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REVIEW

In-hospital delirium risk assessment, diagnosis and management; medications to avoid

Il delirium nel paziente ricoverato: valutazione del rischio, diagnosi, terapia, farmaci da evitare

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KEYWORDS

Delirium;
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Prevention.

Summary

Background: Delirium is a common, but potentially preventable complication of acute illness that is associated with important adverse outcomes including increased length of hospital admission, risk of dementia and admission to long-term care.

In-hospital risk assessment and diagnosis: Age over 65, severe illness, current hip fracture and presence of cognitive impairment or dementia are important risk factors for delirium. Assess people with any of these risk factors for recent changes or fluctuations in behaviour that might indicate delirium. If any indicators are present, complete a full cognitive assessment to confirm the diagnosis of delirium.

In-hospital risk management: Multicomponent delirium prevention interventions can reduce the incidence of delirium in hospital by around one third and should be provided to people with any of the important risk factors that do not have delirium at admission. A medication review that considers both the number and type of prescribed medications is an important part of the multicomponent delirium prevention intervention.

Which medications to avoid in people at risk of delirium: For people at risk of delirium, avoid new prescriptions of benzodiazepines or consider reducing or stopping these medications where possible. Opioids should be prescribed with caution in people at risk of delirium but this should be tempered by the observation that untreated severe pain can itself trigger delirium. Caution is also required when prescribing dihydropyridines and antihistamine H₁ antagonists for people at risk of delirium and considered individual patient assessment is advocated.

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Conclusion: Delirium is common, distressing to patients, relatives and carers and is associated with important adverse outcomes. Multicomponent delirium prevention interventions can reduce the incidence of delirium by approximately one third and usually incorporate a medication review. Identification of which medications to avoid in people at risk of delirium will help guide evidence-based decision making.

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Background

Delirium is a common, but potentially preventable complication of an acute illness that is characterised by the rapid onset of fluctuating confusion and disturbed awareness [1]. Delirium occurs when susceptible people are exposed to often multiple precipitants, including infections, medications and severe pain. Age over 65, severe illness, hip fracture and presence of cognitive impairment or dementia are important risk factors for delirium [2]. These risk factors cluster in hospital patients and this explains the high delirium rate of approximately 30% in general medical, orthopaedic and vascular surgery wards [2]. Delirium is particularly common in the intensive care unit (ICU), where rates are around 70%.

Delirium is independently associated with important adverse outcomes including increased risk of in-patient complications, length of hospital stay, discharge to long-term care facilities, dementia and death [2,3]. However, although delirium is common, and is associated with important adverse outcomes which carry significant health and socio-economic costs, the diagnosis of delirium is frequently overlooked. Knowledge about delirium and confidence in diagnosis and management amongst healthcare professionals

is low [4], and a recent UK study reported that only 1 in 4 cases of delirium in an acute medical admissions unit were correctly identified [5]. Consequently, a substantial disparity between expected rates of delirium and national recording of delirium has recently been reported [6]. This means that a common, but potentially preventable condition which has implications for a poor outcome and additional resource use, remains invisible to healthcare systems. In the UK, the *National Institute for Health and Clinical Excellence (NICE) Delirium Guideline* has recently been published to help healthcare professionals diagnose, prevent and manage delirium [2].

In-hospital delirium risk assessment and diagnosis

People who present to hospital should first be assessed for the presence of the four important delirium risk factors: age over 65; severe illness; current hip fracture; and presence of cognitive impairment or dementia. If any of these risk factors are present, the person is considered to be at increased risk of delirium [2].

People who are at risk should then be assessed to determine whether they have any clinical indicators of prevalent

In order to be diagnosed with delirium a patient must display all of the following four features:

1. A disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.
2. 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.
3. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
4. There is evidence from the history, physical examination and laboratory findings that:
 - (i) the disturbance is caused by the direct physiological consequences of a general medical condition, (ii) the symptoms in criterion (i) developed during substance intoxication, or during or shortly after, a withdrawal syndrome, or (iii) the delirium has more than one aetiology.

Figure 1 DSM IV criteria for delirium [1].

Confusion Assessment Method (CAM)

To have a positive CAM result the patient must display

1. Presence of acute onset and fluctuating course

and

2. Inattention (e.g. 20-1 test with reduced ability to maintain or shift attention)

and either

3. Disorganised thinking (disorganised or incoherent speech)

or

4. Altered level of consciousness (usually lethargic or stuporous)

Figure 2 The confusion assessment method (CAM) screening tool for delirium [7].

delirium. These are recent changes or fluctuations in behaviour that usually develop over hours or days. The changes can affect cognitive function, perception, physical function and social behaviour (see table 1). These changes can indicate hyperactive delirium, hypoactive delirium or a combination of both. Hyperactive delirium, characterised by symptoms including agitation and wandering, is often easier to detect. Hypoactive delirium, which is more common and associated with worse outcomes, is more difficult to detect as the patient is frequently quiet, withdrawn and sleepy. Observation of the patient is critical and is complemented by a detailed informant history which can provide important clues about the onset and fluctuating nature of any changes.

If any of the clinical indicators are present, a full clinical and cognitive assessment should be completed both to confirm the diagnosis of delirium and to identify the precipitant, or combination of precipitants. The assessment for delirium

should be based on the Diagnostic and Statistical Manual of Mental Disorders Volume IV (DSM-IV) criteria (fig. 1) [1]. An alternative is the Confusion Assessment Method (CAM) which is a brief screening tool to identify delirium that is based on the DSM criteria (fig. 2) [7].

Common precipitants of delirium to consider include infection, medications, severe pain, dehydration and electrolyte disturbance [2,8]. In frail older people with delirium, consideration should be given to the possible presence of multiple contributory causes.

In-hospital risk management

In medical and surgical patients who are at risk, but do not have delirium at admission (prevalent delirium), it is possible to prevent delirium from occurring during the hospital stay (incident delirium) in around one third of cases. This is achieved by delivering a tailored multicomponent delirium prevention intervention to those who are at risk [2,9,10]. The multicomponent delirium prevention intervention targets important clinical factors that have been identified as potential precipitants of delirium. These clinical factors, and associated preventative interventions, are summarised in table 2.

Which medications to avoid in people at risk of delirium

A medication review that considers both the number and type of prescribed medications is an important part of the multicomponent delirium prevention intervention. Ideally, evidence-based decisions should be made about which medications to avoid in people at risk of delirium. An understanding of the pathophysiology of delirium, and knowledge of the important medications that are associated with increased risk of delirium, will help guide evidence-based decision making. Furthermore, identification and management of pain is another important part of the

Table 1 Clinical indicators of delirium [2].

Domain	Clinical indicators
Cognitive function	<ul style="list-style-type: none"> ● worsened concentration ● slow responses ● confusion
Perception	<ul style="list-style-type: none"> ● visual hallucinations ● auditory hallucinations
Physical function	<ul style="list-style-type: none"> ● reduced mobility ● reduced movement ● restlessness ● agitation ● sleep disturbance
Social behaviour	<ul style="list-style-type: none"> ● lack of cooperation ● withdrawal ● altered communication ● altered mood

Table 2 Preventing delirium by providing a multicomponent intervention addressing important clinical factors to those at risk.

Clinical Factor Identified	Preventative Intervention
Cognitive impairment, disorientation, or both	<ul style="list-style-type: none"> • Provide appropriate lighting and clear signage. A clock (potentially a 24 hour clock in critical care) and a calendar should also be easily visible to the person at risk • Reorient the person by explaining where they are, who they are, and what your role is • Introduce cognitively stimulating activities (for example, reminiscence) • Facilitate regular visits from family and friends
Dehydration, constipation, or both	<ul style="list-style-type: none"> • Encourage the person to drink. Consider offering subcutaneous or intravenous fluids if necessary • Seek advice if necessary when managing fluid balance in a person with comorbidities (for example, heart failure or chronic kidney disease)
Hypoxia	<ul style="list-style-type: none"> • Assess for hypoxia and optimise oxygen saturation if necessary
Immobility or limited mobility	<ul style="list-style-type: none"> • Encourage the person to: (a) mobilise soon after surgery; (b) walk (provide walking aids if needed—these should be accessible at all times) • Encourage the person to carry out active range of motion exercises, even if unable to walk
Infection	<ul style="list-style-type: none"> • Look for and treat infection • Avoid unnecessary catheterisation • Implement infection control procedures in line with the NICE guideline on infection control
Multiple medications	<ul style="list-style-type: none"> • Carry out a medication review in a person taking multiple drugs, taking into account both the type and number of medications
Pain	<ul style="list-style-type: none"> • Assess for pain. Look for non-verbal signs of pain, particularly in a person with communication difficulties (for example, a person with learning difficulties or dementia, or a person on a ventilator or who has a tracheostomy) • Start and review appropriate pain management in any person in whom pain is identified or suspected
Poor nutrition	<ul style="list-style-type: none"> • Follow the advice given in the NICE guideline on nutrition • If a person has dentures, ensure they fit properly
Sensory impairment	<ul style="list-style-type: none"> • Resolve any reversible cause of the impairment (such as impacted ear wax) • Ensure working hearing and visual aids are available to and used by those who need them
Sleep disturbance	<ul style="list-style-type: none"> • Promote good sleep patterns and sleep hygiene by: avoiding nursing or medical procedures during sleeping hours, if possible; scheduling medication rounds to avoid disturbing sleep; and reducing noise to a minimum during sleep periods. For more information on sleep hygiene see the NICE guideline on Parkinson's disease

multicomponent delirium prevention intervention. Detailed knowledge of the relationship between opioid medications, pain and delirium is therefore of particular importance.

Pathophysiology of delirium

The pathophysiology of delirium is complex. Multiple neurotransmitter pathways are involved, but the cholinergic and dopaminergic pathways are considered to be of key importance and can be influenced by medication effects [11]. Many medications exhibit anticholinergic or dopaminergic activity. Tricyclic antidepressants (TCAs), antihistamine H₁ antagonists, H₂ antagonists, steroids and digoxin all demonstrate in vitro anticholinergic activity, and neuroleptics, angiotensin converting enzyme (ACE) inhibitors, dihydropyridines and antiparkinson medications demonstrate dopaminergic activity [12–14].

Medications to avoid in people at risk

A recent systematic review investigated the risk of delirium that is associated with individual medications [15]. The review identified an approximately three fold increased risk of delirium with benzodiazepine medications. These medications should therefore be avoided, reduced or stopped in people at risk of delirium where possible. When reducing or stopping benzodiazepines, consideration should always be given to the likelihood of provoking benzodiazepine withdrawal symptoms prior to dose adjustment.

There is evidence to support a 2.5 fold increased risk of delirium with opioid medications. These medications should therefore be prescribed with caution in people at risk of delirium. However, opioids should not be avoided in people with acute severe pain as this can itself trigger delirium. Oxycodone appears to be associated with a lower risk of delirium when compared with other opioid medications. Conversely, pethidine appears to be associated with a higher

risk of delirium. It can accumulate in people with impaired renal function and is converted to an active metabolite with anticholinergic properties. In people at risk of delirium, and particularly those with impaired renal function, pethidine should therefore be avoided where possible.

Lower quality evidence exists to suggest an increased risk of delirium with dihydropyridines (e.g. amlodipine) and anti-histamine H₁ medications (e.g. diphenhydramine). Caution is advised when considering prescription of these medications for people at risk of delirium.

Reassuringly, good quality evidence exists to suggest that there is no increased risk of delirium associated with neuroleptic medications such as haloperidol. Low quality evidence exists to suggest no increased delirium risk with digoxin.

There remains significant uncertainty regarding the risk of delirium with H₂ antagonists, TCAs, antiparkinson medications, steroids, non-steroidal anti-inflammatory drugs (NSAIDs) and antimuscarinic agents (e.g. oxybutinin). This uncertainty reflects an absence of evidence due to underpowered observational studies. Large, well designed, adequately powered prospective studies that investigate the risk of delirium with different classes of medication and control for important confounding variables will help guide evidence-based decision making.

Conclusion

Delirium is common but preventable. It is distressing to patients, relatives and carers and is associated with important adverse outcomes that have significant health and socioeconomic costs. Awareness of delirium amongst health-care professionals is low and delirium is frequently undetected in hospitals.

Age over 65, severe illness, current hip fracture and presence of cognitive impairment or dementia are important risk factors for delirium. These risk factors should be identified at hospital admission and those at risk should be assessed for clinical indicators of delirium. If clinical indicators are present, the diagnosis of delirium should be confirmed on the basis of the DSM IV criteria or using the CAM. If the diagnosis of delirium is confirmed, the precipitant, or combination of precipitants, should be identified and treated. Common precipitants include infections, new medications, dehydration and electrolyte disturbance.

In people who are at risk but who do not have delirium at admission, multicomponent delirium prevention interventions have been shown to reduce the incidence of delirium during the hospital stay by around one third. An important component of these interventions is a medication review that addresses both the number and the type of medications.

When conducting a medication review for people at risk of delirium, avoid new prescriptions of benzodiazepines or consider reducing or stopping these medications where possible. Prescribe opioids with caution but remember that untreated severe pain can itself trigger delirium. Exert caution when prescribing dihydropyridines and antihistamine H₁ antagonists. There is uncertainty regarding the risk of delirium that is associated with H₂ antagonists, TCAs, antiparkinsonian medications, steroids, NSAIDs and oxybutinin. A judgment that incorporates the risk of delirium in each individual patient should be taken when prescription of

any of these medications is considered. Future adequately powered prospective studies to investigate the risk of delirium with different classes of medication will help address these uncertainties.

Provenance statement

Andrew Clegg is a member of the *NICE Delirium Guideline Development Group*. John Young is *Chair of the NICE Delirium Guideline Development Group*.

Conflict of interest

John Young is Principal Investigator for a *National Institute for Health Research Programme Grant* investigating delirium prevention in the English NHS.

References

- [1] American Psychiatric Association., American Psychiatric Association. Task Force on DSM-IV. Diagnostic and statistical manual of mental disorders: DSM-IV. 4th ed. Washington, DC: American Psychiatric Association; 1994.
- [2] National Institute for Health and Clinical Excellence Delirium Guidelines 2010. Delirium: diagnosis, prevention and management (CG 103). 2010; Available from: <http://guidance.nice.org.uk/CG103>.
- [3] Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA* 2010;304(4):443–51.
- [4] Davis D, MacLulich A. Understanding barriers to delirium care: a multicentre survey of knowledge and attitudes amongst UK junior doctors. *Age Ageing* 2009;38(5):559–63.
- [5] Collins N, Blanchard MR, Tookman A, Sampson EL. Detection of delirium in the acute hospital. *Age Ageing* 2010;39(1):131–5.
- [6] Clegg A, Westby M, Young J. Under-reporting of delirium in the NHS. *Age Ageing* 2011;40(2):283–6.
- [7] Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;113(12):941–8.
- [8] George J, Bleasdale S, Singleton SJ. Causes and prognosis of delirium in elderly patients admitted to a district general hospital. *Age Ageing* 1997;26(6):423–7.
- [9] Inouye SK, Bogardus Jr ST, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med* 1999;340(9):669–76.
- [10] Marcantonio E, Flacker J, Michaels M, Resnick N. Reducing Delirium After Hip Fracture: a Randomized Trial. *JAGS* 2001;49(5):516–22.
- [11] Alagiakrishnan K, Wiens CA. An approach to drug induced delirium in the elderly. *Postgraduate Medical Journal* 2004;80(945):388–93.
- [12] Brown TM. Drug-induced delirium. *Seminars in Clinical Neuro-psychiatry* 2000;5(2):113–24.
- [13] Tune L, Carr S, Hoag E, Cooper T. Anticholinergic effects of drugs commonly prescribed for the elderly: Potential means for assessing risk of delirium. *American Journal of Psychiatry* 1992;149(10):1393–4.
- [14] Tune LE, Egeli S. Acetylcholine and delirium. *Dementia and Geriatric Cognitive Disorders* 1999;10(5):342–4.
- [15] Clegg A, Young J. Which medications to avoid in people at risk of delirium: a systematic review. *Age & Ageing* 2011;40(1):23–9.