PALLIATIVE CARE

# Delirium in advanced disease

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Delirium in advanced disease, while common, is often not recognised or poorly treated. The aim of management of delirium is to assess and treat reversible causes in combination with environmental, psychological and pharmacological intervention to control symptoms. Delirium presents significant distress and impedes communication between patients and their families at the end of life. A structured approach to recognise, assess and manage delirium is essential for all clinicians caring for patients with terminal illness.

Patients at the end of life develop a number of distressing symptoms. Although delirium is one of the most common neuropsychiatric problems in patients with advanced cancer, it is poorly recognised and poorly treated.[1]

Delirium is prevalent at the end of life, particularly during the final 24–48 h. Prospective data suggest a prevalence of delirium of 28–42% on admission to a palliative care unit and longitudinal studies have documented occurrence rates as high as 88% before death.[1–5] All patients at the end of life can therefore be considered at high risk of delirium.

Delirium presents significant problems: distress for the patient, anxiety and distress for family, and management challenges for health care workers. Delirium interferes dramatically with the identification and control of other physical and psychological symptoms, impedes the ability to make final choices and plans, and for some patients will be a marker of approaching death. Prompt recognition and appropriate treatment of delirium can improve patient comfort and optimise quality of life.[3]

## AETIOLOGY

Delirium is characterised by rapidly emerging disturbance of consciousness and a change in cognition with fluctuating symptoms and evidence of organic aetiology.

The pathogenesis of delirium is complex and poorly understood: abnormalities of several neurotransmitters and endogenous agents have been postulated (including reduced cholinergic transmission, altered γ aminobutyric acid transmission, altered serotonin transmission, cytokine production and altered cortisol levels).[6–8]

Clinically, the presentation of delirium is felt to result from a combination of precipitating and predisposing factors (table 1). Delirium may be[9]:

- a direct effect of cancer on the central nervous system (for example, primary cerebral tumour or cerebral, leptomeningeal metastases)
- indirect effect or treatment related (for example, metabolic changes caused by organ failure, side effects from medication)
- related to cancer and debility (for example, concurrent lower respiratory tract infection)
- unrelated (for example, secondary to renal failure of separate aetiology).

If vulnerability at baseline is high then delirium is likely to occur with exposure to relatively minor precipitating factors.[10 11] Delirium may be a marker of the terminal phase of illness and 10–23% of patients in palliative care units require terminal sedation because of delirium.[2] Delirium at this stage is not usually reversible (due to the fact that irreversible processes such as multi-organ failure are occurring).[9]

## ASSESSMENT

When assessing the patient, particular attention should be paid to the medication history: several drugs commonly used in the palliative care setting may precipitate delirium (for example, opiates, steroids and benzodiazepines), particularly in older patients. Recent drug cessation (for example, benzodiazepines) and usual alcohol intake are also important.

A history from a relative or carer regarding the onset and course of confusion and baseline level of cognitive function is also vital.

Examination may reveal signs of precipitating factors—for example, pneumonia, acute alcohol withdrawal or urinary retention.

The decision to proceed to further investigations should take into consideration the stage of disease and likelihood that a reversible cause will be found; metabolic causes of delirium may occur in up to 18% of terminally ill patients with cancer.[3] A targeted assessment may include: renal function, calcium, glucose, liver function, full blood count, thyroid function and B12, adrenal function, urine/blood culture, chest *x* ray, computed tomographic scan of head, and cerebrospinal fluid examination.[3 13]

## DIAGNOSIS

While there are established diagnostic criteria for delirium (table 2), it is frequently under-recognised and mistreated; up to half of delirium episodes are not noted by clinicians.[1–3] It is important to appreciate that delirium may present as one of three subtypes:[3 4 12 13]

**Abbreviations:** DRS, Delirium Rating Scale; MDAS, Memorial Delirium Assessment Scale; MMSE, Mini Mental State Examination

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**Table 1** Predisposing and precipitating factors for delirium[1 3 7 10–13]

| Predisposing | Precipitating |
|---|---|
| Older age | Severe acute illness |
| Presence and severity of dementia | Infection |
| Previous delirium | Operation with general anaesthesia |
| Functional dependence | Electrolyte imbalance (eg, hyponatraemia, hypoglycaemia, hypercalcaemia) |
| Immobility | Liver failure with hepatic encephalopathy |
| Dehydration | Renal failure |
| Polypharmacy | Respiratory failure with hypoxia (eg, secondary to pulmonary embolus, lymphangitis carcinomatosis) |
| Hypoalbuminaemia | Drugs (eg, alcohol withdrawal, opiates, benzodiazepines, steroids, TCAs, chemotherapy, anticholinergics) |
| Renal impairment | Pain |
| Defects in vision or hearing | Haematological (eg, anaemia, disseminated intravascular coagulopathy) |
| Alcoholism | Cerebral causes (primary and secondary tumours, post-ictal seizures, cerebrovascular disease, raised ICP) |
| Severity of physical illness | Urinary retention (and also bladder catheter use) |
| ? Genetics | Faecal impaction |
| | Unfamiliar environment |

ICP, intracranial pressure; TCAs, tricyclic antidepressants.

- *Hyperactive (''agitated'') delirium*—characterised by increased motor activity with agitation, hallucinations and inappropriate behaviour and therefore more likely to be recognised.
- *Hypoactive (''quiet'') delirium*—characterised by reduced motor activity and somnolence and often overlooked.
- *Mixed delirium*—alternating between agitated and quiet forms and also difficult to recognise.

Diagnosing delirium and distinguishing it from other conditions can be problematic. For example, the hypoactive subtype may be misdiagnosed as depression due to misinterpretation of slowed psychomotor function, lethargy and reduced awareness/interaction with the environment.[4 6] While the Mini Mental State Examination (MMSE) is able to identify patients with cognitive problems it does not distinguish delirium from other diagnoses (both dementia and depressed patients (with ''pseudo dementia'') may have low scores on an MMSE).[16]

A number of other tools have therefore been developed to distinguish delirium from other causes of altered mental status (for example, Delirium Rating Scale (DRS) and Memorial Delirium Assessment Scale (MDAS)) although these are infrequently used in clinical practice.[4 15 17] The Confusion Assessment Method (table 2) is a simple tool to diagnose delirium which has a high sensitivity and specificity and has been validated for use in the palliative care setting.[4 11 12 15]

Detection of delirium can be improved putting greater emphasis on routine cognitive testing and the use of screening instruments.[11]

## MANAGEMENT

### Treatment of underlying cause

The most important action for the management of delirium is the identification and treatment of the underlying reversible causes (table 1). Delirium may be reversible in up to 50% of patients with advanced cancer, particularly where the precipitant is opiates or other psychoactive medication or metabolic disturbance (for example, dehydration or hypercalcaemia).[1 2] While delirium may have a single cause, a multifactorial aetiology is most commonly found in the palliative care setting.[3]

Of all patients with delirium, medication may be implicated in 12–40% of cases.[7 8 11] Observational studies have shown that the most common drugs associated with delirium are sedative hypnotics (for example, benzodiazepines), analgesics (for example, narcotics) and medication with an anticholingeric effect.[8] Polypharmacy is itself a risk factor for delirium.[8]

A review of all medication is therefore fundamental, with particular attention being paid to any temporal relationship with delirium onset and recent additions or drug dose changes.[8]

### Symptom management

Further management incorporates pharmacological and non-pharmacological measures to reduce the symptoms and prevent complications—for example, falls (table 3).

Non-pharmacological strategies for management are free of adverse effects but are underutilised.[11] In general non-pharmacological measures should be used first and then

**Table 2** Diagnostic criteria for delirium[3 12 14 15]

| DSM IV criteria | Confusion assessment method criteria |
|---|---|
| 1. Disturbance of consciousness with impaired ability to focus or shift attention | 1. Acute onset and fluctuating course: Is there an acute change in mental state from the patient's baseline? Does the abnormal behaviour fluctuate? |
| 2. Change in cognition (memory impairment, disorientation, language disturbances, perceptual disturbances) | 2. Inattention: Does the patient have difficulty focusing attention (ie, easily distracted)? |
| 3. Disturbance evolves over a short period of time (hours/days) and fluctuates during the course of the day | 3. Disorganised thinking: Was the patient's thinking disorganised (ie, rambling or irrelevant conversation, illogical flow of ideas)? |
| 4. Evidence of a general medical condition, substance intoxication or withdrawal judged to be aetiologically related to the disturbance | 4. Altered level of consciousness, eg, hyperalert, lethargic, stupor or comatosed |
| To diagnose delirium all 4 features must be present | To diagnose delirium features 1 and 2 and either 3 or 4 must be present |

DSM IV, *Diagnostic and statistical manual of mental disorders*, 4th ed.

**Table 3** Management of delirium[3 9 10 12 21–23]

**Algorithm for assessment and management of delirium**

**Index of suspicion**
Low threshold for cognitive assessment/using screening tools, particularly where multiple predisposing and/or precipitating factors are present

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**Identification and diagnosis**
Using, for example, DSM IV criteria or a validated tool, eg, Confusion Assessment Method

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**Evaluate reversibility and treat reversible causes**
Review all medication. Assess, examine and investigate for reversible causes to a level appropriate for the patient

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**Pharmacological and non-pharmacological management**
Make optimal use of non-pharmacological strategies and make the environment safe and comfortable. Where pharmacological agents required aim to use one drug at the lowest possible dose

| Non-pharmacological | Pharmacological |
|---|---|
| Appropriate lighting for the time of day | *Predominantly neuroleptic effects:* |
| Clocks and calendars to improve orientation | Haloperidol 0.5–1 mg initially titrated to effect (use first line*) |
| Hearing/visual aids to reduce sensory impairment | Olanzapine 2.5–5 mg daily |
| Encourage mobility and engagement in activities with other people | Risperidone 0.5 mg twice daily |
| Avoid physical restraint, eg, cot sides | Quietiapine 25 mg twice daily |
| Continuity of care from nursing staff | *Predominantly sedative effects:* |
| Presence of family members, familiar objects, pictures of home and family | Lorazepam 0.5 mg-1 mg 4 hourly |
| Reduced abnormal distractions, eg, noise | Midazolam 2.5 mg subcutaneously |
| Encourage adequate fluid intake to prevent dehydration and constipation | Levopromazine 12.5 mg–25 mg |
| | *except alcohol/drug withdrawal or Lewy body dementia where benzodiazepines are preferable |

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**Involve family and carers**
Explain, discuss and support. Involve in non-pharmacological management. Obtain background and additional history, eg, pre-admission cognitive status, drug and alcohol use

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**Review and reassess frequently**

pharmacological agents if unsuccessful (sedation may be required in 9–26% of patients with delirium at the end of life[3]).

The use of ward transfers, physical restraints, anticholinergic drugs and catheters should be avoided where possible. Cot sides have not been shown to reduce the risk of falls and may increase the risk of injury.[12]

If required, the aim of drug treatment is to reduce distressing or dangerous behavioural disturbance (for example, agitation and hallucinations). Use only one drug if possible, haloperidol being currently recommended as first line (although evidence to form the basis of guidelines on drug treatment for delirium in terminally ill patients is very limited).[11 18] Notable exceptions are alcohol withdrawal and Lewy body dementia where a benzodiazepine is more preferable; in other patients with delirium benzodiazepines can paradoxically worsen the confusion if used alone.[2 4 12 18]

Delirium in the last few days of life (often referred to as terminal restlessness or terminal agitation) is often ongoing and irreversible. Evidence suggests that delirium in cancer patients with terminal disease may require more than a single drug treatment, and 10–20% of terminally ill patients experience delirium that can be controlled only by sedation to significantly decreased levels of consciousness.[13 19]

Explanation and discussion with family is essential.

## Decision making

Issues of capacity and informed consent will arise in relation to the treatment of delirium. Interventions needed to prevent serious deterioration or death, or which are necessary in the interests of patient safety, are covered by common law in the UK.[5] The new Mental Capacity Act 2005 endorses the principle of clinicians acting in ''best interests'' and is a statutory codification of the existing common law position.[20]

There are other important implications of the Act (which will become law in April 2007), particularly the presumption that all patients have capacity unless it is proven to the contrary: an adult can be deemed to have capacity to consent or refuse treatment if they: (a) understand the information relevant to the decision; (b) retain the information relevant to the decision; (c) use or weigh the information; and (d) communicate the decision (by any means).[20]

The Act also provides statutory clarification of the role of advance decision making but restricts this to advance decisions to refuse treatment stipulated for particular situations. Broader ''advance directives'' and ''living wills'' will have relevance when deciding ''best interests'' but are not legally binding.[5]

Finally, the current provision of appointing an Enduring Power of Attorney relates only to property and affairs; however, Lasting Powers of Attorney appointed under the new Act will have power to make health care decisions on behalf of the incapacitated person (this does not extend to refusing life-sustaining treatment unless this is explicitly stated).[5]

## Main points

- Delirium is common among patients with advanced disease
- Delirium is characterised by a global disturbance in cerebral function affecting consciousness, attention, cognition and perception with a course that may fluctuate over a period of hours
- Delirium is conceptualised as a reversible process; however, it may not be reversible in the last two days of life
- Management incorporates identifying reversible causes and then pharmacological and non-pharmacological measures to reduce the symptoms and prevent complications

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## CONCLUSION

Delirium is common in advanced disease and has a significant detrimental effect on quality of life for patients and their families. Patients with advanced disease are at high risk of developing delirium, particularly those with multiple predisposing and precipitating risk factors. Clinicians should be vigilant in order to recognise delirium when it occurs and use a structured approach to assess and manage the patient.

Management of delirium in the terminally ill involves treatment of the underlying cause if possible (and eliminating non-essential drugs which may be contributing), environmental strategies, and the use of medication to control symptoms and behaviour.

## MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AFTER THE REFERENCES

### Regarding recognition and assessment of delirium in advanced disease:

(A) Delirium is a rare (but important) complication in patients with advanced disease

(B) Delirium is present in over 75% patients in the last 24–48 h of life

(C) Delirium is reversible in over 75% of palliative care patients

(D) There is often a single identifiable cause—for example, hypercalcaemia

(E) A Mini-Mental Structured Examination (MMSE) is a useful tool to distinguish delirium from dementia and depression

### 2. Regarding management of delirium in advanced disease:

(A) Cot sides are an effective non-pharmacological measure to reduce falls in patients with delirium

(B) Haloperidol is currently favoured as the pharmacological agent of first choice

(C) Benzodiazepines should be used in preference for patients with alcohol withdrawal or Lewy body dementia

(D) Multiple randomised controlled trials have provided an evidence base for drug treatment of delirium in advanced disease

(E) Hypoactive delirium is more likely to require the use of sedative drugs than hyperactive delirium

Conflict of interest: None

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## ANSWERS

1. (A) F: delirium is common in advanced disease; (B) T; (C) F: up to 50%; (D) F: usually multifactorial; (E) F: all may have low MMSE scores
2. (A) F (B) T (C) T (D) F (E) F