

Current concepts in the management of delirium

'Delirium is like a baby crying – you have no idea what is wrong. Babies have only one way to communicate: they cry. You pick them up, investigate what is wrong and then deal with it.'
– Professor Rosemary S Browne

I Butler, MB ChB, FCP; **L Sinclair**, MB ChB, FCP; **B Tipping**, MB ChB, MMed, MPhil, FCP

University of the Witwatersrand/Wits Donald Gordon Medical Centre, Johannesburg, South Africa

Corresponding author: I Butler (butler.india@gmail.com)

Introduction and definition

Delirium can be defined as an acute disorder of attention and global cognitive function that represents a change or stress to the steady state. Delirium represents a state of acute brain failure and should be seen as a medical emergency. Delirium is a common manifestation of a diverse array of causes, especially in cognitively vulnerable individuals, or it may be the sole presenting feature of severe neurological illness.

The DSM-5 criteria for the diagnosis of delirium are as follows (available from <http://www.dsm5.org>):

- (a) Disturbance in attention (i.e. reduced ability to direct, focus, sustain and shift attention) and orientation to the environment.
- (b) The disturbance develops over a short period of time (usually hours to a few days) and represents an acute change from baseline that is not solely attributable to another neurocognitive disorder, and tends to fluctuate in severity during the course of a day.
- (c) A change in an additional cognitive domain, such as memory deficit, disorientation, or language disturbance, or perceptual disturbance, that is not better accounted for by a pre-existing, established or evolving other neurocognitive disorder.
- (d) The disturbances in criteria (a) and (c) must not be occurring in the context of a severely reduced level of arousal such as coma.

Four important conditions can mimic delirium: dementia, depression, deafness (or blindness) and dysphasia (inability to communicate) – together known as 'the five Ds'. Importantly, delirium may co-exist with these conditions. As the presence of delirium implies significant physiological derangement, when in doubt it is safer to assume that confusion is due to delirium and look for reversible factors.

Occurrence and cost

Delirium is common and the occurrence rates vary among different settings. A systematic review found rates of 11 - 42% in medical inpatients depending on the diagnostic criteria used.^[1] Post-operatively, the occurrence rate is higher (15 - 53%) and very high in intensive care (70 - 83%).^[2,3] Non-detection rates are 33 - 66%; therefore,

these numbers are likely to under-represent the scale of the problem.^[1]

The costs of delirium are high. In the US it is estimated that delirium leads to \$64 421 in additional costs per delirious patient per year and that the total cost attributable to delirium per year is in the range of \$143 - 152 billion.^[3] The costs continue to add up in the

Table 1. Predisposing and precipitating factors for delirium^[6]

| Characteristic | Patient factors | Environmental and other factors |
|-------------------|---|---|
| Demographic | Older Male Socially isolated | Older-unfriendly hospitals |
| Cognitive | Dementia Cognitive impairment Prior delirium Depression | Absence of time-orientating methods and devices |
| Physical | Dependent Immobile Falls Inactive | Tethering with catheters or IV lines Restraints Not mobilising to chair |
| Sensory | Visual Hearing | Sensory deprivation Withholding assistive devices |
| Nutritional | Dehydration Malnutrition Electrolyte abnormalities Low serum albumin | No assistance with feeding Unpalatable food Unable to swallow or not given dentures Restraints Prolonged nil <i>per os</i> for procedures |
| Drugs | Multiple psychoactive drugs Polypharmacy Alcohol abuse | Sedatives Narcotics Anticholinergics Anaesthesia Polypharmacy |
| Medical | Severe illness Multi-morbidity Chronic liver or renal disease Previous stroke Neurological disease Metabolic derangements Fracture or trauma Terminal illness HIV infection | Iatrogenesis Hypoxia Anaemia Fever or hypothermia Shock Surgery Prolonged cardiac bypass Multiple procedures Pain |
| Sleep deprivation | | Intensive care unit admission Woken up for investigations Noise |

months after discharge as these patients have a higher risk of death (OR 1.95; 95% CI 1.51 - 2.52), institutionalisation (OR 2.41; 95% CI 1.77 - 3.29) and incident dementia (OR 12.52 95% CI 1.86 - 84.21) independent of other factors.^[4] Loss of function from baseline is also increased (OR 1.91; 95% CI 1.3 - 2.8).^[5]

Predisposing factors/precipitants

Certain risk factors predispose an individual to the development of delirium. These include, but are not limited to, visual impairment, severe illness, pre-existing cognitive disorders and dehydration. Predisposing factors can predict which patients are vulnerable to the development of delirium.

Vulnerable individuals are then exposed to precipitants – these include the use of physical restraints, polypharmacy, bladder catheterisation, poor nutrition and any in-hospital adverse event. It has been established that 30 - 40% of cases of delirium are potentially preventable and so it is at this point that one needs to intervene by identifying those who are at risk and being vigilant about not provoking an episode of delirium (Tables 1 and 2). Medications are often implicated in worsening or causing delirium (Table 3).

Pathophysiology

Delirium is poorly understood and multifactorial, but there are some hypotheses:

- Inflammation alters the permeability of the blood-brain barrier via cytokines.
- Neurotransmission is disrupted with cholinergic deficiency and dopaminergic excess, worsened by anticholinergic and dopaminergic medication. Other neurotransmitters such as norepinephrine, serotonin, GABA, glutamate and melatonin are thought to play a role as well.
- A stress response leads to hypercortisolism and disrupts serotonin receptors.^[6]

Table 2. Most common precipitants of delirium^[6]

| |
|---------------------------------------|
| Drugs and drug withdrawal |
| Electrolyte imbalance |
| Low cardiovascular perfusion states |
| Infection |
| Reduced sensory input |
| Intracranial |
| Urinary retention or faecal impaction |
| Metabolic |

Vulnerable people with a predisposition to delirium will require a less noxious precipitant to manifest symptoms of what is essentially global brain dysfunction.

Diagnosis

The assessment of mental state is so important that it has been referred to as the '6th vital sign'.

Delirium can be hyperactive (agitated), hypoactive (quiet) or cycle between the two – this is called mixed delirium. Hypoactive delirium is less well recognised and is associated with greater morbidity and mortality.

There is no specific biomarker associated with delirium, so the diagnosis is mainly clinical.

Table 3. Medications commonly associated with delirium^[13]

| Medication class | Examples | Anticholinergic activity (+ mild, ++ mod, +++ severe) |
|--|------------------|---|
| Benzodiazepines and other sedative hypnotics | Alprazolam | + |
| | Chlodiazepoxide | |
| | Clonazepam | |
| | Diazepam | + |
| | Lorazepam | |
| | Oxazepam | |
| | Temazepam | |
| | Triazolam | |
| | Zolpidem | |
| | Zopiclone | |
| Corticosteroids | Prednisone | + |
| H2-Receptor antagonists | Cimetidine | + |
| | Ranitidine | + |
| Antihistamines (first generation) | Chlorpheniramine | +++ |
| | Diphenhydramine | +++ |
| | Promethazine | +++ |
| | Hydroxyzine | +++ |
| Anti-parkinsons | Benzotropine | +++ |
| | Trihexyphenidyl | +++ |
| Muscle relaxants | Orphenadrine | +++ |
| Antidepressants (tricyclic antidepressants) | Amitriptyline | +++ |
| | Clomipramine | +++ |
| | Imipramine | +++ |
| | Desipramine | +++ |
| | Paroxetine | +++ |
| Antipsychotics | Thioridazine | +++ |
| | Chlorpormazine | +++ |
| | Haloperidol | + |
| | Trifluoperazine | +++ |
| | Clozapine | +++ |
| | Olanzapine | +++ |
| | Quetiapine | +++ |
| | Risperidone | +++ |
| | Ziprasidone | + |
| Antispasmodics and antimuscarinics | Hyoscine | +++ |
| | Meperidine | ++ |
| | Oxybutinin | +++ |
| | Darifenacin | +++ |
| | Solifenacin | +++ |
| | Tolterodine | +++ |
| Antibiotics | Levofloxacin | |
| | Moxifloxacin | |
| | Ertapenem | |
| | Cefepime | |
| Antihypertensives | Reserpine | |
| | Methyldopa | |
| | Clonidine | |

There are various tools that clinicians and researchers can use to diagnose delirium. The Confusion Assessment Method (CAM) is one of the most frequently used standardised methods to diagnose delirium and has been adapted for use in other settings such as the intensive care unit (ICU). It is highly specific and sensitive for the diagnosis of delirium.^[7] To use the CAM, a clinician or trained layperson first interviews the patient and performs a brief bedside cognitive test such as the modified mini-cog test, a digit span test or a Folstein's mini mental state examination. The interviewer then rates the patient by answering a series of questions about the patient's mental state as observed during the interview. The features of delirium taken into account by the CAM include: acute onset, inattention, disorganised thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbances, psychomotor agitation, psychomotor retardation and altered sleep-wake cycle. A shortened version of the CAM includes only the first four features and is shown in Table 4.

Prevention and management

The effective prevention and management of delirium requires non-pharmacological and pharmacological strategies

Non-pharmacological treatment and prevention

Non-pharmacological measures are the mainstay of delirium treatment and the same measures can be used to prevent delirium in vulnerable patients.

The seminal trial of non-pharmacological delirium prevention intervened with 6 risk factors for delirium: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment and dehydration. A significant reduction in the number and duration of delirium episodes was achieved (OR 0.6; 95% CI 0.39 - 0.92).^[8] The findings of the study have been expanded into patient care programmes and incident delirium is not only a driver of cost and morbidity but also considered a measure of poor quality hospital care.

The following recommendations are based on this study as well as several subsequent trials:^[9]

- Screen: vulnerable patients regularly for delirium using the CAM or another validated tool.
- Geriatrics or nurse liaison consultation: proactive geriatrics or nurse liaison consultation in high-risk patients, if available, can reduce delirium.
- Review medications: as below.

- Orientation: using orientating devices such as calendars and clocks, re-orientating the patient frequently, re-introducing yourself, allowing friends and family members to visit and bringing familiar objects from home will help to 'reconnect' the patient with the world.
- Avoid restraints/immobilisation: early mobilisation post-operatively and early referral to physiotherapy, using low beds (rather than high beds with cot-sides) to mitigate possible falls at night, trying not to 'tether' the patients down with IV lines, restraints or catheters if they are not necessary, and daily mobilisation to a chair for meals will reduce delirium. Boxing gloves and a sheet tied around the waist while the patient is in a chair are more acceptable forms of restraints that still allow mobilisation.
- Sensory impairment: if the patient needs devices such as spectacles or hearing aids, then allow the patient to use them.
- Setting: promote a calm, comfortable reassuring environment and consider the much higher occurrence rate of delirium in the intensive care setting when deciding whether an ICU admission is warranted. The 'delirium room' is a zoned area that provides a restraint-free environment with 24-hour nursing care that uses non-pharmacological measures to contain and reduce delirium.
- Sleep deprivation: avoid waking patients up for medication and procedures at night as they can be rescheduled; promote noise-reduction strategies within the unit, use non-pharmacological sleep hygiene measures such as a warm drink and a back massage at bedtime.
- Pain: untreated pain as well as over-treatment of pain causes delirium. Analgesic agents recommended include paracetamol, weaker opioids and opioids. Non-steroidal anti-inflammatory use may be limited by side-effects. Doses of opioids are usually lowered and drug-interactions should be considered.
- Promote bladder and bowel function: assess and treat urine retention and faecal impaction; remember that constipation is a common side-effect of many drugs especially opioids, and laxatives should be considered prophylactically.
- Nutrition, hydration and electrolyte balance: maintaining optimal nutrition and encouraging oral hydration, correcting vitamin deficiencies such as B12, thiamine and nicotinic acid, correcting electrolytes

Table 4. The Confusion Assessment Method (CAM)^[7]

| | |
|-----------|---|
| Feature 1 | Acute onset and fluctuating course Evidence of an acute change in mental status from the patient's baseline. Fluctuating course of the abnormal behaviour during the day (i.e. tend to come and go or increase and decrease in severity) |
| Feature 2 | Inattention Difficulty focusing attention (e.g. being easily distractible or having difficulty keeping track of what was being said) |
| Feature 3 | Disorganised thinking Disorganised or incoherent thought processes, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject |
| Feature 4 | Altered level of consciousness Alert (normal), vigilant (hyper-alert), lethargic (drowsy, easily aroused), stupor (difficult to arouse) or coma (unresponsive) |

Diagnosis of delirium requires the presence of both features 1 and 2 and either 3 or 4.

Table 5. The 'tolerate, anticipate and don't agitate' approach^[10]

| | |
|---------------|--|
| Tolerate | Try re-orientation once; if not effective do not continue Allow the patient to act naturally under close observation Observe behaviour to get clues about specific patient needs |
| Anticipate | Discontinue any unnecessary attachments; hide necessary attachments |
| Don't agitate | Avoid short-term questions Affirm disorientation instead of re-orientating |

and ensuring use of adaptive eating devices such as dentures is important for healing as well as delirium reduction.

- Optimise brain conditions: correct hypoxia, anaemia and blood pressure to maximise cerebral perfusion.
- Infections: diagnose and manage infections early, common infection sites include the urinary and respiratory tracts, cellulitis, diverticulitis and the biliary tree.

Pharmacological treatment

Pharmacological treatment of delirium is NOT the mainstay of management and should be reserved for patients who are a danger to themselves (e.g. agitated and removing endotracheal tube) or a danger to others. Restraints should be avoided as they are associated with increased mortality, morbidity and worsening of delirium.^[10] The patient should be approached calmly and quietly using the 'tolerate, anticipate and don't agitate' approach (T-A-DA)^[11] (Table 5).

No drug has been approved for safe use in delirium. The best agent for acute agitated delirium is probably haloperidol and it can be administered orally, intramuscularly or intravenously. The doses used for delirium are much lower than doses used for psychosis. The starting dose is 0.5 - 1 mg, which can be repeated provided the total daily dose does not exceed 3 mg. The dose should be tapered as the symptoms improve. Patients should be monitored for muscle rigidity, dysphagia, aspiration pneumonia, orthostasis and QT prolongation predisposing to cardiac arrhythmias. Alternative agents include ziprasidone 20 - 40 mg once or twice daily or quetiapine 25 mg at night. There are some data to show that peri-operative delirium prophylaxis with low-dose haloperidol (1.5 mg daily in divided doses) in patients with hip fractures may reduce the severity and duration (but

not the incidence) of delirium.^[10] Haloperidol should NOT be used in patients with Lewy body dementia, idiopathic Parkinson's disease or alcohol withdrawal where low-dose, short-acting benzodiazepines such as lorazepam 0.5 - 1 mg could be used with caution.

Anticholinesterase inhibitors do not improve delirium and may cause harm.^[11] Melatonin is being studied as an attractive alternative agent; the MAPLE A trial is currently underway and will examine the effects of melatonin v. placebo on the occurrence of delirium in hip-fracture patients.

Medication review

All patients with delirium should have their prescriptions reviewed and potentially delirogenic drugs discontinued unless they are essential (Table 3).

The Beer's criteria is a recently updated list of drugs that are thought to be inappropriate in elderly patients, and this can be used as a clinical tool to aid the medication review.^[12]

Conclusion

Delirium is common, costly, under-recognised and associated with short- and long-term morbidity and mortality. It is a highly preventable condition. The mainstay of prevention and treatment includes non-pharmacological measures and clinicians should endeavour to promote a culture of delirium-reduction strategies within health care.

References

1. Siddiqi N, House, AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: A systematic literature review. *Age and Ageing* 2006;35(4):350-364.
2. McNicoll L, Pisani M, Zhang Y. Delirium in the intensive care unit: Occurrence and clinical course in older patients. *J Am Geriatr Soc* 2003;51(5):591-598. [http://dx.doi.org/10.1034/j.1600-0579.2003.00201.x/full]

2003;51(5):591-598. [http://dx.doi.org/10.1034/j.1600-0579.2003.00201.x/full]

3. Leslie DL, Marcantonio ER, Zhang Y, et al. One-year health care costs associated with delirium in the elderly population. *Arch Intern Med* 2008;168(1):27-32.
4. Witlox J, Eurelings L. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization and dementia. *JAMA* 2010;304(4):443-451.
5. Rudolph JL, Inouye SK, Jones RN, et al. Delirium: An independent predictor of functional decline after cardiac surgery. *JAMA* 2010;304(4):643-649.
6. Inouye SK. Delirium in older persons. *New Engl J Med* 2006;354(11):1157-1165.
7. Inouye S, Van Dyck C. Clarifying confusion: The confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;113:941-948.
8. Inouye SK, Bogardus ST, Charpentier P, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med* 1999;340(9):669-676.
9. Cotter VT. Restraint free care in older adults with dementia. *Keio J Med* 2005;54(2):80-84.
10. Flaherty JH, Little MO. Matching the environment to patients with delirium: Lessons learned from the delirium room, a restraint-free environment for older hospitalized adults with delirium. *J Am Geriatr Soc* 2011;59(Suppl 2):S295-S300.
11. Kalisvaart KJ, De Jonghe JFM, 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(10):1658-1666.
12. Van Eijk MMJ, Roes KCB, Honing MLH, 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(9755):1829-1837.
13. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2012;60(4):616-361.

SUMMARY

- Poor awareness – clinician awareness of this serious condition.
- Poor recognition – clinical under-detection rates of delirium remain high at 50 - 66%. This is mainly accounted for by poor knowledge of cognitive evaluation and practice of healthcare practitioners.
- Prevention – 40% of delirium is preventable and caused by iatrogenic exposure. Protocols for care lessen incidence, and impact of delirium.
- Poor management – delirium represents a state of acute brain failure as such management should be performed as an emergency and medical providers should be familiar with standard care of such patients.
- Polypharmacy – inappropriate medications will precipitate and perpetuate delirium. Rarely should medication be needed to palliate a patient with delirium.
- Prognosis - 1-year mortality of a frail older person who has suffered an episode of delirium is up to 30 - 40%.