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%. Post-operative delirium occurs in 15-53% of patients over 65 and the incidence in ICU older patients is as high as 70-87%. 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%. 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. 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). More patients undergoing aortic surgery developed POD as compared to other vascular surgery. The risk of developing POD increases with use of general anaesthesia and the presence of post-operative pain.

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

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. 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. 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. 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. Two studies demonstrated prolonged delirium in APOE E4 carriers but the studies were underpowered.

Prevention
There is increasing evidence that delirium can be prevented. Up to 30-40% of delirium episodes may be preventable. 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. 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). 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. 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 centres and has been positively embraced by patients, families and staff. A similar programme (ReViVe) has been successfully trialled in Australia.

Marcantonio et al. demonstrated effectiveness of geriatric consultation in reducing delirium in hip fracture patients. 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.

There have been several publications showing that delirium education programmes directed at health care workers in hospital significantly reduce the prevalence of delirium. 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. 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). Haloperidol and donepezil 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 beside observation is required for detection, otherwise it is easily missed.

Detection
Various bedside screening tools have been validated to detect delirium. 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. The most widely used is the Confusion Assessment Method (CAM), a four-item instrument based on the DSM-III-R criteria. 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. 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. Multicomponent geriatric intervention has been shown to reduce duration of delirium, length of stay and length of hospitalization. This approach also improves health related quality of life and can be done without increasing overall inpatient cost. 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. 56, 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 stroke 61 and evidence that atypical antipsychotics also increase risk of prolongation of QT interval and
sudden cardiac death\textsuperscript{62} and pneumonia.\textsuperscript{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.\textsuperscript{64}

There are case reports of benefits in using acetylcholinesterase inhibitors\textsuperscript{65-67} and the serotonin 5HT antagonist (trazadone). However, there is no evidence from controlled trials showing benefit from donepezil in treatment of delirium.\textsuperscript{43} Rivastigmine did not decrease duration of delirium and might have increased mortality in critically ill delirious patients.\textsuperscript{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).

**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.\textsuperscript{73} Patients also spend more time in acute hospital care in the subsequent year after onset of delirium.\textsuperscript{73} In one study, the relative risk of developing dementia after delirium over 3 years was trebled.\textsuperscript{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.\textsuperscript{75} Rates of falls, incontinence and pressure sores are more than trebled in hospital patients with delirium.\textsuperscript{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.\textsuperscript{76} Eeles

**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\%.\textsuperscript{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.\textsuperscript{70, 71} This may be due to persisting chronic illness, irreversible neuronal dysfunction or delirium becoming a chronic disorder in some people.\textsuperscript{72}
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). Persistent delirium (lasting for more than 6 months) is a significant independent predictor of 1 year mortality (HR 2.9). 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). Delirium superimposed on dementia during hospitalisation more than doubles the risk of mortality in the 12 months following discharge. Overlap of depressive symptoms and delirium is associated with worse functional outcome, higher institutionalisation and death.

Given the significant adverse outcomes following delirium, rates of delirium would make a good quality indicator of the care that older people receive. The economic impact of delirium is substantial, with total direct one year healthcare costs estimated at US$143 – 152 billion in the USA. 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**

22. Olsson T. Activity in the hypothalamic-pituitary-adrenal axis


78. Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated with 1-