

PALLIATIVE PEARLS

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Recognizing Delirium in Home Hospice October 2022

This month's Palliative Pearls serves as a refresher, pulling key points from a popular case, [Polypharmacy Management](#).

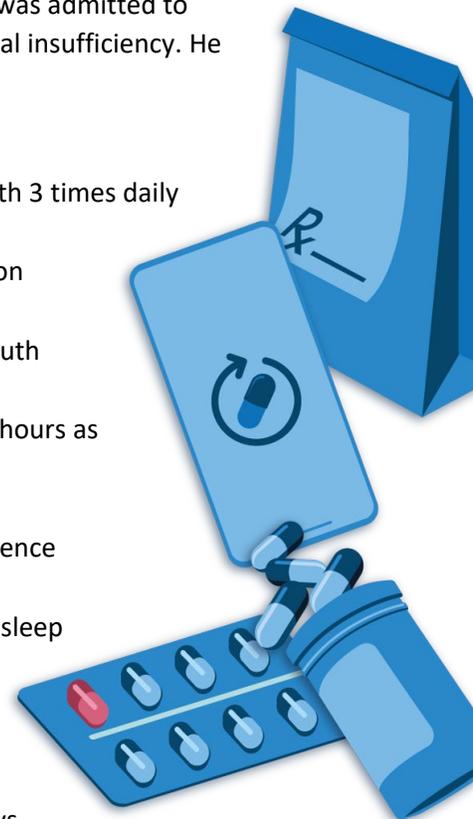
PATIENT CASE

JK is a 72-year-old male with a primary diagnosis of end-stage heart failure, who was admitted to hospice services 2 weeks ago. Comorbid conditions include hypertension and renal insufficiency. He has no known drug allergies and resides in a long-term care nursing facility.

MEDICATIONS:

- Calcium carbonate (TUMS®) chewable 500mg chewable; 1 tablet by mouth 3 times daily as a supplement
- Furosemide (Lasix®) 40mg; 1 tablet by mouth twice daily for fluid retention
- Lisinopril (Zestril®) 20mg; 1 tablet by mouth daily for the heart
- Metoprolol succinate (Toprol XL®) 50mg; One-half tablet (12.5mg) by mouth daily for the heart
- Morphine 20 mg/ml oral concentrate; 0.75 ml (15 mg) by mouth every 3 hours as needed for breakthrough pain
- MS Contin® 60 mg; 1 tablet by mouth every 12 hours for pain
- Oxybutynin (Ditropan®) 5mg; 1 tablet by mouth daily for urinary incontinence
- Senna; 1 tablet by mouth at bedtime as needed for constipation
- Lorazepam (Ativan®) 0.5mg; 1 tablet by mouth at bedtime as needed for sleep

JK's daughter has noticed her father becoming increasingly irritable over the past 2 days; he seems confused and even angry at times. Vital signs are within normal limits and pain management is at goal. It is noted that while he is not experiencing any nausea or cramping, he has not had a bowel movement in 5 days despite administration of Senna nightly. Recent changes to his medications include an increase in his long-acting morphine from 30mg twice daily to 60mg twice daily and short-acting morphine to 15mg per dose. JK has also had trouble sleeping the past 3 nights, with nursing staff chart notes of wakefulness for long stretches of those nights and difficulty following nurse instructions in the mornings. Despite an order for "as needed" lorazepam at bedtime, no doses have been administered in the past week.



DELIRIUM: SIGNS & SYMPTOMS

Delirium is a disturbance in attention and awareness due to an underlying condition or substance/ medication toxicity or withdrawal. Patients present acutely with sudden onset of cognitive changes, perceptual disturbances, and behavioral agitation.^{1,2}

- Cognitive changes including altered level of consciousness, confusion, disorganized thinking, inattention, labile affect and psychosis
- Diagnostic failure - a diagnostic workup fails to identify a reversible etiology
- Therapeutic failure - a time-limited therapeutic trial is unsuccessful at reversing the delirium

Delirium is categorized as one of the following subtypes:

- Hyperactive - Psychomotor agitation, perceptual disturbances and changes in level of consciousness that may be accompanied by mood lability and/or refusal to cooperate with medical care
- Hypoactive - Psychomotor retardation, withdrawal and depressed mood that may be accompanied by sluggishness and lethargy that approaches stupor
- Mixed – Most prevalent but often unrecognized; features of both hyperactive and hypoactive subtypes; also includes individuals whose activity level rapidly fluctuates.

CAUSES IN THE PALLIATIVE CARE SETTING

Nearly any disturbance of normal physiology can cause delirium. Patients with serious illness are at particularly high risk for development because they have complex, changing medical problems, are often receiving multiple medications and are subject to interventions.²

Common, usually can be removed/resolved:

- Medications (e.g., opioids, steroids, benzodiazepines, anticholinergic medications)
- Withdrawal (e.g., from benzodiazepines, opioids, alcohol)
- Constipation
- Urinary retention
- Dehydration

Less common, usually can be removed/resolved if aligned with goals of care:

- Metabolic disturbance (e.g., hyponatremia)
- Anemia
- Hypoxemia

Less common, usually cannot be removed/resolved:

- Path to reversal is incompatible with goals of care (e.g., blood draws for labs, procedures)
- Organ failure (e.g., renal, hepatic, respiratory)
- CNS pathology (e.g., tumor/metastasis, non-convulsive status epilepticus)
- Diagnostic failure - a diagnostic workup fails to identify a reversible etiology
- Therapeutic failure - a time-limited therapeutic trial is unsuccessful at reversing the delirium

PREVENTION³

Preventing delirium begins with identifying patients at high risk for delirium. Attributes include:

- Age ≥ 65 years
- Baseline cognitive impairment or dementia
- Poor vision or hearing
- Poor functional status
- Severe or critical illness
- Alcohol misuse
- Depression
- Current hip fracture
- Post-surgery

Next, review medications:

- Attempt to reduce the number of total medications
- Discontinue medications that may cause constipation or dehydration
- Avoid scheduling medication administration that interrupts patient's normal sleep-wake cycle
- Limit the use, if possible, of medications associated with delirium (e.g., anticholinergics (e.g., diphenhydramine, scopolamine), benzodiazepines (e.g., lorazepam), opioids (e.g., morphine), corticosteroids (e.g., dexamethasone)). When avoidance is not feasible for optimal care of the patient, reduce dose(s) to the smallest and most effective.

Use non-drug measures:

- Equip patient with visible clocks and calendars
- Make accessible glasses and/or hearing aids
- Encourage ambulation
- Support normal sleep-wake cycle

Monitor for these signs and symptoms and consider screening tools to trigger further assessment:

- Reduced clarity or awareness of the environment
- Reduced ability to focus, sustain, or shift attention
- A change in cognition such as memory deficit, disorientation, language disturbance, or a perceptual disturbance such as hallucinations or delusions
- Sleep disturbances
- Abnormal psychomotor activity
- Emotional disturbances such as fear, anxiety, anger, depression, apathy, or euphoria

SCREENING

Screening tools identify the presence of cognitive impairment but may not diagnose delirium without further assessment. Mental status examination and review of diagnostic criteria is required to confirm diagnosis of delirium.⁴⁻⁶

The Confusion Assessment Method (CAM) is one of the most widely used screening tools for delirium. The presence of features 1 and 2, and either 3 or 4 below, may lead to a delirium diagnosis.

- Feature 1: Acute Onset or Fluctuating Course
- Feature 2: Inattention
- Feature 3: Disorganized Thinking
- Feature 4: Altered Level of Consciousness^{6,7}

The Memorial Delirium Assessment Scale (MDAS) is a 10-item, four-point observer-rated scale designed to quantify the severity of delirium with serial observations. It includes assessment of disturbances in consciousness (awareness), orientation, short-term memory, digit span, attention capacity, organized thinking, perception, delusions, psychomotor activity, and arousal in a way that reflects all the main diagnostic criteria according to the Diagnostic and Statistical Manual for Mental Illness. In many institutions, this tool has replaced the Mini-Mental Status Examination (MMSE) for assessment and monitoring of delirium.⁷

The bedside confusion scale is another tool to screen and longitudinally follow delirium in palliative care. The scale assesses ability to recite the 12 months in reverse order and of consciousness state. Serial-sevens and spelling a word such as “farm” or “world” backward are other simple tests of attention.⁷

MANAGEMENT

In the confines of a hospital setting, and in the absence of advanced disease, delirium manifests with multiple opportunities to reverse the underlying cause(s); however, in the palliative care setting, especially near the end of life, reversible causes are not plentiful, leaving even the astute clinician with little option but to manage symptomatically.¹ Palliative care clinicians are called upon to quickly quell patient symptoms and provide reassurance to families and caregivers.

- Workup should be based on the individual patient’s status and prognosis
- Review the medication list and try to correlate changes in medication to the onset of the symptoms; address polypharmacy, discontinue medications contributing to impairment and taper medications that could precipitate additional problems
- Treat reversible causes such as drug withdrawal and infections, when aligned with goals of care
- For some patients, it may be more efficacious to try to treat the delirium rather than search for the underlying cause
- When the correction of underlying disorders and/or causes of delirium is no longer feasible, the standard of care shifts to symptom management.⁸

Non-pharmacological management includes consistent patient reorientation and reassurance, reliable presence of family members and/or close friends, creation of a calm and familiar environment, as well as proper assessment and management of sensory deficits, e.g., hearing loss (functionality of hearing aids) and vision (need for eye glasses).^{2,9}

- Ensure safety
- Maintain adequate nutrition and hydration
- Avoid physical restraints
- Reduce excessive stimulation
- Regularly orient and assure the patient of his or her safety
- Encourage family to be at bedside¹⁰

Pharmacological interventions include antipsychotics, typically haloperidol (however, second-generation antipsychotics have been cited more recently), benzodiazepines in select situations, and sedatives. Use the lowest effective dose of a medication for the shortest duration possible.^{2,9,10}

Antipsychotics are considered first line for potentially reversible delirium and may be used in combination with benzodiazepines and other sedatives for irreversible delirium. Haloperidol (Haldol®) is the preferred medication and chlorpromazine (Thorazine®), an alternative.¹¹

Benzodiazepines are indicated for irreversible delirium and should be avoided for potentially reversible, hyperactive delirium unless agitation is uncontrolled by antipsychotic. Recall that benzodiazepines are often culprits in delirium precipitation and may worsen delirium arising from other causes. Benzodiazepines are ineffective as monotherapy and recommended as adjunct only. Examples include lorazepam (Ativan®) and midazolam (Versed®).¹¹

Other sedatives may be useful for irreversible delirium and are reserved for control of agitation that is refractory to all other measures. Medication examples include phenobarbital and propofol (Diprivan®).¹¹

THE ANTIPSYCHOTIC DEBATE

While some clinicians relay experience with antipsychotics as useful remedies in low doses to provide temporary, palliative relief bandwidth while non-pharmacological measures are introduced, others hold the perspective that pharmacological management of delirium with antipsychotics has trended as a fast-track means to chemical restraint and is largely ineffective.⁹

Historically, the antipsychotic class is no stranger to public concern over unwanted adverse effects. In 2005, the FDA issued a black box warning for all antipsychotic labeling based on findings associated with increased mortality in elderly patients with dementia. Risk of death in drug-treated patients was 1.6 to 1.7 times the risk in placebo group and the most causative condition was cardiovascular (e.g., heart failure, sudden death) or infection (e.g., pneumonia).^{8,12} Coupled with the lack of sufficient trial evidence to support the routine use of antipsychotics to prevent or treat delirium, there is ample reason to pause before selecting an antipsychotic for the management of delirium.¹³

In 2017, findings of a randomized, controlled trial prompted renewed discussion on the subject. The study group included patients with mild to moderate delirium in a hospital setting and investigators found no benefit from low dose of risperidone or haloperidol compared to placebo.^{14,15} The findings were thought-provoking, however the patient population, setting, and outcomes measured made it difficult to broadly extrapolate. Nevertheless, the trial's publication led to numerous meta-analyses and systematic reviews in the past 3 years on the pharmacological management of delirium.¹⁶⁻²⁰

A recent systematic review was published in the *Annals of Internal Medicine*, where investigators sought to evaluate antipsychotic treatment benefit and harm in hospitalized adult patients with delirium. In all, 16 randomized controlled trials and 10 observational studies with publications ranging from 2004 to 2017 were reviewed.²¹ Investigators found no difference in sedation status, delirium duration, hospital length of stay, or mortality between haloperidol and second-generation antipsychotics versus placebo and no difference in delirium severity and cognitive functioning for haloperidol versus second-generation antipsychotics, with insufficient or no evidence for antipsychotics versus placebo. Although "there was little evidence demonstrating neurologic harms associated with short-term use of antipsychotics for treating delirium in adult inpatients," they found that "potentially harmful cardiac effects tended to occur more frequently" in those administered antipsychotics.

PATIENT CASE REVISIT

Assessment

Delirium risk factors for JK include age > 65 years, opioid use, constipation, renal insufficiency, and lack of sleep. His symptoms of agitation, anger and confusion manifested acutely and have a temporal relationship to a recent medication change. Medication therapy review offers several potential reversible causes for delirium. Decision-making must be based on patient-specific goals of care and prognosis:

- JK is prescribed oxybutynin for urinary incontinence that has anticholinergic properties that may precipitate both constipation and symptoms of delirium²²
- The calcium carbonate in TUMS[®] contributes to constipation and is a candidate for discontinuation²²
- Constipation is a common side effect of opioid therapy for which tolerance does not develop. Titrating appropriate laxative therapy (e.g., senna, bisacodyl, Miralax[®]) with changes in opioid therapy prevents constipation in most patients.²²
- Morphine may accumulate in patients with renal insufficiency warranting careful consideration of its use in this patient population. Morphine has been adequately managing pain in JK and is being titrated gradually. If delirium symptoms continue despite other interventions, it may need to be converted to an opioid with less renal concern such as methadone or fentanyl.²³⁻²⁴

Recommendations

- Assess necessity of incontinence management; if warranted, replace oxybutynin with therapy associated with fewer anticholinergic side effects such as mirabegron (Myrbetriq®)
- Assess calcium carbonate use and necessity of continuation; if used as an antacid, recommend “as needed” use and monitor, or if confirmed to be a supplement only, discontinue
- Initiate bisacodyl 10mg suppository, 1 suppository rectally now, and then every 3 days if no bowel movement
- Change senna to scheduled administration and increase to 2 tablets by mouth at bedtime
- Monitor JK for resolution of constipation and delirium symptoms
- Consider converting morphine oral therapy to fentanyl transdermal therapy if symptoms do not resolve

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