Delirium in elderly people

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Delirium is an acute disorder of attention and cognition in elderly people (ie, those aged 65 years or older) that is common, serious, costly, under-recognised, and often fatal. A formal cognitive assessment and history of acute onset of symptoms are necessary for diagnosis. In view of the complex multifactorial causes of delirium, multicomponent non-pharmacological risk factor approaches are the most effective strategy for prevention. No convincing evidence shows that pharmacological prevention or treatment is effective. Drug reduction for sedation and analgesia and non-pharmacological approaches are recommended. Delirium offers opportunities to elucidate brain pathophysiology—it serves both as a marker of brain vulnerability with decreased reserve and as a potential mechanism for permanent cognitive damage. As a potent indicator of patients' safety, delirium provides a target for system-wide process improvements. Public health priorities include improvements in coding, reimbursement from insurers, and research funding, and widespread education for clinicians and the public about the importance of delirium.

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See Online for appendix

Introduction

Despite first being described more than 2500 years ago, delirium remains frequently unrecognised and poorly understood. Delirium—an acute decline in cognitive functioning—is a common, serious, and often-fatal disorder that affects as much as 50% of elderly people (ie, those aged 65 years or older) in hospital, and costs more than US$164 billion per year in the USA[1] and more than $182 billion per year[2,3] in 18 European countries combined (2011 estimates; appendix). Delirium is preventable in 30–40% of cases,[4,5] and thus holds substantial public health relevance as a target for interventions to prevent the associated burden of downstream complications and costs.[6] Accordingly, delirium is now included on patients' safety agendas[7] and has been increasingly used as an indicator of health-care quality for elderly people.[8,9]

Delirium can be thought of as acute brain failure—ie, a multifactorial syndrome analogous to acute heart failure—and might provide a novel approach to elucidation of brain functioning and pathophysiology. Delirium can have acute onset in response to noxious insults (such as major surgery or sepsis), and might help to shed light on cognitive reserve—ie, the brain's resilience to external factors.[10] In this context, delirium could be a marker of the vulnerable brain with diminished reserve capacity. Evidence suggests that the trajectory of normal cognitive ageing might not be a linear decline, but rather a series of punctuated declines and recoveries in the face of delirium and major medical insults.[11,12] Furthermore, accumulating evidence suggests that delirium itself might lead to permanent cognitive decline and dementia in some patients. We provide a state-of-the-art review of delirium to guide clinical practice and elucidate important topics for future research.

Epidemiology

On the basis of a systematic review of medical literature published between Jan 1, 2004, and Aug 31, 2012, we selected articles about the incidence and outcomes of delirium by the following criteria: sample size of 100 or more, prospective sampling framework, satisfaction of Strengthening the Reporting of OBservational Studies in Epidemiology (STROBE) criteria for setting, participants, measurement, and statistical methods,[13] and use of a validated delirium instrument. We chose this timeframe to update information gathered for a previous comprehensive review.[14] An additional inclusion criterion for incidence studies was serial delirium assessments with intervals of no longer than 3 days by trained research staff or clinicians. Table 1 presents the prevalence rates (present on admission) and incidence rates (new onset) of delirium across different populations as described in 35 selected studies (appendix). The sum of prevalence and incidence yields the overall occurrence rate in each setting. The highest incidence rates were noted in intensive-care unit ICU and in postoperative and palliative care settings. Because many of these 35 studies excluded patients with cognitive impairment or dementia at baseline, true incidence is probably underestimated. In general medical and old age medicine wards, the prevalence of delirium (present on admission) of 18–35% should be added to the incidences, yielding an overall occurrence in these settings of 29–64% (table 1). The prevalence of delirium in the community is low (1–2%), but onset usually brings the patient to emergency care.

Search strategy and selection criteria

We comprehensively searched Medline, PubMed, and reference lists from relevant original articles and systematic reviews (appendix) with the terms "delirium", "acute confusion", and "organic brain syndrome" for papers published in English between Jan 1, 1990, and Aug 31, 2012. To provide an overview of epidemiology, causes, and non-pharmacological and pharmacological management of delirium, we reviewed work published between Jan 1, 2004, and Dec 31, 2012, to update a previous comprehensive review, with the exceptions of validated risk prediction models and non-pharmacological studies, for which we expanded our search to include original articles published between Jan 1, 1990, and Dec 31, 2012. All data presented are taken from original papers, and we did not do meta-analyses. The pathophysiology search used the same search terms with the addition of "etiology", "pathophysiology", "physiopathology", or "pathogenesis". Our goal was to provide a comprehensive review of primary articles, and thus systematic reviews and meta-analyses were not routinely included; however, we checked the reference lists of such papers to ensure the comprehensive inclusion of primary articles in our review process (appendix).

	Prevalence (%)*	Incidence (%)*	Outcomes (adjusted RR†)
Surgical			
Cardiac	..	11–46	Cognitive dysfunction 1·7; functional decline 1·9
Non-cardiac	..	13–50	Functional decline 2·1; cognitive dysfunction 1·6
Orthopaedic	17	12–51	Dementia or cognitive dysfunction 6·4–41·2; admission to institution 5·6
Medical			
General medical	18–35	11–14	Mortality 1·5–1·6; functional decline 1·5
Old age medicine	25	20–29	Falls 1·3; mortality 1·9; admission to institution 2·5
Intensive care	7–50	19–82	Mortality 1·4–13·0; longer length of stay 1·4–2·1; extended mechanical ventilation 8·6
Stroke	..	10–27	Mortality 2·0; any of increased length of stay, functional impairment, or death 2·1
Dementia	18	56	Cognitive decline 1·6–3·1; admission to an institution 9·3; mortality 5·4
Palliative care, cancer	..	47	..
Nursing home or postacute care	14	20–22	Mortality 4·9
Emergency department	8–17	..	Mortality 1·7

Some data are provided as ranges. All values were derived from selected articles with sample sizes of 100 or more that satisfied the Strengthening the Reporting of OBservational studies in Epidemiology (STROBE) criteria for setting, participants, measurement, and statistical methods, and included a validated delirium instrument. An additional inclusion criterion for incidence studies was serial delirium assessments no more than 3 days apart by trained research staff or clinicians. The appendix contains a complete list of references and further details on all articles. RR=relative risk. *Sum of prevalence and incidence yields overall occurrence rates of delirium in each setting. †Derived from studies that provided adjustment for at least one covariable.

Table 1: **Incidence of delirium and associated outcomes, by population**

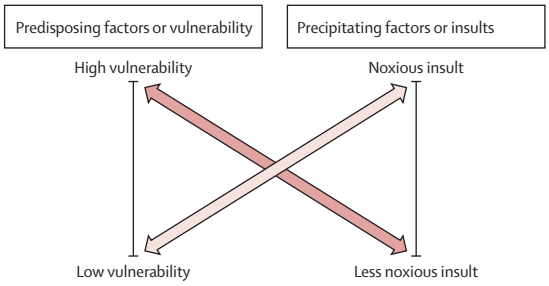

Figure: **Multifactorial model of delirium in older people**
Onset of delirium is dependent on a complex interaction between the patient's baseline vulnerability (predisposing factors) at admission and precipitating factors or noxious insults occurring during hospital admission. Adapted from Inouye and Charpentier,[31] by permission of the *Journal of the American Medical Association*.

On presentation to the emergency department, delirium is present in 8–17% of all elderly people and 40% of nursing home residents.

Table 1 lists adverse outcomes associated with delirium drawn from selected studies that included adjustment for confounders. Delirium is consistently associated with increased mortality across all non-surgical populations of patients, including those in general medicine or old age medicine wards; ICUs or stroke or dementia units; nursing homes; and emergency departments. Compared with those who do not develop delirium, patients who develop delirium in the ICU have a two-to-four-times increased risk of death both in and out of hospital,[15–18] those who develop delirium on general medicine or old age medicine wards have a one-and-a-half times increased risk for death in the year after hospital admission,[19–21] and those with delirium who present in the emergency department have a roughly 70% increased risk of death during the first 6 months after the visit.[22] Cognitive impairment is common (>50%) in surgical patients who develop delirium, and impairments last as long as a year postoperatively.[12,23,24] Physical function is impaired for 30 days or more after discharge in surgical and non-surgical patients who develop delirium.[20,25,26] Delirium at admission to postacute care is associated with a five-times increased risk of mortality at 6 months.[27] In elderly patients with dementia, delirium is associated with increased rates of cognitive decline,[28–30] admission to institutions,[29] and mortality.[29]

Causes

Although a single factor can lead to delirium, usually delirium is multifactorial in elderly people. The multifactorial model of the cause of delirium has been well validated and widely accepted.[31] Development of delirium is dependent on complex inter-relationships between vulnerable patients with several predisposing factors and exposure to noxious insults or precipitating factors (figure). Thus, in vulnerable patients, such as those with underlying dementia and multimorbidity, a seemingly benign insult—eg, a dose of a sedative–hypnotic drug—might be enough to precipitate delirium. Conversely, in a young, healthy patient, delirium will develop only after exposure to a series of noxious insults, such as general anaesthesia, major surgery, several psychoactive drugs, a stay in an ICU, or sleep deprivation. Clinically, the implications of this multifactorial causation are that addressing of a single risk factor is unlikely to resolve delirium, and that multicomponent approaches will be most effective for both prevention and treatment.

Many risk factors for delirium have been identified.[14,32] Table 2 shows predisposing and precipitating factors identified from 11 studies that had prospectively validated prediction models for delirium across different clinical populations, including medical, surgical (non-cardiac and cardiac), and intensive care. The leading risk factors consistently identified at admission in both medical and non-cardiac surgery populations were dementia or cognitive impairment, functional impairment, visual impairment, history of alcohol misuse, and advanced age (>70 years). Comorbidity burden or presence of specific comorbidities (eg, stroke, depression) were associated with an increased risk in all populations. In an ICU-based study, younger patients (ie, those younger than 65 years) were included and baseline factors (eg,

dementia, functional impairment) were not significant independent predictors.

Precipitating factors vary across populations. In medical patients, polypharmacy, use of psychoactive drugs, and physical restraints were the leading factors, conferring as much as a four-and-a-half-times increased risk. Abnormal laboratory measurements were risk factors in all populations, and conferred between a 40% and 500% increased risk. Although a complete list of the medical and neurological diseases that can cause or contribute to delirium is beyond the scope of this Review, clinicians should remain aware that both common and rare disorders can present with delirium.

Predictive models for delirium are useful to identify high-risk patients for proactive implementation of preventive strategies, patients who need close monitoring, and vulnerability factors for intervention; for prognostic decision making; and for determination of clinical trial eligibility. The ability to stratify risk can help physicians to explain risks to patients and families and can help families to better understand the recovery process and potential outcomes.

	General medicine	Surgery		Intensive-care unit
		Non-cardiac	Cardiac	
Predisposing factors				
Dementia	2·3–4·7	2·8	..	..
Cognitive impairment	2·1–2·8	3·5–4·2	1·3	..
History of delirium	..	3·0	..	..
Functional impairment	4·0	2·5–3·5	..	..
Visual impairment	2·1–3·5	1·1–3·0	..	..
Hearing impairment	..	1·3	..	..
Comorbidity or severity of illness	1·3–5·6	4·3	..	1·1
Depression	3·2	..	1·2	..
History of transient ischaemia or stroke	..	..	1·6	..
Alcohol misuse	5·7	1·4–3·3	..	..
Older age (≥75 years)	4·0	3·3–6·6	..	1·1
Precipitating factors				
Drugs				
Several drugs used	2·9	..	..	..
Psychoactive drugs	4·5	..	..	..
Sedatives or hypnotics	..	..	..	4·5
Use of physical restraints	3·2–4·4	..	..	..
Use of bladder catheter	2·4	..	..	..
Physiological				
Increased serum urea	5·1	..	..	1·1
Increased BUN:creatinine ratio	2·0	2·9	..	..
Abnormal serum albumin	..	..	1·4	..
Abnormal sodium, glucose, or potassium	..	3·4	..	..
Metabolic acidosis	..	..	..	1·4
Infection	..	..	..	3·1
Any iatrogenic event	1·9	..	..	..
Surgery				
Aortic aneurysm	..	8·3	..	..
Non-cardiac thoracic	..	3·5	..	..
Neurosurgery	..	..	..	4·5
Trauma admission	..	..	..	3·4
Urgent admission	..	..	..	1·5
Coma	..	..	..	1·8–21·3

Data are relative risks. Some data are reported as ranges. The appendix contains a complete list of references. BUN=blood urea nitrogen.

***Table 2*: Risk factors for delirium from validated predictive models**

Pathophysiology

In view of the complex multifactorial causation of delirium, each individual episode probably has a unique set of component contributors; each set represents a discrete yet sufficient causal mechanism. Thus, a single cause or mechanism for delirium will probably not be discovered. Rather, accumulating evidence suggests that several different sets of interacting biological factors result in disruption of large-scale neuronal networks in the brain, leading to acute cognitive dysfunction.[33] Some of the leading mechanisms postulated to contribute to delirium include neurotransmitters, inflammation, physiological stressors, metabolic derangements, electrolyte disorders, and genetic factors (table 3). Many factors can interfere directly with neurotransmission or cellular metabolism,[34] including drugs,[35] and biological factors such as hypercortisolism,[36] electrolyte disturbances,[37] hypoxia,[38] and impaired glucose oxidation.[39] Many neurotransmitters are potentially implicated,[40] but cholinergic deficiency or dopamine excess, or both, are the most frequently linked to delirium,[41,42] and correlate with the adverse effects of anticholinergic or dopaminergic drugs.[43]

Other causal mechanisms interfere with neurotransmission more indirectly. For instance, the systemic inflammatory response in sepsis can result in a cascade of local (brain) neuroinflammation triggered by inflammatory cytokines, leading to endothelial activation, impaired blood flow, and neuronal apoptosis. Neuroinflammation can lead to microglial overactivation, resulting in a neurotoxic response with further neuronal injury.[44] Peripheral inflammation can activate the CNS by several routes, including vagal afferents, circulating proinflammatory cytokines,[45] endothelial activation with disruption of the blood–brain barrier,[46] and microglial activation.[47] Distinction between local and distant pathological changes might not be possible, however, because the different inflammatory factors and neurotransmitters are closely intertwined.[48]

Advanced neuroimaging techniques might provide further insights into pathophysiology. Local and distant factors together account for overall and regional perfusion abnormalities noted in brains of people with delirium.[49,50] Total cerebral and regional perfusion are decreased as a result of impaired cardiac output[51] and loss of cerebral autoregulation in the damaged brain,[52] both of which are hallmarks of sepsis per se.[53] Furthermore, rapidly evolving

	Type of data available	Review published
Neurotransmitters		
Acetylcholine	Experimental and observational	Yes
Dopamine	Experimental and observational	Yes
γ-aminobutyric acid	Experimental and observational	No
Melatonin	Experimental and observational	Yes
Tryptophan or serotonin	Observational	Yes
Glutamate	Observational	No
Epinephrine or norepinephrine	Hypothetical	No
Proinflammatory markers		No
Interferon α or β	Experimental	Yes
Interleukin 6	Observational	Yes
Interleukin 8	Observational	Yes
Interleukin 10	Observational	No
Tumour necrosis factor α	Hypothetical	Yes
Interleukin 1β	Hypothetical	Yes
Prostaglandin E	Hypothetical	Yes
Physiological stressors		No
Cortisol	Observational	No
S100β	Observational	No
Neopterin	Observational	No
Hypoxia	Observational	No
Metabolic disorders		No
Lactic acidosis	Experimental and observational	No
Hypoglycaemia or hyperglycaemia	Observational	No
IGF1	Observational	Yes
Hypercapnia	Hypothetical	Yes
Electrolyte disorders		No
Sodium, calcium, magnesium	Experimental and observational	No
Genetic factors		
Apolipoprotein E	Observational	Yes
Glucocorticoid receptor	Observational	No
Dopamine transporter or receptor	Observational	Yes
Toll-like receptor 4	Hypothetical	No

Experimental means that controlled data—eg, from clinical trials or inference from unintended side-effects in human beings, or both—are available. Observational means that only observational data are available in human beings. Hypothetical means that that studies in human beings are not yet available to support the mechanism. The appendix contains a complete list of references.

***Table 3*: Potential pathophysiological contributors to delirium**

functional imaging techniques might help to differentiate pre-existing changes and newly acquired structural damage related to delirium.[54]

Although delirium can occur at any age, children and elderly people carry the highest risks. In children, neuronal networks that are underdeveloped and less complex might be easily perturbed.[55] In old people, gradual accumulation of permanent damage to neurons, dendrites, receptors, and microglia,[56] and the effects of cerebrovascular disease or head trauma, can render them susceptible to delirium when biologically stressed, especially when they have underlying cognitive impairment.[57] Depending on the underlying causal mechanism, patients might overcome a delirious state without any residual effects or, alternatively, develop permanent neurological sequelae.[58,59] Understanding of the pathophysiological basis for the stressors and the substrates leading to permanent damage from delirium will advance the notion of cognitive reserve, which will open new avenues for risk stratification and treatment.[60]

Diagnosis

Delirium is a clinical diagnosis, which is often unrecognised and easily overlooked. Recognition of the disorder necessitates brief cognitive screening and astute clinical observation. Key diagnostic features include an acute onset and fluctuating course of symptoms, inattention, impaired consciousness, and disturbance of cognition (eg, disorientation, memory impairment, language changes).[61,62] Supportive features include disturbance in sleep–wake cycle, perceptual disturbances (hallucinations or illusions), delusions, psychomotor disturbance (hypoactivity or hyperactivity), inappropriate behaviour, and emotional lability. The current reference standard diagnostic criteria are the 5th edition of American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5)[63] and WHO's International Classification of Diseases, 10th Revision (ICD-10)[64] (appendix). More than 24 delirium instruments have been used in published studies.[65,66] The most widely used instrument for identification of delirium is the Confusion Assessment Method (CAM; appendix),[6,61,66,67] which has been validated in high-quality studies including more than 1000 patients, with sensitivity of 94%, specificity of 89%, and high inter-rater reliability. Cognitive testing and training are recommended for optimum use. CAM, which has been used in more than 4000 published studies so far and translated into at least 12 languages, has been adapted for use in ICUs,[68] emergency departments,[69] and nursing homes, where it is now included as part of the Minimum Data Set[70] (a standardised comprehensive assessment of all residents in US long-term care facilities). Behavioural checklists for delirium symptoms, such as delirium observation screening,[71] nursing delirium screening checklist,[72] and NEECHAM,[73] are used particularly in nursing-based studies. The most widely used instruments to measure the severity of delirium are the delirium rating scale[74,75] and memorial delirium assessment scale.[76] Summation of items from CAM has been used as a severity indicator.[4,77,78] A validated chart review method for identification of delirium has been developed for retrospective identification,[79] but its sensitivity is more limited than that of CAM. The Family Confusion Assessment Method (FAM-CAM) has been developed to identify delirium symptoms on the basis of reports from

	Actions
Assessment	
History	Check baseline cognitive function and recent (within past 2 weeks) changes in mental status (eg, family, staff) Recent changes in disorder, new diagnoses, complete review of systems Review all current drugs (including over-the-counter and herbal preparations); pay special attention to new drugs and drug interactions Review alcohol and sedative use Assess for pain and discomfort (eg, urinary retention, constipation, thirst)
Vital signs	Measure temperature, oxygen saturation, fingerstick glucose concentration Take postural vital signs as needed
Physical and neurological examination	Search for signs of occult infection, dehydration, acute abdominal pain, deep vein thrombosis, other acute illness; assess for sensory impairments Search for focal neurological changes and meningeal signs
Targeted laboratory assessment (selected tests based on clues from history and physical)*	Consider full blood count; urinalysis; measurement of concentrations of electrolyres, calcium, and glucose; measurement of renal, liver, and thyroid function; taking cultures of urine, blood, sputum; measurement of drug concentrations; measurement of concentrations of ammonia, vitamin B12, and cortisol Measure arterial blood gas Do electrocardiography Chest radiography Lumbar puncture should be reserved for assessment of fever with headache and meningeal signs or suspicion of encephalitis
Targeted neuroimaging (selected patients)	Assess focal neurological changes (stroke can present as delirium) Test for suspected encephalitis (for temporal lobe changes) Assess patients with histories or signs of head trauma
Electroencephalography (selected patients)	Assess for occult seizures Differentiate psychiatric disorder from delirium
Management	
Drug adjustments	Reduce or remove psychoactive drugs (eg, anticholinergics, sedatives or hypnotics, opioids); lower dosages; avoid as required dosing Substitute less toxic alternatives Use non-pharmacological approaches for sleep and anxiety, including music, massage, relaxation techniques
Address acute medical issues	Treat problems identified in work-up (eg, infection, metabolic disorders) Maintain hydration and nutrition Treat hypoxia
Reorientation strategies	Encourage family involvement; use companions as needed Address sensory impairment; provide eyeglasses, hearing aids, interpreters
Maintain safe mobility	Avoid use of physical restraints, tethers, and bed alarms Ambulate patient at least three times per day; active range-of-motion Encourage self-care and regular communication
Normalise sleep–wake cycle	Discourage napping and encourage exposure to bright light during the day Try to provide uninterrupted period for sleep at night Provide non-pharmacological sleep protocol and quiet room at night with low level lighting
Pharmacological management	Reserve for patients with severe agitation that interrupts essential treatment (eg, intubation) or severe psychotic symptoms Start with low doses and titrate until effect achieved; haloperidol 0·25–0·5 mg orally or intramuscularly twice a day is preferred; atypical antipsychotics close in effectiveness

*Not all of these tests should be done in all patients; rather, specific tests should be guided by history, physical examination, and previous results.

***Table 4*: Assessment and management of suspected delirium**

family and informal caregivers, and could help with early recognition of delirium.[80]

Assessment and work-up

The most important step is establishment of the diagnosis of delirium by obtaining a history from an informed observer (eg, family member, caregiver, or staff member) and doing a brief cognitive assessment. To differentiate delirium from dementia, an accurate history is crucial to establish the patient's baseline and acuity of mental status change, to recognise the fluctuations in cognition and other symptoms typical of delirium, and to identify possible causes. Formal cognitive screening tests, such as the short portable mental status questionnaire,[81] the mini-cog,[82] or the Montreal cognitive assessment,[83] should be done. When time is very scarce, assessment of orientation and an attention task, such as naming of days of the week (no errors should be allowed) or months of the year (one error should be allowed) backwards, serial sevens (one error should be allowed for five subtractions), or recitation of digit spans (normally three or more) backwards can substitute for basic screening. These cognitive tests are needed to establish if the patient fulfils criteria for delirium.

In view of the high rates of adverse outcomes and mortality, any suspected or uncertain cases (including

patients with lethargy or those who are unable to complete an interview) should be treated as delirium until proven otherwise. Initial management has three simultaneous priorities—specifically, maintenance of the patient's safety, identification of the cause or causes, and management of symptoms. In terms of safety, efforts should focus on protection of the airway and prevention of aspiration, maintenance of hydration and nutrition, prevention of skin breakdown, and provision of safe mobility while preventing falls. Restraints and bed alarms increase risk and persistence of delirium and injury and should be avoided.[84,85]

Table 4 summarises the suggested work-up and initial management of delirium. Several fundamental points should be emphasised. First, delirium can be the harbinger of a medical emergency, and thus all patients presenting with delirium should be screened for acute physiological disturbances—eg, hypoxaemia, hypoglycaemia, and high arterial carbon dioxide concentrations. Second, the disease can have occult or atypical presentation in older people—eg, in octogenarians, myocardial infarction presents more often as delirium than as the classic presentation of chest pain or shortness of breath. Thus, a family member's non-specific complaint that the patient is not himself or herself should never be taken lightly. Third, diagnostic assessments (eg, laboratory testing, neuroimaging) should be targeted on the basis of the patient's history and physical examination—untargeted testing will probably have low yields.[86]

Electroencephalography (EEG) has little sensitivity and specificity in the diagnosis of delirium. However, delirium does have a characteristic pattern of diffuse slowing with increased theta and delta activity and poor organisation of background rhythm, which correlates with severity of delirium. EEG can be particularly useful in the differentiation of organic causes from functional or psychiatric disorders in difficult-to-assess patients, assessment of deteriorating mental status in patients with dementia, and identification of occult seizures (eg, non-convulsive status epilepticus, atypical complex partial seizures).[87,88] Quantitative and spectral EEG might be of use in assessments of delirium, but their performance characteristics need further investigation. Neuroimaging, including non-contrast head CT and MRI, is low yield in unselected patients. It is recommended to assess acute focal neurological findings (because patients with strokes or haemorrhages can present with delirium) and in patients with a history or signs of recent fall or head trauma, fever and suspected encephalitis, or decreased consciousness of unidentified cause.[89,90] Brain scans are normal in more than 98% of patients whose delirium has an identified medical cause or who have pre-existing dementia.[91] Lumbar puncture should be considered[92] when meningitis, encephalitis, or subarachnoid hemorrhage is suspected, and might be indicated when delirium is persistent or no cause can be identified.

For initial symptom management, non-pharmacological approaches are the first-line strategy and include discontinuation or dose reduction of anticholinergic and psychoactive drugs, family or companion involvement for reorientation and comfort, non-pharmacological approaches to sleep and relaxation (eg, a glass of warm milk or herbal tea, relaxation music, back rubs),[93] creation of a quiet, soothing, warm environment, and pain management. Drugs should be used only in severely agitated patients in whom interruption of essential medical therapies (eg, mechanical ventilation, dialysis catheters) or self-harm is a risk, or in patients with extremely distressing psychotic symptoms (eg, hallucinations, delusions).

Non-pharmacological prevention and treatment

Primary prevention with non-pharmacological multicomponent approaches is widely accepted as the most effective strategy for delirium.[6,14,67] The appendix lists non-pharmacological approaches from 13 studies, each of which included 25 or more patients in both intervention and control groups, applied a prospective sampling framework, included a validated delirium assessment, and achieved a modified Jadad (0–6) score[94] of at least 4 points. Two reviewers rated each article independently and reached consensus.

The most widely disseminated approach is the Hospital Elder Life Program (HELP),[4,95,96] a multicomponent intervention strategy with proven effectiveness and cost-effectiveness in the prevention of delirium and functional decline[97,98] through targeting of risk factors for delirium. The interventions include reorientation, therapeutic activities, reduced use and doses of psychoactive drugs, early mobilisation, promotion of sleep, maintenance of adequate hydration and nutrition, and provision of vision and hearing adaptations. The programme should be implemented by a skilled interdisciplinary team, who should be assisted by either nursing staff or trained volunteers. Although originally assessed in a large-scale controlled clinical trial, more than ten follow-up studies have shown that the programme is effective in diverse settings and populations.[99–101] HELP is now implemented in more than 200 hospitals worldwide, but adaptations and alternatives may be necessary in some settings because of resource constraints or poor availability of skilled interdisciplinary old age medicine professionals. Factors crucial to initiate and sustain the programme are internal support, effective champions, programme fidelity while adapting to local circumstances, documentation of positive outcomes, and long-term funding and resources.[102,103] Savings of roughly $9000 per patient per year have been estimated.[1,98,101]

Proactive old age medicine consultation is another successful approach that has been assessed in a randomised controlled trial.[5] Old age medicine specialists make recommendations before and after surgery on the basis of ten structured modules, including hydration,

pain management, nutrition, and mobilisation. The success of this strategy, however, is integrally linked to adherence to his or her recommendations.

Other non-pharmacological interventions that have been studied (appendix) include multifactorial targeted interventions, delirium screening and intervention on old age medicine units, staff training or educational programmes, and interdisciplinary consultation. Approaches in the past 6 years have included interventions delivered by family members and mobility or rehabilitation interventions, both of which are effective in the prevention of delirium. The use of earplugs at night was moderately efficacious in an ICU-based trial,[104] and might be a useful adjunct to non-pharmacological sleep protocols.[93] Delirium rooms[105]—spaces that provide restraint-free care for patients with delirium, are staffed with specially trained nurses, and promote non-pharmacological management approaches—are an intriguing idea for provision of specialised management for patients with delirium, but have not yet been assessed in a controlled trial. Many studies of non-pharmacological approaches have been hampered by issues such as an absence of comparator groups or of prospective balanced allocation to study groups, or unmasked assessment of outcomes.

Pharmacological prevention and treatment

The appendix lists 16 studies of pharmacological approaches to delirium prevention and treatment that included at least 25 patients in both the intervention and control groups, applied a prospective sampling framework, included a validated delirium assessment, and achieved a modified Jadad score[94] of at least 4 points. No convincing, reproducible evidence of effectiveness has been reported for any of these treatments. In six of the trials, rates of delirium did not differ significantly between groups. In eight of the trials, treatment reduced delirium rates but this reduction either had no effect on clinical outcomes (such as ICU admission, length of hospital stay, complications, or mortality) or clinical outcomes were not measured. In two trials, treatment resulted in potentially worse outcomes compared with placebo. Olanzapine reduced the incidence but increased the duration and severity of delirium (without reported clinical outcomes), and rivastigmine resulted in increased duration and mortality. Different approaches were used to assess delirium in all 16 trials, and the populations investigated were diverse. Thus, to generalise findings is difficult. Because of the preponderance of evidence, however, pharmacological approaches to prevention and treatment are not recommended at this time.[6,106]

Controversies

Need for increased research

Although delirium research has expanded greatly in the past 30 years, many key aspects of the disorder remain poorly understood. Some biomarkers associated with delirium have been identified, but the fundamental pathophysiological basis remains obscure. Important knowledge gaps need to be addressed.

Delirium and dementia

Is delirium simply a marker of vulnerability to dementia, or does delirium itself lead to dementia? This question is the subject of much controversy, but ultimately both hypotheses are probably true. An episode of delirium can signal vulnerability of the brain, with decreased cognitive reserve and increased risk for future dementia, and delirium can bring previously unrecognised cognitive impairment to medical attention. Delirium and dementia frequently coexist, and dementia is a leading risk factor for delirium (table 2). Furthermore, a growing body of evidence, ranging from epidemiological studies to tissue culture and animal studies, suggests that delirium leads to permanent cognitive impairment and dementia. A 2010 meta-analysis[107] of two studies (total n=241) showed that delirium was associated with an increased rate of incident dementia (adjusted relative risk, 5·7, 95% CI 1·3–24·0). In a sample of 225 cardiac surgery patients,[12] delirium was associated with a severe punctuated decline in cognitive functioning, followed by recovery during 6–12 months in most patients. However, a substantial proportion of patients, particularly those with prolonged delirium, never regained their baseline cognitive level. In 263 patients with Alzheimer's disease,[30] delirium was associated with a doubling of the rate of cognitive decline during the year after hospital admission and accelerated decline persisting during 5 years' follow-up.

Further evidence supports a direct role for delirium in dementia. In an important study of 553 people who were aged 85 years or older at baseline,[58] the findings of which were neuropathologically confirmed, delirium increased the risk of incident dementia (odds ratio 8·7, 95% CI 2·1–35·0). Alzheimer's pathology was significantly associated with dementia in patients without delirium, whereas no such relationship was noted in those with delirium, suggesting alternative pathological mechanisms for dementia after delirium. This study was limited, however, by a high rate of loss to follow-up.

Previous studies in animal models and human neuronal cell cultures have shown that exposure to inhaled anaesthetics can induce neurotoxic effects, including apoptosis, caspase activation, Aβ oligomerisation and accumulation, neuroinflammation, and mitochondrial dysfunction.[108,109] Preliminary results in human beings[110] suggest that some inhaled anaesthetics (eg, isoflurane) might be more neurotoxic than others. Important work[111] in animal models of delirium has shown that, in vulnerable animals, systemic inflammatory insults can cause punctuated cognitive decline typical of delirium, followed by acceleration in disease progression typical of dementia. Furthermore, a dose of lipopolysaccharide, which induces an inflammatory insult similar to that induced by a

	Research priorities	Public health priorities
Recognition	Improve measurement for delirium—diagnosis, phenomenology, severity, and subtypes Develop cost-effective approach for assessment and work-up	Improve coding and reimbursement Educate clinicians and public about the importance and recognition of delirium
Epidemiology	Long-term follow-up studies of delirium to establish outcomes Patient's experience; distress, post-traumatic stress disorder Genetic determinants of delirium risk Risk stratification to identify high risk	Assess economic and societal costs Policy incentives to improve recognition and management Address caregiver burden
Pathophysiology	Neuroimaging approaches So-called deliriomics to identify biomarkers Animal models for delirium	Improve funding for delirium research overall Encourage interdisciplinary scientists to address the topic
Prevention and treatment	Assess long-term effects of non-pharmacological prevention Trials of drug reduction, more prudent and individualised approaches to sedation, anesthaesia, and analgesia Combined approaches to management, such as music, massage, exercise, cognitive rehabilitation, and sleep enhancement	Incentives for system-wide process and quality improvements in detection, prevention, and treatment Provider education about prevention and management approaches Public education about avoiding of psychoactive drugs (including over-the-counter drugs), limiting of alcohol use, and enhancement of cognitive reserve; encourage exercise

Table 5: **Research and public health priorities for delirium**

moderate infection in human beings, induces neuronal death, microglial activation, decreased regional blood flow, and loss of cholinergic activation in animal models.[112] Such accumulating evidence strongly suggests that delirium contributes to, or mediates, or both, permanent cognitive impairment. Future human studies that carefully establish baseline cognitive function, control for confounding factors, and include long-term follow-up, including neuropsychological testing and neuroimaging, will help to elucidate the relation further.

Disorder of cognition or arousal?

Historically, delirium was first categorised as a mental status problem—a disorder of arousal with varying degrees of obtundation. However, as a result of medical advances and more sophisticated observation, delirium is now deemed mainly a disorder of cognition, with attention and global cognitive impairments as the key features, rather than a primary disorder of arousal alone.[61,112] This distinction is important in the identification of delirium that is most associated with poor long-term outcomes.

Clearly, delirium includes impairments in both cognition and arousal in many cases. To distinguish an oversedated patient from a delirious patient can be challenging but is clinically relevant. Delirium lasting for 2–3 days or longer has been associated with poorer outcomes than have more transient episodes, which are often caused by psychoactive drugs.[62,113] Sedation scales, such as the Richmond agitation and sedation scale,[68,114] which are neither sensitive nor specific for delirium, should not be used alone, but rather in conjunction with tests of attention and cognition (in patients with verbal ability) or other diagnostic assessments. Furthermore, the cause, pathophysiology, and management of oversedation, which has its own prognostic risks, should be thought of as distinct from the management of delirium.

Pathophysiological or prognostic differences

Delirium has two major psychomotor forms—hypoactive and hyperactive. Although these two forms are distinctive clinically, patients can wax and wane between them during the course of a day or the course of the disorder. Patients with acute alcohol withdrawal are more likely to present with the hyperactive than the hypoactive form. The mainly hypoactive form is more common in elderly patients, and has been generally associated with a worse prognosis.[32]

EEG manifestations of hypoactive and hyperactive delirium do not differ reliably.[115] Delirium severity instruments tend to have more hyperactive symptoms represented in their summative scores than hypoactive symptoms, which tends to lead to weighting of hyperactive delirium as more severe. Whether different causal mechanisms can be separated by clinical signs and symptoms is unclear—ie, are there different, recognisable phenotypes of delirium beyond the hypoactive and hyperactive forms?[116, 117] Do specific clinical manifestations, such as hallucinations, suggest separate pathophysiology or outcomes? Clarification of these issues through improved delirium measurement methods and application of sophisticated neuroimaging and pathophysiological approaches would have substantial ramifications for understanding of both the phenomenology and treatment of delirium.

Treatment strategies

Clinical trials for delirium management have focused mainly on antipsychotic or sedating drugs. Although such drugs can reduce the agitation and behavioural symptoms associated with delirium, which are often vexing to health-care professionals, no evidence shows that antipsychotics or sedatives effectively improve prognosis. In view of the limitations of measurement instruments, these treatments might result in the patient's delirium switching from the hyperactive to the

***Panel*: Summary messages for clinicians**

- Assess for delirium in all elderly patients (ie, aged 65 years or older) admitted to hospital. Use simple cognitive screening and the Confusion Assessment Method, and get the history or timecourse of any cognitive changes from an informed proxy.
- Assessment of drugs is a high-yield procedure. Reduce psychoactive drugs as a first step whenever possible.
- Use non-pharmacological approaches to manage sleep, anxiety, and agitation.
- Reserve pharmacological approaches for patients with severe agitation who risk interruption of essential medical treatment (eg, intubation) or self-injury, or have severe, distressing psychotic symptoms (eg, hallucinations, delusions).
- Involve family members in care, particularly for reorientation and prevention of self-harm.
- Avoid bedrest orders; encourage mobility and self-care.
- Ensure that, if needed, patients have glasses, hearing aids, and dentures (being able to see, hear, and eat is important in all health-care settings).
- Let patients know their schedule and keep them involved in their care. Communicate regularly with patients and their families.

hypoactive form (which is then not measured), contributing to these poor outcomes. A growing body of evidence suggests that antipsychotics and sedatives can prolong the duration of delirium and associated cognitive impairments, and worsen clinical outcomes. Thus, to consider other approaches—including non-pharmacological strategies, cognitive rehabilitation, drug reduction, drug-sparing approaches (ie, substitution for less toxic alternatives), and treatments targeted towards inflammation, neuroprotection, sleep enhancement (eg, melatonin), or reduction of pain and stress (including complementary and alternative medicine)—is crucial. Management of delirium should be focused on treatments that enhance recovery, maximise functional status, and improve clinical outcomes.

Future directions and recommendations

Although many knowledge gaps remain, available evidence in delirium provides a clear path to move forward. Table 5 outlines some of the research priorities in delirium and the concomitant public health priorities necessary for progress. Each research domain should be coupled with translation into practice and policy to effect change.

Important public health and policy priorities should include more logical coding and insurance-based reimbursement strategies for delirium. At least 11 codes for delirium are included in the International Classification of Diseases, 9th Revision, Clinical Modification, and 23 in ICD-10, but only about 3% of delirium cases are coded in medical records.[79] Without a logical system to record delirium in health-care systems, large-scale public health efforts will be severely limited.

Comprehensive efforts to educate clinicians and the public about delirium, including about the disorder's importance, recognition, risk factors, prevention, and management, will be crucial to remedy under-recognition and mismanagement (panel). Delirium is as a potent and well recognised indicator of health-care quality across many settings, and creation of incentives for system-wide process improvement to address the disorder will result in high-quality old age medical care overall. Because delirium is highly multifactorial and linked to many other common syndromes of old age (such as falls, pressure ulcers, functional decline, and incontinence), addressing delirium provides a highly practical and effective strategy to improve outcomes, decrease costs, and raise the quality of health care system wide.

Contributors

All authors contributed to selection of articles, synthesis of information identified in the search, and drafting and editing of the paper or relevant sections thereof. RGJW focused on the pathophysiology section and JSS on the epidemiology, cause, and non-pharmacological-management sections. All authors have seen and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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References

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

2 WHO Regional Office for Europe. European hospital morbidity database. Copenhagen: World Health Organization, 2012.

3 Organisation for Economic Co-operation and Development. OECD health data 2012. Paris: Organisation for Economic Co-operation and Development, 2012.

4 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:** 669–76.

5 Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *J Am Geriatr Soc* 2001; **49:** 516–22.

6 O'Mahony R, Murthy L, Akunne A, Young J. Synopsis of the National Institute for Health and Clinical Excellence guideline for prevention of delirium. *Ann Intern Med* 2011; **154:** 746–51.

7 Wachter RM. Understanding patient safety, 2nd edn. New York: McGraw-Hill Medical, 2012.

8 Agency for Healthcare Research and Quality (AHRQ). National quality clearinghouse measure: delirium: proportion of patients meeting diagnostic criteria on the confusion assessment method (CAM). http://www.qualitymeasures.ahrq.gov/content.aspx?id=27635 (accessed Jan 3, 2013).

9 Shekelle PG, MacLean CH, Morton SC, Wenger NS. Acove quality indicators. *Ann Intern Med* 2001; **135:** 653–67.

10 Jones RN, Fong TG, Metzger E, et al. Aging, brain disease, and reserve: implications for delirium. *Am J Geriatr Psychiatry* 2010; **18:** 117–27.

11 Wilson RS, Hebert LE, Scherr PA, Dong X, Leurgens SE, Evans DA. Cognitive decline after hospitalization in a community population of older persons. *Neurology* 2012; **78:** 950–56.

12 Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. *N Engl J Med* 2012; **367:** 30–39.

13 Von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370:** 1453–57.

14 Inouye SK. Delirium in older persons. *N Engl J Med* 2006; **354:** 1157–65.

15 Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004; **291:** 1753–62.

16 Lin SM, Liu CY, Wang CH, et al. The impact of delirium on the survival of mechanically ventilated patients. *Crit Care Med* 2004; **32:** 2254–59.

17 Van den Boogaard M, Schoonhoven L, van der Hoeven JG, van Achterberg T, Pickkers P. Incidence and short-term consequences of delirium in critically ill patients: a prospective observational cohort study. *Int J Nurs Stud* 2012; **49:** 775–83.

18 Veiga D, Luis C, Parente D, et al. Postoperative delirium in intensive care patients: risk factors and outcome. *Rev Bras Anestesiol* 2012; **62:** 469–83.

19 Pitkala KH, Laurila JV, Strandberg TE, Tilvis RS. Prognostic significance of delirium in frail older people. *Dement Geriatr Cogn Disord* 2005; **19:** 158–63.

20 Buurman BM, Hoogerduijn JG, de Haan RJ, et al. Geriatric conditions in acutely hospitalized older patients: prevalence and one-year survival and functional decline. *PLoS One* 2011; **6:** e26951.

21 Leslie DL, Zhang Y, Holford TR, Bogardus ST, Leo-Summers LS, Inouye SK. Premature death associated with delirium at 1-year follow-up. *Arch Intern Med* 2005; **165:** 1657–62.

22 Han JH, Shintani A, Eden S, et al. Delirium in the emergency department: an independent predictor of death within 6 months. *Ann Emerg Med* 2010; **56:** 244–52.

23 Bickel H, Gradinger R, Kochs E, Forstl H. High risk of cognitive and functional decline after postoperative delirium. A three-year prospective study. *Dement Geriatr Cogn Disord* 2008; **26:** 26–31.

24 Krogseth M, Wyller TB, Engedal K, Juliebo V. Delirium is an important predictor of incident dementia among elderly hip fracture patients. *Dement Geriatr Cogn Disord* 2011; **31:** 63–70.

25 Rudolph JL, Inouye SK, Jones RN, et al. Delirium: an independent predictor of functional decline after cardiac surgery. *J Am Geriatr Soc* 2010; **58:** 643–49.

26 Oldenbeuving AW, de Kort PL, Jansen BP, Algra A, Kappelle LJ, Roks G. Delirium in the acute phase after stroke: incidence, risk factors, and outcome. *Neurology* 2011; **76:** 993–99.

27 Marcantonio ER, Kiely DK, Simon SE, et al. Outcomes of older people admitted to postacute facilities with delirium. *J Am Geriatr Soc* 2005; **53:** 963–69.

28 Fong TG, Jones RN, Shi P, et al. Delirium accelerates cognitive decline in Alzheimer disease. *Neurology* 2009; **72:** 1570–75.

29 Fong TG, Jones RN, Marcantonio ER, et al. Adverse outcomes after hospitalization and delirium in persons with Alzheimer disease. *Ann Intern Med* 2012; **156:** 848–56.

30 Gross AL, Jones RN, Habtemariam DA, et al. Delirium and long-term cognitive trajectory among persons with dementia. *Arch Intern Med* 2012; **172:** 1–8.

31 Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA* 1996; **275:** 852–57.

32 Marcantonio ER. Postoperative delirium: a 76-year-old woman with delirium following surgery. *JAMA* 2012; **308:** 73–81.

33 Watt D, Budding DE, Koziol LF. Delirium. In: Noggle CA, Dean RS, eds. The neuropsychology of psychopathology. New York: Springer, 2013: 425–40.

34 Maclullich AM, Ferguson KJ, Miller T, de Rooij SE, Cunningham C. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. *J Psychosom Res* 2008; **65:** 229–38.

35 Alagiakrishnan K, Wiens CA. An approach to drug induced delirium in the elderly. *Postgrad Med J* 2004; **80:** 388–93.

36 Joels M. Impact of glucocorticoids on brain function: relevance for mood disorders. *Psychoneuroendocrinology* 2011; **36:** 406–14.

37 Marcantonio ER, Rudolph JL, Culley D, Crosby G, Alsop D, Inouye SK. Serum biomarkers for delirium. *J Gerontol A Biol Sci Med Sci* 2006; **61:** 1281–86.

38 Schoen J, Meyerrose J, Paarmann H, Heringlake M, Hueppe M, Berger KU. Preoperative regional cerebral oxygen saturation is a predictor of postoperative delirium in on-pump cardiac surgery patients: a prospective observational trial. *Crit Care* 2011; **15:** R218.

39 Caplan GA, Kvelde T, Lai C, Yap SL, Lin C, Hill MA. Cerebrospinal fluid in long-lasting delirium compared with Alzheimer's dementia. *J Gerontol A Biol Sci Med Sci* 2010; **65:** 1130–36.

40 Gaudreau JD, Gagnon P. Psychotogenic drugs and delirium pathogenesis: the central role of the thalamus. *Med Hypotheses* 2005; **64:** 471–75.

41 Young BK, Camicioli R, Ganzini L. Neuropsychiatric adverse effects of antiparkinsonian drugs. Characteristics, evaluation and treatment. *Drugs Aging* 1997; **10:** 367–83.

42 Hshieh TT, Fong TG, Marcantonio ER, Inouye SK. Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence. *J Gerontol A Biol Sci Med Sci* 2008; **63:** 764–72.

43 Lauretani F, Ceda GP, Maggio M, Nardelli A, Saccavini M, Ferrucci L. Capturing side-effect of medication to identify persons at risk of delirium. *Aging Clin Exp Res* 2010; **22:** 456–58.

44 Hughes CG, Patel MB, Pandharipande PP. Pathophysiology of acute brain dysfunction: what's the cause of all this confusion? *Curr Opin Crit Care* 2012; 18: 518–26.

45 MacLullich AM, Edelshain BT, Hall RJ, et al. Cerebrospinal fluid interleukin-8 levels are higher in people with hip fracture with perioperative delirium than in controls. *J Am Geriatr Soc* 2011; **59:** 1151–53.

46 Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 2008; **9:** 46–56.

47 Jalleh R, Koh K, Choi B, Liu E, Maddison J, Hutchinson MR. Role of microglia and toll-like receptor 4 in the pathophysiology of delirium. *Med Hypotheses* 2012; **79:** 735–39.

48 Van Gool WA, van de Beek D, Eikelenboom P. Systemic infection and delirium: when cytokines and acetylcholine collide. *Lancet* 2010; **375:** 773–75.

49 Fong TG, Bogardus ST Jr, Daftary A, et al. Cerebral perfusion changes in older delirious patients using 99mTc HMPAO SPECT. *J Gerontol A Biol Sci Med Sci* 2006; **61:** 1294–99.

50 Pfister D, Siegemund M, Dell-Kuster S, et al. Cerebral perfusion in sepsis-associated delirium. *Crit Care* 2008; **12:** R63.

51 Siepe M, Pfeiffer T, Gieringer A, et al. Increased systemic perfusion pressure during cardiopulmonary bypass is associated with less early postoperative cognitive dysfunction and delirium. *Eur J Cardiothorac Surg* 2011; **40:** 200–07.

52 Sabayan B, Jansen S, Oleksik AM, et al. Cerebrovascular hemodynamics in Alzheimer's disease and vascular dementia: a meta-analysis of transcranial doppler studies. *Ageing Res Rev* 2012; **11:** 271–77.

53 Zampieri FG, Park M, Machado FS, Azevedo LC. Sepsis-associated encephalopathy: not just delirium. *Clinics (Sao Paulo)* 2011; **66:** 1825–31.

54 Choi SH, Lee H, Chung TS, et al. Neural network functional connectivity during and after an episode of delirium. *Am J Psychiatry* 2012; 169: 498–507.

55 Hatherill S, Flisher AJ. Delirium in children and adolescents: a systematic review of the literature. *J Psychosom Res* 2010; **68:** 337–44.

56 Izaks GJ, Westendorp RG. Ill or just old? Towards a conceptual framework of the relation between ageing and disease. *BMC Geriatr* 2003; **3:** 7.

57 Cole MG. Delirium in elderly patients. *Am J Geriatr Psychiatry* 2004; **12:** 7–21.

58 Davis DH, Muniz Terrera G, Keage H, et al. Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study. *Brain* 2012; **135:** 2809–16.

59 Kolanowski AM, Fick DM, Clare L, Therrien B, Gill DJ. An intervention for delirium superimposed on dementia based on cognitive reserve theory. *Aging Ment Health* 2010; **14:** 232–42.

60 Soiza RL, Sharma V, Ferguson K, Shenkin SD, Seymour DG, Maclullich AM. Neuroimaging studies of delirium: a systematic review. *J Psychosom Res* 2008; **65:** 239–48.

61 Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990; **113:** 941–48.

62 American Psychiatric Association. Task force on DSM-IV, diagnostic and statistical manual of mental disorders: DSM-IV (text revision), 4th edn. Washington, DC: The Association, 2000.

63 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th edn. Washington, DC: American Psychiatric Association, 2013.

64 WHO. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. Geneva: World Health Organization, 1993.

65 Adamis D, Sharma N, Whelan PJ, Macdonald AJ. Delirium scales: a review of current evidence. *Aging Ment Health* 2010; **14:** 543–55.

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

67 Wei LA, Fearing MA, Sternberg EJ, Inouye SK. The confusion assessment method: a systematic review of current usage. *J Am Geriatr Soc* 2008; **56:** 823–30.

68 Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the confusion assessment method for the intensive care unit (CAM-ICU). *Crit Care Med* 2001; **29:** 1370–79.

69 Han JH, Zimmerman EE, Cutler N, et al. Delirium in older emergency department patients: recognition, risk factors, and psychomotor subtypes. *Acad Emerg Med* 2009; **16:** 193–200.

70 Center for Medicare & Medicaid Services (CMS). Minimum data set, version 3.0. Washington, DC: Centers for Medicare & Medicaid Services, 2010.

71 Schuurmans MJ, Shortridge-Baggett LM, Duursma SA. The delirium observation screening scale: a screening instrument for delirium. *Res Theory Nurs Pract* 2003; **17:** 31–50.

72 Gaudreau JD, Gagnon P, Harel F, Tremblay A, Roy MA. Fast, systematic, and continuous delirium assessment in hospitalized patients: the nursing delirium screening scale. *J Pain Symptom Manage* 2005; **29:** 368–75.

73 Neelon VJ, Champagne MT, Carlson JR, Funk SG. The NEECHAM confusion scale: construction, validation, and clinical testing. *Nurs Res* 1996; **45:** 324–30.

74 Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. *Psychiatry Res* 1988; **23:** 89–97.

75 Trzepacz PT, Mittal D, Torres R, Kanary K, Norton J, Jimerson N. Validation of the delirium rating scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. *J Neuropsychiatry Clin Neurosci* 2001; **13:** 229–42.

76 Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S. The memorial delirium assessment scale. *J Pain Symptom Manage* 1997; **13:** 128–37.

77 Cole MG, Dendukuri N, McCusker J, Han L. An empirical study of different diagnostic criteria for delirium among elderly medical inpatients. *J Neuropsychiatry Clin Neurosci* 2003; **15:** 200–07.

78 Milisen K, Foreman MD, Abraham IL, et al. A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. *J Am Geriatr Soc* 2001; **49:** 523–32.

79 Inouye SK, Leo-Summers L, Zhang Y, Bogardus ST Jr, Leslie DL, Agostini JV. A chart-based method for identification of delirium: validation compared with interviewer ratings using the confusion assessment method. *J Am Geriatr Soc* 2005; **53:** 312–18.

80 Steis MR, Evans L, Hirschman KB, et al. Screening for delirium using family caregivers: convergent validity of the family confusion assessment method and interviewer-rated confusion assessment method. *J Am Geriatr Soc* 2012; **60:** 2121–26.

81 Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc* 1975; **23:** 433–41.

82 Borson S, Scanlan J, Brush M, Vitaliano P, Dokmak A. The mini-cog: a cognitive 'vital signs' measure for dementia screening in multi-lingual elderly. *Int J Geriatr Psychiatry* 2000; **15:** 1021–27.

83 Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005; **53:** 695–99.

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

85 Park M, Tang JH. Changing the practice of physical restraint use in acute care. *J Gerontol Nurs* 2007; **33:** 9–16.

86 Hirano LA, Bogardus ST Jr, Saluja S, Leo-Summers L, Inouye SK. Clinical yield of computed tomography brain scans in older general medical patients. *J Am Geriatr Soc* 2006; **54:** 587–92.

87 Jacobson S, Jerrier H. EEG in delirium. *Semin Clin Neuropsychiatry* 2000; **5:** 86–92.

88 Jenssen S. Electroencephalogram in the dementia workup. *Am J Alzheimers Dis Other Demen* 2005; **20:** 159–66.

89 Hardy JE, Brennan N. Computerized tomography of the brain for elderly patients presenting to the emergency department with acute confusion. *Emerg Med Australas* 2008; **20:** 420–24.

90 Lai MM, Wong Tin Niam DM. Intracranial cause of delirium: computed tomography yield and predictive factors. *Intern Med J* 2012; **42:** 422–27.

91 Hufschmidt A, Shabarin V. Diagnostic yield of cerebral imaging in patients with acute confusion. *Acta Neurol Scand* 2008; **118:** 245–50.

92 Marcantonio ER. In the clinic. Delirium. *Ann Intern Med* 2011; **154:** ITC6-1–15.

93 McDowell JA, Mion LC, Lydon TJ, Inouye SK. A nonpharmacologic sleep protocol for hospitalized older patients. *J Am Geriatr Soc* 1998; **46:** 700–05.

94 Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17:** 1–12.

95 Inouye SK, Bogardus ST Jr, Baker DI, Leo-Summers L, Cooney LM Jr. The Hospital Elder Life Program: a model of care to prevent cognitive and functional decline in older hospitalized patients. Hospital Elder Life Program. *J Am Geriatr Soc* 2000; **48:** 1697–706.

96 Inouye SK, Baker DI, Fugal P, Bradley EH. Dissemination of the hospital elder life program: implementation, adaptation, and successes. *J Am Geriatr Soc* 2006; **54:** 1492–99.

97 Rizzo JA, Bogardus ST Jr, Leo-Summers L, Williams CS, Acampora D, Inouye SK. Multicomponent targeted intervention to prevent delirium in hospitalized older patients: what is the economic value? *Med Care* 2001; **39:** 740–52.

98 Leslie DL, Zhang Y, Bogardus ST, Holford TR, Leo-Summers LS, Inouye SK. Consequences of preventing delirium in hospitalized older adults on nursing home costs. *J Am Geriatr Soc* 2005; **53:** 405–09.

99 Caplan GA, Harper EL. Recruitment of volunteers to improve vitality in the elderly: the REVIVE study. *Intern Med J* 2007; **37:** 95–100.

100 Chen CC, Lin MT, Tien YW, Yen CJ, Huang GH, Inouye SK. Modified hospital elder life program: effects on abdominal surgery patients. *J Am Coll Surg* 2011; **213:** 245–52.

101 Rubin FH, Neal K, Fenlon K, Hassan S, Inouye SK. Sustainability and scalability of the hospital elder life program at a community hospital. *J Am Geriatr Soc* 2011; **59:** 359–65.

102 Bradley EH, Schlesinger M, Webster TR, Baker D, Inouye SK. Translating research into clinical practice: making change happen. *J Am Geriatr Soc* 2004; **52:** 1875–82.

103 Bradley EH, Webster TR, Baker D, Schlesinger M, Inouye SK. After adoption: sustaining the innovation. A case study of disseminating the hospital elder life program. *J Am Geriatr Soc* 2005; **53:** 1455–61.

104 Van Rompaey B, Elseviers MM, Van Drom W, Fromont V, Jorens PG. The effect of earplugs during the night on the onset of delirium and sleep perception: a randomized controlled trial in intensive care patients. *Crit Care* 2012; **16:** R73.

105 Flaherty JH, Steele DK, Chibnall JT, Vasudevan VN, Bassil N, Vegi S. An ACE unit with a delirium room may improve function and equalize length of stay among older delirious medical inpatients. *J Gerontol A Biol Sci Med Sci* 2010; **65:** 1387–92.

106 Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; **41:** 263–306.

107 Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA* 2010; **304:** 443–51.

108 Xie Z, Dong Y, Maeda U, et al. Isoflurane-induced apoptosis: a potential pathogenic link between delirium and dementia. *J Gerontol A Biol Sci Med Sci* 2006; **61:** 1300–06.

109 Zhang Y, Xu Z, Wang H, et al. Anesthetics isoflurane and desflurane differently affect mitochondrial function, learning, and memory. *Ann Neurol* 2012; **71:** 687–98.

110 Zhang B, Tian M, Zhen Y, et al. The effects of isoflurane and desflurane on cognitive function in humans. *Anesth Analg* 201; **114:** 410–15.

111 Cunningham C, Campion S, Lunnon K, et al. Systemic inflammation induces acute behavioral and cognitive changes and accelerates neurodegenerative disease. *Biol Psychiatry* 2009; **65:** 304–12.

112 Cunningham C. Systemic inflammation and delirium: important co-factors in the progression of dementia. *Biochem Soc Trans* 2011; **39:** 945–53.

113 Chedru F, Geschwind N. Disorders of higher cortical functions in acute confusional states. *Cortex* 1972; **8:** 395–411.

114 Chester JG, Beth Harrington M, Rudolph JL. Serial administration of a modified Richmond agitation and sedation scale for delirium screening. *J Hosp Med* 2012; **7:** 450–53.

115 Koponen H, Partanen J, Paakkonen A, Mattila E, Riekkinen PJ. EEG spectral analysis in delirium. *J Neurol Neurosurg Psychiatry* 1989; **52:** 980–85.

116 Khoury M, Beaty T, Cohen H. Fundamentals of genetic epidemiology. Oxford: Oxford University Press, 1993.

117 Maldonado JR. Pathoetiological model of delirium: a comprehensive understanding of the neurobiology of delirium and an evidence-based approach to prevention and treatment. *Crit Care Clin* 2008; **24:** 789–856.