Management of delirium

Delirium occurs in up to 50% of general hospital inpatients and is even more common in terminal illness. It is associated with a high morbidity and mortality, regularly missed and importantly is often either preventable or treatable.

Delirium is an important complication of physical illness, particularly in the acutely unwell medical, and the perioperative surgical, patient. It is also very common in palliative care settings as a result of a range of factors, including older age, advanced disease and exposure to iatrogenic factors such as polypharmacy. The incidence is approximately 30% in palliative care patients (range 20–44%) but has been found to be as high as 90% in the terminal phase of illness (Leonard et al, 2008). This article explains how to diagnose and treat delirium with an emphasis on palliative care settings, but perhaps more importantly how to avoid causing it and when to be vigilant for its presence, particularly the hypoactive variant which can be less obvious to clinicians.

Clinical features and diagnosis

The diagnosis of delirium is based on the key features of an acute onset of disturbed cognition in the context of a physical illness. Classically, delirium runs a fluctuating course. Agreement on the boundaries of the syndrome and its core components are elusive and reflect our poor understanding of the effects of severe systemic illness on the functioning of the brain. Although the American (*Diagnostic and Statistical Manual of Mental Disorders* 4th edition, DSM-IV; American Psychiatric Association, 1994) and European (*International Classification of Diseases* 10th revision, ICD-10; World Health Organization, 1993) classification systems generally concur, they differ on which core features must be present to make the diagnosis. Of the five features required by ICD-10 (*Table 1*) only two are shared by DSM-IV, which requires that acute onset and evidence of a physiological cause are also present. A mnemonic for the key features of delirium is given in *Figure 1*.

It is important to appreciate that there is a range of motor activity level in delirium. Hyperactive variants are characterized by high levels of arousal, distractibility, restlessness and wandering – most clinicians have seen such patients. However, hypoactive variants are at least as common, particularly in palliative care populations where they account for 40–78% of all cases (Leonard et al, 2008). Such patients have slowed or reduced movement, speech and awareness and are often missed as they rarely cause a disturbance or appear distressed. They may be misdiagnosed as having exhaustion or depression. Psychosis is equally prevalent in hypoactive delirium as in the hyperactive form (Meagher et al, 2007) but seems to respond less well to treatment. 'Mixed' presentations are also common where rapid fluctuations occur between hyperactive and hypoactive states.

Terminology

ICD-10 defines delirium as an 'aetiologically non-specific organic cerebral syndrome' and acknowledges the other terminology used for this condition, including 'acute brain syndrome'. The terms 'acute brain dysfuntion' and 'acute

Table 1. Features and diagnosis of delirium

ICD-10 criteria require all of the following in the context of an underlying physical or brain disease:	
1. Consciousness (i.e. Glasgow Coma Scale) and attention (e.g. serial 7s, 20-1, digit span*) impairment	
2. Cognition disturbance (global)	Perceptual disturbance (visual > other senses)
	↓Memory: especially immediate recall/recent memory
	Disorientation: time +/- place +/- person
3. Emotional disturbance, e.g. depression, anxiety, fear, irritability, euphoria or apathy	
4. Sleep–wake cycle disturbance	
5. Psychomotor disturbance: hyper- or hypo-activity (or speech)	
Other important criteria mentioned by DSM-IV	Acute onset
	Evidence of physiological cause (i.e. physical illness)

*See ***Figure 2*** for details. N.B. ICD-10 criteria for delirium exclude the same symptoms caused by psychoactive drugs (including alcohol) either as a result of intoxication or withdrawal. DSM-IV = ***Diagnostic and Statistical Manual of Mental Disorders*** (4th edition) (American Psychiatric Association, 1994); ICD-10 = ***International Classification of Diseases*** (10th revision) (World Health Organization, 1993)

Figure 1. Mnemonic for the features of delirium.

Acute onset, and often (diurnally) fluctuating, disturbance of:	
Activity	Psychomotor (increase or decrease) Sleep–wake cycle
Behaviour	Emotions: anxiety/fear, anger, mood change (depression > mania) Psychosis: hallucinations (mostly visual) or delusions (poorly formed)
Cognition	Conscious level (i.e. Glasgow Coma Scale) Attention Memory Orientation

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brain failure' also allude to the syndrome being the result of a gross and non-specific insult to the brain. The term 'brain failure' reminds us that the brain is another highly complex major organ, similar to the kidneys, heart, liver and lungs, and is affected by severe systemic illness of any cause. The term 'intensive care syndrome' is also widely used to describe essentially the same syndrome in a setting where, by definition, patients are severely unwell and often have many other risk factors for delirium (*Table 2*).

Table 2. Aetiological factors in delirium

Predisposing factors	Increasing age
	Pre-morbid cognitive impairment (e.g. dementia)
	Sensory (e.g. visual or auditory) impairment
	Advanced or severe physical disease
	Malnutrition or low serum albumin
Precipitating factors	Metabolic derangement
	Hypoxia
	Infection (especially sepsis)
	Dehydration
	Constipation (N.B. iatrogenic,e.g. opiate induced)
	Medication*
	Postoperative
	Emotional or psychological
	Pain

* Consider in any drug with psychotropic or anticholinergic action (***Table 3***)

Table 3. Drugs that can precipitate delirium

Opioids*	
Benzodiazepines*	'Paradoxical' reaction (agitating rather than sedating, common in the elderly) or withdrawal
Anticholinergics	Common action of many drug classes; easy to spot if the main (therapeutic) action of drug but less so when this is 'side effect'
Antihistamines	Antiemetics, e.g. cyclizine, cinnarizine, prochlorperazine
	Sleeping tablets, e.g. promethazine
	Allergies, e.g. cetirizine, loratadine, chlorphenamine
Antispasmodics, e.g. hyoscine, procyclidine	
Bladder stabilizers, e.g. oxybutinin	
Bronchodilators, e.g. atropine, ipratropium, aminophylline, theophylline	
Antidepressants*, especially tricyclics, e.g. amitriptylline, lofepramine, dosulepin	
Antihypertensives	Diuretics (e.g. furosemide) and alpha agonists
Antiarrhythmic (digoxin)	
Steroids, especially high dose and/or potency	
Chemotherapy, e.g. asparginase, cytosine, chlorambucil, ifosfamide, interleukins, vinblastine and vincristine	

*These drugs can all cause 'discontinuation syndrome' if stopped abruptly (by patient or clinician) and either precipitate or exacerbate delirium

Improving the terminology and diagnostic criteria for this condition remains a source of active debate (Meagher et al, 2007) and this process will be informed by ongoing research into the phenomenology and pathophysiology of delirium. There has been an attempt to establish a common international terminology in this confusing area (Morandi et al, 2008).

Aetiology

The causes of delirium are most helpfully categorized into predisposing and precipitating factors (*Table 2*).

Predisposing factors, particularly older age and cognitive impairment, lower the 'threshold' for delirium. The term 'cognitive reserve' is useful in conceptualizing the severity of insults required to precipitate delirium in a specific individual. For example, only a small insult (e.g. minor chest infection) would be required in someone with advanced dementia, but a collection of severe insults (e.g. road traffic accident with subsequent brain and skeletal injuries, operations and polypharmacy) may all be required in a young healthy person. Risk factors often co-exist or sit on the same causal pathway – metabolic derangement may be caused by sepsis and pain may be related to constipation. In oncology patients specific risk factors have been identified and these included bone metastases and, perhaps less intuitively, haematological malignancies (Ljubisavljevic and Kelly, 2003).

Iatrogenic precipitants are common, particularly medications (*Table 3)*. This might be as a direct action of the drug, a side effect, or as a discontinuation effect following abrupt cessation. Opiates can do this via all three mechanisms as intoxication (even at relatively low doses in the elderly or those naive to opiates), constipation as a side effect and withdrawal are all common.

The pathophysiology of delirium is not well understood. There is good evidence for the role of central cholinergic underactivity (Hshieh et al, 2008), consistent with anticholinergic drugs precipitating delirium. There is evidence for dopaminergic overactivity, consistent with dopaminergic antagonism being effective for the treatment of delirium. There is also some evidence for the role of increased activity in the hypothalamic–pituitary axis (especially increased cortisol levels) and of inflammation, particularly via pro-inflammatory cytokines (e.g. interleukin-6 and interleukin-8). Associations have been found with many other biomarkers (e.g. insulin-like growth factor-1) and some genes (e.g. APOE-4 allele) with logical connections to possible mechanisms. It is likely that genetic susceptibility plays a role, similar to other common psychiatric disturbances.

However, no clear unifying mechanistic pathway has yet been identified. Delirium is the final outcome of a range of biological mechanisms. It is likely that there are several deliriums each with a smaller number of final common pathways.

Screening, assessment and monitoring tools

Several tools exist that aid either the screening, assessment or monitoring of delirium. Tools for the latter tend to be more specific to delirium and some require training for their use.

The 10-point (Abbreviated) Mental Test Score and the 30-point Mini Mental State Examination are commonly used tools for screening for cognitive dysfunction. They are well validated, familiar and available to most clinicians. However, they are not very specific or sensitive for delirium as they focus on testing domains such as orientation, which are relatively spared in delirium. Despite this they remain good baseline tests although it is helpful to perform additional tests if any cognitive impairment is detected or where delirium is anticipated. For example the reverse digit span test is specific for attention and the clock face test has been validated in a variety of settings, including palliative care (Henderson and Hotopf, 2007); *Figure 2* shows how to perform these tests.

Several specific tools for delirium have been developed, such as the Confusion Assessment Method which is a short (4-item) tool validated for both screening and diagnosis (Inouye et al, 1990) and designed for use by (trained) non-specialists. It has even been adapted and validated for use on intensive care patients who are often mechanically ventilated or for other reasons unable to communicate verbally. The Memorial Delirium Assessment Scales is used for monitoring symptoms and has been validated in patients with advanced cancer (Lawlor et al, 2000) but is designed for use by experienced mental health professionals.

Investigations

Delirium is a clinical diagnosis. Nonetheless ICD-10 recommends that if the diagnosis is in doubt evidence of cerebral dysfunction may be required, for example an abnormal electroencephalogram. In reality such tests are hardly ever required and more basic investigations can support the diagnosis, reveal the underlying cause(s) and prompt appropriate treatment. Investigations should be tailored to the clinical scenario (*Table 4*). It is worth looking for multiple causes, especially if the patient is severely unwell or not responding to initial treatments.

Figure 2. Useful tests for delirium to add to basic screening procedures.

1. Reverse digit span test

Read the following series of numbers to patients in constant rhythm and ask them to repeat them to you in reverse order:

1-4-6	6-4-1
2-7-4-8	8-4-7-2
3-1-9-2-5	5-2-9-1-3

2. Clock drawing test

Give patient sheet of paper with a large circle drawn on it
Ask patient to add numbers to create a clock-face
Ask patient to add the hands to show a specific time (e.g. half past four)
Several scoring systems exist

Treatment

The management of delirium may be divided into pharmacological and non-pharmacological approaches. There have been several attempts to generate specific guidance, such as the British Geriatrics Society guidelines for prevention and treatment of delirium (Potter and George, 2006) and a more recent Swiss-French collaboration (the Delirium Guidelines Development Group; Michaud et al, 2007). There is broad consensus on treatment options but it is less clear when, and often exactly how, these should be applied. National Institute for Health and Clinical Excellence guidelines are currently in development (expected publication date 2010) which should clarify this area, at least in terms of UK practice.

Non-pharmacological treatments

There are a number of measures that have been shown to both prevent and treat delirium (*Table 5*). Many of these

Table 4. General approach to investigations in delirium

Basic observations: signs of infection or major organ failure
Physical examination: signs of dehydration, constipation, infection or organ failure
Look at drug chart for possible causes (*Table 3*)
Basic blood tests: full blood count, C-reactive protein, urea, creatinine, estimated glomerular filtration rate, calcium, phosphate
Septic screen: e.g. blood cultures, urine dipstick or mid stream urine, chest X-ray, ultrasound of the abdomen
Neurology screen: computed tomography or magnetic resonance imaging of the brain, lumbar puncture, electroencephalogram

N.B. start with basic observations and tests and consider further tests according to clinical picture. Always consider iatrogenic causes first (especially medications)

Table 5. Non-pharmacological treatment

Remove and/or treat underlying cause; often just standard 'best medical practice' – rationalize medications (especially those potentially contributing to delirium), ensure optimal fluid balance and analgesia, remove non-essential invasive lines (urinary catheters or cannulae) because of the risk of infection, pain, irritation and also injury if the patient pulls them out
Reassurance, good lighting, calm (and ideally) familiar surroundings, attempts to orientate patient (e.g. access to natural light, clocks and calendars). Try to mimimize changes to surroundings (e.g. changes of bed or ward)
Optimize sensory input; check for previously known hearing and/or visual impairment and correct as appropriate. Check for missed or new diagnosis
Check for pain (including psychological) and treat. If possible avoid opiates and if not possible use minimum dose necessary
Normalize sleep–wake cycle. Discourage sleep and provide stimulation during day. Where possible give essential sedative medications in evening (or as close as possible). Consider sleeping tablet in short term to re-establish normal sleep pattern
Non-confrontational approach: intolerance is likely to exacerbate the syndrome and although such patients are often challenging to manage, this is worth bearing in mind

are common sense but it is important to bear these in mind as they are relatively inexpensive and have limited adverse effects.

Pharmacological treatments

Antipsychotics

Antipsychotics are the first-line treatment in delirium, although they may worsen disorders such as Parkinson's disease. A Cochrane review (Lonergan et al, 2007) concluded that low-dose haloperidol (<3.0 mg/day), a typical or first generation antipsychotic, and the atypical or second generation antipsychotics (e.g. olanzapine, quetiapine or risperidone) are effective and there is no clear difference between them. However, this review only found three small studies that were of sufficient quality to merit inclusion, and therefore its conclusions must be treated as preliminary until further evidence is available.

It also concluded that there are no differences in complication rates between the two classes of antipsychotic. There have been concerns from the UK Committee on Safety of Medicines (2006) that atypical antipsychotics are associated with an increased risk of stroke, particularly in those with dementia and perhaps the elderly in general. Despite ongoing evidence for this (Douglas and Smeeth, 2008) the significance of the risk remains controversial. It should also be noted that haloperidol was the comparator in two studies and was also associated with an increased risk of stroke, albeit less than the atypical antipsychotics.

Atypical antipsychotics are also significantly more expensive for low dose tablets (0.5 mg haloperidol = 3p, 0.5 mg risperidone = 35p, 2.5 mg olanzapine = 119p, 25 mg quetiapine = 135p) and if used long term there may be significant metabolic side effects such as impaired glucose control. However, this should be balanced against the evidence that they produce fewer extrapyramidal side effects and perhaps lower overall mortality in the elderly (Wang et al, 2005), probably, at least in part, as a result of the reduced risk of hypotension and falls. However, studies have raised doubts about the extent to which atypical antipsychotics cause fewer extrapyramidal side effects (the large CATIE (Lieberman et al, 2005) and CUtLASS (Jones et al, 2006) trials). In conclusion there is little to suggest the potential risk of stroke and increased monetary cost of atypical antipsychotics is balanced by any benefits. Therefore, until further evidence is available, low dose haloperidol should remain first choice.

Other drugs

Benzodiazepines are the treatment of choice of delirium in the context of known, or suspected, alcohol withdrawal (i.e. delirium tremens) but beyond this a Cochrane review concludes their use should be limited. This relates to their potential, particularly in the elderly, to cause 'paradoxical' agitation. Other circumstances for their use include management of psychomotor complications in those receiving antipsychotics (Michaud et al, 2007), and if benzodiazepine withdrawal is thought to be involved in the cause of delirium.

Cholinesterase inhibitors have been tried with mixed success and another Cochrane review concludes there is currently no evidence backing their use (Overshott et al, 2008). There is some limited evidence for the efficacy of other drugs such as mianserin, ondansetron, clonidine, clomethiazole and melatonin, but currently this is not sufficient to support routine use.

When to use drugs

In general, drug treatment should be reserved for when other measures have failed but there will be times when this is not possible, particularly if there is danger to the patient or others (*Table 6*).

What route to use

Oral medication should be used first unless there are immediate risks requiring rapid pharmacological action or the patient is unwilling or unable to take oral preparations. In such cases intramuscular or intravenous administration may be necessary. In palliative care settings some clinicians advocate the less invasive subcutaneous administration of drugs such as haloperidol and midazolam but this is an off licence route for these drugs.

Table 6. Pharmacological treatment

Indications for drug treatment as recommended by the Delirium Guidelines Development group	Uncontrollable agitation despite non-pharmacological interventions	
	Danger to the patient, staff, or others	
	Anxiety in agitated or hallucinating patients	
	Need to control agitation, to perform an investigation, or to provide (other) treatment	
Choices of medication	Antipsychotic (for most cases of delirium; see text for details)	Typical: haloperidol (oral, intramuscular or intravenous)
		Atypical: olanzapine (oral* or intramuscular), risperidone (oral*) or quetiapine (oral)
	Benzodiazepines (for alcohol or benzodiazepine withdrawal)	Long acting: chlordiazepoxide (oral), diazepam (oral, rectal, intravenous) or clonazepam (oral)
		Short acting: lorazepam (oral, intramuscular, intravenous), midazolam (oral, intramuscular, intravenous)

From Michaud et al (2007). *Available in 'quick dissolving' forms that can improve compliance and avoid need for injections.

Prevention

Delirium should ideally be prevented rather than treated. A Cochrane review (Siddiqi et al, 2007) concluded that, in hip surgery patients, prophylactic low dose haloperidol reduces the severity and duration of a delirium episode and reduces length of stay (Kalisvaart et al, 2005). There is also evidence for a programme of proactive geriatric consultation (daily physician reviews) of postoperative hip fracture patients reducing incidence of delirium by over one third (Marcantonio et al, 2001). In elderly general medical patients a risk-factor intervention study, particularly focusing on correcting sensory impairment and optimizing orientation, sleep and hydration (Inouye et al, 1999), reduced the incidence and duration of delirium by over a third. This suggests over 30% of cases are preventable with basic interventions and this is likely to be cost-effective given that delirium leads to significant increases in costs of care (Milbrandt et al, 2004). Greater awareness of, and skills in managing, delirium in both medical and nursing staff is also likely to improve outcomes.

Conclusions

Delirium is common in palliative care settings, easily missed and responds to treatment. Clinicians should be alert to its presence and ideally have screening procedures in place. Hypoactive cases must be looked for – they are equally likely to be hallucinating. Treatments are effective and should encompass a range of both non-pharmacological and pharmacological therapies. There is evidence for prevention strategies in some settings. Further study is clearly needed into the phenomenology, pathology and treatment of delirium. There is also a need for improved training of all health-care professionals caring for those at risk of delirium. **BJHM**

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KEY POINTS

- Delirium is common in palliative care patients, as in all patients with severe physical illness.
- It is characterized by acute onset, and classically (diurnally) fluctuating, cognitive and behavioural disturbance – attention is particularly affected.
- Delirium is easy to miss, especially if patients are not hyperactive, looking overtly distressed or causing management problems for staff, and is associated with a high morbidity and mortality.
- It is often preventable with minimization of precipitating factors and vigilance in those at high risk, and may be treatable by managing the precipitating cause and, if required, treatment with both non-pharmacological and pharmacological measures.
- Antipsychotics are the drug treatment of choice unless the cause is alcohol withdrawal in which case long-acting benzodiazepines are recommended.