REVIEW

Delirium

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Delirium is a common cause of mortality and morbidity in older people in hospital, and indicates severe illness in younger patients. Identification of risk factors, education of professional carers, and a systematic approach to management can improve the outcome of the syndrome. Physicians should be aware that delirium sufferers often have an awareness of their experience, which may be belied by their varying grasp of reality.

Delirium, as a concept, stretches back to the age of Hypocrates and has survived repeated attempts at definition and redefinition over the last 2000 years. It is a relatively common disorder, especially in older people with physical illness, has a high morbidity and mortality, is often under-recognised and under-treated, and provides a unique opportunity to delve into acute and florid psychiatric symptomatology, which may aid our understanding of phenomenology.¹

In this article we will attempt to bring together some current information about delirium, with a particular emphasis on diagnosis, phenomenology, management, and prevention, building on a previous review in this journal 10 years ago.² While delirium can occur at any age, it is age related and this review will reflect that emphasis, commensurate with the discipline of its authors, while recognising that the principles of investigation, management, and prevention are age independent. The information base for this article consisted of a Medline search with “delirium” as the MeSH heading (from 1988, yielding 1465 references), the review by Taylor and Lewis, from 1993,² and a recent publication.³

TERMINOLOGY

The core features of delirium include altered consciousness, global disturbance of cognition, fluctuating course with a rapid onset, perceptual abnormalities, and evidence of a physical cause. Table 1 outlines the criteria for delirium listed in the current *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR).⁴ These have remained unchanged since the previous version (DSM-IV).⁵ They differ from DSM-III-R⁶ in that they include clouding of consciousness rather than inattention as a core feature. The richness of the phenomenology of delirium is reflected in the *International Classification of Diseases* (ICD 10)⁷ (table 2). For example, impairment of abstract thinking is a core criterion, reflected in the term “confusion,” which was introduced in the 19th century⁸ and pragmatically defined by Lishman⁹

as an “inability to think with one’s customary clarity and coherence.”

DSM-IV recognised the coexistence of delirium and dementia, and DSM-IV-TR includes a code for recording the presence of delirium arising in the course of dementia. The ICD system acknowledges the existence of a minority of people in whom the delirium is of more than six months’ duration, based on observations such as those of Levkoff *et al*,¹⁰ and on reports of prolonged delirium in patients with right middle cerebral artery syndrome observed by Mori and Yamaduri.¹¹

CLINICAL FEATURES

These have been summarised by Taylor and Lewis² and can be described under the headings *impairment of consciousness; thinking; memory; psychomotor behaviour; perception; and emotion*.⁹ The onset is usually rapid and the course diurnally fluctuating, usually lasting less than six months. The clinical picture is so characteristic that a confident diagnosis of delirium can be made even if the underlying cause is not firmly established. In addition to a history of an underlying physical or brain disease, evidence of cerebral dysfunction (such as an abnormal electroencephalogram (EEG), usually but not invariably showing a slowing of the background activity) may be required if the diagnosis is in doubt.

Impairment of consciousness characteristically fluctuates often, with a deterioration in the evening when environmental stimulation is least. Awareness is impaired and alertness to the environment can either be falsely increased or lowered. Characteristically, in delirium tremens a hyperalert state is seen, with the patient attending to all external stimuli without discrimination. Very minor degrees of impaired consciousness can occur, such as difficulty in estimating the passage of time (tested by asking the patient to estimate how long the interview has lasted). Disordered attention is another key clinical feature of delirium. At interview, the patient appears to have impaired concentration and distractibility. Simple tests of concentration include: serial 7s where the patient counts backwards in sevens from 100; spelling the word “world” backwards; saying the months of the year backwards, or counting down from 20 to 1. The interpretation of these assessments should take into account the patient’s age and educational attainment.

The sleep/wake cycle is almost always disturbed, with marked periods of drowsiness, sleep in the day, and insomnia at night. Excessive dreaming with persistence of the experience into wakefulness is common—experiences which

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Table 1 DSM-IV-(Text Revision) criteria for delirium ⁴	
(a)	Disturbance of consciousness (that is, 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 developed over a short period of time (usually hours to days) and tends to fluctuate during the course of the day
(d)	Where the delirium is due to a <u>general medical condition</u> – 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
	Where the delirium is due to <u>substance intoxication</u> – there is evidence from the history, physical examination, or laboratory findings of either 1 or 2: 1. The symptoms in criteria (a) and (b) developed during substance intoxication 2. Medication use – aetiologically related to the disturbance
	Where the delirium is due to <u>substance withdrawal</u> – there is evidence from the history, physical examination, or laboratory findings that the symptoms in criteria (a) and (b) developed during or shortly after the withdrawal syndrome
	Where delirium is due to <u>multiple aetiologies</u> – there is evidence from the history, physical examination, or laboratory findings that the delirium has more than one aetiology (for example, more than one aetiological general medical condition, a general medical condition plus substance intoxication, or medication side effects)
(e)	Delirium not otherwise specified – this category should be used to diagnose a delirium that does not meet criteria for any of the specific types of delirium described. Examples include a clinical presentation of delirium that is suspected to be due to a general medical condition or substance use but for which there is insufficient evidence to establish a specific aetiology, or where delirium is due to causes not listed (for example, sensory deprivation)

have also been described in Lewy body dementia where there is a profound cholinergic deficit, and the associated dopaminergic deficit may underlie the delirium-like states that are a characteristic feature of that condition.^{12 13}

Thinking is progressively disturbed. Initially, speech is slowed or speeded up, with the capacity to make judgements and to grasp abstract concept becoming more obviously impaired as the delirium proceeds. Incoherent and disorganised thoughts supervene with the progression of the illness. The patient may seem to be cut off from the external world, and increasingly occupied with inner thoughts and experiences, which are often abnormal in nature.

Disturbance of memory is another cardinal feature of delirium—short term, immediate, or working memory is demonstrated by tests of attention such as digit span, which examines immediate memory over a period of seconds; long term anterograde memory relates to a period of minutes (for example, the ability to remember a fictitious name and address after two or five minutes); and long term memory relates to recalling days, weeks, and months.¹⁴ One of the most obvious examples of impairment of immediate short term memory is disorientation in time and place, experience suggesting that disorientation in time, in mild impairment, is lost before the sense of place. The failure to track time and the intermittent nature of some of the deficits in delirium can sometimes result in mixing of memories and false recall, with simple rationalisations resulting from an attempt to reconcile experiences.¹⁵

Table 2 ICD 10 diagnostic criteria for delirium ⁷	
For a definite diagnosis, symptoms, mild or severe, should be present in each of the following areas:	
(a)	Impairment of consciousness and attention (ranging from clouding to coma; reduced ability to direct, focus, sustain and shift attention)
(b)	Global disturbance of cognition (perceptual distortions, illusions and hallucinations – most often visual; impairment of abstract thinking and comprehension, with or without transient delusions, but typically with some degree of incoherence; impairment of immediate recall and of recent memory, but with relatively intact remote memory; disorientation for time as well as in more severe cases for place and person)
(c)	Psychomotor disturbances (hypo- or hyperactivity and unpredictable shifts from one to the other; increased reaction time; increased or decreased flow of speech; enhanced startle reaction)
(d)	Disturbance of the sleep/wake cycle (insomnia or, in more severe cases, total sleep loss or reversal of the sleep/wake cycle; daytime drowsiness; nocturnal worsening of symptoms; disturbing dreams or nightmares, which may continue as hallucinations after awakening)
(e)	Emotional disturbances, for example, depression, anxiety or fear, irritability, euphoria, apathy or wandering, perplexity

There may be disturbances of psychomotor behaviour, with little spontaneous activity when the disturbance is mild, although inner experiences such as hallucinations or delusions may result in quick reactions, as in delirium tremens. Purposeless behaviour, such as groping or picking, can occur, with complex stereotyped movements and rarely, the mimicking of a work pattern—occupational delirium.¹²

Lipowski¹⁶ described the hypoactive and hyperactive syndromes, while recognising that a mixed form could occur. Abnormalities of perception are usual and may favour the diagnosis of the hyperactive form of delirium. Initial changes may include disturbances of the perception of shape (micropsia or macropsia) with depersonalisation, derealisation, illusions, and hallucinations—commonest in the visual mode, consisting of flashes of light—but may be fully formed to encompass fantastic scenes of people and animals. Lilliputian hallucinations (where people and objects appear small) are characteristic. Florid and frightening experiences are typical of delirium tremens and of the toxic effects of lysergic acid diethylamide (LSD) or intoxication with cocaine.¹⁷ Visual hallucinations in delirium are more often associated with multiple aetiological factors than is the presence of either auditory hallucinations or delusions,¹⁸ and length of hospital stay is significantly longer in the hypoactive variant.¹⁹

The description of hypoalert and hyperalert subtypes has implications for the detection of delirium (in that patients who are floridly disturbed and hyperactive are more likely to attract a diagnosis than those who are quiet and mildly confused). A factor analytic study supports this subtyping of delirium,²⁰ although the same investigators found few differences in terms of outcome or aetiology.²¹

EPIDEMIOLOGY

Challenges in case identification and sample bias result in variations in estimates of the prevalence and incidence of delirium. The Eastern Baltimore mental health survey has yet to be bettered in providing information about the prevalence in the community of delirium.²² This documented a significant increase in the prevalence of delirium with age: 0.4% in those over the age of 18, 1.1% of those over the age of 55, and 13.6% in those over 85, a figure similar to a more recent study in older people in Finland.²³

In hospital populations most studies report prevalences of between 10% and 20% for medical inpatients. Incidence rates of delirium in medical inpatients range between 5% and 10% (the length of admission being the unit of time²⁴), with one study reporting a rate of over 50% in a mixed group of medical and surgical patients over the age of 60.²⁵ Both the prevalence and the incidence of delirium are particularly high in surgical inpatients, especially in people undergoing cardiothoracic and emergency orthopaedic procedures,²⁶ cataract removal,²⁷ or in intensive care units. Rates in cancer units have also been described, with prevalence and incidence rates of 42% and 45%, respectively.²⁸

RISK FACTORS FOR DELIRIUM

Risk factors in delirium can be categorised according to whether they are predisposing factors (table 3) or more immediate precipitating factors (table 4),²⁹ although a combination of the two may be present. For example, a chest infection (precipitating factor) may be sufficient to cause an episode of delirium in a person with pre-existing cognitive impairment (predisposing factor) but not in a person who is cognitively normal.

Age

It is well accepted that age is a risk factor for the development of delirium, but it is not easy to quantify how much of the association is independent of physical frailty, one study suggesting that being more than 80 years old was an independent risk factor for the development of delirium, with an odds ratio of 5.2,³¹ but independence of age from physical frailty has not been observed in other studies.³² The effects of increased age on the tendency to develop delirium are complex and include the assumed loss of intellectual and physical reserve and the narrowing of mental adaptability. Changes in the metabolism of drugs with age may increase the susceptibility of a person to side effects, particularly in the presence of pre-existing cerebral disease.

Lipowski¹⁶ describes the effect of age throughout the life cycle on the likely aetiology. Bacterial meningitis and HIV/AIDS are commoner in childhood or young adulthood and may cause delirium, whereas these infections are rare in old age. Similarly, drug intoxication in youth is more likely to be caused by recreational drugs, whereas in older people drugs causing delirium are more likely to have been prescribed. A list of drugs that may cause delirium is given in table 5.

Dementia

Dementia is an important risk factor, a meta-analysis suggesting a relative risk of 5.2.³⁵ A later age of onset of vascular dementia was associated with an increased risk of delirium compared with early onset Alzheimer's disease and other dementias.³⁶⁻³⁷ Pre-existing cognitive impairment is a known risk factor for the onset of a delirium, and the two

Table 3 Predisposing factors in delirium³⁰

Older age
Male sex
Visual impairment
Presence of dementia
Severity of dementia
Depression
Functional dependence
Immobility
Hip fracture
Dehydration
Alcoholism
Severity of physical illness
Stroke
Metabolic abnormalities

Table 4 Precipitating factors in delirium³⁰

Narcotics
Severe acute illness
Urinary tract infection
Hyponatraemia
Hypoxaemia
Shock
Anaemia
Pain
Physical restraint
Bladder catheter use
Iatrogenic event
Orthopaedic surgery
Cardiac surgery
Duration of cardiopulmonary bypass
Non-cardiac surgery
Intensive care unit admission
High number of hospital procedures

Only independent associations are listed.

occur together in between 22% and 89% of people aged more than 65 years.³⁸ The presence of delirium during hospital admission increased the risk of developing dementia and of mortality (relative risks 3.2 and 1.8, respectively) in 186 patients followed up for just under three years.³⁹

Physical and mental health

Physical and mental ill health is associated with an increased risk of delirium. Physical impairment has been documented as an important factor in the genesis of delirium in surgical inpatients undergoing elective surgery.⁴⁰ Evidence of biochemical abnormalities with low levels of sodium and potassium and high urea reflects the severity of the underlying precipitating cause, as does a low body mass index and sensory impairment.³⁵⁻⁴¹ Other risk factors include sex (men affected more than women³⁵⁻⁴⁰), depression,³⁵ alcoholism, and bladder catheterisation.⁴² In a study aimed at prospectively identifying delirium and establishing a predictive model for its development, five factors were included in the model—use of physical restraints, malnutrition, adding more than three drugs during admission, bladder catheterisation, and any iatrogenic event.⁴² Others which contributed to the development of delirium but which were not included were: being out of bed less than once a day⁴²; a longer than 12 hour wait in an emergency department; respiratory insufficiency; dehydration; visual impairment; cognitive impairment; impaired renal function; and more severe systemic illness.⁴²

AETIOLOGICAL FACTORS

The aetiology of delirium is usually multifactorial in older people, but a single aetiology can often be more clearly identified—for example, alcohol withdrawal or substance misuse. Table 3 lists those factors that have been identified as predisposing to delirium, and table 4 lists those that independently precipitate delirium.³⁰ An important cause in older people is the distancing of a person from their glasses and hearing aids when they are admitted to hospital.³² Unrecognised faecal impaction and urinary retention should be considered as contributing causes,³⁰ and anecdotal reports have documented the resolution of symptoms with treatment of these conditions.⁴³ Experienced nurses are well versed in this, and the confused elderly patient who leans to the left should first have an examination to exclude faecal impaction in the descending colon. Delirium is universal following coma caused by head injury (including focal injury) and may last from a few minutes to some weeks; it is particularly likely to occur on recovery of consciousness following acute brain injury. Symptoms may vary and be florid.⁹

Table 5 Drugs that may cause delirium

Drugs with high anticholinergic activity	Other drugs associated with delirium	Over the counter drugs
Cimetidine	Benzodiazepines	Diphenhydramine (eg, Benlyn)
Prednisolone	Narcotics	Triprolidine (eg, Actifed)
Theophylline	Antiparkinsonian agents (eg, L-dopa)	Chlorpheniramine (eg, Piriton)
Tricyclic antidepressants (eg, amitriptyline)	Non-steroidal anti-inflammatory drugs	Promethazine (eg, Night Nurse, Phenergan)
Digoxin	Laxatives	Anti-diarrhoeal agents (containing belladonna)
Nifedipine	Antibiotics	Irritable bowel syndrome treatments with hyoscine (eg, Buscopan)
Antipsychotics (eg, chlorpromazine)	Haloperidol	
Furosemide		
Ranitidine		
Isosorbide dinitrate		
Warfarin		
Dipyridamole		
Codeine		
Diazepam (triamterene with thiazide)		
Captopril		

Adapted from Mintzer and Burns³³ and Tune *et al.*³⁴

PATHOPHYSIOLOGY

Two main neuronal networks underlie attention, the first being diffuse, involving thalamic and bihemispheric pathways, and the second being focal, involving frontal and parietal cortex in the right hemisphere.⁴⁴ There is widespread disruption of higher cortical function in delirium, with evidence of dysfunction in several brain areas—subcortical structures, brain stem and thalamus, non-dominant parietal lobe, fusiform, and pre-frontal cortices, as well as the primary motor cortex.⁴⁴ Right sided lesions have been suggested as important in the final common pathway for delirium^{45–47} and right cerebral artery and middle cerebral artery infarctions are associated with an agitated delirium.^{11–48}

There is evidence for a cholinergic deficiency in delirium.⁴⁷ First, risk factors for delirium include metabolic and structural brain abnormalities associated with decreased acetylcholine activity. Second, high serum anticholinergic activity is associated with severity of delirium.^{33–41–46} Third, there is anecdotal evidence to suggest that anticholinesterase drugs used in the treatment of Alzheimer's disease may also be of benefit in treating the symptoms of delirium.⁴⁹ Gorwood⁵⁰ reported an association of the dopamine transporter gene (nine copy repeat) in 120 alcohol dependent patients and the presence of alcohol withdrawal fits and delirium tremens.

THE SUFFERER'S EXPERIENCE OF DELIRIUM

Accounts suggest that patients may recall the experience of delirium more vividly than might be supposed from the profound disturbances in consciousness and awareness described above.⁵¹ Crammer⁵² describes a personal experience of delirium caused by renal failure, but his symptoms may have arisen from fragmented memories of recalled perceptual disorders rather than recall of contemporaneous experiences.¹ Two reports of 19 and 40 patients, respectively,^{53–54} found that 80% recalled their experience (often in great detail) without prompting, and experienced as reality unreal impressions of all kinds. The similarity between the experience of delirium and the recall of dreams has been noted. These observations may have implications for the management of delirium—for example, in the use of reassurance.

MANAGEMENT

Delirium is a medical emergency, and prompt attention to obvious precipitating factors should be the first aim of management. Four key steps in management have been

described⁵⁵—addressing the underlying causes, maintaining behavioural control, preventing complications, and supporting functional needs. In practice, the commonest causes are drugs, infections, fluid balance and metabolic disorders, cerebral hypoxia, pain, sensory deprivation, urinary retention, and faecal impaction (especially in people with pre-existing dementia). Many drugs may cause delirium, but particularly psychotropic agents. Anticholinergic drugs (or drugs with anticholinergic side effects like tricyclic antidepressants) are particularly potent causes, and a careful drug history is essential. A raised white blood cell count or specific symptoms (such as a fever) may direct attention towards an infection, one caveat being that asymptomatic bacteriuria is common in older people, and the finding of a urinary tract infection does not necessarily mean that it is the cause of the symptoms. Dehydration can easily be treated with subcutaneous fluids.⁵⁶ Congestive cardiac failure is another common cause of delirium, particularly in older people, its deleterious effect being mediated through cerebral hypoxia. Severe pain is a relatively unrecognised and readily treatable cause of delirium and is particularly associated with elective surgery.⁵⁷

Environmental interventions

While there are no randomised controlled trials of interventions such as noise control, light intensity, reassurance, and stimulus modification, these environmental manipulations are still recommended as an integral part of the management of delirium.⁵⁸

Drug treatment

A careful analysis of the risks and benefit of drug treatment should be carried out before embarking on treatment. In some patients, the cessation of “deliriogenic” drugs may be effective. Early identification of the symptoms of delirium results in a reduced use of medicines.⁵⁹ Antipsychotic drugs are the mainstay of treatment and are effective in all types of delirium. Except in cases of delirium caused by alcohol or sedative hypnotic withdrawal, neuroleptics are the treatment of choice, resulting in improvement before elucidation of the underlying cause.⁶⁰ Haloperidol in doses of 0.5 to 10 mg a day (intramuscularly or intravenously) improves most symptoms of delirium and is especially effective in the control of more severely disturbed and aggressive patients. Meagher⁶¹ suggested up to 100 mg of haloperidol intravenously for over 24 hours—a regimen that has been criticised and is certainly inappropriate for older patients.⁶² In many older patients, oral drug treatment is

accepted and obviously preferable to a parenteral route. Formulations such as liquid or velotabs are available for risperidone and olanzapine.

The adage in psychopharmacology in older people is "start low, go slow" and, if the patient's clinical condition allows, starting doses of 0.5 mg a day of haloperidol and risperidone and 2.5 mg a day of olanzapine are appropriate. Atypical antipsychotics such as olanzapine and risperidone have been used with success, although no controlled trials have been carried out and they are only available in the oral form.^{63, 64} Benzodiazepines may be particularly helpful where the delirium is caused by withdrawal of alcohol or sedatives. Benzodiazepines with rapid onset and short duration of action, such as lorazepam, are preferred and may be given orally or intravenously, with a recommended upper limit of 2 mg intravenously every four hours.⁶¹

Other treatments such as anticholinesterase drugs have been used with some success,⁴⁹ and serotonin antagonists such as trazodone may be helpful.⁶⁵

PREVENTION OF DELIRIUM

Prevention of delirium, particularly in older people, is now a reality. Education of medical and nursing staff can increase the recognition of the syndrome⁶⁶ and knowledge of risk factors is probably the most important information to have. The fact that delirium is often multifactorial in origin necessitates a broad intervention strategy. Many studies have attempted to prove the effectiveness of interventions in various different settings but have suffered from being underpowered, non-blinded, or without identified and valid outcome measures.

Any consideration of the prevention of delirium should be influenced by an appreciation that there are predisposing and precipitating factors for the illness, and that the traditional view that any acute illness can be the cause of the syndrome ignores the fact that delirium not infrequently arises when a person is already in hospital. If there is too fulsome a concentration on the acute problem, the opportunity to intervene to ameliorate other risk factors may be missed.⁶⁷ With this in mind, it makes sense that interventions should address a range of problems rather than single issues. Seventeen trials have been carried out assessing interventions that purport to prevent delirium in hospital inpatients, ranging through psychiatric assessment and support, specialist nursing care, different types of anaesthesia, patient controlled anaesthesia, specialist assessment (including cognitive monitoring), and specific care protocols.⁶⁶ Few have been randomised or properly blinded. Inouye *et al* reported the results of a major trial on patients aged 70 years and over admitted to the Yale New Haven teaching hospital.²⁹ They matched 852 patients before randomisation to a standardised protocol for the management of six previously defined risk factors⁴²—cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration. They found that 9.9% of the intervention group developed a delirium compared with 15% of the control group (that is, the intervention had to be provided to 19 patients to prevent one developing delirium). Both the number of the episodes of delirium and the number of days of illness were significantly reduced in the intervention group. A health economic analysis has shown that the intervention was cost-effective for those regarded as at intermediate risk of developing a delirium.⁶⁸

CONCLUSIONS

Delirium is a common cause of mortality and morbidity in older people in hospital, and indicates severe illness in

younger patients. Identification of risk factors, education of professional carers, and a systematic approach to management can improve the outcome of the syndrome. Physicians should be aware that delirium sufferers often have an awareness of their experience, which may be belied by their varying grasp of reality.

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