Delirium

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Historical Context

Disturbed brain function in the context of physical or bodily illness has been recognised in the medical literature for over two millennia. The actual term *delirium* was not introduced until the first century AD, when Aulus Cornelius Celsus, a Roman, described it in his medical encyclopedia De Medicina. The word is thought to originate from the Latin de (meaning 'out of') and lira (meaning 'furrow'). In his work, Celsus used the term *delirium* to describe the acute confusional states that could occur after wound infections or head injuries. However, more than 400 years before that, Hippocrates used about 16 different words to describe to the clinical syndrome that we now call delirium, with the terms *lethargus* and *phrenitis* largely consistent with the present-day concepts of hypoactive and hyperactive clinical presentations [1]. These early descriptions emphasised the occurrence of psychosis and impaired arousal in patients with morbidity that was often distant from the brain (typically infectious). They thus include an awareness of the connection between body wellness and brain function that has been somewhat downplayed until relatively recent times with the greater recognition of the inherent connectivity of mind and body – an interface that is exemplified by the delirious state where pathology often very peripheral to the central nervous system (CNS) can cause globalised cognitive and neuropsychiatric disturbances.

Thereafter, the clinical meaning of delirium remained quite consistent until the nineteenth century where, partly for linguistic reasons, especially in France where 'delire' was used to refer to a variety of psychotic states, the term *confusion mentale* was applied by Chaslin [2] to distinguish causes with an organic basis. In fact, the Irish psychiatrist Conolly Norman [3] had provided a compelling description of delirium as 'acute confusional insanity' a full two years prior to this and the term *confusion* as a synonym for *delirium* remains in widespread use in all countries to this day. Also in the nineteenth century, there was greater focus upon the distinct psychopathology of delirium, which prompted the German clinician Georg Greiner to introduce the concept of 'clouding of consciousness' (*Verdunkelung des Bewusstseins*) to denote the altered mental state of delirious patients [4]. Greiner believed that fever caused disturbances in the organ of consciousness in the brain and that delirium represented a state of dreaming whilst awake.

In the twentieth century, with increased specialisation of medical activity, a plethora of labels (e.g., acute confusional state, brain failure, toxic encephalopathy, intensive care psychosis: see Box 5.1) emerged to describe patients with acute widespread disturbance of brain function [5], but it was recognised that these mostly reflected the population, clinical setting or presumed etiology for the delirium with little evidence to support such concepts as separate scientific entities (i.e., they merely reflect the syndrome of delirium occurring in

different clinical contexts). As such, *delirium* has been adopted as the accepted umbrella term to denote acute disturbances of global cognitive function that occur in physically ill patients.

Box 5.1   Synonyms used to denote delirium

Acute brain failure/syndrome
Acute cerebral insufficiency
Acute dementia
Acute organic psychosis
Acute reversible psychosis
Acute secondary psychosis
Confusional state
Dysergastic reaction
Encephalopathy
Exogenous psychosis
Infective-exhaustive psychosis
Intensive care unit (ICU) psychosis
Metabolic encephalopathy
Oneiric state
Organic brain syndrome
Posttraumatic confusion
Reversible cerebral dysfunction
Reversible cognitive dysfunction
Reversible dementia
Reversible toxic psychosis
Subacute befuddlement
Toxic confusion state
Toxic encephalopathy

Definition and Classification

Delirium is a complex neuropsychiatric syndrome characterised by acute or subacute generalised disturbance of brain function that occurs in the context of one or more physical aetiologies. It is deemed 'complex' by virtue of its heterogenous clinical presentation that can include a broad range of cognitive and neurobehavioural disturbances that are thought to reflect widespread disruption of neural function. The introduction of the term *delirium* in DSM-III [6] as the umbrella term to subsume other synonyms for acute generalised disturbance of brain function has brought a consistency of definition that in turn has promoted more coherent clinical practice and more meaningful research effort. This, along with the increasing agedness of our society, has generated heightened awareness of the frequency and impact of delirium and it is now recognised as a key target within modern healthcare.

Since DSM-III in 1980, the definition of *delirium* has undergone a series of revisions through DSM-IIIR and DSM-IV [7,8], but the key diagnostic features have remained quite consistent and include altered consciousness, inattention and generalised disturbance of cognition, all of which are of relatively acute onset, often fluctuate and occur in the context of a physical insult. The current definition of *delirium* as per the fifth edition of the

Diagnostic and Statistical Manual (DSM-5) [9] categorises delirium as an acute neurocognitive disorder characterised by prominent disturbance of attention, awareness and other cognitive and perceptual functions. Although delirium lacks a pathognomonic feature and its symptoms are lacking in specificity for delirium, it should be noted that the context and combination of these disturbances is highly characteristic in that they develop over a short period (typically hours or days), tend to fluctuate over short periods and are temporally linked to physical illness, brain insult or pharmacological factors.

A further clarifying feature for delirium is that disturbances should not be primarily accounted for by other neurocognitive disorders, such as dementia, depression or coma. In the case of dementia this can be a challenging distinction because approximately 50% of cases of delirium occur against a background of pre-existing brain impairment such as dementia and reflect the so-called acute on chronic comorbid delirium-dementia cases [10]. In general, where there is a change from baseline that includes altered consciousness with prominent inattention, it is prudent to attribute this to probable delirium in the first instance due the relative urgency of diagnosis.

DSM-5 also includes specifying characteristics for delirium according to underlying cause (substance intoxication, substance withdrawal, medication induced, other medical condition, multiple aetiologies), course (acute lasting hours/days vs. persistent lasting weeks or longer) and phenomenological subtype (hyperactive vs. hypoactive vs. mixed). In addition, the concept of subsyndromal delirium is classified in DSM-5 as 'attenuated delirium syndrome' in recognition that such states are intermediate between no-delirium and syndromal delirium in terms of phenomenological intensity and prognosis [11]. In many cases, subsyndromal illness occurs as part of the evolution or resolution of a delirious episode. DSM-5 lacks specific criteria-based descriptions of these variants within the syndrome of delirium, but other detailed phenomenological work has produced criteria that can be used where more formal diagnosis is warranted (e.g., within research) [11].

The ICD-10 [12] description of delirium includes a greater breadth of symptoms that can occur, but has more required features and is thus less inclusive and not typically preferred by either clinicians or researchers [13].

Epidemiology

The development of delirium reflects the interaction between precipitating events (such as acute illness or drug exposure) and baseline vulnerability, with the latter a particularly strong factor. As such, although delirium can occur at any age if faced within response to sufficiently significant precipitating stresses, it is particularly common at age extremes where the developing or aged brain is more vulnerable to decompensation when faced with deliriogenic stressors. Most epidemiologic studies focus on the elderly, which is unsurprising given the particular vulnerability to delirium in this group along with population projections that emphasise increasing agedness and prolonged frailty over the coming decades where delirium rates are set to increase substantially and in parallel with dementia prevalence. For example, by 2040, nearly one in four people in the United Kingdom will be aged 65 or over and almost one in five people currently in the United Kingdom will live to see their 100th birthday, all of which has direct relevance to the importance of responding to the challenge of delirium [14].

Most studies of the incidence and prevalence of delirium report general hospital populations consisting of either referral samples or consecutive admissions to a given

service with relatively less quality information regarding delirium rates in the general population and in community-based settings such as nursing homes. Delirium is common across healthcare settings – for example, it is present on admission of one-half of elderly medicine admissions, while a further third of elderly develop delirium during their hospital stay. Similarly, post-operative delirium (POD) is common with a relationship between the risk of delirium and the type of surgery. The incidence of POD is reported as varying, in increasing order, from otolaryngological (12%), general surgery (13%), aortic (up to 29%), major abdominal (up to 50%) to cardiac surgery (up to 51%). In addition, emergency versus elective surgery, increased requirement for blood transfusion and increased surgical duration all have increased risk of POD 15. Delirium is frequent in older emergency department (ED) patients, affecting an estimated 8–10% of patients. The prevalence of delirium in ICU cohort studies ranges from as low as 20% to 70–80% or more, with the frequency of incident delirium variously described as ranging from 22% to 83%. In palliative care, delirium incidence ranges from 3% to 45%, while delirium prevalence varies from 13–42% at admission, 26–62% during admission, and increasing to 58–88% in the weeks or hours preceding death [16].

A clinical rule of thumb seems to be that approximately one in five general hospital patients have delirium at some time during their hospitalisation [17]. In long-term residents of care homes, 5–10% typically have delirium at any time with rates as high as 50% in those in post-acute care facilities [18]. Moreover, rates of subsyndromal delirium are as high as one-third of elderly residents in community-based facilities. These figures highlight how delirium has almost unrivalled penetration of our healthcare settings and this frequency, along with its negative impact upon a variety of important healthcare outcomes, has made it a somewhat belated target for improved healthcare management.

Aetiology

Delirium is a complex disorder with multifactorial causation that develops as a consequence of the interaction of predisposing factors with a variety of precipitants that challenge 'cognitive reserve'. Importantly, baseline vulnerability is a particularly potent factor such that in young healthy adults delirium is uncommon except with severe illness or physical insult, while in older patients relatively minor stressors can precipitate an episode of delirium [19]. Elderly populations are more vulnerable to developing delirium due to pre-existing impairments such as a vulnerable brain in the context of dementia and also chronic physical health disorders [20]. Additionally, older people with a prior history of delirium and ongoing sensory impairment, for example, visual or hearing difficulties, are also predisposed to developing a delirium. However, no cause for delirium is found in approximately 10–20% of cases. For a summary of risk factors for delirium, refer to Box 5.2 [21].

> **Box 5.2   Risk factors for delirium**
>
> Development of delirium depends on a complex interaction of multiple risk factors. Some of these factors are modifiable and are potential targets for prevention. Among elderly patients, dementia is the most prominent risk factor, being present in up to two-thirds of all cases of delirium.

Box 5.2 (*cont.*)

- Potentially modifiable risk factors

  - Sensory impairment (hearing or vision)
  - Immobilisation (catheters or restraints)
  - Medications (e.g., sedative hypnotics, narcotics, anticholinergic drugs)
  - Corticosteroids, polypharmacy, withdrawal of alcohol or other drugs
  - Acute neurological diseases (e.g., acute stroke [usually right parietal])
  - Intracranial hemorrhage, meningitis, enkephalitis
  - Intercurrent illness (e.g., infections, iatrogenic complications, severe)
  - Acute illness, anemia, dehydration, poor nutritional status, fracture or trauma
  - HIV infection
  - Metabolic derangement
  - Surgery
  - Environment (e.g., admission to an intensive care unit)
  - Pain
  - Emotional distress
  - Sustained sleep deprivation

- Nonmodifiable risk factors

  - Dementia or cognitive impairment
  - Advancing age (>65 years)
  - History of delirium, stroke, neurological disease, falls or gait disorder
  - Multiple comorbidities
  - Male sex
  - Chronic renal or hepatic disease

Common precipitants for delirium include medical illness (particularly infection), post-operative surgical status and drug effects, especially with exposure to opioids, benzodiazepines and agents with anticholinergic effects [21]. Common precipitants whether at home, long-term care or in a hospital environment include pain, constipation, dehydration, malnutrition, impaired metabolic/electrolyte regulation and infections (e.g., urinary tract infection, pneumonia, sepsis). Possible environmental causes of delirium include an unfamiliar environment such as a being on a hospital ward and away from home or family, experiencing sleep deprivation while at intensive care units or absence of hearing/visual aids. In the intensive care unit setting, mechanically ventilated patients are at increased risk of delirium [22] and intensive care units have particularly high rates of delirium for a variety of reasons including pre-existing cognitive impairment and severity of illness [23].

Post-operative (e.g., hip fractures) and palliative care settings have increased rates of delirium due to frailty, severity of illness and opioid medication [24,25]. Systemic organ failure such as chronic renal, heart or liver impairment also increase the likelihood of developing a delirium in the elderly. Additionally, cerebral insults such as cerebrovascular accidents or head injuries can be commonly associated with delirium. Subcortical strokes and basal ganglia abnormalities contribute, and underlying structural abnormalities such as white matter lesions, cortical atrophy and ventricular dilatation have been found [21,26]. Impairment in global cortical function also occurs, as shown on an electroencephalogram (EEG) as slowing of the dominant posterior alpha rhythm and the appearance of abnormal

slow-wave activity [27]. An exception is delirium accompanying alcohol and sedative medication withdrawal; this is represented by low-voltage, fast-wave activity.

Furthermore, the elderly are at increased risk of developing delirium due to potential interactions of prescribed medications. Polypharmacy in the form of sedative medication (e.g., opioids and benzodiazepines) are not uncommon. Apart from prescribed medications, intoxication on or withdrawal from psychoactive agents after a period of dependence can precipitate delirium whereby a common example is alcohol. Moreover, anticholinergic effects [28] can arise for a variety of reasons including hypoxia, hypoglycaemia, thiamine deficiency, psychotropic medication and drugs; these can also worsen cognitive functioning [29]. There is evidence of cholinergic deficits in both delirium and dementia [30] as well as increased levels of dopamine [31] due to amino acids being shunted down the dopamine production pathway. Increased levels of cortisol, which is associated with chronic stress, trauma or disease states, has also been suggested to contribute to delirium arising [32].

Neuroinflammation and inflammatory cytokines have been reported to be raised in delirium in the elderly and in post-operative populations [33–35]. Pro-inflammatory cytokines produced by microglia [36] are thought to contribute to endothelial damage, increased vascular permeability and enhanced crossing of the blood brain barrier but reduced cerebral blood flow overall. Apolipoprotein E4 (APOE4) polymorphism has been suggested to contribute to the development and prolonged duration of delirium [37], but overall the association is inconsistent [38,39].

Clinical Features

Delirium manifests with acute onset of impaired cognitive functioning, inattention, fluctuating mental state or perceptual abnormalities and disturbances of the sleep-wake cycle or levels of consciousness [31]. Alterations in cognitive functioning can manifest as acute confusion (with diminished grasp of surroundings and disorientation), reduced concentration and slowed responses in combination with language or visuospatial abnormalities.

Perceptual abnormalities can involve any of the sensory modalities, but these are typically visual and include hallucinations, illusions or misinterpretations. Delirium may also be associated with acute changes in behaviour that differs from a person's baseline, and there is often a fluctuating course and the need for a high index of suspicion. Changes from baseline can include agitation, restlessness, uncooperativeness, social withdrawal or shifts in communication. These can be associated with changes in physical functioning and contribute to reduced movement, impaired mobility, changes in appetite and sleep disturbance.

There is variation in how delirium can present and a psychomotor classification has been suggested [40,41] to include hypoactive, hyperactive and mixed forms of delirium. With hyperactive delirium, there is restlessness, agitation, aggression, perceptual abnormalities or hyperarousal, which contrasts with the hypoactive form that manifests with lethargy, sleepiness, inactivity, lack of interest and withdrawal. The hypoactive form may mimic depression or dementia and is often very poorly recognised despite its association with poorer outcomes [42]. This is, in part, because the stereotyped image of delirium is of an agitated and psychotic patient (e.g., delirium tremens) while in reality, the hypoactive and mixed forms are the most common in everyday real-world practice in most clinical settings [43,44].

While delirium is typically considered as a highly reversible state, it can last for several weeks to months [45]. Delirium can also be potentially life-threatening and associated with

increased rates of morbidity. For example, prolonged hospital stays, hospital-acquired complications and a higher incidence of dementia and long-term care [46]. With regard to cognitive and functional recovery, there is evidence to suggest that delirium is associated with poorer outcomes following acute care and especially with persisting delirium symptoms [47–49].

Assessment and Diagnosis

During an episode of delirium, people are often unable to communicate their symptoms coherently and the diagnosis of delirium therefore requires careful consideration of collateral history, elicited cognitive deficits, observation of behaviour and its fluctuation over time, supplemented by relevant investigations. Of note, investigations can support the possibility of an underlying delirium but are not specific to or diagnostic of delirium. Some units more frequently encounter delirium, e.g., orthopaedic surgery, intensive care, emergency department and hospice settings, but overall delirium is ubiquitous across healthcare settings and there should always be a high degree of suspicion in the elderly or in those with pre-existing CNS compromise. Delirium can be misdiagnosed as depression or dementia especially when the hypoactive form of delirium is present [50] and excluding the presence or absence of depression during an episode of delirium is difficult.

Features supporting a diagnosis of delirium include behavioural disturbances such as hypoactivity, hyperactivity and sleep disturbance while emotional disturbances, such as fear or perplexity, can also be suggestive of a delirium.

As there is much variation in how delirium presents, assessment tools can be used to help standardise its evaluation. For example, the confusion assessment method (CAM) [51] is a validated, relatively quick and standardised bedside tool to assess and track delirium in clinical settings. Its use can be triggered when there is a change in orientation, behaviour or levels of consciousness and should be integrated alongside other sources of information such as a thorough medical assessment and collateral information from family/carers. The short version of the CAM assesses whether there has been an acute onset, fluctuating course, inattention, disorganised thinking and altered levels of consciousness. The CAM-ICU which was adapted from the CAM and the ICDSC (intensive care delirium screening checklist) have shown validity and are most frequently used in ICU settings in comparison to other delirium tools [52,53]. However, assessment tools such as the CAM require end-user training for them to be utilised accurately.

Other quick and popular screening tools include the 4AT and Nu-DESC. The 4AT which stands for the 4 A's Test was developed as a rapid screening tool (1–2 minutes) by non-specialists in everyday clinical practice and has been validated in a geriatric and rehabilitation inpatient sample. The 4AT includes items for levels of alertness, orientation, attention (listing months of the year backwards) and acute onset or fluctuating course. The test's sensitivity and specificity are 89.7% and 84.1%, respectively, and it maintains good accuracy in comorbid delirium and dementia [54].

The Nursing Delirium Screening Scale (Nu-DESC) is an observational instrument designed especially for rapid screening for possible delirium by nurses [55]. It includes five items (each rated on a two-point scale) – orientation, behaviour, communication, illusions/hallucinations and psychomotor retardation. The total score ranges between 0 and 10, where a score greater than 2 indicates probable delirium. It is typically completed in less than 2 minutes. Studies have indicated a sensitivity of 32–96% and a specificity of 69–92%

for DSM-IV– defined delirium [52–57]. The large variability in sensitivity is partly due to it being assessed at different thresholds.

Management

Delirium is a complex syndrome characterised by high morbidity and mortality. Delirium increases deterioration in function and results in longer hospital stays and increases mortality. Although earlier descriptions of delirium highlighted the potential reversibility of the disorder if the underlying condition was treated appropriately, more recent studies have, however, emphasised that delirium can persist at the time of discharge from hospital and well into community-based care settings [24,58,59]. While it is evident that patients with delirium have a worse prognosis than those who are not delirious, it is not fully understood why some patients recover from delirium and others do not.

In view of its poor prognosis, it is paramount that delirium is identified, and a management plan put in place as soon as possible. Because of its serious nature, delirium is best managed in hospital because further investigation and treatment can be facilitated; however, this advantage must be balanced against the potentially deleterious disorientating effects of a sudden change in environment on elderly people with cognitive impairment [60].

Management of delirium should commence with identification of the underlying cause. Polypharmacy is frequently implicated as a cause and medication review to identify potential culprits should be undertaken. Infections (particularly respiratory and urinary tract) should be identified and treated. Pain management is crucial and non-opioid agents are often preferred to minimise any aggravating effects on delirium, although undertreated pain is also a potent deliriogenic stressor such that careful and repeated clinical assessment is needed.

Environmental management strategies are important but are underutilised despite their relative safety. These include management in an adequately lit and uncluttered area; clear and succinct communication; frequent reassurance; providing orientation aids, for example, large clock and a calendar; instituting consistent staff as far as possible, for example, a key nurse; and involving relatives in patient care. It is also crucial that adequate fluid and dietary intake is ensured.

Pharmacological management of delirium requires careful consideration. The clinician needs to balance the need to alleviate distress with the potential harm that can result, for example, increased incidence of falls. Drug treatment in delirium is primarily based on observational studies and expert consensus because randomised trials are difficult in this subgroup of patients. In any case, the use of pharmacological agents should be short term and at lowest effective doses [61].

Antipsychotic Agents

Antipsychotic agents are the most commonly used drugs in the pharmacological management of delirium [62]. Haloperidol is regularly used largely due to long experience with this agent, low sedative potential and ability to use different routes of administration, whereas the evidence, appropriate dosing and efficacy for atypical antipsychotics is still being established [63]. It is recommended that low doses are used and initial dosage of 0.5–1 mg/day is reasonable, and this can be increased further but incidence of extrapyramidal effects is higher at doses greater than 4.5 mg/day [64]. There is little evidence that haloperidol in low dosage has different efficacy in comparison to the atypical antipsychotics olanzapine and risperidone in the management of delirium or has a greater frequency of

adverse drug effects than these agents. Because evidence suggests higher mortality with haloperidol compared to atypical antipsychotic agents in people with dementia [65]. Risperidone (1.5–4 mg/day) or olanzapine (5–10 mg/day) are viable options [65].

Benzodiazepines

The role of benzodiazepines in the treatment of delirium is limited to cases of sedative drug and alcohol withdrawal or when neuroleptic drugs are contraindicated. But benzodiazepines are still often used inappropriately [66]. Their use may be appropriate if prescribed carefully and shown to relieve marked agitation.

Prevention

A number of agents have been looked at for prophylaxis of delirium including haloperidol, risperidone, olanzapine and the cholinesterase inhibitor rivastigmine [67]. At present there is no convincing, reproducible evidence that any of these are clearly effective in the prevention of delirium. A recent study [68] shows some promise in using low-dose dexmedetomidine (an alpha 2 adrenergic receptor agonist that has shown some promise in neuro-protection in animal models of brain injury) for delirium prophylaxis. It appears to. Further research is needed in this area.

Prognosis

Delirium increases the length of hospitalisation, functional decline and institutionalisation, and worsens prognosis for a long period after discharge [69]. A recent study found that in patients with delirium, the overall rate of recovery was poor and was approximately 70% [70]. This study also suggested that older age, impaired functioning in activities of daily living, the presence of renal failure, hypoxia and delirium were independently associated with increased risk of poor recovery.

Other studies have demonstrated an association between increasing delirium severity, older age, functional dependence and hypoxia with persistent symptoms, institutionalisation or death [71]. Prognosis in delirium is at best guarded [70].

Future Directions

There is increasing interest in the role of melatonin neurotransmission in delirium. Indeed, sleep-wake cycle disturbance is a prominent symptom in delirium and novel agents such as suvorexant, which is a potent orexin receptor antagonist and ramelteon (a melatonin agonist), have been investigated with encouraging results in the context of both efficacy and safety for the prevention of delirium [72].

Studies have shown an association between neuro-inflammatory response and delirium when the body is exposed to a variety of conditions especially those that involve destruction of tissue, systemic inflammation and infection [73]. Further research in this area is needed.

Tools to detect delirium are available but delirium continues to be under-recognised. An emphasis on earlier detection is needed. There is also an urgent need to elucidate the pathophysiology of delirium as it can inform effective treatments [74]. Because it is well known that many patients continue to display symptoms of delirium at the time of discharge and indeed for a long period after discharge, greater focus is needed on long-term care of delirious patients [31].

References

1   Adamis, D., Treloar, A., Martin, F. C., Macdonald, A. J. (2007) 'A brief review of the history of delirium as a mental disorder'. *Hist Psychiatry* 18: 459–69.

2   Chaslin, P. (1892) 'La confusion mentale primitive'. *Ann Med Psychol (Paris)* 16: 225–73.

3   Norman, C. (1890) 'Acute confusional insanity'. *Dublin J Med Sci* 89: 506–18.

4   Greiner, G. F. C. (1817) Der Traum und das fi eberhafte Irreseyn. Ein physiologisch-psychologischer Versuch, Altenburg und Leipzig, F. A. Brockhaus.

5   Morandi, A., Pandharipande, P., Trabucchi, M., et al. (2008) 'Understanding international differences in terminology for delirium and other types of acute brain dysfunction in critically ill patients'. *Intensive Care Med* 34: 1907–15.

6   American Psychiatric Association (1980) *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed. Washington, DC: American Psychiatric Publishing.

7   American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders*. 3rd rev. ed. Washington, DC: American Psychiatric Publishing.

8   American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Publishing.

9   American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders*. Washington DC: American Psychiatric Publishing.

10 Bellelli, G., Morandi, A., Di Santo, S. G., et al. (2016) '"Delirium Day": A nationwide point prevalence study of delirium in older hospitalized patients using an easy standardized diagnostic tool'. *BMC Med* 14: 106.

11 Meagher, D., O'Regan, N., Ryan, D., et al. (2014) 'Frequency of delirium and subsyndromal delirium in an adult acute hospital population'. *Br J Psychiatry* 205: 478–85.

12 World Health Organization (1992) *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization.

13 Morandi, A., Davis, D., Taylor, J. K., et al. (2013) 'Consensus and variations in opinions on delirium care: A survey of European delirium specialists'. *Int Psychogeriatr* 25: 2067–75.

14 Office for National Statistics (2015) National population projections for the UK, 2014-based, www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections.

15 Vasilevskis, E. E., Han, J. H., Hughes, C. G., Ely, E. W. (2012) 'Epidemiology and risk factors for delirium across hospital settings'. *Best Pract Res Clin Anaesthesiol* 26: 277–87.

16 Hosie, A., Davidson, P. M., Agar, M., et al. (2013) 'Delirium prevalence, incidence, and implications for screening in specialist palliative care inpatient settings: A systematic review'. *Palliat Med* 27: 486–98.

17 Ryan, D. J., O'Regan, N. A., Caoimh, R. O., et al. (2013) 'Delirium in an adult acute hospital population: Predictors, prevalence and detection'. *BMJ Open* 3(1).

18 Flaherty, J. H., Morley, J. E. (2013) 'Delirium in the nursing home'. *J Am Med Dir Assoc* 14: 632–4.

19 Inouye, S. K., Charpentier, P. A. (1996) 'Precipitating factors for delirium in hospitalized elderly persons: Predictive model and interrelationship with baseline vulnerability'. *JAMA* 275: 852–7.

20 Cole, M. G., Mccusker, J., Dendukuri, N., Han, L. (2002) 'Symptoms of delirium among elderly medical inpatients with or without dementia'. *J Neuropsychiatry Clin Neurosci* 14: 167–75.

21 Fong, T. G., Tulebaev, S. R., Inouye, S. K. (2009) 'Delirium in elderly adults: Diagnosis, prevention and treatment'. *Nat Rev Neurol* 5: 210–20.

22 Cavallazzi, R., Saad, M., Marik, P. E. (2012) 'Delirium in the ICU: An overview'. *Ann Intensive Care* 2: 49.

23 Pisani, M. A., Mcnicoll, L., Inouye, S. K. (2003) 'Cognitive impairment in the intensive care unit'. *Clin Chest Med* 24: 727–37.

24 Siddiqi, N., House, A. O., Holmes, J. D. (2006) 'Occurrence and outcome of delirium in medical in-patients: A systematic literature review'. *Age Ageing* 35: 350–64.

25 Sagawa, R., Akechi, T., Okuyama, T., et al. (2009) 'Etiologies of delirium and their relationship to reversibility and motor subtype in cancer patients'. *Jpn J Clin Oncol* 39: 175–82.

26 Fong, T. G., Bogardus, S. T., Jr., Daftary, A., et al. (2006) 'Cerebral perfusion changes in older delirious patients using 99mTc HMPAO SPECT'. *J Gerontol A Biol Sci Med Sci* 61: 1294–9.

27 Jacobson, S., Jerrier, H. (2000) 'EEG in delirium'. *Semin Clin Neuropsychiatry* 5: 86–92.

28 Flacker, J. M., Cummings, V., Mach, J. R., Jr., et al. (1998) 'The association of serum anticholinergic activity with delirium in elderly medical patients'. *Am J Geriatr Psychiatry* 6: 31–41.

29 Campbell, N., Boustani, M., Limbil, T., et al. (2009) 'The cognitive impact of anticholinergics: A clinical review'. *Clin Interv Aging* 4: 225–33.

30 Hshieh, T. T., Fong, T. G., Marcantonio, E. R., Inouye, S. K. (2008) 'Cholinergic deficiency hypothesis in delirium: A synthesis of current evidence'. *J Gerontol A Biol Sci Med Sci* 63: 764–72.

31 Young, J., Inouye, S. K. (2007) 'Delirium in older people'. *BMJ* 334: 842–6.

32 Inouye, S. K. (2006) 'Delirium in older persons'. *N Engl J Med* 354: 1157–65.

33 De Rooij, S. E., Van Munster, B. C., Korevaar, J. C., Levi, M. (2007). 'Cytokines and acute phase response in delirium'. *J Psychosom Res* 62: 521–5.

34 Vasunilashorn, S. M., Ngo, L., Inouye, S. K., et al. (2015) 'Cytokines and postoperative delirium in older patients undergoing major elective surgery'. *J Gerontol A Biol Sci Med Sci* 70: 1289–95.

35 Munster, B. C., Aronica, E., Zwinderman, A. H., et al. (2011) 'Neuroinflammation in delirium: A postmortem case-control study'. *Rejuvenation Res* 14: 615–22.

36 Cerejeira, J., Lagarto, L., Mukaetova-Ladinska, E. B. (2014) 'The immunology of delirium'. *Neuroimmunomodulation* 21: 72–8.

37 Ely, E. W., Girard, T. D., Shintani, A. K., et al. (2007) 'Apolipoprotein E4 polymorphism as a genetic predisposition to delirium in critically ill patients'. *Crit Care Med* 35: 112–7.

38 Vasunilashorn, S., Ngo, L., Kosar, C. M., et al. (2015) 'Does apolipoprotein E genotype increase risk of postoperative delirium?' *Am J Geriatr Psychiatry* 23: 1029–37.

39 Chu, C.-L., Liang, C.-K., Lin, Y.-T., et al. (2011) 'Biomarkers of delirium: Well evidenced or not?' *J Clin Gerontol Geriatr* 2: 100–4.

40 Lipowski, Z. J. (1983) 'Transient cognitive disorders (delirium, acute confusional states) in the elderly'. *Am J Psychiatry* 140: 1426–36.

41 Meagher, D. J., Leonard, M., Donnelly, S., et al. (2012) 'A longitudinal study of motor subtypes in delirium: Frequency and stability during episodes'. *J Psychosom Res* 72: 236–41.

42 O'Keeffe, S. T., Lavan, J. N. (1999) 'Clinical significance of delirium subtypes in older people'. *Age Ageing* 28: 115–9.

43 Meagher, D. (2009) 'Motor subtypes of delirium: Past, present and future'. *Int Rev Psychiatry* 21: 59–73.

44 Peterson, J. F., Pun, B. T., Dittus, R. S., et al. (2006) 'Delirium and its motoric subtypes: A study of 614 critically ill patients'. *J Am Geriatr Soc* 54: 479–84.

45 Roche, V. (2003) 'Southwestern Internal Medicine Conference: Etiology and management of delirium'. *Am J Med Sci* 325: 20–30.

46 NICE (2010) *Delirium: Diagnosis*. London: Prevention and Management.

47 Marcantonio, E. R., Simon, S. E., Bergmann, M. A., et al. (2003) 'Delirium

symptoms in post-acute care: Prevalent, persistent, and associated with poor functional recovery'. *J Am Geriatr Soc* 51: 4–9.

48 Van Den Boogaard, M., Schoonhoven, L., Evers, A. W., et al. (2012) 'Delirium in critically ill patients: Impact on long-term health-related quality of life and cognitive functioning'. *Crit Care Med* 40: 112–8.

49 Cole, M. G., Ciampi, A., Belzile, E., Zhong, L. (2009) 'Persistent delirium in older hospital patients: A systematic review of frequency and prognosis'. *Age Ageing* 38: 19–26.

50 Farrell, K. R., Ganzini, L. (1995) 'Misdiagnosing delirium as depression in medically ill elderly patients'. *Arch Intern Med* 155: 2459–64.

51 Inouye, S. K., Van Dyck, C. H., Alessi, C. A., et al. (1990) 'Clarifying confusion: The confusion assessment method. A new method for detection of delirium'. *Ann Intern Med* 113: 941–8.

52 Luetz, A., Heymann, A., Radtke, F. M., et al. (2010) 'Different assessment tools for intensive care unit delirium: Which score to use?' *Crit Care Med* 38: 409–18.

53 Bergeron, N., Dubois, M. J., Dumont, et al. (2001) 'Intensive Care Delirium Screening Checklist: Evaluation of a new screening tool'. *Intensive Care Med* 27: 859–64.

54 Bellelli, G., Morandi, A., Davis, D. H., et al. (2014) 'Validation of the 4AT, a new instrument for rapid delirium screening: A study in 234 hospitalised older people'. *Age Ageing* 43: 496–502.

55 Gaudreau, J. D., Gagnon, P., Harel, F., et al. (2005) 'Fast, systematic, and continuous delirium assessment in hospitalized patients: The nursing delirium screening scale'. *J Pain Symptom Manage* 29: 368–75.

56 Leung, J., Leung, V., Leung, C. M., Pan, P. C. (2008) 'Clinical utility and validation of two instruments (the Confusion Assessment Method Algorithm and the Chinese version of Nursing Delirium Screening Scale) to detect delirium in geriatric inpatients'. *Gen Hosp Psychiatry* 30: 171–6.

57 Neufeld, K. J., Leoutsakos, J. S., Sieber, F. E., et al. (2013) 'Evaluation of two delirium screening tools for detecting post-operative delirium in the elderly'. *Br J Anaesth* 111: 612–8.

58 Inouye, S. K., Westendorp, R. G., Saczynski, J. S. (2014) 'Delirium in elderly people'. *Lancet* 383: 911–22.

59 Cole, M. G. (2010) 'Persistent delirium in older hospital patients'. *Curr Opin Psychiatry* 23: 250–4.

60 Meagher, D. J. (2001) 'Delirium: Optimising management'. *BMJ* 322: 144–9.

61 Young, J., Murthy, L., Westby, M., et al. (2010) 'Diagnosis, prevention, and management of delirium: Summary of NICE guidance'. *BMJ* 341: c3704.

62 Trzepacz, P. T. (1996) 'Delirium: Advances in diagnosis, pathophysiology, and treatment'. *Psychiatr Clin North Am* 19: 429–48.

63 Gilchrist, N. A., Asoh, I., Greenberg, B. (2012) 'Atypical antipsychotics for the treatment of ICU delirium'. *J Intensive Care Med* 27: 354–61.

64 Lonergan, E., Britton, A. M., Luxenberg, J., Wyller, T. (2007) 'Antipsychotics for delirium'. *Cochrane Database Syst Rev*: CD005594.

65 Kales, H. C., Kim, H. M., Zivin, K., et al. (2012) 'Risk of mortality among individual antipsychotics in patients with dementia'. *Am J Psychiatry* 169: 71–9.

66 Carnes, M., Howell, T., Rosenberg, M., et al. (2003) 'Physicians vary in approaches to the clinical management of delirium'. *J Am Geriatr Soc* 51: 234–9.

67 De Pont, A. C., Van Geer, M. A., Schultz, M. J. (2011) 'Cholinesterase inhibitor treatment in patients with delirium'. *Lancet* 377: 899.

68 Su, X., Meng, Z. T., Wu, X. H., et al. (2016) 'Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: A randomised, double-blind, placebo-controlled trial'. *Lancet* 388: 1893–1902.

69 Francis, J., Kapoor, W. N. (1992) 'Prognosis after hospital discharge of older

medical patients with delirium'. *J Am Geriatr Soc* 40: 601–6.

70 Dasgupta, M., Brymer, C. (2014) 'Prognosis of delirium in hospitalized elderly: Worse than we thought'. *Int J Geriatr Psychiatry* 29: 497–505.

71 Kiely, D. K., Jones, R. N., Bergmann, M. A., et al. (2006) 'Association between delirium resolution and functional recovery among newly admitted postacute facility patients'. *J Gerontol A Biol Sci Med Sci* 61: 204–8.

72 Hatta, K., Kishi, Y., Wada, K., et al. (2017) 'Preventive effects of suvorexant on delirium: A randomized placebo-controlled trial'. *J Clin Psychiatry* 78: e970–979.

73 Cerejeira, J., Firmino, H., Vaz-Serra, A., Mukaetova-Ladinska, E. B. (2010) 'The neuroinflammatory hypothesis of delirium'. *Acta Neuropathol* 119: 737–54.

74 Avramescu, S., Wang, D. S., Choi, S., Orser, B. A. (2017) 'Preventing delirium: Beyond dexmedetomidine'. *Lancet* 389: 1009.