

DELIRIUM IN ADVANCED CANCER

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Abstract

Delirium is a distressing and under-diagnosed syndrome of acute alteration in mental state. It occurs frequently in patients with advanced cancer and is often associated with a worsening of prognosis and difficult challenges in symptom management. Given its associations with older age, recognition and management of delirious patients are likely to become an even more important aspect of oncological practice in the future. The potential for prevention of delirium is being studied, and protocols which involve modifications in hospital care, in addition to screening and rapid identification and treatment of precipitants, may reduce the burden of the condition. However, such approaches require further study and validation in an advanced cancer population. Routine use of appropriate and validated screening tools is a low burden strategy which is likely to improve diagnosis, care and understanding of delirium. The evidence to guide pharmacological management is not strong. Well designed clinical trials are urgently needed in order to improve supportive care outcomes for delirious patients and to clarify the role of antipsychotic and other medications in symptomatic management.

For cancer patients and their families, delirium is a devastating, frequent and often under-recognised complication of their disease.¹ Delirium is a complex neuropsychiatric syndrome causing acute alteration in mental status.

Core features of the condition as described in the Diagnostic and Statistical Manual IV² are:

- disturbed consciousness, with reduced ability to focus, sustain or shift attention

- altered cognition (memory, orientation, language) or the development of a perceptual disturbance that is not better accounted for by dementia

- disturbance develops over hours to days and tends to fluctuate during the course of the day

- there is evidence of an aetiological cause.

There is no pathognomonic feature of delirium. Presentations include diverse cognitive and non-cognitive symptoms (table 1).³

Table 1. Delirium symptomatology

Features	Hypoactive delirium	Hyperactive delirium
Disturbance of arousal	Hypoaroused, hypoalert, drowsy, reduced awareness of surroundings.	Hypervigilant, distractible, easy startling.
Temporal onset	Abrupt onset, fluctuating course.	Abrupt onset, fluctuating course.
Perceptual disturbance	Visual hallucinations, misperceptions, illusions.	Visual hallucinations, misperceptions, illusions.
Disturbance of thought content	Paranoid delusions. Vague and not systematised.	Persistent thoughts and delusions more common in hyperactive delirium.
Mood symptoms	Sad, depressed irritable, mood labile, disinhibition.	Mood lability – may include a wide range of mood states from combative or impatient through to euphoric.
Psychomotor activity	Hypoactive, withdrawn, quiet.	Restless, agitated.
Past psychiatric history	Previous episode of delirium may be present.	Correlated with alcohol and/or drug withdrawal. Previous episode of delirium may be present.
Sleep wake disturbance	Increased daytime sleepiness.	Prominent sleep-wake cycle disturbance, nightmares.
Neurological examination	Asterixis, frontal release signs may be elicited; EEG may show slowing.	Asterixis, frontal release signs may be elicited; EEG may show slowing.

The existence of hyperactive, hypoactive and mixed subtypes is clinically significant, as delirium can range from subtle hypoactivity or altered mood through to dramatic onset of psychosis. Hypoactive delirium is a diagnosis which is frequently missed, but nonetheless causes significant distress to patients and may be associated with worse outcomes than hyperactive presentations.^{4,5} Of all the potential features of delirium, inattention is crucial to the diagnosis, occurring in 97-100% of cases.⁶

Despite the frequency and severity of delirium, it is not well studied and current clinical management strategies lack a robust evidence base. This review addresses evolving understandings of the condition, potential for prevention, outcomes of delirium and how it impacts on prognosis, clinical strategies for screening and assessment, and emerging clinical approaches to pharmacological management.

Epidemiology

The prevalence of delirium at admission to hospital for patients with advanced cancer has been estimated at between 28% and 48%, rising to around 90% in the last days of life.⁷ However, evaluation of the degree of error in recognition and diagnosis in such settings has been limited.^{8,9} Due to poor ascertainment of delirium in routine clinical practice,¹⁰ these prevalence figures are likely to underestimate the true burden of the problem.

Delirium is conceptualised as having predisposing and precipitating features.^{11,12} The threshold for an episode relates to the interplay of these factors. Vulnerable patients with many predisposing factors, particularly the elderly, require fewer, less noxious precipitants to trigger an

Pathophysiology – current understandings

The physiological basis of delirium is not well understood, and the syndrome is likely to be the final common pathway of a diverse group of pathophysiological mechanisms.²⁹

The best studied hypothesis proposes that delirium can be caused by relative neurotransmitter imbalance, with decreased cholinergic transmission and corresponding overactivity of dopaminergic pathways. Central nervous system cholinergic pathways are involved in arousal, attention, memory and sleep, all functions affected in delirium. Supporting evidence for this model includes demonstration of a dose response relationship between exposure to anticholinergic medications and delirium in vulnerable populations and the discovery of endogenous anticholinergic activity in sera and cerebrospinal fluid of delirious patients.³⁰⁻³² This hypothesis also suggests a theoretical link with the cholinergic deficit model for dementia, perhaps accounting for the frequent co-occurrence of these two conditions. Finally, the model provides theoretical support for the use of dopamine blocking neuroleptic agents as treatments for delirium. There is also evidence for dysregulation of other neurotransmitter pathways in delirium. These include serotonin, melatonin, cortisol, endogenous opioids and glutamate.³³⁻³⁵

The role of inflammatory mediators and cytokines within the delirium process are also being explored.³⁴

episode of delirium. In clinical practice, the epidemiology is consistent with this model, with delirium occurring predominantly in older patients or the most severely ill. Also increasingly recognised is the overlap with dementia, with both pre-existing cognitive impairment predisposing to delirium occurrence and ongoing cognitive change common after delirium resolution.¹³⁻¹⁷ As one of the most important predisposing factors is cognitive impairment, delirium has been identified as a “geriatric syndrome.”¹⁸

Advanced cancer brings specific vulnerability and precipitating factors for delirium. Chemotherapy and its complications are potential precipitants,¹⁹ while some treatments, such as stem cell transplants and high dose interferon, are recognised as being associated with a particularly high risk of delirium.²⁰⁻²² Given that improved treatment of cancer has led to more frequent and prolonged active treatment of elderly patients, who may have pre-existing cognitive fragility or even dementia, these distinct epidemiologies of delirium – as geriatric syndrome and as comorbid with cancer – can be expected to increasingly overlap in oncological practice in future.

Observational studies in palliative care settings have shown that, when carefully screened for, the hypoactive subtype predominates – occurring in as many as 86% of patients with delirium.²³ A series of studies looking at potential for delirium reversibility in palliative care have demonstrated that up to 50% of cases may be reversible.^{9,24,25} However, in those patients in whom delirium persists, mortality is higher and outcomes are worse.^{9,25,26} The impact of hospital practices on the incidence of delirium have led to the suggestion of using delirium as a marker of quality of care.^{27,28}

The evidence related to these is less well established, however these mechanisms may potentially explain how diverse (and sometimes seemingly trivial) precipitants without obvious link to central neurotransmission (for example mild urinary tract infection), might trigger the often disproportionate and global neuropsychiatric response of delirium. Another important area of research attempts to identify biomarkers and/or physiological predictors of delirium. Attention has focused on inflammatory mediators such as interleukins IL-6 and IL-8, markers of neuronal injury such as neuron-specific enolase and S 100 beta, presence of APOE4 genotype, cerebral blood flow, neuropeptide Y, brain-derived neurotrophic factor and glutamate transport.³⁶ A consistent picture has yet to emerge from the literature.

Modifiable versus non-modifiable factors

In considering the potential for both prevention and reversibility of delirium, distinguishing between modifiable and non-modifiable factors is useful (table 2). The presence of numerous non-modifiable predisposing factors defines a high risk population. It is suggested that these patients require routine screening for cognitive changes, with a high level of clinical alertness for onset of delirium, careful attention to their environment, to minimising polypharmacy, and rapid identification and treatment of reversible problems.³⁷

Table 2. Risk factors for delirium

Non-modifiable individual factors	Potentially modifiable individual factors	Institutional factors ³⁸
Age >65	Treatable medical condition (eg. infection, metabolic syndrome, anaemia, uncontrolled cardiovascular or respiratory condition)	Number of room changes
Known/documentated cognitive impairment	Psychoactive medications: <ul style="list-style-type: none"> ■ opioids ■ benzodiazepines ■ steroids ■ SSRIs ■ tricyclic antidepressants ■ neuroleptics 	Absence of clock or watch
Severe underlying illness eg. advanced cancer, trauma, end-stage organ failure	Anticholinergic load	Absence of usual visual aids
Intracranial disease / damage: <ul style="list-style-type: none"> ■ primary and metastatic brain neoplasms ■ leptomeningeal metastases ■ paraneoplastic encephalitis ■ cerebrovascular accident ■ postictal state ■ CNS radiotherapy 	Poorly treated pain	Absence of a family member
Low albumin	Dehydration	Use of restraints (physical or pharmacological)
Post-operative state	Malnutrition	Catheterisation

It is important to recognise that most cases of delirium, particularly in older patients, are likely to have multiple precipitants.^{39,40} In a study of causes of delirium in a cohort of patients with advanced cancer, a median of three precipitants was identified for each episode (range 1 – 6). Potential for reversibility was associated with specific aetiologies. Episodes related to opioids or other psychoactive medications (corticosteroids and benzodiazepines), or dehydration, were more likely to be treatable, while delirium attributed to hypoxic encephalopathy or metabolic causes was associated with refractoriness.⁹ Managing psychoactive medication and delirium is a fine balance between adequate symptom control and contribution to delirium. While medications used for supportive care are often implicated in the onset of delirium, there may be limited alternatives to these if they are being used to treat distressing symptoms such as pain. Strategies such as opioid rotation,⁴¹ gentle hydration, and attempting to select adjuvant medications with less psychoactive or anticholinergic properties, or use of more specific therapies such as radiation for bone pain, may all be used to try to alter the balance between analgesia and adverse effects. Pharmacovigilance is especially required in caring for the deteriorating patient.

Potential for preventability

Evidence has been accumulating in relation to the potential preventability of delirium. A number of factors which may be amenable to primary prevention approaches have been identified (see box).⁴²

Elements of multicomponent interventions to prevent delirium

- Modifying processes of care: minimising room changes and staff changes; providing regular re-orientation to time and place and access to a clock; ensuring cognitive stimulation; ensuring access to aids such as glasses, hearing aids and dentures.
- Minimisation of polypharmacy - medication review
- Focus on maintaining mobility, hydration and nutrition, preventing constipation and promoting natural sleep.
- Treat infection and other precipitants.

Clinical trials testing this concept have shown that multicomponent interventions addressing delirium risk factors may reduce the incidence of delirium by up to a third, while in some studies there were

reductions in severity of delirium.³⁷ These findings have led to considerable interest in developing clinical protocols for primary prevention of delirium, focusing on minimisation of risk factors. A multicomponent intervention protocol addressing major geriatric delirium risk factors (sleep deprivation, cognitive function, reduced mobility, visual impairment, dehydration) using a case control study method (N = 852) reduced the incidence of delirium (9.9% v 15% p = 0.02), the number of delirium episodes (62 v 90 p = 0.03) and the total number of days of delirium (105 v 161 days p = 0.02).⁴²

The possibility of using neuroleptics and other medications for prophylaxis for delirium is also being explored, however has not yet shown definitive results.⁴³⁻⁴⁵ Studies relating to delirium prevention have so far been performed in aged care and orthopaedic surgical populations almost exclusively. The extent to which similar benefits could be expected if prevention strategies were implemented in in-patient cancer care has not been studied. As in aged care, for patients with advanced cancer the balance of predisposing and precipitating factors and the extent to which the dominant precipitants are ultimately reversible, determine the outcomes. For example, risk factors identified in a population of patients receiving haematopoietic stem cell transplant included poor cognitive function, increased creatinine, type of malignancy, total body irradiation, older age and history of drug or alcohol misuse, most of which are not easily reversible.^{20,46} However, any strategies that raise the threshold at which delirium may be triggered may still deliver overall benefits across a

population.

Screening and diagnostic tools

Under-diagnosis of delirium is a significant barrier to improvements in care and to improving our understanding of the problem. Identifying acute alterations in mental state often does not carry the sense of clinical urgency which the problem merits. Delirium is frequently described with one of a multitude of synonyms which have no diagnostic specificity – ‘confused,’ ‘agitated,’ ‘muddled’ or ‘drowsy’. Under-diagnosis and under-treatment go hand in hand. As the diagnosis of delirium is a clinical one, and its presentation is so varied, healthcare providers need to maintain a high index of suspicion, especially in high risk patients. This is particularly true for the hypoactive subtype, which may commonly be mistaken for depression.^{8,47}

Screening for baseline cognitive function and acute alterations in mental state have been shown to improve outcomes for patients with delirium in terms of length of hospital stay and mortality.⁴⁸ However, there are challenges in using some of the available cognitive assessment tools, especially in unwell patients with advanced cancer. For instance the Mini-Mental Status Examination is widely used, but provides a non-specific assessment of cognitive function, and is physically difficult for sick patients to complete. Several tools which are more specific for delirium and less burdensome for both patients and staff have been developed (table 3), and can potentially be recommended for routine clinical use in cancer care settings.¹⁹

Table 3. Cognitive assessment tools

Tool	Description	Comments
Confusion Assessment Method (CAM) ⁴⁹	A brief four-item tool, validated in a variety of settings for the screening and diagnosis of delirium.	Despite good psychometric properties when used by trained clinicians, the tool is less specific if used by those who are untrained. Versions of the CAM exist for ICU patients. Does not include an item to specifically capture hypoactive delirium.
Memorial Delirium Assessment Scale (MDAS) ⁵⁰	A 10 item instrument for diagnosis and monitoring severity of delirium.	Developed and validated in cancer care settings. The score can also be used as a measure of the degree of confidence with which a diagnosis of delirium can be made. Scoring is standardised, but the assessment is intrusive and may be impossible to complete with an unwell patient.
Blessed Orientation Memory and Concentration Test (BOMCT) ⁵¹	A brief oral test which is able to be used both for screening and monitoring severity of delirium.	Excellent psychometric characteristics. Less burdensome than the Mini-Mental State Examination in a cancer population.
Nursing Delirium Screening Scale (NuDESC) ⁵²	An observational five-item scale useful for both screening and monitoring severity.	Sensitivity 85.7% and specificity 86.8% in a palliative care validation study. High degree of clinical utility and acceptability to staff, and a non-intrusive assessment.

Management strategies for delirium symptomatology

As well as appropriate non-pharmacological management, patients experiencing delirium symptoms may require pharmacological treatment to reduce distress and prevent injury to themselves or caregivers. Whether such treatment may also modify the underlying condition is not yet well established by evidence, despite an increase in trials undertaken in recent years. Many are methodologically flawed (non-blinded, not placebo controlled or not adequately powered).^{16,45} Both typical and atypical antipsychotics have been studied, and most evidence is from retrospective or open label studies and case reports. While these studies appear to support a clinical role for antipsychotic medications, due to lack of any placebo arm demonstrated improvements cannot be clearly separated from the natural history of delirium itself.⁵³ Benzodiazepines are frequently given in caring for delirious patients to reduce symptoms of agitation, but no evidence supports their use in delirium, except if due to benzodiazepine or alcohol withdrawal, and a single trial has been done which suggests they may worsen cognitive function.⁵⁴

Therefore pharmacological management of delirium, including which drug to use and how to titrate, continues to be based on expert opinion, and continues to be controversial. There is enormous variation in practice between different disciplines in medicine and different settings of care.⁵⁵ Due to the fluctuating nature of delirium, well designed, adequately powered, randomised placebo-controlled trials are required.⁵⁶ Studies designed to separate the impact of various antipsychotics and other medications on distressing target symptoms versus overall delirium severity, as well as the impact on duration and mortality outcomes from delirium, are greatly needed. They should be able to ascertain the frequency and effect of any adverse effects of these medications in patients with advanced cancer, or perhaps on various specific aetiologies of delirium.

Outcomes for patients with delirium

For patients with advanced cancer, even with careful management of all reversible precipitants, delirium is a generally reliable marker of poorer prognosis.³ Hypoactive subtype and severity of cognitive impairment are correlated with worse outcomes, and for refractory delirium the life expectancy in advanced cancer is likely to be days or weeks. One study in a palliative care unit showed that for patients with reversible delirium (n=33) the mean time to death was 39.7 days, while for refractory delirium (n=88) it was 16.8 days.²⁶ The costs of delirium are substantial – both to the patient and to health services. Although not quantified for cancer patients specifically, these include loss of ability to communicate and reduced quality of life, increased length of stay in hospital with requirement for more intense nursing care, and admission to hospital for patients who can no longer be cared for at home by their families. The suffering of families of delirious patients is also significant, and witnessing severe or terminal delirium may add to their distress in the bereavement period,^{1,3,4} while unrelieved and distressing symptoms of delirium at the end of life may be an ethically appropriate justification for

initiating palliative sedation.⁵⁷

Given the prevalence and impact of delirium in cancer, it is remarkable how little evidence is available to support clinicians in making the difficult decisions required in caring for delirious patients. These include: how much to investigate and what burden of tests and treatments is appropriate and acceptable for a given episode of delirium; when and how to manage pharmacologically the kinds of psychological care and institutional arrangements needed by delirious patients; and how best to support their families. Research focused on the cancer population is urgently required in order to improve screening, diagnosis, and management of delirious patients and to minimise avoidable distress.

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