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Delirium

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Delirium (acute confusional state) is a common and unpleasant condition in older people that can have serious short- and long-term consequences. It is often misdiagnosed or unrecognised by doctors and nurses, and management is often poor.[1]

Clinical features and diagnosis

A diagnosis of delirium should be considered when a patient is described as, or thought to be, 'confused', 'vague', 'a poor historian' or 'unco-operative'.

Delirium is characterised by a change of cognition that develops over hours or days (Table 1). Symptoms fluctuate throughout the day and are worst at night. Disturbed consciousness and inability to attend to the environment are cardinal features: patients are highly distractable and find it difficult to focus or sustain concentration. They are often disoriented with rambling, incoherent speech and may be tearful or anxious. Persecutory delusions and visual hallucinations are common.

Table 1. Diagnostic criteria for delirium.

- Disturbance of consciousness (reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention
- A change in cognition (such as memory deficit, disorientation, language disturbance or perceptual disturbance) not better explained by a pre-existing or evolving dementia
- The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate over the course of the day
- There is often evidence from the history, physical examination or laboratory findings that the disturbance is due to one or more medications or general medical conditions

Two distinct clinical subtypes of delirium are recognised:

- an *agitated variant* with psychomotor overactivity, such as plucking at bedclothes or aggression, and
- a *quiet variant* where patients appear apathetic and withdrawn; this is easily missed or misdiagnosed as depression.

A history from a carer of the onset of the cognitive disturbance is invaluable in distinguishing between dementia and delirium. Delirious patients can often be recognised at the bedside from their characteristic distractability. Impaired attentiveness can be assessed formally with bedside tests such as asking the patient to say the months of the year backwards or to count backwards from 20.

Generalised slowing of the EEG trace is characteristic of delirium (withdrawal states excepted), but the specificity of this finding is reduced with increasing age and in dementia.

The prevalence and incidence of delirium are shown in Table 2.

Outcome

Delirium is traditionally regarded as a transient disorder, but 30–60% of delirious patients still have clinically significant new cognitive impairment several weeks later, and subsequently there is an increased risk of developing dementia.[4] It remains uncertain whether delirium is simply a marker for reduced cognitive reserve or whether it may of itself cause structural brain damage.

In reports from widely diverse healthcare systems, even after adjusting for potential confounding factors, delirium has consistently been associated with:[5]

- prolonged hospital stay
- functional decline, and
- increased risk of institutionalisation.

Complications such as pressure sores, falls, infections and urinary incontinence

are more common in delirious patients and may prolong or exacerbate the delirium.

Aetiology

In the past, it was usual to describe the acute illness that led to the patient's admission as the 'cause' of delirium. However, many episodes of delirium develop only after admission to hospital (Table 2) despite the institution of effective therapy for the presenting illness. A better approach is to distinguish between factors that increase the vulnerability of the patient to delirium and those that precipitate delirium.[6] The precipitating insult in vulnerable patients may be as mild as a simple urinary tract infection. Delirium is almost invariably multifactorial in older people, and it is often inappropriate to isolate a single precipitant as 'the' cause.

Predisposing factors

The most important risk factors for delirium have consistently emerged as:

- prior cognitive impairment
- older age
- severity of illness, and
- psychoactive drug use.

Laboratory indices of dehydration or metabolic disturbance, alcohol abuse and visual impairment have also been identified as important risk factors in some studies.[1]

Precipitating factors (Table 3)

Delirium may be the presenting feature of an otherwise clinically silent myocardial infarction or pneumonia. Common precipitants of delirium in hospital patients include:

- chest or urinary infections
- cardiorespiratory disease
- medication toxicity
- dehydration, and
- stroke (especially involving the right hemisphere).

Alcohol withdrawal should always be considered, even in the absence of a history of alcohol abuse. Thiamine deficiency, non-convulsive seizures, intracranial infections and subdural haematoma should be considered in difficult cases. Anticholinergic drugs are important in the genesis of delirium, and metabolites of drugs not usually thought of as having major anticholinergic effects such as digoxin, nifedipine and prednisolone may contribute to the anticholinergic 'burden'.[7] Iatrogenic factors, such as the use of restraints, malnutrition, polypharmacy and bladder catheterisation, are especially important in patients who develop delirium after hospital admission.[6]

Table 2. Prevalence of and incidence of delirium.

- 10–20% of older medical patients are delirious on hospital admission
- a further 10–30% develop delirium after admission[2]

Delirium develops in:

- 5–10% of patients following general surgery
- 33–50% of patients after hip fracture repair
- 20–40% of patients after elective joint replacement surgery

Postoperative delirium is common:

- after major cardiac surgery
- in patients admitted to intensive care[3]

Delirium occurs:

- in up to 60% of patients admitted to palliative care units

Pathophysiology

It appears that delirium represents the clinical manifestation of diffuse, reversible impairment of cerebral oxidative metabolism and neurotransmission.[3] The current dominant theory is that a state of relative cholinergic

Table 3. Selected common precipitating causes of delirium.

Medications	Alcohol or sedative hypnotic withdrawal Substance toxicity Sedative hypnotics Opioids (especially postoperative) Anticholinergics Antiparkinsonian drugs Antidepressants Anticonvulsants Corticosteroids Digoxin
Infections	Pneumonia Urinary tract infections
Metabolic abnormalities	Hypoglycaemia Hypercalcaemia Hypernatraemia Hepatic failure Renal failure Thiamine deficiency
Hypoxaemia	Cardiac failure Myocardial infarction Respiratory failure Pulmonary embolus
Urinary and faecal retention	
Pain	
Neurological illness	Stroke Seizures Subdural haematoma

deficiency and dopaminergic excess is the final common pathway for delirium, although disturbances in other neurotransmitter systems also occur. Another hypothesis is that delirium results from a stress reaction to acute illness, associated with increased levels of and vulnerability to glucocorticoids and cytokines.

Treatment

The general principles of treatment of delirium are:[8,9]

- early diagnosis
- treatment of precipitating factors
- provision of a supportive environment
- maintenance of nutrition and hydration, and
- careful use (if at all) of psychotropic drugs.

Supportive measures

It is important to maintain fluid intake and nutrition. Subcutaneous fluids are a useful option in agitated patients. Multivitamin supplements, especially thiamine, are essential in obviously malnourished or alcoholic patients. Physical restraints, including bedrails, are potentially dangerous in paranoid and agitated patients. Spectacles and hearing aids should be provided to minimise sensory deprivation, and self-care and mobility promoted. Interventions such as bladder catheterisation should be avoided unless essential. Staff should adopt a calm and friendly approach, with frequent reassurance. The presence of family members at the bedside will often improve orientation, reduce agitation and facilitate feeding.

These measures represent a humane approach to dealing with the confused patient. However, randomised trials have found that systematic detection and management of delirium lead to statistically significant, but small, beneficial effects on cognition, behaviour and function without affecting long-term outcomes.[10] In contrast, some similar interventions have been found to be effective in the prevention of delirium in vulnerable patients.

Table 4. Pharmacological management of delirium.

General principles	• Tailor doses according to age, body size, sex and degree of agitation • Titrate doses to effect • Increase scheduled dose if regular 'as-needed' doses required • Maintain effective dose for a few days, then taper and stop
Haloperidol	• Neuroleptic agent • Avoid in withdrawal states, anticholinergic toxicity and hepatic failure • Extrapyramidal side effects, especially if dose >3 mg daily or prolonged • QTc prolongation, especially with higher or parenteral doses. Check electrolytes and baseline and follow-up ECG; consider discontinuation or reduction in dose if QTc >450 msec or >25% increase above baseline • Oral therapy: – bioavailability 66%; time to peak effect 4–6 hours – usually 0.5–1.0 mg bd with additional doses 'as-needed' • Intramuscular therapy: – bioavailability 100%; time to peak effect 20–40 min – severe agitation, give 0.5–1.0 mg, observe for 30–60 min and repeat if needed
Atypical neuroleptic	• Fewer drug interactions and less extrapyramidal effects than haloperidol • ? Similar effects on QTc • Antipsychotic potency: risperidone > olanzapine > quetiapine • Sedation: olanzapine > quetiapine > risperidone • Extrapyramidal safety: quetiapine > olanazapine > risperidone • Usual starting doses: – risperidone 0.5 mg bd – olanzapine 2.5–5.0 mg daily – quetiapine 25–50 mg daily
Lorazepam	• Benzodiazepine • Use in sedative and alcohol withdrawal, parkinsonism • Sometimes used as adjunct to haloperidol to reduce risk of extrapyramidal side effects • More likely than neuroleptics to cause respiratory depression and paradoxical excitement • Usual starting dose: 0.5–1.0 mg oral (or intravenous in emergency) with additional doses 4-hourly 'as needed'
Trazadone	• Antidepressant • Usual dose 25–150 mg nocte • Limited by sedative side effects

Pharmacological management

Not all patients need psychotropic medications. While they may treat troublesome symptoms, their effect on long-term outcomes is unknown. The need for medication is usually obvious in the agitated, hallucinating patient but even quietly delirious patients can experience considerable distress.

The common errors in managing delirium are to use antipsychotic medications in excessive doses, give them too late and to overuse benzodiazepines. It is kinder and less dangerous to begin regular low-dose therapy early rather than wait for agitation to increase and then resort to a 'chemical cosh'. The only randomised trial to date, albeit in younger AIDS patients, has confirmed that neuroleptic agents are superior to benzodiazepines in the treatment of delirium.[11] Neuroleptics do not impair respiratory function and are less likely than benzodiazepines to cause drowsiness or disinhibition.

Neuroleptics. Haloperidol remains the standard treatment; it is a powerful antipsychotic that can be given orally or parenterally and has limited anticholinergic, sedative, hypotensive or

Key Points

- Delirium in older patients is usually multifactorial in origin, and there is an inverse relationship between the severity of the insult necessary to precipitate delirium and the pre-existing vulnerability of the patient
- Delirium associated with impaired cholinergic neurotransmission is contributed to by metabolites of drugs not usually thought of as having major anticholinergic effects
- The cognitive effects of delirium may resolve only slowly or not at all
- Neuroleptic agents appear to be superior to benzodiazepines in the pharmacological treatment of delirium
- Measures to promote orientation and sleep and to avoid sensory deprivation and dehydration can prevent delirium in high-risk patients

KEY WORDS: agitation, cognitive impairment, delirium, haloperidol, lorazepam, pharmacotherapy

pro-arrhythmic properties (Table 4).[8,12] An initial, regular dose of 0.5–1.0 mg haloperidol twice daily will often suffice in older people, with additional as-needed doses four-hourly.

Although there are few trial data, atypical neuroleptics also seem effective and are less likely to cause extrapyramidal side effects. Of these agents, risperidone has the greatest antipsychotic potency, olanzapine is most likely to cause sedation, and quetiapine is least likely to cause parkinsonism.

The response to treatment should be monitored daily; if as-needed medication is needed regularly, the dose should be increased. When patients are stable, antipsychotics should be continued for a few days, then tapered and stopped.

Prolongation of the rate-corrected QT interval (QTc) can occur with neuroleptics, especially at high doses or if there is concomitant electrolyte disturbance, heart disease or use of other QTc prolonging drugs. Prolonged QTc may increase the risk of developing *torsades de pointes* and sudden death, although the size of the risk with currently favoured neuroleptics is unknown. Baseline electrolyte measurement and ECG seem prudent in high-risk patients. The American Psychiatric Association suggests that cardiac monitoring or discontinuation or reduction in neuroleptic dose should be considered with QTc prolongation greater than 450 msec or more than 25% increase above baseline.[9]

Other agents. Benzodiazepines are the treatment of choice for withdrawal states and for patients with extrapyramidal disease. Lorazepam, which has a relatively short half-life and is available for parenteral use, is particularly useful. The antidepressant trazadone is a useful alternative to benzodiazepines in patients with parkinsonism and delirium, although sedative side effects can occur.

Trials are investigating whether cholinesterase inhibitors such as donepezil may be useful in treating (or preventing) delirium. Psychostimulants have been used to treat hypoactive delirium, but there have been no satisfactory studies.

Prevention

There is now good evidence that delirium in high-risk patients can be prevented by a strategy comprising:

- repeated reassurance and orientation of the patient
- non-pharmacological sleep promotion
- early mobilisation
- provision of visual and hearing aids, and
- avoidance of dehydration.

This strategy reduced the incidence and duration of delirium in a study of 852 elderly patients on acute medical wards. The number of patients needed-to-treat to prevent one episode of delirium was 19 (95% confidence interval 10–134).[13]

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