



Australian and New Zealand Society for Geriatric Medicine

Position Statement 13

Delirium in Older People

Revised 2012

1. Delirium is a syndrome characterized by the rapid onset of impaired attention that fluctuates, together with impaired cognition and / or altered consciousness, perceptual disturbances and behaviour. It may be the only sign of serious medical illness in an older person and should be urgently assessed. Misdiagnosis of delirium may have dire consequences.
2. Better prevention and treatment is needed to avoid the poor outcomes that result from delirium, especially increased rates of cognitive and functional decline, prolonged hospital stay, institutionalisation and mortality.
3. All older persons should be assessed for risk factors for delirium on admission to hospital. These include dementia, polypharmacy, visual and hearing impairment, dehydration, functional disability, alcohol abuse, depression and advanced age. Many precipitating factors are described. Iatrogenic factors particularly medications are unfortunately common and potentially avoidable.
4. Delirium is very common but is often not detected or misdiagnosed. Cognition should be considered a “vital sign” and cognitive assessment routinely performed. Those who display altered cognition should be screened for delirium using a tool such as the Confusion Assessment Method.
5. Preventative strategies have now been demonstrated to be very effective. These are based on multicomponent interventions targeting risk factors which are managed with care protocols and environmental strategies.
6. Education programmes are very effective in prevention. Preventative strategies and Education programmes should be adopted by all healthcare institutions.
7. Investigations for common precipitating factors are usually needed unless clear, recent causes are identified. Specialised investigations may be needed in specific circumstances.
8. Management of delirium involves identifying and treating risk factors and precipitating factors, use of non-pharmacological and pharmacological measures to manage neuropsychiatric

manifestations, preventing complications and monitoring progress.

9. Non-pharmacological measures should always be utilised. These include: correction of dehydration (subcutaneous fluids if needed), malnutrition and sensory deficits; provision of reorientation, good quality communication and undisturbed sleep; encouraging self-care and mobility; avoiding use of restraints or immobilising devices; and limiting room and staff changes. However, current hospital environments and practices rarely facilitate these measures.
10. Pharmacological measures are not always needed but should be considered to control distressing symptoms or when safety is compromised. Small doses of antipsychotics are effective and appropriate in the short term. When patients with an extrapyramidal syndrome require treatment, atypical antipsychotics should be considered. Benzodiazepines are useful in alcohol and benzodiazepine withdrawal.
11. Delirium is best managed by a multidisciplinary team utilising multicomponent interventions in an appropriate environment with adequate staffing levels. Delirium Units provide effective and safe care for older people, can help raise awareness of delirium as a serious condition, and enhance delirium research. They are cost effective but there is no data to purport that they have better outcomes than ACE units.

This Position Statement represents the views of the Australian and New Zealand Society for Geriatric Medicine. This Statement was approved by the Federal Council of the ANZSGM on

May 1 2012. The revision of this paper was coordinated by Drs Teck Yew and Sean Maher. The original paper was coordinated by Dr Sean Maher.

BACKGROUND PAPER

Delirium is a syndrome characterized by the rapid onset of impairment of attention that fluctuates, together with impaired cognition and / or altered consciousness. Behavioural disturbance and psychotic features are common. It is commonly encountered in older people and is associated with increased rates of cognitive and functional decline, prolonged hospital stay, relocation to residential care and mortality. It is often either not diagnosed or is misdiagnosed. There is often a strong element of iatrogenicity in the precipitating factors contributing to many episodes of delirium, emphasizing the need for better quality of care of older people. Good quality studies regarding risk factors, prevention and prognosis exist for hospitalised patients. Comprehensive Geriatric Assessment with a multidisciplinary approach aimed at prevention, and education programmes, improve delirium outcomes. The potential exists for better pharmacological interventions in delirium management.

Epidemiology

The incidence of delirium arising during hospital stay is reported to be as high as 56%.¹ Post-operative delirium occurs in 15-53%² of patients over 65 and the incidence in ICU older patients is as high as 70-87%.³ Reports of the prevalence of delirium in long term care facilities in a small

number of studies range from 0.5-57%, with a mean of 14.2%.⁴ Nursing home residents are more likely (OR 10.2) to present to ED with delirium compared to community dwelling older people.⁵

Aetiology

Delirium represents a true geriatric syndrome with a defined phenotype, with interactions between individual risk or predisposing factors (“vulnerability”) and precipitating factors. Thus, a vulnerable patient may easily develop delirium with a minor event such as a urinary tract infection. A person with few or no risk factors would require severe or multiple precipitating events before their cognitive reserves are overwhelmed. Acutely unwell older patients have an average of 5.2 predisposing and 3 precipitating factors.⁶

Common predisposing factors include old age, frailty, dementia, severe illness, multiple diseases, admission to hospital with infection or dehydration, visual impairment, deafness, polypharmacy, alcohol excess, renal impairment and malnutrition.^{1,7} A predictive model from Inouye et al showed that visual impairment, severe illness and dementia, each treble the risk of delirium while dehydration doubles the risk.⁸ 9% with no risk factors developed delirium as compared to 83% with 3 to 4 risk factors. Multiple risk factors multiply, rather than add, the relative risks for developing delirium. These data point

to approaches for risk stratification as well as prevention.

Precipitants for delirium include infections (especially chest and urinary), constipation, electrolyte disturbance, medications, organ failure, hypoxia, alcohol withdrawal, uncontrolled pain, neurological insults, sleep deprivation and surgery.⁹ Restraint use and malnutrition each quadruple the risk of delirium, whilst adding >3 medications and use of a bladder catheter each nearly treble the risk. Any iatrogenic event doubles the risk.⁸

Medications contribute to about 40% of cases of delirium.¹⁰ Older people have diminished renal excretion and hepatic metabolism and are more likely to have adverse effects even at lower doses. Psychoactive drugs and those that cross the blood brain barrier are most likely to cause delirium. Drugs with anticholinergic properties are particularly likely to cause delirium.¹¹ Additionally, metabolites of some common drugs have anticholinergic properties and add to the total “anticholinergic burden”.¹² Common classes of drugs implicated include antiparkinsonians, benzodiazepines, lithium, antidepressants, antipsychotics, anticonvulsants, antiarrhythmics, antihypertensives, histamine-2 receptor antagonists, corticosteroids, opiate analgesics, non-steroidal anti-inflammatories, over the counter and herbal preparations, antihistamines and antispasmodics.

A cohort study of delirium in stroke patients has shown that 25% of patients developed delirium within 3

days after stroke.¹³ Independent predisposing factors identified include older age, haemorrhagic stroke, metabolic disorders, dementia pre-stroke, an admission GCS <15 or the inability to lift both arms.

Cardioembolic stroke (OR 5.58) and total anterior circulation infarcts (OR 3.42) were more likely to develop delirium. Post-stroke delirium is associated with greater 6 and 12 month mortality, and reduced functional status and higher institutionalisation at 12 months.

The usual predisposing factors contributing to delirium apply to surgical patients however some specific risk factors need consideration. Trauma or unplanned surgery such as fractured neck of femur carries a higher risk of Post-Operative Delirium (POD).^{14, 15} More patients undergoing aortic surgery developed POD as compared to other vascular surgery.¹⁶ The risk of developing POD increases with use of general anaesthesia¹⁷ and the presence of post-operative pain.^{18, 19}

Depression symptoms in older hospitalised patients, in particular dysphoric mood and hopelessness are predictive of incident delirium.²⁰

Pathophysiology

The pathophysiology of delirium is not fully understood. Multiple pathogenic mechanisms contribute to the development of delirium. A relative deficiency of acetylcholine and dopamine excess is well described.²¹ Delirium may also partially be a

response to stress. Steroids can induce delirium and hypothalamic-pituitary-adrenal axis abnormalities have been described in dementia and delirium.²² Inflammatory processes have been shown to play a role. Patients with delirium have significantly higher IL-6 levels (53% vs. 31%) and IL-8 level (45% vs. 22%) as compared with patients who did not have delirium despite adjusting for infection, age, and cognitive impairment.²³ Adamis et al. found that low levels of neuroprotective factors (IGF-I, IL-1RA) are associated with delirium, whilst high IFN- γ and low IGF-I have significant effects on delirium severity.²⁴ Two studies demonstrated prolonged delirium in APOE E4 carriers but the studies were underpowered.²⁵

Prevention

There is increasing evidence that delirium can be prevented. Up to 30-40% of delirium episodes may be preventable.²⁶ The majority of studies rely on non pharmacological measures such as identifying and managing risk factors as well as education programmes. Their efficacy suggests that they should be introduced widely into real world clinical settings.²⁷ In 1999, Inouye et al. published one of the most influential delirium prevention studies targeting 6 key delirium risk factors (cognitive impairment, vision/hearing impairment, immobilisation, psychoactive drug use, dehydration and sleep deprivation).²⁸ Using this protocol, delirium developed in 9.9% of the intervention group as

compared with 15.0% of the usual-care group (matched OR 0.6). The total number of days with delirium (105 vs. 161, $P=0.02$) and the total number of episodes (62 vs. 90, $P=0.03$) were also significantly lower in the intervention group. The Hospital Elder Life Program (HELP) was developed based on the model of screening and targeting these 6 key risk factors.²⁹ This approach is multidisciplinary in nature and includes a geriatric nurse specialist, Elder Life Specialists, trained volunteers, and geriatricians. The HELP programme has been adapted in other centres³⁰ and has been positively embraced by patients, families and staff.³¹ A similar programme (ReViVe) has been successfully trialled in Australia.³²

Marcantonio et al. demonstrated effectiveness of geriatric consultation in reducing delirium in hip fracture patients.³³ Recommendations were made regarding analgesia, fluid/electrolyte balance, adequate oxygen delivery, medication review, bowel/bladder function, nutrition, early mobilisation and rehabilitation, prevention, detection and treatment of post operative complications, appropriate environmental stimuli and treatment of hyperactive delirium. The intervention group had a significantly reduced relative risk of developing delirium (RR 0.64) and even greater benefit for preventing severe delirium (RR 0.40). Multicomponent intervention reduces delirium in hospitalised older patients, improves quality of care, reduces rate of functional decline and can be

implemented without increased cost.^{34, 35}

There have been several publications showing that delirium education programmes directed at health care workers in hospital significantly reduce the prevalence of delirium.³⁶⁻⁴⁰ Providing base-line data on the prevalence and outcome of delirious patients, training in methods of mental assessments and introducing guidelines on medical management through a series of small group meetings and grand rounds prevents delirium.³⁸ A staff education programme focusing on the assessment, prevention, and treatment of delirium and on caregiver-patient interaction reduces delirium and length of hospital stay. In a prospective intervention study based in a general medical ward in Sweden, delirium was equally common on the day of admission at the intervention and control wards, but fewer patients remained delirious on Day 7 on the intervention ward ($n=19/63$, 30.2% vs 37/62, 59.7%, $P=.001$). The mean length of hospital stay was shorter on the intervention ward than on the control ward (9.4 vs 13.4 days, $P<.001$) especially for delirious patients (10.8 vs 20.5 days, $P<.001$).⁴¹

Haloperidol⁴² and donepezil^{43, 44} have been studied for prevention of post-operative delirium. The studies were small and results were mixed therefore their use cannot be recommended at this stage.

Clinical Features

Early symptoms of delirium (prodromal delirium) may include irritability, bewilderment or evasiveness. Delirium develops over hours to days and fluctuates, usually with lucid periods during the day and maximal disturbance at night. Impaired attention may result in a distractible or inert patient. Disorientation to time and short-term memory impairment are apparent. Thinking is disordered and is reflected by rambling, incoherent speech. Patients may exhibit obvious distress with paranoid delusions, misperceptions and visual hallucinations. Altered consciousness is reflected by impaired clarity of awareness and alertness ranging from vigilant through to coma.

Its clinical presentation can be divided into hyperactive or hypoactive subtypes although the presentation can be mixed. Hyperactive delirium is easily recognised. There is hyperarousal with increased sensitivity to immediate surroundings to the point where patients can be verbally and physically aggressive. Restlessness and wandering are common features. Psychotic symptoms may also be present. Patients with hypoactive delirium may appear lethargic, sluggish, confused and with discernibly low mood. Hypoactive delirium is more common and careful bedside observation is required for detection, otherwise it is easily missed.

Detection

Various bedside screening tools have been validated to detect delirium.⁴⁵

Examples of these screening tools include Global Attentiveness Rating (GAR), Memorial Delirium Assessment Scale (MDAS) and Delirium Rating Scale Revised-98 (DRS-R-98). The most widely used is the Confusion Assessment Method (CAM), a four-item instrument based on the DSM-III-R criteria.^{21, 46}

1. Acute onset & fluctuating course AND
 2. Inattention AND
 3. Disorganised thinking OR
 4. Altered level of consciousness.
- The CAM algorithm has a sensitivity of 94-100% and a specificity of 90-95%. It has a high inter-rater reliability when administered by trained interviewers.

Diagnosis

Delirium remains a clinical diagnosis made on the basis of a detailed history, examination and relevant investigations. Establishing previous functional and cognitive status and recent events such as falls or medication changes is essential. A formal diagnosis can be made by using the Diagnostic and Statistical Manual of Mental Disorders, 4th revision (DSM-IV) criteria or International Classification of Diseases 10 (ICD-10).

Misdiagnosis

Mistaking delirium for the behavioural and psychological symptoms of dementia (BPSD) is common and may have dire consequences. Hypoactive delirium can be erroneously diagnosed as depression. Features of

hyperactive delirium such as agitation and hallucinations can be mistaken for late onset schizophrenia or mania.

Investigations

The clinical picture should guide investigation, but if there are no obvious clues then a routine “screen” should be used to detect common causes. A reasonable screen includes FBE, U&E, glucose, calcium, liver function tests, cardiac enzymes, ESR, CRP, oxygen saturation, MSU if urinalysis is abnormal, CXR and ECG. Other tests to consider include blood cultures, thyroid function tests, arterial blood gases, B12 and folate, CT brain, lumbar puncture and CSF exam, and EEG. CT brain should not be routine unless there is a positive history of falls, anticoagulation or focal neurological signs. Lumbar puncture should be considered (after CT brain) if there is headache, meningism or no other source of fever. EEG may be helpful if the diagnosis is in doubt and occasionally assists in determining aetiology e.g. non-convulsive status epilepticus. Newer neuroimaging techniques, such as volumetric MRI, SPECT and PET scan with a radioisotope tracer specific for cholinergic and dopaminergic activities, have been studied for diagnosing delirium. However, the findings are not yet consistent and at present have not been shown to improve detection of delirium.

Management

The mainstay of managing a patient with delirium is supportive with active identification and treatment of predisposing and precipitating factors. It is important to actively prevent complications such as pressure sores and falls. Patients who deteriorate further or have persistent delirium require active re-evaluation. Delirium care involves a multidisciplinary approach with the use of non-pharmacological and pharmacological interventions. Evidence based clinical practice guidelines have been developed and are widely available.⁴⁷ Every hospital should have local guidelines for prevention, improving detection and management of delirium.

Non Pharmacological Management

Measures recommended in the literature are mainly derived from established risk factors for delirium and follow an empiric approach that improvement is unlikely if risk factors are perpetuated. Dehydration should be corrected, with subcutaneous fluids if needed. One to three litres per day can be given via a butterfly needle easily resited by nursing staff.⁴⁸ Multicomponent geriatric intervention has been shown to reduce duration of delirium, length of stay and length of hospitalization.⁴¹ This approach also improves health related quality of life and can be done without increasing overall inpatient cost.⁴⁹ A multicomponent approach mainly consists of staff education focusing on the assessment, prevention and treatment of delirium and on caregiver-

patient interaction providing individualized care.

There have been a limited number of trials examining the efficacy of cognitive, behavioural and environmental interventions in delirium management.⁵⁰⁻⁵² Reorientation and behavioural interventions are important. Sensory impairments, such as vision and hearing loss should be minimized by use of spectacles and hearing aids. Physical restraints often lead to immobility, increased agitation, prolongation of delirium and higher risk of injury thus should be avoided. Environmental interventions are also important. Room and staff changes should be limited. At night, there should be low-level lighting and a quiet setting to allow undisturbed sleep. Psychoactive medications should be avoided if possible and non-pharmacological sleep protocols should be used instead.⁵³ Family members can be helpful in settling and reassuring agitated patients.

Flaherty et al. described the use of a "Delirium Room" situated within an Acute Care of the Elderly (ACE) unit.⁵⁴ Comprehensive geriatric assessment with multidisciplinary care was standard with 24 hour nursing supervision. Patients were managed free of restraints and needed less sedation. Other benefits include raising awareness of delirium as a serious condition within a hospital, and ensuring a high level of adherence to care protocols. Although cost effectiveness has been demonstrated for delirium units, mainly by reducing the need for patient care assistants,⁵⁵

there are no data showing better outcomes compared to care within an ACE unit. A lower rate of falls than expected has been reported supporting the rationale for close supervision.⁵⁵ Although the emphasis should be on providing effective multicomponent interventions to all older people, delirium units assist with the care of those with significant behavioural disturbance and are still worthy of further evaluation.

Pharmacological Management

There are limited high quality randomised controlled trials on the use of pharmacological agents in delirium management and current practice is mainly based on case series and retrospective studies.⁵⁶ Medications should be reserved for patients whom symptoms are distressing or compromise safety. The lowest starting dose should be used and titrated as necessary. Haloperidol is widely used and its effectiveness established in one randomised controlled trial.⁵⁷ Atypical antipsychotics have been shown to be comparable to haloperidol in terms of efficacy.^{58, 59} There is no significant difference in efficacy within the class of atypical antipsychotic medications.⁶⁰ Atypical antipsychotics have less extrapyramidal side effects and should be considered for delirious patients with an extrapyramidal syndrome.

However, there is evidence of harm from antipsychotics including ischaemic stroke⁶¹ and evidence that atypical antipsychotics also increase risk of prolongation of QT interval and

sudden cardiac death⁶² and pneumonia.^{62, 63} In a large study of American nursing home residents (which included some patients with delirium) antipsychotic use increased the risk of mortality. The increased risk was highest with haloperidol and lowest for quetiapine. This emphasises the need to have a clear indication for antipsychotic use and employ low doses for short durations.⁶⁴

There are case reports of benefits in using acetylcholinesterase inhibitors⁶⁵⁻⁶⁷ and the serotonin 5HT antagonist (trazadone). However, there is no evidence from controlled trials showing benefit from donepezil in treatment of delirium.⁴³ Rivastigmine did not decrease duration of delirium and might have increased mortality in critically ill delirious patients.⁶⁸ Benzodiazepines are appropriate therapy for alcohol and drug withdrawal. However, they are not recommended as first line agents in older patients as they can worsen mental state changes. Agents with a short half-life and no active metabolites are preferable (e.g. lorazepam 0.5mg or oxazepam 7.5mg daily) if needed. Intramuscular midazolam 1mg can be used for excessive agitation not responding to neuroleptic agents or where they are inappropriate (e.g. extrapyramidal disorders).

Duration

Delirium may be very persistent. In one study, delirium was present for up to one week in 60% of patients, two

weeks in 20%, four weeks in 15% and more than four weeks in 5%.⁶⁹ “Subsyndromal” delirium, with disorientation, inattention, and memory impairment may be still present at up to 12 months and associated with poorer functional and cognitive outcomes.^{70, 71} This may be due to persisting chronic illness, irreversible neuronal dysfunction or delirium becoming a chronic disorder in some people.⁷²

Outcomes

Delirium increases the risk of adverse outcomes, including length of stay, complications, cognitive and functional decline, nursing home admission and mortality. A 2010 study of hospital use, institutionalisation rate and mortality in older patients demonstrated that delirious patients have a length of stay twice as long compared to non-delirious patients.⁷³ Patients also spend more time in acute hospital care in the subsequent year after onset of delirium.⁷³ In one study, the relative risk of developing dementia after delirium over 3 years was trebled.⁷⁴ This may reflect early cognitive impairment unmasked by acute illness and/or irreversible neuronal dysfunction. Delirium trebles the rate of cognitive decline in people with dementia.⁷⁵ Rates of falls, incontinence and pressure sores are more than trebled in hospital patients with delirium.⁶⁹ Delirium after hip fracture increases the risk of poor functional outcome, decline in ambulation and death or nursing home admission by nearly 3 times.⁷⁶ Eeles

et al in their study showed median time to death was 162 days for those with delirium compared with 1,444 days for those without ($P < 0.001$).⁷³ Persistent delirium (lasting for more than 6 months) is a significant independent predictor of 1 year mortality (HR 2.9).⁷⁷ The number of days of ICU delirium has been shown to be significantly associated with time to death within 1 year post-ICU admission (HR 1.10).⁷⁸ Delirium superimposed on dementia during hospitalisation more than doubles the risk of mortality in the 12 months following discharge.⁷⁹ Overlap of depressive symptoms and delirium is associated with worse functional outcome, higher institutionalisation and death.⁸⁰

Given the significant adverse outcomes following delirium, rates of delirium would make a good quality indicator of the care that older people receive.⁸¹

The economic impact of delirium is substantial, with total direct one year healthcare costs estimated at US\$143 – 152 billion in the USA.⁸² This fact alone surely warrants the attention of health policy makers.

Conclusion

Delirium carries a high mortality and morbidity and yet it remains a common condition that is underdiagnosed. There is strong evidence that comprehensive geriatric assessment with multicomponent intervention is effective in preventing and managing delirium. Education programmes are a vital part of preventing delirium and

should be obligatory. Implementation of such strategies should be in place at all health care institutions. More effort in prevention, detection and management of delirium would involve expenditure but there should be significant savings from the prevention of delirium with all of its attendant morbidities.

As we cannot prevent all cases of delirium, more research is needed to improve the diagnostic approach to delirium, aimed at early detection and better management and treatment of delirium. Improved understanding of the pathophysiology of delirium and its association with cytokines and inflammation may result in further research into pharmacological treatments. The complex pathophysiology of delirium involving multiple mechanisms may mean that future therapeutic agents will also likely need to target multiple pathways.

The combination of poor outcomes with significant health costs demands that delirium should be a major priority for health policy makers.

References

1. Inouye SK. Delirium in hospitalized older patients: recognition and risk factors. *J Geriatr Psychiatry Neurol* 1998;11:118-25; discussion 57-8.
2. Inouye SK. Delirium in older persons. *N Engl J Med* 2006;354:1157-65.
3. Pisani MA, McNicoll L, Inouye SK. Cognitive impairment in the intensive care unit. *Clin Chest Med* 2003;24:727-37.

4. McCusker J, Cole MG, Voyer P, et al. Prevalence and incidence of delirium in long-term care. *Int J Geriatr Psychiatry* 2011.
5. Han JH, Morandi A, Ely EW, et al. Delirium in the nursing home patients seen in the emergency department. *J Am Geriatr Soc* 2009;57:889-94.
6. Laurila JV, Laakkonen ML, Tilvis RS, Pitkala KH. Predisposing and precipitating factors for delirium in a frail geriatric population. *J Psychosom Res* 2008;65:249-54.
7. Elie M, Cole MG, Primeau FJ, Bellavance F. Delirium risk factors in elderly hospitalized patients. *J Gen Intern Med* 1998;13:204-12.
8. Inouye SK. Prevention of delirium in hospitalized older patients: risk factors and targeted intervention strategies. *Ann Med* 2000;32:257-63.
9. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA* 1996;275:852-7.
10. Flacker JM, Marcantonio ER. Delirium in the elderly. Optimal management. *Drugs Aging* 1998;13:119-30.
11. Han L, McCusker J, Cole M, Abrahamowicz M, Primeau F, Elie M. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. *Arch Intern Med* 2001;161:1099-105.
12. Tune L, Carr S, Hoag E, Cooper T. Anticholinergic effects of drugs commonly prescribed for the elderly: potential means for assessing risk of delirium. *Am J Psychiatry* 1992;149:1393-4.
13. Sheng AZ, Shen Q, Cordato D, Zhang YY, Yin Chan DK. Delirium within three days of stroke in a cohort of elderly patients. *J Am Geriatr Soc* 2006;54:1192-8.
14. Kalisvaart KJ, Vreeswijk R, de Jonghe JF, van der Ploeg T, van Gool WA, Eikelenboom P. Risk factors and prediction of postoperative delirium in elderly hip-surgery patients: implementation and validation of a medical risk factor model. *J Am Geriatr Soc* 2006;54:817-22.
15. Galanakis P, Bickel H, Gradinger R, Von Gumpfenberg S, Forstl H. Acute confusional state in the elderly following hip surgery: incidence, risk factors and complications. *Int J Geriatr Psychiatry* 2001;16:349-55.
16. Bohner H, Hummel TC, Habel U, et al. Predicting delirium after vascular surgery: a model based on pre- and intraoperative data. *Ann Surg* 2003;238:149-56.
17. Sieber FE, Zakriya KJ, Gottschalk A, et al. Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. *Mayo Clin Proc* 2010;85:18-26.
18. Vaurio LE, Sands LP, Wang Y, Mullen EA, Leung JM. Postoperative delirium: the importance of pain and pain management. *Anesth Analg* 2006;102:1267-73.
19. Lynch EP, Lazor MA, Gellis JE, Orav J, Goldman L, Marcantonio ER. The impact of postoperative pain on the development of postoperative delirium. *Anesth Analg* 1998;86:781-5.
20. McAvay GJ, Van Ness PH, Bogardus ST, Jr., et al. Depressive symptoms and the risk of incident delirium in older hospitalized adults. *J Am Geriatr Soc* 2007;55:684-91.
21. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;113:941-8.
22. Olsson T. Activity in the hypothalamic-pituitary-adrenal axis

and delirium. *Dement Geriatr Cogn Disord* 1999;10:345-9.

23. de Rooij SE, van Munster BC, Korevaar JC, Levi M. Cytokines and acute phase response in delirium. *J Psychosom Res* 2007;62:521-5.

24. Adamis D, Lunn M, Martin FC, et al. Cytokines and IGF-I in delirious and non-delirious acutely ill older medical inpatients. *Age Ageing* 2009;38:326-32; discussion 251.

25. van Munster BC, de Rooij SE, Korevaar JC. The role of genetics in delirium in the elderly patient. *Dement Geriatr Cogn Disord* 2009;28:187-95.

26. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age Ageing* 2006;35:350-64.

27. Tabet N, Howard R. Non-pharmacological interventions in the prevention of delirium. *Age Ageing* 2009;38:374-9.

28. 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.

29. 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.

30. Inouye SK, Baker DI, Fugal P, Bradley EH. Dissemination of the hospital elder life program: implementation, adaptation, and successes. *J Am Geriatr Soc* 2006;54:1492-9.

31. Sandhaus S, Zalon ML, Valenti D, Dzielak E, Smego RA, Jr., Arzamasova U. A volunteer-based Hospital Elder Life Program to reduce delirium. *Health Care Manag (Frederick)* 2010;29:150-6.

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

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

34. Vidan MT, Sanchez E, Alonso M, Montero B, Ortiz J, Serra JA. An intervention integrated into daily clinical practice reduces the incidence of delirium during hospitalization in elderly patients. *J Am Geriatr Soc* 2009;57:2029-36.

35. Bo M, Martini B, Ruatta C, et al. Geriatric ward hospitalization reduced incidence delirium among older medical inpatients. *Am J Geriatr Psychiatry* 2009;17:760-8.

36. Brymer C, Cavanagh P, Denomy E, Wells K, Cook C. The effect of a geriatric education program on emergency nurses. *J Emerg Nurs* 2001;27:27-32.

37. Tabet N, Hudson S, Sweeney V, et al. An educational intervention can prevent delirium on acute medical wards. *Age Ageing* 2005;34:152-6.

38. Naughton BJ, Saltzman S, Ramadan F, Chadha N, Priore R, Mylotte JM. A multifactorial intervention to reduce prevalence of delirium and shorten hospital length of stay. *J Am Geriatr Soc* 2005;53:18-23.

39. Pierre JS. Delirium: a process improvement approach to changing prescribing practices in a community teaching hospital. *J Nurs Care Qual* 2005;20:244-50; quiz 51-2.

40. Lundstrom M, Olofsson B, Stenvall M, et al. Postoperative delirium in old patients with femoral neck fracture: a randomized intervention study. *Aging Clin Exp Res* 2007;19:178-86.

41. Lundstrom M, Edlund A, Karlsson S, Brannstrom B, Bucht G, Gustafson Y. A multifactorial

intervention program reduces the duration of delirium, length of hospitalization, and mortality in delirious patients. *J Am Geriatr Soc* 2005;53:622-8.

42. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. *J Am Geriatr Soc* 2005;53:1658-66.

43. Liptzin B, Laki A, Garb JL, Fingerroth R, Krushell R. Donepezil in the prevention and treatment of post-surgical delirium. *Am J Geriatr Psychiatry* 2005;13:1100-6.

44. Sampson EL, Raven PR, Ndhlovu PN, et al. A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. *Int J Geriatr Psychiatry* 2007;22:343-9.

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

46. 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.

47. Tropea J, Slee JA, Brand CA, Gray L, Snell T. Clinical practice guidelines for the management of delirium in older people in Australia. *Australas J Ageing* 2008;27:150-6.

48. O'Keeffe ST, Lavan JN. Subcutaneous fluids in elderly hospital patients with cognitive impairment. *Gerontology* 1996;42:36-9.

49. Pitkala KH, Laurila JV, Strandberg TE, Kautiainen H, Sintonen H, Tilvis RS. Multicomponent geriatric intervention for elderly inpatients with delirium: effects on costs and health-related quality of life. *J Gerontol A Biol Sci Med Sci* 2008;63:56-61.

50. Cole MG, Primeau FJ, Bailey RF, et al. Systematic intervention for elderly inpatients with delirium: a randomized trial. *CMAJ* 1994;151:965-70.

51. Meagher DJ, O'Hanlon D, O'Mahony E, Casey PR. The use of environmental strategies and psychotropic medication in the management of delirium. *Br J Psychiatry* 1996;168:512-5.

52. Williams MA, Campbell EB, Raynor WJ, Mlynarczyk SM, Ward SE. Reducing acute confusional states in elderly patients with hip fractures. *Res Nurs Health* 1985;8:329-37.

53. McDowell JA, Mion LC, Lydon TJ, Inouye SK. A nonpharmacologic sleep protocol for hospitalized older patients. *J Am Geriatr Soc* 1998;46:700-5.

54. Flaherty JH, Tariq SH, Raghavan S, Bakshi S, Moinuddin A, Morley JE. A model for managing delirious older inpatients. *J Am Geriatr Soc* 2003;51:1031-5.

55. Wong Tin Niam DM, Geddes JA, Inderjeeth CA. Delirium unit: our experience. *Australas J Ageing* 2009;28:206-10.

56. Flaherty JH, Gonzales JP, Dong B. Antipsychotics in the treatment of delirium in older hospitalized adults: a systematic review. *J Am Geriatr Soc* 2011;59 Suppl 2:S269-76.

57. Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. *Am J Psychiatry* 1996;153:231-7.

58. Han CS, Kim YK. A double-blind trial of risperidone and haloperidol for the treatment of delirium. *Psychosomatics* 2004;45:297-301.

59. Kim JY, Jung IK, Han C, et al. Antipsychotics and dopamine transporter gene polymorphisms in

delirium patients. *Psychiatry Clin Neurosci* 2005;59:183-8.

60. Kim SW, Yoo JA, Lee SY, et al. Risperidone versus olanzapine for the treatment of delirium. *Hum Psychopharmacol* 2010;25:298-302.
61. Laredo L, Vargas E, Blasco AJ, Aguilar MD, Moreno A, Portoles A. Risk of cerebrovascular accident associated with use of antipsychotics: population-based case-control study. *J Am Geriatr Soc* 2011;59:1182-7.
62. Setoguchi S, Wang PS, Alan Brookhart M, Canning CF, Kaci L, Schneeweiss S. Potential causes of higher mortality in elderly users of conventional and atypical antipsychotic medications. *J Am Geriatr Soc* 2008;56:1644-50.
63. Knol W, van Marum RJ, Jansen PA, Souverein PC, Schobben AF, Egberts AC. Antipsychotic drug use and risk of pneumonia in elderly people. *J Am Geriatr Soc* 2008;56:661-6.
64. Huybrechts KF, Gerhard T, Crystal S, et al. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. *BMJ* 2012;344:e977.
65. Slatkin N, Rhiner M. Treatment of opioid-induced delirium with acetylcholinesterase inhibitors: a case report. *J Pain Symptom Manage* 2004;27:268-73.
66. Noyan MA, Elbi H, Aksu H. Donepezil for anticholinergic drug intoxication: a case report. *Prog Neuropsychopharmacol Biol Psychiatry* 2003;27:885-7.
67. Wengel SP, Roccaforte WH, Burke WJ. Donepezil improves symptoms of delirium in dementia: implications for future research. *J Geriatr Psychiatry Neurol* 1998;11:159-61.
68. van Eijk MM, Roes KC, Honing ML, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol

on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. *Lancet* 2010;376:1829-37.

69. O'Keeffe S, Lavan J. The prognostic significance of delirium in older hospital patients. *J Am Geriatr Soc* 1997;45:174-8.
70. Levkoff SE, Evans DA, Liptzin B, et al. Delirium. The occurrence and persistence of symptoms among elderly hospitalized patients. *Arch Intern Med* 1992;152:334-40.
71. McCusker J, Cole M, Dendukuri N, Han L, Belzile E. The course of delirium in older medical inpatients: a prospective study. *J Gen Intern Med* 2003;18:696-704.
72. McCusker J, Cole M, Dendukuri N, Belzile E, Primeau F. Delirium in older medical inpatients and subsequent cognitive and functional status: a prospective study. *CMAJ* 2001;165:575-83.
73. Eeles EM, Hubbard RE, White SV, O'Mahony MS, Savva GM, Bayer AJ. Hospital use, institutionalisation and mortality associated with delirium. *Age Ageing* 2010;39:470-5.
74. Rockwood K, Cosway S, Carver D, Jarrett P, Stadnyk K, Fisk J. The risk of dementia and death after delirium. *Age Ageing* 1999;28:551-6.
75. Fong TG, Jones RN, Shi P, et al. Delirium accelerates cognitive decline in Alzheimer disease. *Neurology* 2009;72:1570-5.
76. Marcantonio ER, Flacker JM, Michaels M, Resnick NM. Delirium is independently associated with poor functional recovery after hip fracture. *J Am Geriatr Soc* 2000;48:618-24.
77. Kiely DK, Marcantonio ER, Inouye SK, et al. Persistent delirium predicts greater mortality. *J Am Geriatr Soc* 2009;57:55-61.
78. Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated with 1-

year mortality in an older intensive care unit population. *Am J Respir Crit Care Med* 2009;180:1092-7.

79. Bellelli G, Frisoni GB, Turco R, Lucchi E, Magnifico F, Trabucchi M. Delirium superimposed on dementia predicts 12-month survival in elderly patients discharged from a postacute rehabilitation facility. *J Gerontol A Biol Sci Med Sci* 2007;62:1306-9.

80. Givens JL, Jones RN, Inouye SK. The overlap syndrome of depression and delirium in older hospitalized patients. *J Am Geriatr Soc* 2009;57:1347-53.

81. Inouye SK, Schlesinger MJ, Lydon TJ. Delirium: a symptom of how hospital care is failing older persons and a window to improve quality of hospital care. *Am J Med* 1999;106:565-73.

82. Leslie DL, Inouye SK. The importance of delirium: economic and societal costs. *J Am Geriatr Soc* 2011;59 Suppl 2:S241-3.