Delirium in the Hospitalised Elderly

Juli A Moran, Michael I Dorevitch

ABSTRACT

Delirium is a clinically diagnosed, diffuse brain disorder characterised by a variety of cognitive and behavioural disturbances. It is a common and serious problem in a hospital setting and frequently remains unrecognised in elderly patients. Delirium is usually caused by multiple factors, many of which are preventable. There is an inverse relationship between patient vulnerability and the severity of insult required to induce delirium. Although previously considered to be a self-limiting condition, complete reversibility is the exception rather than the rule. The prognosis is often poor, with significant inpatient mortality, substantially increased care costs and the need for additional home care, rehabilitation and long-term residential care.

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INTRODUCTION

Delirium (also known as acute brain syndrome) is a clinically diagnosed, diffuse brain disorder characterised by a variety of cognitive and behavioural disturbances (Table 1). It is a particularly common problem among hospitalised patients[2-4] and the incidence increases with age.[5] Whilst delirium has previously been considered to be largely a self-limiting condition,[6] it is now clear that it has a poor prognosis, causing substantially increased care costs[5] and increased need for institutionalisation, rehabilitation and home care. Despite its seriousness, delirium frequently remains unrecognised, particularly among the hospitalised elderly.

EPIDEMIOLOGY

Delirium affects 14-56% of hospitalised patients[2-4] with a further 30% of patients having evidence of a 'partial syndrome'[6] (exhibiting some features of delirium, without fulfilling the DSM-IV criteria for diagnosis). The average age of patients developing delirium is 75 years old, with only a moderate proportion of patients affected on admission to hospital, and many more developing signs three or more days after admission or surgery.[7] Levkoff et al., in a study of 325 elderly patients admitted to a teaching hospital, reported that only 10% had delirium at presentation, while a further 31% developed it during their admission.[6] Similarly, in a study of 225 patients admitted to an acute geriatric unit, reported by O'Keeffe and Lavan, 18% had delirium on admission, with a further 29% developing it thereafter.[8] The mean duration of symptoms fulfilling DSM-III criteria was seven days, although 5% persisted for more than four weeks after diagnosis. Thirty-eight per cent of those patients with new onset impairment of orientation and memory still had impairment at one month, while 32% of survivors still had symptoms on discharge.

Table 1. Diagnostic and statistical manual of mental disorders 4th edition [DSM-IV] criteria[1]

A.	Disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
B.	A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing established or evolving dementia.
C.	The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
D.	There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

PATHOPHYSIOLOGY

The diverse range of clinical features seen with delirium is due to widespread cortical and subcortical involvement.[2] The pathophysiology of delirium is poorly understood, but may be due to reduced cerebral oxidative metabolism causing altered neurotransmitter levels in prefrontal and subcortical areas.[9] There is evidence of reduced cholinergic and increased dopaminergic activity, while the significance of serotonin and GABA levels remains unclear. Alternatively, delirium may be the effect of stress-induced increased plasma cortisol levels on the brain.

AETIOLOGY

Delirium is caused by a complex interplay between predisposing (Table 2) and precipitating factors (Table 3). Patients with several predisposing factors are more likely to develop delirium than those patients with none. There is an inverse relationship between host predisposition and precipitant severity, with more vulnerable patients often developing delirium as a result of seemingly trivial insults.[11] Patients with no risk factors usually require quite severe insults (e.g. significant brain injury)

Juli A Moran, FRACP, **Michael I Dorevitch,** MD, Bundoora Extended Care Centre, Bundoora, Victoria
Address for correspondence: Dr Michael Dorevitch, Senior Geriatrician, Bundoora Extended Care Centre, 1231 Plenty Road, Bundoora Vic. 3083
E-mail: michael.dorevitch@nh.org.au

to induce delirium, although it is important to remember that patients who develop delirium as a result of an apparently minor insult may have unrecognised underlying dementia.[3,12]

Table 2. Predisposing factors

Dementia
Multiple medications
Advanced age
Cerebral damage e.g. stroke, Parkinson's disease
Visual and hearing impairment[10]
Functional disability[8]
Living in institution[6]
Alcohol abuse
Social isolation
Multiple co-morbid conditions
Depression
History of previous postoperative delirium

Table 3. Precipitating factors

Severe acute illness (including but not limited to those conditions listed below)
Chest, urine, other infections 10-35%[3]
Intoxication with drugs/poisons 22-39%[3]
Benzodiazepine withdrawal
Alcohol withdrawal ± thiamine deficiency
Metabolic encephalopathies (25%)[3]
• acid-base and electrolyte disorders • hypoglycaemia • hypoxia or hypercapnia • hepatic/renal failure
Polypharmacy
Surgery and anaesthesia
Poorly controlled postoperative pain
Neurological 8% (anoxia, stroke, epilepsy etc.)
Change from familiar environment
Sleep deprivation
Low serum albumin[2]
Fever/hypothermia
Perioperative hypotension
Use of physical restraints
Use of indwelling catheter
Cardiovascular 3%[3]
No cause found 10%[3]

DRUGS AND DELIRIUM

Pharmaceutical preparations, both prescribed and over-the-counter, are a particularly common cause of delirium in the elderly and have been shown to cause 11-30% of hospital admissions.[13] In a study of 432 patients over the age of 65 in a university hospital, Rudberg et al. demonstrated that at least 43% of cases of delirium were related to medication.[7] Lindley et al. showed that 26 of 416 (6.3%) admissions of elderly patients to a teaching hospital were a result of adverse drug reactions, 50% of which were due to inappropriate medications.[14]

Elderly people are more vulnerable to the effects of drugs at lower doses and are especially at risk of developing delirium when more than three medications are commenced during an admission. Drugs that cross the blood-brain barrier are particularly likely to cause delirium. Delirium due to drug toxicity is also commonly caused by drugs with a narrow therapeutic index, although some drugs, e.g. digoxin, have been reported to cause delirium even at normal levels. Patients with alcohol intoxication may present with delirium on admission, although alcohol withdrawal can cause delirium one to three days after admission, as can hypnotic and sedative withdrawal. Drugs which are commonly associated with delirium are listed in Table 4. The most common drugs to cause delirium are sedatives and hypnotics, anticholinergic drugs and narcotics. The use of these agents should be carefully considered in the elderly, especially in those with pre-existing cognitive impairment. If these drugs must be used, then they should be commenced at low doses and increased slowly.[13] Hypoglycaemic drugs, especially long-acting agents can cause prolonged hypoglycaemia, which may present as confusion.[16]

Table 4. Drugs causing delirium[3,11,15]

Sedatives/hypnotics
• Benzodiazepines (starting or withdrawal) • Chloral hydrate, barbiturates
Anticholinergics
• benztropine, oxybutynin • antihistamines e.g. diphenhydramine • antispasmodics e.g. belladonna, propantheline • phenothiazines e.g. thioridazine
Tricyclic antidepressants
Antiparkinsonian drugs e.g. levodopa, amantadine, pergolide, bromocriptine
Analgesics e.g. opiates (especially pethidine), less commonly non-steroidal anti-inflammatory drugs, aspirin
Anaesthetic agents
Antipsychotics, especially those with anticholinergic effects e.g. clozapine
Steroids – may be dose related
Histamine$_2$-antagonists, especially cimetidine, but also others including ranitidine
Antibiotics e.g. aminoglycosides, penicillins, cephalosporins, sulfonamides and, in particular, fluoroquinolones such as ciprofloxacin
Cardiovascular drugs and antihypertensives
• quinine, digoxin (even at normal levels), amiodarone • propanolol, methyldopa
Anticonvulsants e.g. phenytoin, carbamazepine, valproate, primidone, clonazepam, clobazam
Miscellaneous
• lithium, fluoxetine, metoclopramide, immunosuppressants

CLINICAL

The diagnosis of delirium is made clinically.[2] The hallmark feature of delirium is fluctuation of cognition, with

some patients alternating between confusion, usually worst at night, and relative lucidity.[17] There are usually multiple cognitive effects, including deficits in attention, memory and higher order functions that develop acutely over hours to days. Perceptual disturbances including hallucinations (especially visual) and delusions (usually persecutory) and evidence of abnormal thought processes are common. There is often disruption of the sleep-wake cycle, with early features of insomnia and vivid nightmares. Classical features of delirium include restlessness, excitability, pressured speech, shouting, laughing and autonomic hyperactivity (such as diaphoresis, tachycardia and anxiety). This behaviour can be extremely disruptive in hospital or residential care, and at times very difficult to manage.

Although delirium is a primary cognitive problem, it can cause other somatic complaints, including gait and balance disturbance, with a marked increase in falls, depression,[18] impaired swallowing[19] (increasing the risk of aspiration), and urinary and faecal incontinence.

Up to two-thirds of delirious patients may remain undiagnosed by treating physicians.[3,19] In a prospective study of 229 elderly patients admitted to a tertiary hospital, Francis et al. found that physicians had diagnosed only 8 of 50 (16%) patients who met DSM-III criteria for the presence of delirium.[12] Several other studies have suggested that 32-67% of delirious patients remain undiagnosed.[3] A key reason for the underdiagnosis of delirium is that many patients do not exhibit the more recognisable hyperalert psychomotor behaviour described above.[3] A large proportion of delirious older patients are actually hypoalert, presenting as quiet and motionless, frequently drifting off to sleep, with slow and often incoherent speech. In a busy hospital environment they can be considered to be 'model patients' and the diagnosis of delirium overlooked. Francis et al. showed that less than half of the 22% of patients who developed delirium actually had disruptive behaviour, although more than 50% became incontinent of urine.[12]

The fluctuating course of delirium can also confound the diagnosis,[20] as patients who are often more disruptive at night may appear normal to their doctors on the morning ward round.[3] This is compounded by the fact that cognitive testing is rarely done on admission to hospital. In a study of 100 patients undergoing elective or emergency surgery at a university hospital, Ni Chonchubhair et al. performed the 10-point Abbreviated Mental Test Score (AMTS) routinely on admission and three days later.[21] They found that a reduction of more than 2 points postoperatively had a 93% sensitivity and 84% specificity for detecting delirium, as diagnosed by DSM-III. Similarly, a good history of premorbid cognitive function is rarely taken by hospital staff, who should make the effort to obtain a full history from a reliable informant in order to distinguish delirium from dementia.[22] There are carer questionnaire tools available, for example the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), which may help diagnose dementia in older medical inpatients.[23]

MANAGEMENT

The management of delirium in hospital involves prevention, early diagnosis, a thorough search for and treatment of precipitating factors, supportive measures and, if necessary, medication.

Prevention

Delirium is a common and serious problem that is best prevented, although early identification of established delirium can help reduce the duration of symptoms.[24] High risk patients should be identified as soon as possible through screening at or before admission (Table 2). This is especially important prior to surgery[22] and should become routine at preoperative clinics. In a study of 100 delirious older patients O'Keeffe and Lavan showed that the coexistence of pre-existing cognitive impairment, severe illness and elevated serum urea predicted the onset of delirium in 100% of patients.[24] Similarly, Francis et al. in a study of 229 elderly patients showed that those with three or more specific risk factors (abnormal sodium, severe illness, dementia, fever or hypothermia, psycho-active drug use and uraemia) had a 60% incidence of delirium.[12] It is clear that assessment tools are required to diagnose and monitor delirium and to assess the effectiveness of treatment.

The Confusion Assessment Method (Table 5) has been developed by Inouye et al. for use by non-psychiatric clinicians.[25] It was based on the DSM-IIIR criteria and validated against ratings by psychiatrists.

Table 5. Confusion Assessment Method (CAM)[25]

1. Acute onset and fluctuating course AND
2. Inattention (e.g. easily distractible) AND
3. Disorganised thinking OR
4. Altered level of consciousness (includes drowsy or hyperalert)

Intervention studies to reduce the incidence of delirium have been based on general geriatric medical approaches, nursing care, family interventions and changes in anaesthetic practice, including perioperative blood pressure maintenance.[22] Whilst most types of intervention have been shown to be beneficial, few have been statistically significant. However, many of these studies had limitations (for example, small numbers), and most focused on treatment rather than prevention.[22] Gustafson et al. developed an intervention program for 111 elderly patients with fractured necks of femur, comprising pre- and postoperative physician assessment, early surgery, aggressive management of perioperative hypoxia and hypotension and treatment of postoperative complications.[26] They found that the incidence, severity and duration of delirium were reduced, with associated reduction in postoperative complications and length of stay. Similarly, in a study of 852 general medical inpatients over 70 years old, Inouye et al. showed that protocols to manage six risk factors for delirium (cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment and dehydration) significantly reduced the risk of developing delirium (odds ratio 0.60).[5] They also showed that once delirium was present, the intervention did not alter the severity or duration, suggesting that primary prevention of delirium is the best approach.

Investigation

Once a patient has been diagnosed with delirium it is important to establish the cause. In the elderly, delirium may be the only evidence of an underlying medical problem. A detailed history and examination should be performed, as well as a thorough review of medications,

especially psychoactive and over-the-counter preparations.[22] In particular, any new treatment commenced in hospital, especially perioperatively, should be reviewed and all unnecessary medications should be discontinued. Visual hallucinations, if present, suggest an identifiable problem such as drugs or dementia.[2] Routine blood tests should be ordered (Table 6), as well as a thorough search for infections, particularly of the chest or urinary tract, which may otherwise be asymptomatic.[3] Other targeted investigations should be performed as appropriate, including thyroid function tests, electrocardiograph, arterial blood gases, vitamin B12 and folate. The routine use of electroencephalogram (EEG), computerised tomography (CT) of the brain and lumbar puncture are controversial, due to their low specificity.[3] Although many clinicians order a CT brain in the initial investigation of delirium, the yield is low unless an intracranial cause of delirium is suspected, based on focal neurology, signs of increased intracranial pressure, anticoagulation or the development of confusion after a fall or head injury.[3,11] The specificity of the EEG falls with increasing age and dementia[27] and it is generally not indicated.[11] Lumbar puncture has a limited role due to its very low yield, unless there are specific features to suggest meningitis.[3]

Table 6. Routine investigations for delirium[3]

Urea and electrolytes (UEC)
Glucose
Full blood examination (FBE)
Calcium
Phosphate
Liver function tests (LFTs)

Supportive Measures

Supportive measures include removing factors that exacerbate the confusion, providing familiarity and optimising environmental stimulation.[18] It is important to maximise sensory perception by ensuring that patients wear their glasses or hearing aids and that nightlights are used to avoid sensory misperception.[18] Patients should be frequently reoriented and reassured by staff, while room and staff changes should be kept to a minimum.[18] Staff should use simple instructions and explanations when caring for patients and should approach gently. Ideally, patients should be placed in a private room and physical restraints and interruptions to sleep should be avoided.[22] Orientation should be maximised by the use of a clock or calendar, and by placing familiar objects at the bedside. The frequent presence of family members should be encouraged and it is important to educate and reassure them of the usually temporary nature of delirium.[18]

It is essential to aggressively prevent and treat the many complications associated with delirium.[11] When required, analgesia should be administered on a strict schedule. Fluid and food intake should be closely monitored, with early consideration of nutritional supplements or a dietitian consult.[11,18,28] Patients may require assistance with feeding or subcutaneous or intravenous fluids.[27,29] Dose reduction of diuretics and renally excreted medications may be required. Constipation should be prevented with the use of bulking agents.[11,29] Indwelling catheters should be avoided due to the risk of trauma and infection; incontinence alone is not an indication for indwelling catheter insertion.[11] Patients should be mobilised early to avoid the significant risks of atelectasis, pressure areas, contractures and deconditioning,[11,29] which all may contribute to increased morbidity and length of stay. In cases where consent is required, guardianship may be required.[18]

Pharmacological Measures

Despite supportive measures, pharmacological management of delirium to reduce anxiety and agitation may be required to ensure the safety of the patient or staff. Patients with a hypoactive delirium usually do not require sedation, although low dose antipsychotics may be required if there is evidence of distressing hallucinations.[27] Agitated or disruptive patients are often seen to interfere with the ward routine, especially at night, and requests may be made for sedation.[30]

Unfortunately, there are few well-designed trials regarding the drug treatment of delirium.[11,27] Most authors recommend antipsychotics, especially haloperidol, as first line treatment for delirium.[11] The Australian *Therapeutic Guidelines: Psychotropic* recommend benzodiazepines first line if delusions or hallucinations are not present.[28] Breitbart et al. conducted a randomised trial of 30 AIDS patients fulfilling DSM criteria for delirium.[31] Haloperidol and chlorpromazine were shown to be equally effective, while lorazepam therapy was limited by side effects.[31]

Although there are multiple medications available for the treatment of delirium, there are several principles which should be followed for all agents. Medications should ideally be given orally in low doses, with further doses administered as required. Patients requiring multiple doses should be closely monitored.[28] It is essential that any regular orders for medication are frequently reviewed for patient response, side effects, and the continuing need for the medication.[11,28]

Haloperidol is popular due to its rapid onset of action, effectiveness and low side effect profile, although it may not be appropriate for patients with pre-existing extrapyramidal gait or balance disorders. It has minimal cardiovascular toxicity but can cause extrapyramidal side effects (EPSE), akathisia (which may mimic increased agitation), tardive dyskinesia and neuroleptic malignant syndrome. These effects are more likely with increasing age, dose and duration of treatment.[11] The peak onset of action is 20 to 40 minutes after intramuscular injection and several hours after oral dosing.[29] It has a half-life of 10-19 hours and there are no active metabolites,[18] although the EPSE can potentially last longer than the drug half-life. Practice guidelines published in the *American Journal of Psychiatry* and *Therapeutic Guidelines: Psychotropic* recommend using small doses of haloperidol orally, such as 0.25-1.5 mg every four hours, although younger or more agitated patients may require higher doses at more frequent intervals.[18,28] Due to its increased potency, intramuscular haloperidol needs to be used in smaller doses, e.g. 0.125-0.25 mg.[11] It is clear that the 5 mg intramuscular doses that are often used for elderly patients in hospital settings are inappropriate. Cardiac monitoring is essential in the rare cases when a continuous infusion is required.[18]

Droperidol is an alternative agent for parenteral use. It is faster acting, more sedating, has a shorter half-life, and is possibly more effective than haloperidol with less EPSE.[18] The usual starting dose in the elderly is 2 mg.[28] However, sedation may be a problem in older patients, and there is a higher risk of hypotension, especially when given intravenously.[18]

Older phenothiazines, such as thioridazine and chlorpromazine, at doses of 12.5-25 mg initially, have also been used due to their effectiveness and sedating properties, although their popularity is declining due to cardiotoxicity. Other side effects are anticholinergic, extreme sedation and postural hypotension.[17,21,29] Chormethiazole, a short-acting sedative, may be useful for withdrawal syndromes, although prolonged therapy brings its own risk of dependence,[17] and it is not routinely used.

There have now been multiple studies and case reports showing the effectiveness of atypical agents such as risperidone, olanzapine, clozapine and quetiapine in the treatment of agitation or psychosis associated with Alzheimer's disease or dopaminergic therapy for Parkinson's disease.[32] These medications have generally been well tolerated with a lower incidence of EPSE than traditional antipsychotics.[32] However, there are only a few case reports and no trials regarding their use in delirium.[18] With further evidence these may be a useful alternative to the more traditional antipsychotics.

The role of benzodiazepines in the treatment of delirium is controversial, possibly due to the lack of data available on monotherapy.[18] The *Therapeutic Guidelines: Psychotropic* recommend 5-10 mg diazepam (2 mg in the very old or frail) orally as first line therapy to control anxiety and agitation.[28] However, the majority of authors feel benzodiazepines are less appropriate than antipsychotics,[17,29] and some even suggest that benzodiazepines are contraindicated due to their side effects and brief duration of peak effect.[22,33]

Most authors agree that benzodiazepines of choice should be short acting with no active metabolites e.g. lorazepam (half-life of 10-15 hours), and able to be given parenterally. There are few studies regarding optimal doses.[22] Oxazepam, another short acting agent, is also frequently used at oral doses of 15-30 mg, especially if there is hepatic insufficiency.[18]

When an intramuscular benzodiazepine is required for acute agitation, the *Therapeutic Guidelines: Psychotropic* recommend intramuscular midazolam, at a dose of 1.25 mg in the very old or frail.[28] Midazolam is more commonly used in palliative care and acute psychiatry and its use should be closely monitored.[28] Intramuscular absorption can be unpredictable, limiting its use in the elderly.

Although the role of benzodiazepines as first line treatment for all causes of delirium is unclear, there is no question that they are the most appropriate first line agents for drug or alcohol withdrawal where higher doses of longer acting agents are more appropriate.[18] If there is a history of recent alcohol use, regular diazepam 5-10 mg orally should be given, with thiamine 100 mg daily.[28] Benzodiazepines may also have a role in patients with known epilepsy (as most antipsychotic medications are known to lower seizure threshold), or if patients have parkinsonism.

Side effects of benzodiazepines include sedation, behavioural inhibition, respiratory depression, ataxia, falls, amnesia, depression, dependence, rebound insomnia, withdrawal and delirium.[18,34] Benzodiazepines can uncommonly cause a paradoxical response, where patients actually become more agitated and confused.[34] They should be avoided in patients with hepatic encephalopathy and respiratory insufficiency.[18]

PROGNOSIS

Although traditionally regarded as a self-limiting condition, it is now clear that there are multiple adverse outcomes associated with the development of delirium. During the hospital admission it has been shown to be responsible for functional decline, increased risk of hospital-acquired complications such as falls, pressure sores and urinary incontinence[8] and prolonged hospital stay.[6,8,20,26] At discharge, studies have shown that there is increased risk of functional decline in activities of daily living,[2,20] increased admission to long-term care facilities,[6,8,10] and increased risk of readmission.[10] Far from the short-lived inconvenience it has previously been considered, multiple studies have demonstrated the persistence of delirium post-discharge.[6,8] Levkoff et al. showed that of 125 delirious elderly patients, only 4% had complete resolution of clinical features at the time of discharge,[6] and less than 25% had resolution of all new symptoms at 3 and 6 months after discharge. Delirium has also been associated with increased mortality, although it is unclear whether this is due to underlying medical illness and co-morbidities or due to delirium itself.[2] The overall mortality of delirium approaches 30%,[20,35] with a 12-month mortality of 35-40% and 5-year mortality of 50%.[2]

CONCLUSION

Delirium is a common and serious problem that affects a significant proportion of elderly hospital inpatients. It is associated with poor outcome in terms of increased length of stay and healthcare costs, in-hospital complications, discharge functional state and destination, and mortality. The cause of delirium is usually multifactorial, with many potentially preventable precipitating factors. It needs to be appreciated that a more vulnerable patient may require only very minor insults to induce delirium. There should be an aggressive search for and correction of all potential causes, including infections and metabolic abnormalities. Medications should be thoroughly reviewed with cessation of all unnecessary agents. There needs to be a much greater emphasis on prevention and early detection of delirium. Hospital staff should be aware of those patients likely to develop delirium, and it is strongly recommended that all patients have a comprehensive cognitive assessment on admission, supplemented by an adequate pre-morbid history, particularly in those expected to undergo surgery. Known precipitants of delirium, especially iatrogenic and environmental factors, should be avoided, and staff should monitor patients carefully for signs of delirium, particularly hypo-active features. Once delirium has been identified, the appropriate supportive and pharmacological measures should be instituted. Delirium is a potentially devastating disorder that is likely to continue to increase in prevalence with the ageing of the population. However, with careful attention to patient, illness and hospital factors, it should be possible to minimise its impact on the hospitalised elderly.

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