



# Emergent Management of Delirium in Cancer Patients

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Delirium is an unwelcome syndrome seen often in patients with advanced cancer, especially those who are older and taking opioids. This comprehensive article considers causes and contributors, screening and diagnosis in the emergency department, and interventions and outcomes.

**D**elirium, an acute confusional state resulting from global brain dysfunction, is one of the most common neuropsychiatric syndromes in patients with advanced cancer.<sup>1-3</sup> Delirium is more common in older patients and among those receiving opioid analgesics.<sup>4,5</sup>

The exact incidence of delirium in patients with advanced cancer at presentation to the emergency department is unknown. Authors have reported rates of 8% to 17% in elderly patients seen in general emergency departments,<sup>6-8</sup> and in a study of patients older than 70 years, a 24% prevalence was reported.<sup>9</sup> Furthermore, authors have reported delirium prevalence rates of 25% to 44% in elderly hospitalized patients,<sup>2,10-12</sup> with rates as high as 44% in elderly nursing home residents.<sup>13</sup> The

highest rates are seen in those near the end of life; in one study, 88% of patients with advanced cancer who were treated in an inpatient palliative care unit were reported to experience terminal delirium.<sup>14</sup> Fann et al reported a cumulative incidence of delirium of 50% in the 4-week period following hematopoietic stem cell transplant.<sup>15</sup>

Delirium is classified into three subtypes based on psychomotor activity: (1) hyperactive or agitated, mimicking psychosis or mania and associated with hallucinations and delusion; (2) hypoactive or withdrawn, resembling depression; and (3) mixed subtype, with features of the first and second subtypes. Emergency physicians are very familiar with signs of agitated delirium (eg, delirium tremens); however, hypoactive- and mixed-subtype delirium are most common.<sup>6,16,17</sup> Consequently, delirium is frequently missed or misdiagnosed as anxiety, worsening pain, depression, psychosis, or dementia.<sup>6,18,19</sup> In fact, in a recent study from a single emergency department, Han et al reported that the diagnosis of delirium was missed by emergency physicians in 76% of cases.<sup>6</sup>

Missing a diagnosis of delirium may result in therapeutic errors as well as significant distress to patients,

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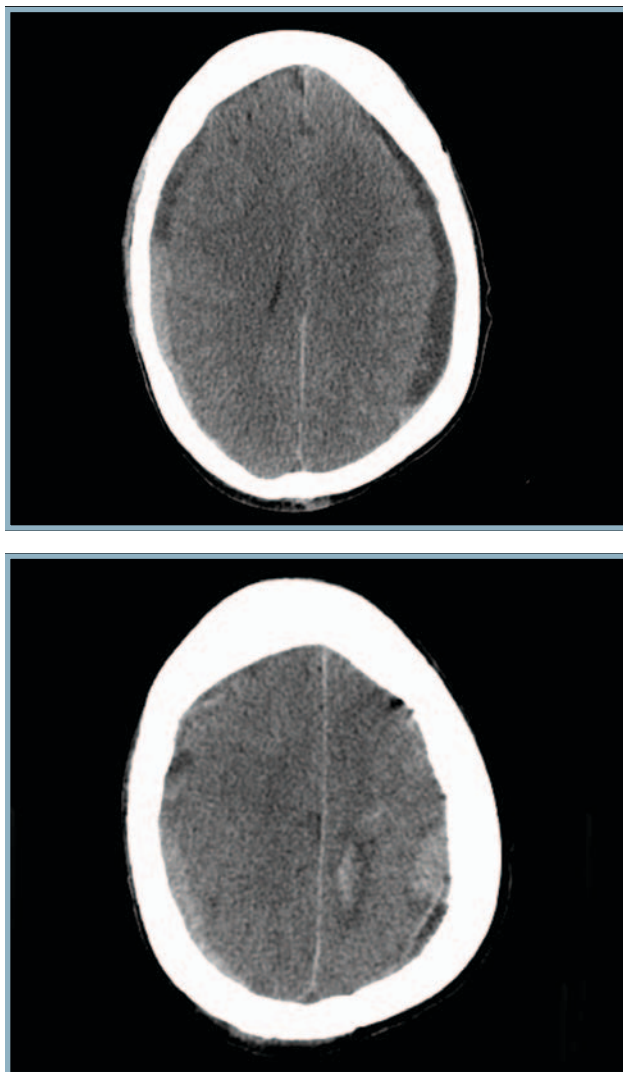
their families, and nursing staff.<sup>17,20,21</sup> In this article, we review the complex syndrome of delirium and its causes and pathophysiology and suggest approaches to delirium assessment and management in the emergency department.

## CASE

A 70-year-old woman with advanced breast cancer presented to our emergency department with increasing back pain, fatigue, somnolence, and insomnia. She had received her last round of chemotherapy treatment 1 week earlier and was taking hydromorphone (6 mg every 4 hours). She had taken the maximum dose for the last 4 days. She was unable to sleep because of increasing pain and anxiety, and her husband had given her a sleeping pill the previous night. He stated that she was unable to eat or drink (except when taking her pain medication) because of drowsiness. Physical examination demonstrated a chronically ill-appearing patient with dehydration and cachexia. She was easily arousable and, when asked, reported a pain intensity of 10 out of 10. She was tachycardic, but her other vital signs were normal. Her husband, who was exhausted, left her in the emergency department and went home. Laboratory tests revealed that the patient had hypercalcemia and a high blood urea nitrogen level. We initiated intravenous hydration and the patient received intravenous hydromorphone. Shortly after, she fell off her stretcher, striking her head on the floor. She screamed for help and held her hands to her head before losing consciousness. Head CT without contrast (Figure 1) revealed acute and subacute subdural hemorrhage. Subsequently, her platelet count was  $5,000 \times 10^3/\mu\text{L}$ . The patient died 3 days later.

## CAUSES AND PATHOPHYSIOLOGY

The precise cause of delirium is unknown, but the syndrome tends to occur in predisposed individuals who have underlying comorbid conditions and experience additional acute insults.<sup>16,22</sup> Old age, advanced cancer, and prior cognitive impairment (eg, prior episodes of delirium or dementia) predispose individuals to delirium. Other predisposing factors include residing in an unfamiliar environment (such as a nursing home),

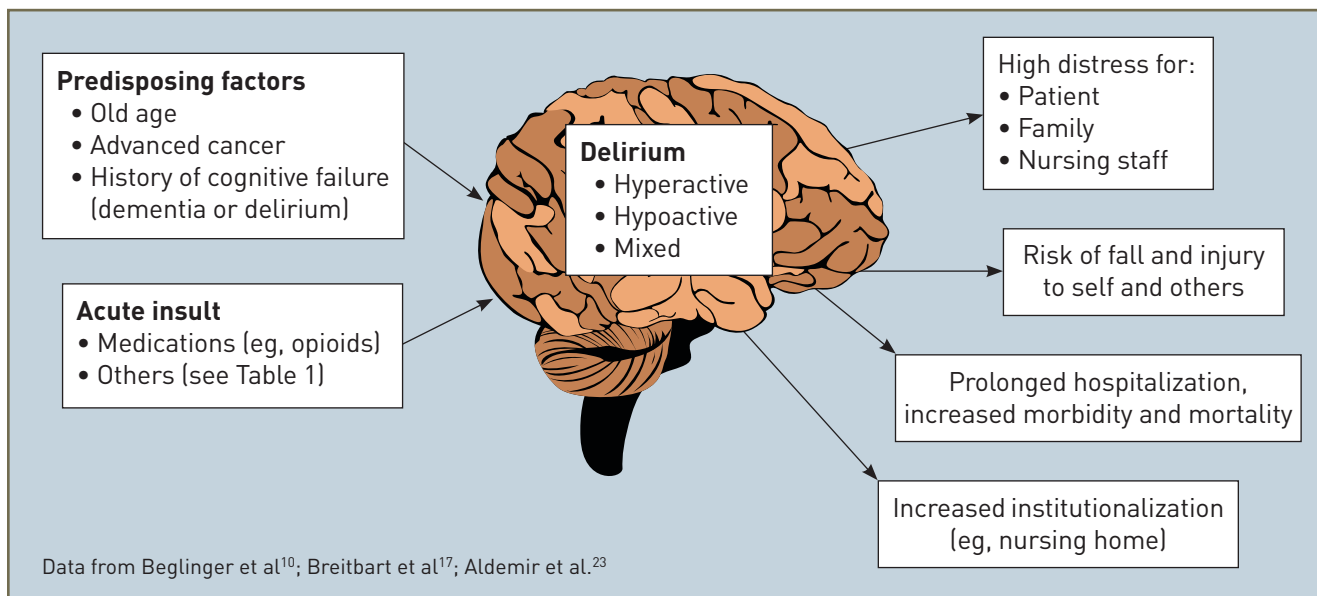


**FIGURE 1.** Non-contrast-enhanced head CT obtained in the case patient after she fell off her gurney in the ED. Acute and subacute subdural hemorrhage is seen.

social isolation, and hearing or vision impairment. Figure 2 demonstrates some predisposing factors and acute insults that are associated with delirium, as well as some of its consequences.<sup>10,17,23</sup> In addition, Table 1 lists conditions that can cause or contribute to delirium. Medications, particularly opioids, are a frequent proximal cause of delirium in patients with advanced cancer.

Central neurotransmitter disturbances are believed to be the final common pathophysiologic mechanism causing delirium. Cholinergic mechanisms are frequently implicated, owing to observations of reductions in acetylcholine and increases in dopamine levels

**FIGURE 2.** Causes and consequences of delirium



in patients with delirium.<sup>24,25</sup> Other neurotransmitter abnormalities that may contribute to delirium include excess levels of serotonin and cortisol and reductions in GABA (γ-aminobutyric acid) levels. More recently, increasing attention has been given to the role of cytokines, such as interleukins 1 and 6, tumor necrosis factor, and pro-inflammatory markers, such as C-reactive protein, in causing delirium.<sup>26,27</sup> Whether advanced cancer causes or contributes to delirium via cytokines or other mechanisms remains to be determined.

Neurotoxicity is a known complication of chronic opioid therapy that may be manifested by delirium, hallucinations (particularly visual hallucinations), myoclonus, and hyperalgesia.<sup>28</sup> Chronic high-dose opioid therapy and coadministration of opioids and other psychoactive drugs such as benzodiazepines are common predisposing factors for delirium. Opioid-induced neurotoxicity is believed to be caused by opioid end-products, such as morphine-3-glucuronide (in the case of morphine). These opioid metabolites are usually excreted by the kidneys<sup>29</sup> and accumulate with renal insufficiency; therefore, dehydration or acute or chronic renal failure may decrease their clearance. The majority of opioids have similar active metabolites. Opioids may exert their toxic effects via the cholinergic system.

Other medications besides opioids are known to cause or contribute to delirium (Table 2). In a study of

261 hospitalized patients with cancer, Gaudreau et al<sup>30</sup> found that the risk of delirium doubled when the daily dosages exceeded 90 mg of subcutaneous morphine, 2 mg of oral lorazepam, or 15 mg of oral dexamethasone.

**DIAGNOSIS**

Early recognition is critical to the appropriate management of delirium. The gold standard for diagnosis is the criteria set forth in the *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition–Text Revision*.<sup>2</sup> According to this text, a diagnosis of delirium requires the following: disturbance of consciousness with reduced awareness, attention, and focus; acute cognitive changes (such as memory deficits, hallucinations, or delusions) that are not attributed to dementia; occurrence of these symptoms over a short period of time (hours to days) with fluctuation throughout the day; history, examination, and workup findings indicating that the changes are the result of a specific physical cause (eg, medication or medical condition).

A number of screening and diagnostic tools utilizing these criteria have been developed. Table 3 lists some commonly used screening and diagnostic tools.<sup>3,31-38</sup> Some patients with delirium may appear cognitively normal and follow commands appropriately; thus, use of a screening tool can provide valuable guidance toward an accurate diagnosis of the condition. It is

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**Table 1. Causes/Conditions That May Contribute to Delirium**

- Medications (including certain chemotherapies)<sup>a</sup>
- Infection (eg, sepsis)
- Electrolyte imbalance (hypercalcemia, hyponatremia)
- Uncontrolled pain
- Organ failure (renal, hepatic, pulmonary [with hypoxia], cardiac)
- Dehydration
- CNS insults (primary or metastatic brain tumors, cerebrovascular accidents)
- Alcohol or benzodiazepine withdrawal
- Others (malnutrition, anemia, hypothyroidism, paraneoplastic syndrome, tethers, change in environment/stimulation)

<sup>a</sup>See Table 2. CNS = central nervous system.

advisable for the clinician to be familiar with at least one of these tools. The CAM (Confusion Assessment Method)<sup>33</sup> is the most validated diagnostic tool for delirium in the emergency department setting.

The emergency physician should maintain a high index of suspicion for delirium in patients with advanced cancer. The patient or surrogate may report cognitive symptoms. In addition, the astute clinician will be alert for evidence of insomnia and nighttime restlessness, sleepiness during the day, anxiety or restlessness that worsens at night, picking at bed sheets or clothing, talking while asleep, raising hands while asleep as if trying to reach for something, new or worsened memory deficits, and rapidly fluctuating symptoms.

A detailed medication history should include over-the-counter medications. Further history-taking should focus on urinary symptoms, constipation, symptoms of pneumonia or other infections, oral intake, sleep, and headache or double vision. The physical examination can eliminate possible etiologies of the delirium. Laboratory tests may reveal electrolyte abnormalities (eg, hypercalcemia, renal failure). Brain imaging studies should be reserved for patients with a probable central nervous system etiology based on findings from history and physical examination and knowledge of the specific malignancy

**Table 2. Common Medications That Could Contribute to Delirium**

Medication	Examples
Opioids	Morphine, hydromorphone, oxycodone, fentanyl, meperidine
Benzodiazepines	Lorazepam, diazepam
Corticosteroids	Dexamethasone, prednisone
Anticholinergics	Scopolamine
Antihistamines	Diphenhydramine, dimenhydrinate, hydroxyzine
Antiemetics	Prochlorperazine
Antidepressants	TCAs, SSRIs, lithium
Antibiotics	Fluoroquinolones
Antivirals	Acyclovir
Muscle relaxants	Baclofen
Cardiac medications	Antiarrhythmics, digitalis, some antihypertensives
Chemotherapeutics	Ifosfamide, 5-fluorouracil

TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor.

potential of brain metastasis. Figure 3 provides a delirium assessment and management algorithm.

## TREATMENT

### Nonpharmacologic

The most important nonpharmacologic intervention for delirium is to ensure the safety of the patient, caregiver, and health care staff.<sup>16,22</sup> A family member (if available) or surrogate should be encouraged to stay with the patient, and surrounding noise and visual stimuli should be minimized. Pain levels and the patient's need to use the bathroom should be addressed. The bed should be lowered to minimize fall-related injury, and the patient and surrogate should be advised to call the nurse if the patient would like to leave the bed for any reason, including going to the restroom. If no caregiver is available, a sitter should be assigned to assist the patient; however, a familiar face is preferable to that of a stranger. Use of restraints or any teth-

**Table 3. Delirium Screening and Diagnostic Tools**

Tool	Purpose	Main Features
Nu-DESC <sup>3</sup>	Screening	<ul style="list-style-type: none"> <li>• Based on Confusion Rating Scale<sup>31</sup></li> <li>• Simple, used by nurses at bedside.</li> <li>• Brief (5 items, requires &lt;2 min)</li> </ul>
MMSE <sup>32</sup>	Screening	<ul style="list-style-type: none"> <li>• Test of cognitive failure</li> <li>• Simple</li> <li>• 30 items (score &lt;24 signifies greater cognitive failure)</li> <li>• Commonly used for dementia, but may be used as screening tool for delirium</li> <li>• Most clinicians are familiar with this tool</li> </ul>
CAM <sup>33</sup>	Diagnostic	<ul style="list-style-type: none"> <li>• Based on <i>DSM-III-R</i><sup>34</sup> criteria</li> <li>• Brief (4 features, could be completed in &lt;5 min)</li> <li>• Simple, but users need training.</li> <li>• Does not rate severity</li> <li>• Most validated tool in the ED setting</li> </ul>
MDAS <sup>35</sup>	Severity rating	<ul style="list-style-type: none"> <li>• Differentiates among types of delirium</li> <li>• 10 items, 30-point scale (higher scores signify greater severity)</li> <li>• Some groups use cutoff score &gt;7 to diagnose delirium<sup>36</sup></li> </ul>
CAM-ICU <sup>37</sup>	Diagnosis in ICU, screening in ED	<ul style="list-style-type: none"> <li>• Based on CAM</li> <li>• Originally validated to assess delirium in ICU</li> <li>• Recently evaluated in ED setting<sup>38</sup></li> </ul>

Nu-DESC = Nursing Delirium Screening Scale; MMSE = Mini-Mental State Examination; CAM = Confusion Assessment Method; *DSM-III-R* = *Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised*; ED = emergency department; MDAS = Memorial Delirium Assessment Scale; CAM-ICU = Confusion Assessment Method for the Intensive Care Unit. Data from: Gaudreau et al<sup>3</sup>; Williams et al<sup>31</sup>; Anthony et al<sup>32</sup>; Inouye et al<sup>33</sup>; American Psychiatric Association<sup>34</sup>; Breitbart et al<sup>35</sup>; Lawlor et al<sup>36</sup>; Ely<sup>37</sup>; Han et al.<sup>38</sup>

ering agent, such as Foley catheters, ECG leads, and oxygen saturation or blood pressure monitor lines, is discouraged. These items may worsen agitation in the delirious patient. Familiar items such as photographs of family members may help calm the patient. Delirious patients require frequent orientation by the caregiver or nursing staff to their surroundings and situation. Calm explanations to patients and their family members of all planned interventions are critical to avoid misinterpretation or violent reactions.<sup>16,28</sup>

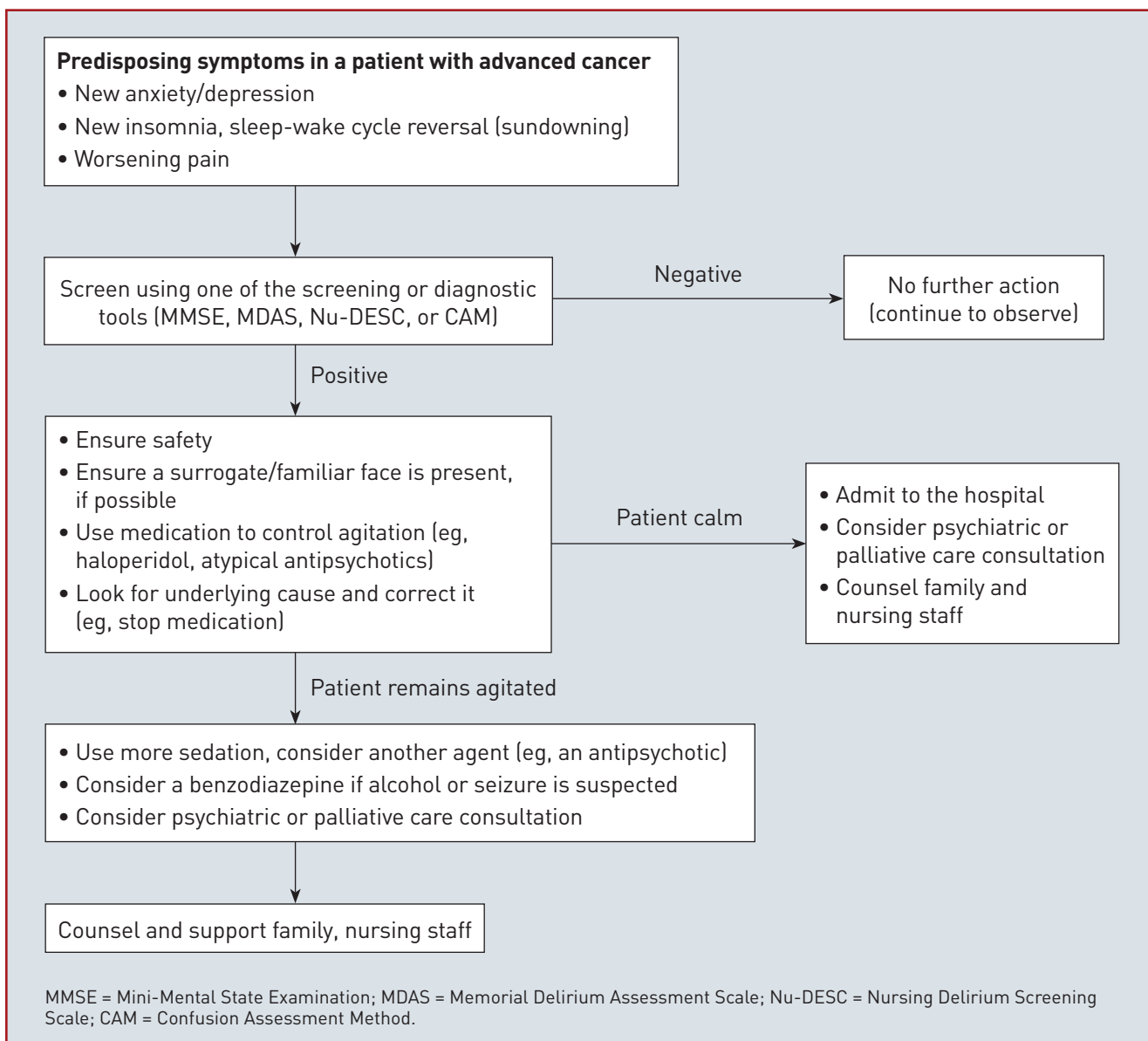
### Pharmacologic

The goal of delirium treatment is to correct underlying causes and contributors to the episode, if possible. In many cases, multiple contributors may be evident, and all of them should be addressed. As illustrated in the case

vignette, patients should be hydrated, infection should be treated, and the offending opioid should be discontinued to allow the body to eliminate active metabolites. In many cases, a different opioid should be instituted to control pain; the new opioid should be administered in equianalgesic doses. A 30% reduction of the new opioid dose may be necessary to account for cross-tolerance.<sup>39</sup>

Table 4 highlights some interventions to correct the underlying pathology causing delirium. In elderly patients, minor interventions such as hearing aids, eyeglasses, or treating constipation may be sufficient to treat an episode of delirium.<sup>40</sup> One study of elderly patients showed that use of restraints, malnutrition, adding three medications or more, and use of Foley catheters were associated with the development of delirium in hospitalized patients.<sup>41</sup>

**FIGURE 3.** Algorithm for management of agitated or mixed delirium in the ED



**Symptomatic Management**

Medications are often needed to control delirium-associated agitation in patients with the hyperactive or mixed subtypes. Table 5 includes a list of medications used to treat agitation, as well as their available forms and most common side effects. In the emergency department setting, agitated patients may require parenteral administration of antipsychotic medications.

Haloperidol is the drug of first choice.<sup>42</sup> It is a high-potency agent that can be initiated at 0.5 to 2 mg IV or SC every few hours.<sup>43</sup> One of the main side effects of

haloperidol is extrapyramidal symptoms, which could be confused with worsening agitation. If agitation persists with increasing doses of haloperidol, agents providing more sedation, such as chlorpromazine or an atypical antipsychotic (eg, olanzapine), may be considered. Benzodiazepines are not recommended for use as a single agent to manage agitation, except in alcohol withdrawal, and could worsen the symptoms of delirium.<sup>43-46</sup> A small study by Breitbart et al<sup>47</sup> compared haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in patients with HIV/AIDS. The

study was stopped early because of worsening of symptoms in patients in the lorazepam arm and an equally good response to haloperidol and chlorpromazine.

Chlorpromazine is a more-sedating antipsychotic, but its use is limited by significant side effects, such as orthostatic hypotension and anticholinergic effects.<sup>47,48</sup>

The atypical antipsychotics have gained attention in the management of delirium<sup>49</sup>; however, most of these agents are unavailable in parenteral form. For atypical antipsychotic agents available in parenteral form, such as olanzapine and ziprasidone, administration via intramuscular injection is recommended. Such routes may not be suitable for the advanced cancer patient, who frequently suffers from muscle wasting and cachexia or has thrombocytopenia or other hematologic abnormalities. Our group studied the use of subcutaneous olanzapine in 24 patients with advanced cancer in the acute palliative care unit. We found olanzapine given subcutaneously to be well tolerated, without evidence of injection site reactions.<sup>50</sup> Time of onset with subcutaneously administered agents is generally similar to that of agents given by intramuscular injection; however, additional pharmacokinetic studies should be conducted to compare time of onset and half-life of the drug. A major limitation of atypical antipsychotics is their high cost compared to the cost of the typical agents.

Some studies have reported increased mortality in elderly patients receiving atypical antipsychotic medications, perhaps resulting from their effect on cardiac conduction. The US Food and Drug Administration issued a boxed warning about this serious side effect in 2005.<sup>51</sup> Wang et al found that mortality risks were similarly elevated in patients taking typical antipsychotics such as haloperidol.<sup>52</sup> In 2007, the FDA issued a similar boxed warning on haloperidol.<sup>53</sup>

Again, this mortality may be related to prolonged QT intervals and resultant arrhythmias. Therefore, it is important to obtain a baseline ECG, if possible. If conduction abnormalities are evident at baseline, antipsychotics should be used sparingly. Follow-up ECGs after antipsychotic administration should be considered on an individual basis.

Antipsychotic side effects depend on the receptor targeted or blocked by the medication. For example, chlorpromazine's action on histamine and  $\alpha_1$ -adrenergic

**Table 4. Specific Interventions to Correct Underlying Causes of Delirium**

Condition	Intervention
Side effect of a medication (eg, opioids, benzodiazepines)	Stop offending drug (with opioids, consider reducing dose/switching to different opioid)
Infection, fever	Treat underlying pathology (antibiotics, antivirals, etc)
Dehydration, ARF, hypercalcemia	Hydration, bisphosphonate or calcitonin (for hypercalcemia)
Brain metastasis	Corticosteroids (consider radiation therapy or chemotherapy)
Alcohol or benzodiazepine withdrawal	Benzodiazepines
Constipation	Laxatives, disimpaction
Hearing or vision impairment	Provide aids

ARF = acute renal failure.

receptors results in more sedation and orthostatic hypotension, respectively, than does haloperidol. Conversely, haloperidol has more extrapyramidal side effects because of its action at dopamine receptors.<sup>16,28,54</sup>

In cases of persistent agitation in patients with advanced cancer, consultation with a palliative care specialist may be required, as such symptoms may herald death and palliative sedation may be indicated. Delirium is the main indication for palliative sedation. In such advanced cases, benzodiazepines, particularly midazolam (given its shorter half-life) is the drug of first choice. Other agents used in this setting include lorazepam and propofol.

## OUTCOMES

Delirium complicates the assessment and management of other symptoms. For example, while cancer patients with delirium tend to experience more pain and have higher opioid requirements at night as compared to those without delirium, increased opioid consumption

**Table 5. Common Medications for Management of Agitated Delirium**

Medication	Main Receptors Affected	Forms Available	Major Side Effects/Disadvantages
Haloperidol	<ul style="list-style-type: none"> <li>• Dopamine D<sub>2</sub>, D<sub>1</sub></li> </ul>	Tablets, liquid, IV, SC, IM depot	<ul style="list-style-type: none"> <li>• Extrapyramidal</li> <li>• QT-interval prolongation</li> <li>• Seizure</li> </ul>
Chlorpromazine	<ul style="list-style-type: none"> <li>• Dopamine D<sub>2</sub>, D<sub>1</sub></li> <li>• α<sub>1</sub>-Adrenergic</li> </ul>	Tablets, IV, suppositories	<ul style="list-style-type: none"> <li>• Orthostatic hypotension</li> <li>• Anticholinergic</li> <li>• QT-interval prolongation</li> <li>• Arrhythmia</li> </ul>
Risperidone	<ul style="list-style-type: none"> <li>• Serotonin 5-HT<sub>2A</sub></li> <li>• α<sub>1</sub>-, α<sub>2</sub>- Adrenergic</li> <li>• Histamine H<sub>1</sub></li> </ul>	Tablets, IM depot	<ul style="list-style-type: none"> <li>• Arrhythmia</li> <li>• Dysphagia</li> <li>• Seizure</li> <li>• Expensive</li> </ul>
Olanzapine	<ul style="list-style-type: none"> <li>• Serotonin 5-HT<sub>2A</sub></li> <li>• Histamine H<sub>1</sub></li> <li>• Muscarinic M<sub>1</sub></li> </ul>	Tablets, IM	<ul style="list-style-type: none"> <li>• Arrhythmia</li> <li>• Weight gain</li> <li>• Sedation</li> <li>• Expensive</li> </ul>
Quetiapine	<ul style="list-style-type: none"> <li>• Serotonin 5-HT<sub>2A</sub></li> <li>• Dopamine D<sub>2</sub></li> </ul>	Tablets	<ul style="list-style-type: none"> <li>• Arrhythmia</li> <li>• Orthostatic hypotension</li> <li>• Expensive</li> </ul>
Ziprasidone	<ul style="list-style-type: none"> <li>• Serotonin 5-HT<sub>2A</sub></li> <li>• Dopamine D<sub>2</sub></li> </ul>	Capsules, IM	<ul style="list-style-type: none"> <li>• Arrhythmia</li> <li>• Orthostatic hypotension</li> <li>• Expensive</li> </ul>

IM = intramuscular; IV = intravenous

may also worsen existing delirium.<sup>55,56</sup> Clinical decision-making in this complex scenario benefits from prior observations of treatment response, a luxury that is rarely available to the emergency physician.

With early identification and prompt treatment of delirium, at least 50% of patients will recover cognitive function.<sup>14,17,20,57</sup> However, they remain at increased risk for subsequent episodes.<sup>57,58</sup> In patients with advanced cancer, Lawlor et al<sup>14</sup> found that dehydration and opioid use were associated with reversibility of delirium, while hypoxic encephalopathy and metabolic factors were associated with nonreversible terminal delirium. Delirium is a significant prognostic marker and is associated with prolonged hospitalization, increased hospital mortality, and increased 6-month mortality.<sup>14,58</sup> Also, as in the vignette presented, delirium is associated with an increased risk of falls.<sup>59</sup>

Upon hospital discharge, many patients with delirium need long-term care in nursing homes or assisted-living facilities.<sup>9,60</sup> The overall cost of care is significantly higher for patients with delirium than that for patients without it.<sup>61</sup> In a study of patients undergoing hematopoietic stem cell transplant for malignancy, more than half were diagnosed with delirium in the month following transplant.<sup>15</sup> Fann et al<sup>62</sup> compared patients who developed delirium after stem cell transplantation with those who did not; they found that those with delirium had significantly worse depression, anxiety, and fatigue 30 days after transplant and significantly worse cognitive and executive functions 80 days after transplant. Han et al<sup>8,38</sup> reported delirium diagnosed in the emergency department to be an independent predictor of 6-month mortality and prolonged hospital length-of-stay.



## CONCLUSION

Delirium is a common neuropsychiatric syndrome in patients with cancer, particularly in elderly patients, those receiving opioids, and those with advanced disease. The significant morbidity and mortality associated with this syndrome lead to high levels of distress for patients, their families, and medical staff. The diagnosis of delirium is difficult, especially in the emergency department setting. We therefore strongly support the use of delirium screening tools in the emergency department. With prompt management of the underlying etiology, the majority of patients will recover from an episode of delirium, although they will remain at risk for future occurrences. More research is needed to understand the outcomes of early emergency department interventions in this population. **EM**

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