studies have examined the association of delirium with the apolipoprotein E4 allele. Majority of these studies (4 of the 5) did not confirm the association between apolipoprotein E4 allele and delirium.[28] The study of the genetics of delirium due to alcohol withdrawal have found positive associations for 3 different candidate genes involved in dopamine transmission.[29] One gene was involved in the glutamate pathway along with 1 neuropeptide gene and 1 cannabinoid gene. Variations in 2 candidate genes involved in the dopamine transmission (the dopamine receptor D3 and the dopamine transporter) were validated in independent study populations. These analyses suggest that dopaminergic neurotransmission may play an important role in alcohol withdrawal delirium. However, the findings in the *DRD3* gene were not confirmed in an elderly population with delirium.[30] In the *SLC6A3* gene, the variable number of tandem repeats was associated with alcohol withdrawal delirium but again this variation was not confirmed in elderly patients with delirium.[28] Two other single nucleotides polymorphisms (SNPs), rs393795 and rs1042098, in this gene were associated with delirium.[28]

Clinical Subtypes

Based on the motor activity, delirium can be classified broadly into 3 subtypes; hypoactive, hyperactive, and mixed types.[31] Patients with hyperactive delirium are restless, agitated, hypervigilant, and with active hallucinations and delusions. The hypoactive subtype presents with lethargy, sedation, and with slowed motor response. Patients with mixed delirium demonstrate both hyperactive and hypoactive features. Under or misdiagnosis is a considerable problem with delirium with psychosis, hypomania, anxiety disorders, and akathisia being important differential diagnoses for the hyperactive and mixed profile patients. Patients with the hypoactive form are often misdiagnosed as having depression or dementia. The hypoactive form is the most frequently seen subtype in the elderly.[31] The hypoactive subtype is also least likely to be detected by clinicians as compared with the hyperactive or mixed subtypes. There is some evidence that each delirium subtype results from a different pathophysiological mechanism and carries a different prognosis.[31] Overall, the balance of evidence suggests that the hypoactive form of delirium is associated with a relatively poorer prognosis although this is probably more relevant in patients with dementia.[32]

Subsyndromal Delirium

Subsyndromal delirium (SSD) is the term used to denote the clinical condition where the patients present with one or more delirium symptoms but do not meet the full criteria for delirium.[33] It occurs in 21% to 76% of older medical inpatients.[34] Such symptoms may precede or follow an episode of full-blown delirium or may never progress to full-blown delirium.[34] It is unclear whether this condition constitutes a stage in the spectrum of brain dysfunction severity which varies from normal to subsyndromal delirium to delirium.[35] In 1 study, patients with prevalent SSD had longer acute care hospital stay, increased postdischarge mortality, more symptoms of delirium, and a lower cognitive and functional level at follow-up than patients with no SSD.[33] In a more recent study, the investigators compared the 6- and 12-month outcomes of older medical inpatients who recovered from SSD by 8 weeks with the outcomes of patients who did not recover or did not have an index episode of SSD. The primary and secondary outcomes of patients in the SSD-recovered group were better than the outcomes of patients in the SSD-not recovered group and, for the most part, intermediate between the outcomes of patients in the SSD-not recovered and no-SSD groups.[33]

Table 1. Most Commonly Used Rating Scales to Detect Delirium[7,44,48]

Rating Scales	Description
Confusion Assessment Method (CAM)	It assesses the presence, severity, and fluctuation of delirium. Includes acute onset, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbances, psychomotor agitation or retardation, and altered sleep-wake cycle. Criteria for delirium: features 1 (acute onset and fluctuating course) and 2 (inattention) are essential features, and feature 3 (disorganized thinking) or 4 (altered level of consciousness) is supported by expert judgment and clinical practice, in which the first 2 and either of the latter 2 are required for diagnosis. It has a sensitivity of 94%-100% and specificity of 90%-95%. It closely correlates with the *DSM-IV* criteria for delirium. It can be completed by any trained clinician. Can be administered in 5 minutes.
Confusion Assessment Method-Intensive Care Unit (CAM-ICU)	It is a nonverbal adaptation of the confusion assessment method (CAM). The instrument includes a series of nonverbal tasks to rate the 4 key criteria: acute change from baseline or fluctuating course, inattention, disorganized thinking, and altered level of consciousness. All tasks and questions were designed to be completed by nonverbal, mechanically ventilated, or restrained patients in ICU settings. The CAM-ICU is not performed in patients who are nonarousable. It can be completed by any trained clinician. Can be administered in 5 minutes.
Delirium Rating Scale (DRS)	It is a 10-item observational scale. Each of 10 items is scored from 0 to a maximum of 2, 3, or 4 points. Range: 0-32. Recommended cutoff score is about 12 points. Rates patients on temporal onset, perceptual disturbance, hallucinations, delusions, psychomotor behavior, cognitive status, physical disorder, sleep-wake cycle disturbance, lability of mood, and variability of symptoms. It has a sensitivity of 0.82 and specificity of 0.94 with a cut-point of 10. It is to be completed by a psychiatrically trained clinician.
Nursing Delirium Screening Scale (Nu-DESC)	Administered by a nurse based on clinical observation in routine practice. Range: 0-10 Five symptoms are rated: disorientation, inappropriate behavior, inappropriate communication, hallucination, and psychomotor retardation. Score of 2 or more indicates delirium. Can be completed in 1 minute.

Persistent Delirium

The traditional description of delirium is that of being transient with recovery being complete if the underlying etiological factors are promptly treated.[6] However, among the elderly, many patients do not recover from an episode of delirium and develop a condition called persistent delirium.[36] In an excellent systematic review, Cole et al sought to determine the frequency and prognosis of persistent delirium in older hospital patients. The investigators found that the combined proportions with persistent delirium at discharge at 1, 3, and 6 months were 44.7%, 95% CI, 26.8% to 63.7%, 32.8%, 95% CI, 18.4% to 47.2%, 25.6%, 95% CI, 7.9% to 43.4%, and 21%, 95% CI, 1.4% to 40.6%, respectively.[37] The outcomes (mortality, nursing home placement, function, cognition) of patients with persistent delirium were consistently worse than the outcomes of patients who had recovered from delirium in terms of skilled nursing facility placement, cognitive and activities of daily living decline, and mortality. In another study, Kiely et al evaluated the association between persistent delirium and 1-year mortality in newly admitted postacute care (PAC) facility patients.[38] They found that nearly one third of the participants remained delirious at 6 months. Cumulative 1-year mortality was 39%. Independent of age, sex, comorbidity, functional status, and dementia, participants with persistent delirium were 2.9, 95% CI, 1.9 to 4.4 times as likely to die during the 1-year follow-up as participants whose delirium resolved. This association remained strong and significant in groups with and without dementia. Additionally, when delirium resolved, the risk of death diminished thereafter. The investigators concluded that patients who were delirious at the time of PAC admission, persistent delirium was a significant independent predictor of 1-year mortality.[38] These studies indicate that in a significant minority of elderly patients, delirium may persist and in those patients the prognosis is grim. A recent systematic review indicated that persistence of delirium was associated with dementia, increasing numbers of medical conditions, increasing severity of delirium, hypoactive symptoms, and hypoxic illnesses..[39]

Nocturnal Delirium (Sundowning or Sundowning Syndrome)

Disruptive behaviors worsening in the late afternoon or evening time are often seen in patients with cognitive impairment.[40] The terms used to describe this phenomenon is "nocturnal delirium," "sundowning," or "sundowning syndrome." Recent studies have focused on the potential role of disordered circadian rhythm as an important contributing factor to sundowning syndrome.[40] These changes are consistent with the existence of circadian rhythm abnormalities that progressively worsen with cognitive and functional deterioration. Other theories describe the role of sleep fragmentation in sundowning.[41] Although most commonly seen in patients with dementia, sundowning syndrome has also been seen in patients with acute delirium.[41] Certain environmental factors have been

Table 2. Differential Diagnoses for Delirium

Clinical Features	Delirium	Dementia	Depression	Primary Psychotic Disorders
Onset	Acute	Insidious	Acute or insidious	Acute or insidious
Duration	Hours to weeks	Months to years	Weeks to months	Weeks to months
Course	Fluctuating	Chronic and progressive	May be chronic	May be chronic
Progress	Usually reversible	Irreversible	Usually reversible	Usually reversible
Level of consciousness	Altered	Usually clear	Clear	Clear
Orientation	Variable	Disoriented	Oriented	Oriented
Attention and concentration	Poor	Normal except in late stage	May be impaired	May be impaired
Speech	Incoherent	Coherent until the late stage	Usually normal	May be pressured
Thought process	Disorganized	Limited	Usually organized	May be disorganized
Perception	Hallucinations are frequent especially visual	May have hallucinations especially visual	May have hallucinations especially auditory	May have hallucinations especially auditory
Psychomotor activity	Variable	Normal	May be slow	Variable

shown to worsen the behavioral symptoms of sundowning. These include changes in the environment, amount of daily light exposure, activities during the day, noise level, disruptions at night, medications, and the patient's medical comorbidities. Sundowning syndrome has been noted in literature to be associated with increased caregiver stress/burnout and institutionalization for the patient.[40]

Assessment

Delirium is consistently underdiagnosed in clinical practice.[42] About one-third to two thirds of delirium goes unrecognized.[43] Reasons for underdiagnosis include a lack of awareness of the clinical features of delirium, its fluctuating nature, its overlap with dementia, the lack of formal cognitive assessment as a routine, and the failure to consider either the possibility of the condition or its consequences.[2] Inadequate information regarding the patient's premorbid level of cognition and function and, ageist attitudes toward older people with an "expectation" of confusion can lead to missed diagnoses.[2]

Currently, the diagnosis of delirium is made on the basis of clinical information, behavioral observations, and cognitive assessment.[7,44] A thorough history clarifies as to whether the changes observed are acute, subacute, or chronic. It also rules in or rules out underlying medical conditions, medication usage, and substance abuse as etiologies for the observed changes in cognition and behaviors. Bedside cognitive assessment detects impairments in orientation, attention, concentration, and memory. Physical examination helps rule out infectious, metabolic, endocrine, cardiovascular, and cerebrovascular diseases that may cause delirium.[2,7]

Initial investigations should include a complete blood count, blood urea and nitrogen levels, electrolytes, blood sugar, liver function, and thyroid function tests.[2,45] An electrocardiogram (EKG) must be done on all patients with preexisting cardiac disease. C reactive protein (CRP), and erythrocyte sedimentation rate (ESR) may be checked in suspected cases of inflammatory diseases. A clean catch urine analysis and culture, blood cultures, arterial blood gases, and chest X-ray (CXR) are also appropriate in suspected infectious etiology. A urine toxicology screen should be done to rule illicit drug use. Serum vitamin B12 and folate levels are tested to rule out nutritional causes for cognitive impairment. An EEG is useful in ruling out seizures and metabolic encephalopathy. Computed tomography (CT) scan and magnetic resonance imaging (MRI) scan of the brain rule out cerebral and cerebrovascular diseases. A lumbar puncture (LP) should only be reserved for cases of suspected meningitis causing delirium.[2,45]

Because of the transient and fluctuating nature of its symptoms, just using the clinical information may lead to an underdiagnosis of delirium.[46] The study by Zou et al suggested that one clinical assessment by a psychiatrist may not be the best method for detecting and diagnosing delirium in the elderly. The investigators opined that a consensus diagnosis or diagnosis by a trained rater using the Confusion Assessment Method (CAM) and multiple observation points may be a more sensitive approach for the diagnosis of delirium in the elderly.[46] Given this data, it is most advisable to use validated assessment scales to support and enhance the clinical evaluation and rate the severity of delirium.[2] A formal diagnosis can be confirmed by using the *DSM-IV-TR* criteria.[6]

In an excellent review, Wong et al systematically evaluated the evidence on the accuracy of bedside instruments in diagnosing the presence of delirium in adults.[44] They concluded that the CAM has the best available supportive data as a bedside delirium instrument. The mini-mental state examination (MMSE; score <24) was the least useful for identifying a patient with delirium.[44] In another study, the investigators compared the validity and reliability of 3 instruments for detection and assessment of delirium in ICU patients.[47] Trained staff members performed daily and independently the Confusion Assessment Method for the ICU (CAM-ICU), the Nursing

Delirium Screening Scale (Nu-DESC), and the Delirium Detection Score (DDS), and these evaluations were compared against the reference standard conducted by a delirium expert (blinded to the study), who used delirium criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition; *DSM-IV*). The investigators concluded that the CAM-ICU showed the best validity of the evaluated scales to identify delirium in ICU patients. The Nu-DESC might be an alternative tool for detection of ICU delirium. The DDS should not be used as a screening tool.[48] These 2 studies indicate that the CAM and the CAM-ICU are the 2 best instruments that are available at the present time to detect delirium at the bedside (Table 1).[44,47]

Differential Diagnoses

Delirium should be differentiated from dementia, depression, and primary psychotic disorder.[2,7] Table 2 indicates the clinical features of these disorders that help distinguish them from one another.[2,7]

Outcomes

Delirium contributes to poor patient outcomes irrespective of baseline patient characteristics and etiological factors.[7] Agitation or lethargy occurring in delirium can increase the risk of aspiration, pressure ulcers, pulmonary emboli, and decreased oral intake.[7] Some patients with delirium never recover to their baseline level of cognitive function following an episode of delirium and demonstrate persistent functional and cognitive losses.[7] A recent study by Fong et al showed a significant acceleration in the slope of cognitive decline occurring following an episode of delirium in a cohort of patients with Alzheimer disease (AD).[49] Across groups, the rate of change in cognitive scores occurred about 3 times faster in those who had delirium compared to those who did not.[49] Such findings indicate that the pathological processes involved in delirium can cause direct neuronal injury causing persistent cognitive changes.[7] Outcomes in patients with dementia who develop delirium are also worse than in those patients who do not develop this condition.[7,50] Patients with dementia who experience delirium had higher rates of hospitalization, institutionalization, and death.[7,51]

Delirium has also been shown to increase nursing time per patient, higher per-day hospital costs, and an increased length of hospital stay.[7,43] The meta-analysis by Witlox et al indicated that delirium is associated with an increased risk of dementia, institutionalization, and death independent of age, sex, comorbid illness or illness severity, and baseline dementia.[52] The economic burden of delirium in the United States is also staggering with a total of approximately $6.9 billion in Medicare hospital expenditure (2004 figures).[7,53] In a recent study, following adjustment for pertinent demographic and clinical characteristics, the average costs per day survived among patients with delirium were more than 2.5 times the costs among patients without delirium.[54] The total cost estimates attributable to delirium ranged from $16,303 to $64,421 per patient. When translated, the national burden of delirium on the health care system ranged from $38 billion to $152 billion each year. When comparing the national annual health care costs for delirium, it is higher than the cost for hip fracture ($7 billion) and nonfatal falls ($19 billion) and comparable to the cost for diabetes mellitus ($91.8 billion).[54]

Prevention

Some investigators estimate that 30% to 40% of cases of delirium are preventable and that prevention is the most effective strategy for minimizing the occurrence of delirium and its adverse outcomes.[7] In a pivotal study, Inouye et al described the multicomponent targeted risk factor intervention (MTI) strategy that used standardized protocols for the management of 6 risk factors for delirium: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration.[55] Delirium developed in 9.9% of the intervention group as compared with 15% of the usual-care group, matched odds ratio, 0.60, 95% CI, 0.39-0.92. The total number of days with delirium (105 vs. 161, $P = .02$) and the total number of episodes (62 vs 90, $P = .03$) were significantly lower in the intervention group. However, the severity of delirium and the recurrence rates were not significantly different between the 2 groups. The total number of targeted risk factors per patient was significantly reduced. Intervention was also associated with significant improvement in the degree of cognitive impairment among patients with cognitive impairment at admission and a reduction in the rate of use of sleep medications among all patients. Among the other risk factors per patient, there were trends toward improvement in immobility, visual impairment, and hearing impairment. The investigators opined that the risk-factor intervention strategy resulted in significant reductions in the number and duration of episodes of delirium in hospitalized older patients; however, the intervention had no significant effect on the severity of delirium or on recurrence rates indicating that primary prevention of delirium is probably the most effective treatment strategy.[56] This intervention showed a short-term cost savings of $831 per hospitalization for intermediate-risk patients and the long-term cost savings approaching $10,000 per year from the prevention of long-term nursing home days.[56,57]

A recent controlled trial indicated that home rehabilitation after acute hospitalization in elderly individuals was associated with a lower risk of delirium and greater patient satisfaction when compared with the inpatient hospital setting.[58] A meta-analysis by Siddiqi et al indicates that a program of proactive geriatric consultation may reduce delirium incidence and severity in patients undergoing surgery for hip fracture.[59] They also found that prophylactic low-dose haloperidol may reduce severity and duration of delirium episodes and shorten length of hospital admission in hip surgery.[59] In the only English language systematic review specific to the prevention of delirium in the elderly, investigators concluded that multicomponent interventions to prevent delirium are effective and should be

Table 3. Summary of Important Meta-Analyses and Systematic Reviews in the Pharmacotherapy of Delirium

Class of Drug	Name of Study	Type of Study	Comparators	Outcomes	Side-Effects	Limitations
Antipsychotics	Lonergan et al[65]	Meta-analysis	Haloperidol with risperidone, olanzapine, and quetiapine	Haloperidol in low dosage has similar efficacy in comparison with the atypical antipsychotics olanzapine and risperidone in the management of delirium.	There is no greater frequency of adverse effects with haloperidol in low doses compared to the other drugs. Higher doses haloperidol was associated with a greater incidence of side effects, mainly parkinsonism, than the atypical antipsychotics.	Only 3 studies met the inclusion criteria.
	Lacasse et al[66]	Systematic review	Antipsychotic therapy with placebo or comparing 2 antipsychotic treatments in an acute care setting	Antipsychotic drugs are efficacious when compared with baseline and safe for the treatment of delirium.	Oral haloperidol was associated with more frequent extrapyramidal side effects, but overall, all agents were well tolerated.	Only 4 studies met the inclusion criteria.
	Seitz et al[67]	Systematic review	Haloperidol, chlorpromazine, olanzapine, risperidone, and quetiapine.	Improvements in delirium severity were reported with all of these antipsychotic medications.	Serious adverse events attributable to antipsychotic medication were uncommon.	No study included a placebo group
	Ozbolt et al[68]	Systematic review	Atypical antipsychotics for the treatment of delirium in the elderly.	Atypical antipsychotic medications demonstrate similar rates of efficacy as haloperidol for the treatment of delirium in the elderly.	In comparison to haloperidol, the frequency of adverse reactions and side effects was found to be much lower with the use of atypical antipsychotic medications.	No double-blind placebo trials exist.
Cholinesterase inhibitors	Overshott et al[17]	Meta-analysis	Blinded randomized controlled trials with cholinesterase inhibitors compared with alternative interventions	One trial of donepezil found no significant difference between the treatment and placebo groups was found in the duration of delirium.	Donepezil was well tolerated.	Only 1 study met the inclusion criteria.
Benzodiazepines	Lonergan et al[71]	Meta-analysis	Lorazepam versus dexmedetomidine, alprazolam versus neuroleptics and lorazepam versus haloperidol and chlorpromazine	Dexmedetomidine had greater efficacy than lorazepam, no advantage of alprazolam compared to neuroleptics and decreased effectiveness of lorazepam and increased adverse effects when compared with neuroleptics.	Benzodiazepines have higher side effects than compartors compounds.	No adequately controlled trials could be found to support the use of benzodiazepines in the treatment of non-alcohol withdrawal related delirium.

(continued)

Table 3 (continued)

Class of Drug	Name of Study	Type of Study	Comparators	Outcomes	Side-Effects	Limitations
Others	Campbell et al[72]	Systematic review	Second-generation antipsychotics, first-generation antipsychotics, cholinergic enhancers, an antiepileptic agent, an inhaled anesthetic, injectable sedatives, and a benzodiazepine.	No superiority for second-generation antipsychotics over haloperidol in managing delirium.	No significant difference between the various compounds.	Data available is limited.

Table 4.

Medication group	Dosage	Side-effects
1. Typical antipsychotics Haloperidol Excessive agitation	0.25–1.0 mg PO BID/TID 0.25–1.0 mg PO or IM; can repeat every 30-60 minutes if needed	Extrapyramidal symptoms, sedation, prolonged QTc interval
2. Atypical antipsychotics	0.25 mg-0.5 mg PO BID/TID 0.25–0.5 mg PO; can repeat every 30-60 minutes if needed 2.5–5.0 mg PO BID 2.5–5.0 mg PO or IM; can repeat every 30-60 minutes if needed 25-50 mg BID/TID 25-50 mg PO; can repeat every 30-60 minutes if needed	Metabolic dysfunction, extrapyramidal symptoms hyperglycemia, prolonged QTc interval
A. Risperidone Excessive agitation		As for Risperidone
B. Olanzapine Excessive agitation		As for risperidone and Olanzapine
C. Quetiapine Excessive agitation		
3. Benzodiazepines Lorazepam Excessive agitation	0.25–1.0 mg PO BID/TID 0.25–1.0 mg PO or IM; can repeat every 30-60 minutes if needed	Paradoxical agitation, sedation, motor incoordination, worsening confusion, respiratory depression
4. Cholinesterase inhibitors Donepezil	5-10 mg PO once daily	Gastrointestinal disturbances

Abbreviations: PO, per oral; BID, bis in die, two times a day; TID, ter in die, three times a day; IM, intramuscular.

implemented through synergistic cooperation between the various health care disciplines.[60] A recent structured-analysis on prevention strategies for delirium showed that interventions to prevent delirium are generally effective.[61]

These studies indicate that strategies to prevent delirium are efficacious in reducing its incidence in both surgical and medical patients. They may reduce the duration and severity of delirium and its effect on functional status. However, these interventions have not produced beneficial effects on the length of stay or mortality due to delirium.

Treatments

Nonpharmacological

Nonpharmacological treatments are the first line of management for patients with delirium.[7,45] They include frequent reorientation, making eye contact, frequent touching, and using clear verbal instructions when talking to patients.[7] Sensory impairments including vision and hearing loss should be minimized by use of corrective devices.[7] The use of physical restraints should be minimized.[7] Treatment should be provided in a nonstimulating environment where noise levels are minimized with the provision for adequate soft lighting.[46] Room and staff changes should be minimized. Although the data for the use of these interventions is limited, they have become part of standard treatment protocols for delirium given their efficacy in clinical practice.[62,63]

Pharmacological

Pharmacotherapy in delirium is mainly targeted toward the treatment of its underlying causes.[2] However, it may also be needed when the patient's behaviors cannot be controlled by nonpharmacological means.[7] They are prescribed when the patient exhibits agitation, aggression, paranoia, and hallucinations that place them and those caring for them at risk of imminent harm.[7] Recent data indicates that the evidence base for effective drug treatment of delirium is restricted by the limitations in many of the studies that have been conducted to date.[64] Given this concern, we chose to only use data from meta-analytics studies and systematic reviews to evaluate the efficacy of pharmacotherapeutic agents for the treatment of delirium.

In an excellent meta-analysis, Lonergan et al compared the efficacy and incidence of adverse effects of haloperidol with risperidone, olanzapine, quetiapine and placebo in the

treatment of delirium.[65] Decrease in delirium scores were not significantly different comparing the effect of low-dose haloperidol (<3.0 mg per day) with the atypical antipsychotics olanzapine and risperidone odds ratio, 0.63, 95% CI, 1.029 to 1.38, $P = .25$. Low-dose haloperidol did not have a higher incidence of adverse effects than the atypical antipsychotics. High-dose haloperidol (>4.5 mg per day) in one study was associated with an increased incidence of extrapyramidal adverse effects compared with olanzapine. Low-dose haloperidol decreased the severity and duration of delirium in postoperative patients, although not the incidence of delirium when compared to placebo controls in one study. There were no controlled trials comparing quetiapine with haloperidol. There investigators concluded that there is no evidence that haloperidol in low dosage has different efficacy in comparison with the atypical antipsychotics olanzapine and risperidone in the management of delirium or has a greater frequency of adverse drug effects than these drugs. High-dose haloperidol was associated with a greater incidence of side effects, mainly parkinsonism, than the atypical antipsychotics.[65]

In a systematic review by Lacasse et al evaluated the efficacy and safety of antipsychotics in the management of delirium in medically or surgically ill patients.[66] The investigators found that antipsychotic agents, either atypical or typical, were effective compared with baseline for the treatment of delirium in medically or surgically ill patients without underlying cognitive disorders. Oral haloperidol was associated with more frequent extrapyramidal side effects, but overall, all agents were well tolerated. They concluded that antipsychotic drugs are efficacious when compared with baseline and safe for the treatment of delirium. Haloperidol remains the most studied agent. Recommendation of one antipsychotic over another as a first-line pharmacologic intervention in the treatment of hospital-associated delirium is limited by the quality and quantity of data available.[66] In another systematic review, Seitz et al evaluated the evidence for the efficacy and safety of antipsychotics in treating delirium.[67] Study medications included haloperidol, chlorpromazine, olanzapine, risperidone, and quetiapine. Improvements in delirium severity were reported with all of these antipsychotic medications. No study included a placebo comparison to account for spontaneous improvements in delirium. Other methodological limitations included inadequate blinding, randomization, and handling of participant withdrawals. The improvements in delirium tended to occur soon after the initiation of treatment, and most of the studies examined used relatively low doses of antipsychotic medication. Serious adverse events attributable to antipsychotic medication were uncommon in studies, although the side effects were not evaluated systematically in most studies. The investigators concluded that to date, there are no published double-blind, randomized, placebo-controlled trials to establish the efficacy or safety of any antipsychotic medication in the management of delirium. There is limited evidence from uncontrolled studies that supports the use of low-dose, short-term treatment of delirium with some antipsychotics.[67]

In a systematic review specific to the elderly, the investigators examined the literature on atypical antipsychotics and summarize the results from published trials in order to evaluate the efficacy and potential benefits of atypical antipsychotics for the treatment of delirium in the elderly population.[68] They found that risperidone was the most thoroughly studied atypical antipsychotic and was found to be approximately 80% to 85% effective in treating the behavioral disturbances of delirium at a dosage of 0.5 to 4 mg daily. Studies of olanzapine indicated that it was approximately 70% to 76% effective in treating delirium at doses of 2.5 to 11.6 mg daily. Although very few studies have been conducted using quetiapine; it also appears to be a safe and effective alternative to high-potency antipsychotics. In comparison to haloperidol, the frequency of adverse reactions and side effects was found to be much lower with the use of atypical antipsychotic medications. In the limited number of trials comparing atypical antipsychotics to haloperidol, haloperidol consistently produced a higher rate (an additional 10% to 13%) of extrapyramidal side effects. The investigators concluded that a review of current literature supports the conclusion that atypical antipsychotic medications demonstrate similar rates of efficacy as haloperidol for the treatment of delirium in the elderly patient, with a lower rate of extrapyramidal side effects. There is limited evidence of true efficacy since no double-blind placebo trials exist.[68]

Although the data on the use of antipsychotics in elderly patients with cognitive impairment is growing, their use is limited by their efficacy and prominent adverse effects. In the most comprehensive study done to date, Schneider et al compared the efficacy of olanzapine, quetiapine, risperidone or placebo for the treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease.[69] The investigators found that there were no significant differences noted among the groups with regard to improvements in symptoms but the time to discontinuation of treatment due to adverse events and intolerability favored the placebo group. They concluded that adverse effects offset the advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease.

Recent evidence indicates that the use of antipsychotics is not very safe in the elderly patients, especially in those with dementia. Concerns include the development of cerebrovascular adverse events (CVAEs) and death. In a recent literature review of evidence, Mittal et al reviewed the risk of cerebrovascular adverse events (CVAEs) and death with antipsychotic medications when used to treat elderly patients with dementia.[70] The available data indicates that the risk of CVAEs is higher in the drug-treated group compared to placebo. Although preliminary, existing data for atypical versus typical antipsychotics indicate that the risk of CVAEs is similar in both groups. No one drug has been found to be safer than the other in terms of the CVAEs. A higher than median doses of a drug, older age, a diagnosis of dementia especially vascular dementia, and comorbid atrial fibrillation have been noted as risk factors for CVAEs. It appeared that the time frame for which the risk of CVAEs remains elevated is about 20 months.

Preliminary data indicates that risk of death with atypical and typical antipsychotics is greater than when compared to the placebo group or the group that did not use these medications. Existing data for atypical versus typical antipsychotics indicate that the risk of death is similar in both groups. No one drug has been found to be safer than the other in terms of the death. Older age, male gender, severe dementia, and functional impairment are associated with a higher risk of death. The risk remains elevated in the first 30 days and possibly to 2 years. The investigators concluded that in the elderly, judicious use of these medications with careful assessment of the risk benefit ratio and close monitoring of the risk factors is needed to ensure the safety and well-being of these patients.[70] Given these risks, antipsychotic medications should be used very carefully in elderly patients with delirium and dementia as these 2 conditions are highly comorbid.

Cholinesterase inhibitors. In a meta-analysis, Overshott et al evaluated the efficacy and safety of cholinesterase inhibitors in the treatment of delirium.[17] They found one trial of donepezil compared with placebo in 15 patients. No significant difference between the treatment and placebo groups was found in the duration of delirium. The mean duration of postoperative delirium for the donepezil group was 1.0 day (standard error 0.0), while for the placebo group it was 1.3 days (standard error 0.19). No other outcomes were measured for the patients who developed delirium. The investigators opined that there is currently no evidence from controlled trials that donepezil is effective in the treatment of delirium.[17]

Benzodiazepines. In a meta-analysis, Lonergan et al determined the effectiveness and incidence of adverse effects of benzodiazapines in the treatment of nonalcohol withdrawal-related delirium.[71] Only one trial met their selection criteria. In this trial comparing the effect of the benzodiazepine lorazepam with dexmedetomidine, a selective alpha-2-adrenergic receptor agonist, on delirium among mechanically ventilated ICU patients, dexmedetomidine treatment was associated with an increased number of delirium- and coma-free days compared with lorazepam-treated patients (dexmedetomidine patients, average 7 days; lorazepam patients, average 3 days, $P = .01$). One partially controlled study showed no advantage of a benzodiazepine (alprazolam) compared with neuroleptics in treating agitation associated with delirium, and another partially controlled study showed decreased effectiveness of a benzodiazepine (lorazepam), and increased adverse effects, compared with neuroleptics (haloperidol, chlorpromazine) for the treatment of acute confusion. The investigators concluded that no adequately controlled trials could be found to support the use of benzodiazepines in the treatment of nonalcohol withdrawal-related delirium among hospitalized patients and at this time benzodiazepines cannot be recommended for the control of this condition.[71]

Others. In another systematic review, Campbell et al reviewed the efficacy and safety of pharmacologic interventions targeting either prevention or management of delirium.[72] The investigators identified 13 studies that met their inclusion criteria and evaluated 15 compounds: second-generation antipsychotics, first-generation antipsychotics, cholinergic enhancers, an antiepileptic agent, an inhaled anesthetic, injectable sedatives, and a benzodiazepine. Four trials evaluated delirium treatment and suggested no differences in efficacy or safety among the evaluated treatment methods (first and second generation antipsychotics). Neither cholinesterase inhibitors nor procholinergic drugs were effective in preventing delirium. Multiple studies, however, suggest either shorter severity and duration or prevention of delirium with the use of haloperidol, risperidone, gabapentin, or a mixture of sedatives in patients undergoing elective or emergent surgical procedures. The investigators concluded that the existing limited data indicates no superiority for second-generation antipsychotics over haloperidol in managing delirium. Although preliminary, results suggest delirium prevention may be accomplished through various mechanisms, but further studies are necessary to prove effectiveness (Table 3).[72]

The American Psychiatric Association (APA) recommends low-dose haloperidol as a first-line agent in the symptomatic management of delirium episodes, with few comparisons of newer second-generation antipsychotic medications included in their evaluation.[62] The second-generation antipsychotics may be an alternative in patients who are not candidates for or who do not tolerate first-generation antipsychotics, although the class has shown no benefit over the first-generation antipsychotics on either efficacy or safety parameters in delirium trials.[72] Because of the risks of cerebrovascular and cardiovascular adverse effects, the use of antipsychotics in patients with delirium should be continuously evaluated to minimize the potential for adverse outcomes.[72] Currently, there is limited data to recommend cholinesterase inhibitors for the treatment of delirium.[17] Evidence indicates that benzodiazepines should not be considered in delirium in patients without a history of psychiatric illness or alcohol withdrawal due to poor outcomes and limited use in the literature (Figure 1).[72]

Conclusion

Delirium is a common neuropsychiatric syndrome in the elderly characterized by concurrent impairments in cognition and behaviors. The etiologies for delirium are often multifactorial and are due to a complex interplay between the various underlying predisposing and precipitating factors. The known etiologic factors for delirium appear to cause changes to the neuronal membrane function which in turn leads to a number of neurotransmitter aberrations. The diagnosis of delirium is often missed in elderly patients and this condition may often be mislabeled as depression or dementia. Untreated, delirium can have devastating consequences in the elderly, with high rates of morbidity and mortality. Standardized screening tools are currently available that can aid in the diagnosis and the assessment of severity of this condition. Current data although limited, supports the use of nonpharmacological treatment

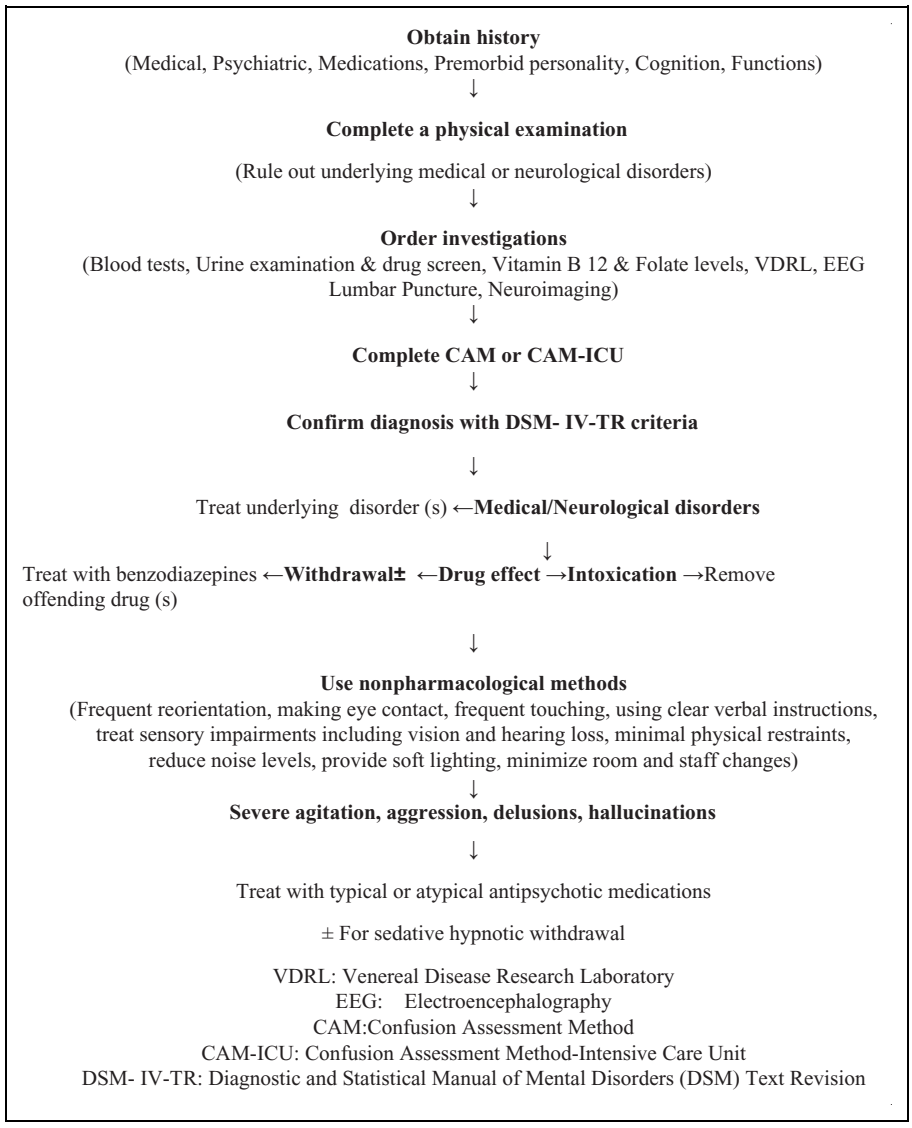

Figure 1. Algorithm for the treatment of delirium.

protocols and some psychotropic medications both in the prevention and the treatment of this condition. Available evidence indicates that early detection, proper correction of risk factors, and better management of symptoms can decrease the morbidity rates for this condition, thereby reducing undue suffering for the patients and their families.

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References

1. Khan RA, Kahn D, Bourgeois JA. Delirium: sifting through the confusion. *Curr Psychiatry Rep*. 2009;11(3):226-234.
2. Saxena S, Lawley D. Delirium in the elderly: a clinical review. *Postgrad Med J*. 2009;85(1006):405-413.
3. Morandi A, Pandharipande P, trabucchi M, et al. Understanding international differences in terminology for delirium and other types of acute brain dysfunction in critically ill patients. *Intensive Care Med*. 2008;34(10):1907-1915.
4. Brown TM, Boyle MF. Delirium. *BMJ*. 2002;325(7365):644-647.
5. Pisani MA, Araujo KL, Van Ness PH, et al. A research algorithm to improve detection of delirium in the intensive care unit. *Crit Care*. 2006;10(4):R121.
6. *Quick Reference to the Diagnostic Criteria from DSM-IV-TR*. Washington, DC: American Psychiatric Association; 2000:83-87.
7. Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. *Nat Rev Neurol*. 2009;5(4):210-220.
8. Miller MO. Evaluation and manegement of delirium in hospitalized older patients. *Am Fam Physician*. 2008;78(11): 1265-1270.

9. Inouye SK. Predisposing and precipitating factors for delirium in hospitalized older patients. *Dement Geriatr Cogn Disord*. 1999;10(5):393-400.
10. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA*. 1996;275(11):852-857.
11. Maldonado JR. Pathoetiological model of delirium: comprehensive understanding of the neurobiology of delirium and an evidence-based approach to prevention and treatment. *Crit Care Clin*. 2008;24(4):789-856.
12. Hshieh TT, Fong TG, Marcantonio ER, et al. Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence. *J Gerontol A Biol Sci Med Sci*. 2008;63(7):764-772.
13. Trzepacz PT. Anticholinergic model for delirium. *Semin Clin Neuropsychiatry*. 1996;1(4):294-303.
14. Tune LE, Damlouji NF, Holland A, et al. Association of postoperative delirium with raised serum levels of anticholinergic drugs. *Lancet*. 1981;2(8248):651-653.
15. Han L, McCusker J, Cole M, et al. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. *Arch Intern Med*. 2001;161(8): 1099-1105.
16. Flacker JM, Cummings V, Mach JR, Jr, et al. The association of serum anticholinergic activity with delirium in elderly medical patients. *Am J Geriatr Psychiatry*. 1998;6(1):31-41.
17. Overshott R, Karim S, Burns A. Cholinestrase inhibitors for delirium. *Cochrane Database Syst Rev*. 2008;(1):CD005317.
18. Flacker JM, Lipsitz LA. Neural mechanisms of delirium: current hypothesis and evolving concepts. *J Gerontol A Biol Sci Med Sci*. 1999;54(6):B239-B246.
19. Gaudreau JD, Gagnon P. Psychotogenic drugs and delirium pathogenesis: the central role of the thalamus. *Med Hypotheses*. 2005;64(3):471-475.
20. Hála M. Pathophysiology of postoperative delirium: systemic inflammation as a response to surgical trauma causes diffuse microcirculatory impairment. *Med Hypotheses*. 2007;68(1): 194 -196.
21. Dimitrijevic OB, Stamatovic SM, Keep RF, et al. Effects of the chemokine CCL2 on blood-brain barrier permeability during ischemia-reperfusion injury. *J Cereb Blood Flow Metab*. 2006;26(6):797-810.
22. Rudolph JL, Ramlawi B, Kuchel GA, et al. Chemokines are associated with delirium after cardiac surgery. *J Gerontol A Biol Sci Med Sci*. 2008;63(2):184-189.
23. Simone MJ, Tan ZS. The role of inflammation in the pathogenesis of delirium and dementia in older adults. *CNS Neurosci Ther*. 2010. doi:10.1111/j1755-5949.2010.00173.x.
24. Maclullich AM, Ferguson KJ, Miller T, et al. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress response. *J Psychosom Res*. 2008;65(3):229-238.
25. Pearson A, de Vries A, Middleton SD, et al. Cerebrospinal fluid cortisol levels are higher in patients with delirium versus controls. *BMC Res Notes*. 2010;8(3):33.
26. Van Munster BC, Bisschop PH, Zwinderman AH. Cortisol, interleukins and S100B in delirium in the elderly. *Brain Cogn*. 2010;74(1):18-23.
27. Soiza RL, Sharma V, Ferguson K, et al. Neuroimaging studies of delirium: a systematic review. *J Psychosom Res*. 2008;65(3):239-248.
28. Van Munster BC, de Rooij SE, Korevaar JC. The role of genetics in delirium in the elderly patient. *Dement Geriatr Cogn Disord*. 2009;28(3):187-195.
29. Van Munster BC, Korevaar JC, de Rooij SE, et al. Genetic polymorphisms related to delirium tremens: a systematic review. *Alcohol Clin Exp Res*. 2007;31(2):177-184.
30. Van Munster BC, Yazdanpanah M, Tanck MW, et al. Genetic polymorphisms in the DRD2, DRD3, and SLC6A3 gene in elderly patients with delirium. *Am J Med Genet B Neuropsychiatr Genet*. 2010;153B(1):38-45.
31. Meagher DJ, Trzepacz PT. Motoric subtypes of delirium. *Semin Clin Neuropsychiatry*. 2000;5(2):75-85.
32. Yang FM, Marcantonio ER, Inouye SK, et al. Phenomenological subtypes of delirium in older persons: patterns, prevalence, and prognosis. *Psychosomatics*. 2009;50(3):248-254.
33. Cole MG, McCusker J, Dendukuri N, et al. The prognostic significance of subsyndromal in delirium in elderly medical inpatients. *J Am Geriatr Soc*. 2003;51(6):754-760.
34. Cole MG, McCusker J, Ciampi A, et al. The 6- and 12-month outcomes of older medical inpatients who recover from subsyndromal delirium. *J Am Geriatr Soc*. 2008;56(11):2093-2099.
35. Ouimet S, Riker R, Bergeron N, et al. Subsyndromal delirium in the ICU: evidence for a disease spectrum. *Intensive Care Med*. 2007;33(6):1007-1013.
36. Cole MG. Persistent delirium in older hospital patients. *Curr Opin Psychiatry*. 2010;23(3):250-254.
37. Cole MG, Ciampi A, Belzile E, et al. Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. *Age Ageing*. 2009;38(1):19-26.
38. Kiely DK, Marcantonio ER, Inouye SK, et al. Persistent delirium predicts greater mortality. *J Am Geriatr Soc*. 2009;57(1):55-61.
39. Dasgupta M, Hillier LM. Factors associated with prolonged delirium: a systematic review. *Int Psychogeriatr*. 2010;22(3):373-394.
40. Bachman D, Rabins P. "Sundowning'' and other temporally associated agitation states in dementia patients. *Ann Rev Med*. 2006;57(1):499-511.
41. Kim P, Louis C, Muralee S, Tampi RR. Sundowning in the elderly patient. *Clin Geriat*. 2005;13(4):32-36.
42. Inouye SK, Foreman MD, Mion LC, et al. Nurses' recognition of delirium and its symptoms: comparison of nurse and researcher ratings. *Arch Intern Med*. 2001;161(20):2467-2473.
43. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age Ageing*. 2006;35(4):350-364.
44. Wong CL, Holroyd-Leduc J, Simel DL, et al. Does this patients have delirium?: value of bedside instruments. *JAMA*. 2010;304(7):779-786.
45. Cole MG. Delirium in elderly patients. *Am J Geriatr Psychiatry*. 2004;12(1):7-21.
46. Zou Y, Cole MG, Primeau FJ, et al. Detection and diagnosis of delirium in the elderly: psychiatris diagnosis, confusion assessment method, or consesensus diagnosis? *Int Psychogeriatr*. 1998;10(3):303-308.

47. Luetz A, Heymann A, Radtke FM, et al. Different assessment tools for intensive care unit delirium: which score to use? *Crit Care Med*. 2010;38(2):409-418.
48. McNicoll L, Pisani MA, Ely EW, et al. Detection of delirium in the intensive care unit: comparison of confusion assessment method for the intensive care unit with confusion assessment method ratings. *J Am Geriatr Soc*. 2005;53(3):495-500.
49. Fong TG, Jones RN, Shi P, et al. Delirium accelrates cognitive decline in Alzheimer disease. *Neurology*. 2009;72(18):1570-1575.
50. Fick D, Foreman M. Consequences of not recognizing delirium superimposed on dementia in hospitalized elderly individuals. *J Gerontol Nurs*. 2000;26(1):30-40.
51. Rockwood K, Cosway S, Carver D, et al. The risk of dementia and death after delirium. *Age Ageing*. 1999;28(6):551-556.
52. Witlox J, Eurelings LS, de Jonghe JF, et al. Delirium in elderly patients and the risk of postdischarge mortality, institutionalisation, and dementia: a meta-analysis. *JAMA*. 2010;304(4):443-451.
53. Young J, Inouye SK. Delirium in older people. *BMJ*. 2007;334(7598):842-846.
54. Leslie DL, Marcantonio ER, Zhang Y, et al. One-year healthcare costs associated with delirium in the elderly population. *Arch Intern Med*. 2008;168(1):27-32.
55. Inouye SK, Bogardus ST Jr, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med*. 1999;340(9):669-676.
56. Rizzo JA, Bogardus ST, Leo-Summers L, et al. Multicomponent targeted intervention to prevent delirium in hospitalized older patients: what is the economic value? *Med Care*. 2001;39(7):740-752.
57. Leslie DL, Zhang Y, Bogardus ST, et al. Consequences of preventing delirium in hospitalized older adults on nursing home costs. *J Am Geriatr Soc*. 2005;53(3):405-409.
58. Caplan GA, Coconis J, Board N, et al. Does home treatment affect delirium? A randomised controlled trial of rehabilitation of elderly and care at home or usual treatment (The REACH-OUT trial). *Age Ageing*. 2006;35(1):53-60.
59. Siddiqi N, Stockdale R, Britton AM, et al. Interventions for preventing delirium in hospitalised patients. *Cochrane Database Syst Rev*. 2007;(2):CD005563.
60. Milisen K, Lemiengre J, Braes T, et al. Multicomponent intervention strategies for managing delirium in hospitalized older people: systematic review. *J Adv Nurs*. 2005;52(1):79-90.
61. Hempenius L, van Leeuwen BL, van Asselt DZ, et al. Structured analyses of interventions to prevent delirium. *Int J Geriatr Psychiatry*. 2010. n/a. doi:10.1002/gps.2560.
62. Treatment of Patients With Delirium. http:// www.psychiatryonline.com/pracGuide/pracGuideTopic_2.aspx. Accessed October 4, 2010.
63. British Geriatric Society. Clinical guidelines for the prevention, diagnosis and management of delirium in older people in hospital. January 2006. http://www.bgs.org.uk/Publications/Clinical%20Guidelines/ clinical_1-2_fulldelirium.htm. Accessed October 4, 2010.
64. Bourne RS, Tahir TA, Borthwick M, et al. Drug treatment of delirium: past, present and future. *J Psychosom Res*. 2008;65(3):273-282.
65. Lonergan E, Britton AM, Luxenberg J, et al. Antipsychotics for delirium. *Cochrane Database Syst Rev*. 2007;(2):CD005594.
66. Lacasse H, Perreault MM, Williamson DR. Systematic review of antipsychotics for the treatment of hospital-associated delirium in medically or surgically ill patients. *Ann Pharmacother*. 2006;40(11):1966-1973.
67. Seitz DP, Gill SS, van Zyl LT. Antipsychotics in the treatment of delirium: a systematic review. *J Clin Psychiatry*. 2007;68(1):11-21.
68. Ozbolt LB, Paniagua MA, Kaiser RM. Atypical antipsychotics for the treatment of delirious elders. *J Am Med Dir Assoc*. 2008;9(1):18-28.
69. Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med*. 2006;355(15):1525-1538.
70. Mittal V, Kurup L, Williamson D, et al. Risk of cerebrovascular adverse events and death in elderly demented patients when treated with antipsychotic medications: a literature review of evidence. *Am J Alzheimers Dis Other Demen*. IN PRESS.
71. Lonergan E, Luxenberg J, Areosa Sastre A. Benzodiazepines for delirium. *Cochrane Database Syst Rev*. 2009;(4):CD006379.
72. Campbell N, Boustani MA, Ayub A, et al. Pharmacological management if delirium in hospitalized adults—a systemic evidence review. *J Gen Intern Med*. 2009;24(7):848-853.