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TITLE: Delirium: non-pharmacological and pharmacological management

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Delirium is an acute onset, fluctuant, confusional state with cognitive, emotional, perceptual, psychomotor, and sleep–wake cycle disturbances. It is often worse in the evening and at night, particularly with underlying dementia [1]. Delirium is often not diagnosed due to fluctuating signs and symptoms. The most common clinical subtype in palliative care is hypoactive delirium, with reduced psychomotor activity [2]. Delirium is especially common in palliative care, almost ubiquitous towards the end of life; up to 88% of patients develop delirium in the last weeks to hours of life [3].

Older age and dementia are major risk factors. Current and projected demographic changes, with an increased elderly population, signal a need for physicians to have a better awareness of delirium diagnosis and assessment. A high level of suspicion and multidisciplinary team involvement is needed in diagnosis and management.

The primary management is rapid diagnosis, as mortality increases with delay. This includes history (importantly collateral histories from carers, family, and staff), examination, and appropriate investigation (according to goals of care). The aim is to make the diagnosis and if possible confirm the cause(s). It is also important to determine the impact on the patient and family/carer and ascertain their needs.

Delirium screening and diagnostic tools can help improve diagnosis but seldom used [4]. Clinicians should use low burden validated screening tools including the Single Question in Delirium (SQiD), Nursing Delirium Screening Scale (Nu-DESC), Delirium Observation Screening (DOS) Scale, and the Confusion Assessment Method (CAM) [2]. The CAM needs proper training. The 4AT assesses cognition (specifically attention) and is popular in elderly medicine. Currently, it has not been formally

validated in palliative care patients but has been used in a hospice setting [5].
Diagnostic criteria appear in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 and International Classification of Diseases (ICD)-11.
Assessment tools (to confirm diagnosis and rate severity) include the Delirium Rating Scale revised-98 (DRS-R-98) and Memorial Delirium Assessment Scale (MDAS) [1].

Identify and reverse underlying cause(s) of delirium if appropriate/consistent with goals of care and illness trajectory. The cause is often multifactorial, with usually one to six causes (median three) per episode [6]. This is central to management and should be a key part of assessment post-diagnosis. Up to 50% of delirium episodes in palliative care have a cause which can be found and treated [6]. If identified and the patient responds to appropriate treatment, this is the best approach.

Common causes include dehydration; drug/alcohol withdrawal; electrolyte abnormalities (hypercalcaemia, inappropriate antidiuretic hormone secretion (SIADH), abnormal glucose); infection; and metabolic encephalopathy from hepatic, renal, heart or respiratory failure [1].
Communication, education, information, and patient support (reassurance and support when not lucid and education when they are) are vital as delirium can be very distressing [2]. In addition, education and support to family and staff will be needed. Furthermore, family/informal carers often support the patient and can help with non-pharmacological management.

Non-pharmacological management is the mainstay of treatment for most episodes and needs frequent reinforcement (Box 1) [1 7]. Non-pharmacological interventions are

effective in older people [7 8] but still under evaluation in palliative care. In addition, avoid physical restraints and unnecessary urinary catheterisation.

Box 1: Non-pharmacological delirium management [1 7].
Correction of predisposing conditions (hearing, vision)
Encourage mobilisation
Improve sleep–wake patterns (day: exposure to daylight, discourage naps; evening: non-caffeinated drinks, relaxing music, minimise light, noise, disruptions)
Orientation activities (explain where the patient is, who they are, who you are and your role, use orientation board, visible clock, and cognitive stimulation activities, e.g. Reminiscence)
Minimise room changes
Encourage and assist patients to drink (and eat) - provided they can swallow safely

There have been two recent randomised controlled trials of pharmacological management in adult palliative care inpatients. One compared dose-titrated haloperidol and risperidone with placebo over three days in a multisite trial [9]. Regular oral risperidone and oral haloperidol were associated with higher delirium symptom scores and more extrapyramidal side effects in mild-to-moderate severity delirium [1]. Haloperidol was associated with shorter overall survival in long-term follow-up (secondary outcome). This study has focused clinicians away from using antipsychotics to manage delirium, unless patients are a danger to themselves/others, or very distressed (frightening hallucinations) and non-pharmacological management has been ineffective [1 9]. If an antipsychotic is required, use the lowest effective dose for a short time (Box 2). It is best to use as required dosing; use lower doses in frail or older people [1]. Patients should be assessed for

antipsychotic-associated extrapyramidal side effects; the risk is lower with new generation antipsychotics. Haloperidol should be avoided in Lewy body dementia or Parkinson's disease due to an increased risk of extrapyramidal side effects.

The other study was a single-centre randomised placebo-controlled trial in end-of-life severe delirium and agitation on intravenous haloperidol [10]. Patients who were administered intravenous lorazepam added to haloperidol had less agitation than haloperidol and placebo at eight hours [10].

Caution is needed with benzodiazepines as they can exacerbate delirium. The exception is use in alcohol/benzodiazepine withdrawal (reverses the underlying cause). In severe delirium where sedation is required, a patient may respond to a benzodiazepine (in the lowest effective dose) added in second line with an antipsychotic. Further research for the role of medications in delirium management is needed.

In summary, delirium is common, distressing, and underdiagnosed. Diagnosis is key, with an appropriate search for causes, as it is often reversible. Non-pharmacological measures should be optimised. Antipsychotics should be used sparingly but may be indicated in severe distress from delirium/hallucinations. Benzodiazepines may be required in severe agitated delirium unresponsive to prior measures. For optimal care, patient evaluation, investigation and management of reversible delirium precipitants (according to goals of care) is important and should include patient and family education and support, as well as family input into the decision-making process (including the patient whenever possible) [2].

Box 2: Recommendations for medications for delirium symptoms [1 2].

Medications are generally not recommended in most cases. If needed, use the lowest effective dose for the shortest possible time to relieve symptoms.

ANTIPSYCHOTICS: The oral route is preferred; if not possible, then use the subcutaneous route (if parenteral preparations are available). Start with lower doses in elderly or frail patients. Dose reduction of some antipsychotics may be needed in those with renal and hepatic impairment. Antipsychotics do not 'treat' delirium *per se*, but rather the symptoms (underlying cause/s needs to be reversed to treat the delirium).

HALOPERIDOL: If non-pharmacological measures are ineffective and/or the patient has distressing hallucinations, then 0.5mg haloperidol is recommended *as required* orally (alternative subcutaneously). Dose can be increased to 1mg and repeated up to hourly if needed. If a regular dose is needed, this should be the lowest dose (usually given at night or BD). Usual daily maximum: <5mg/24h.

LEVOMEPROMAZINE (METHOTRIMEPRAZINE): This is sometimes used if haloperidol is ineffective. It is more sedating. Starting dose 5-12.5mg orally (alternative subcutaneously) up to every 2 hours *as required*. If a regular dose is needed, this should be the lowest dose (usually given at night). Usual daily maximum: 50-100mg.

NEW GENERATION ANTIPSYCHOTICS: olanzapine (2.5-5mg orally or subcutaneously at night; can titrate up to 10mg), quetiapine (25mg orally BD; up to 50-100mg BD) and aripiprazole (2.5-5mg daily orally; up to 20mg), may provide symptom relief. Some, such as quetiapine, are not available as a parenteral preparation. Risperidone has been shown to be ineffective in a recent RCT [9].

BENZODIAZEPINES: They (e.g. midazolam and lorazepam) are first-line in alcohol or benzodiazepine withdrawal. In severely distressed delirious patients, benzodiazepines may have a role in addition to antipsychotics for sedation and anxiolysis. They should be used with caution as they are deliriogenic and associated with an increased risk of falls. Recommended doses: Midazolam 2.5mg subcutaneously up to hourly *as required*. Usual maximum *as required* dose is 5mg. If repeated doses are needed for refractory agitated delirium, can administer via a continuous subcutaneous infusion (usually 10-20mg/day; usual maximum 40-60mg/day). Lorazepam 0.5-1mg orally or subcutaneously up to hourly *as required* (up to 2mg maximum). If repeated doses are needed, can use regularly, usual effective dose 3-6mg/day.

Use benzodiazepines with caution in the elderly/frail and those with severe liver disease or chronic obstructive airways disease; dose reduction may be needed.

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