Agitation and Delirium at the End of Life: "We Couldn’t Manage Him"

William Breitbart; Yesne Alici


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“‘We Couldn’t Manage Him’”

William Breitbart, MD
Yesne Alici, MD

THE PATIENT’S STORY
Mr L was a 59-year-old man with metastatic non–small cell lung cancer. He was brought to the hospital for progressive lower extremity weakness and gait instability that had developed over several weeks and worsened in the preceding 2 or 3 days. His partner, Ms P, was having difficulty caring for him at home because Mr L continually fell when attempting to get out of bed on his own. She found this extremely frustrating and was concerned about his safety. Mr L’s cancer had been diagnosed 3 years earlier and treated aggressively with multiple chemotherapy regimens and radiation therapy. Two years ago, Mr L developed brain metastases and underwent 3 gamma-knife radiation treatments. One month previously, his oncologist discussed the possibility of additional chemotherapy, but Mr L decided to pursue comfort measures only. He was referred for home hospice for management of pain and debilitating fatigue.

During the following month, his neurological status deteriorated and Ms P noted changes in his personality. She brought Mr L to the emergency department, where he was irritable, uncooperative, and verbally abusive to the staff. Computed tomography and magnetic resonance imaging scans of the brain revealed new mild depression of the cerebellar tonsils, suggesting an increasing mass effect from his brain metastases, and worsening ventriculomegaly, but no new brain lesions. Mr L was treated with lorazepam to control his irritability and verbally abusive behavior. However, after the lorazepam was administered, he became more agitated and restless and fell while attempting to get out of bed. The staff placed him in wrist restraints to control his behavior and admitted him.

On hospital day 2, after a palliative care consultation, he was transferred to a comfort care suite. The restraints were removed, and a 24-hour sitter was engaged to ensure his safety. His agitation was believed to be due in part to uncontrolled pain, so morphine was initiated and titrated to...
control pain. Dexamethasone and insulin were discontinue-
died, given that they were no longer contributing to his com-
and were potentially exacerbating his agitation. Lor-
up. Upon transfer, Mr L’s regimen included the fol-
for agitation; lorazepam, 0.5 to 2 mg intrave-
nously every 3 hours as needed for agitation. Mr L was given intravenous haloperidol just before his am-
universally related to medical causes. Clinical fea-
tures can be quite varied (Box 1). Delirium is the most com-
face, with prevalence estimates ranging from rates as low
achieved by his favorite music, which seemed to calm him. Mr L’s agi-
tion improved and he was transferred to an inpatient hos-
facility. Upon transfer, Mr L’s regimen included the fol-
following medications: fentanyl patch, 37.5 µg/h every 72 hours;
haloperidol, 2 mg intravenously every 6 hours; haloperi-
dol, 0.5 mg intravenously or subcutaneously every 4 hours
as needed for agitation; lorazepam, 0.5 to 2 mg intrave-
nously every 3 hours as needed for insomnia or anxiety.
Mr L was given intravenous haloperidol just before his am-
bulance transfer and morphine was ordered for administra-
during the transport. At the residential hospice faci-
cility, Mr L’s agitation was successfully controlled with
haloperidol and nonpharmacological measures, such as a
sitter and his favorite music. He died there 4 days later.

PERSPECTIVES
In December 2006, a few months after Mr L’s death, a Per-
spectives editor interviewed Dr C, the attending physician of
the hospital’s palliative care consultation team; Ms S, the
team’s social worker; and Dr H, the medical director of the
residential hospice.

Dr C: He was delirious. I thought he was potentially in-
pain. . . . He seemed incredibly frustrated by his condition.

Ms S: The medicine team made the referral to palliative care,
and I was in on the original assessment with the physician about
his prognosis and involved in a family meeting with his part-
ner . . . she was exhausted to the point of dropping.

Dr H: [Delirium] is one of the things that people have diffi-
culty taking care of at home. It’s very scary for family members.

Delirium, often accompanied by agitation, is frequently
the final challenge of palliative care management, as illus-
trated by the case of Mr L. In the palliative care setting, de-
lirium is often the harbinger of impending death; it is dis-
tressing for all concerned; and there are controversies
regarding the goals of management, including appropriate
assessment and pharmacological and nonpharmacological
approaches. Determining and securing the best care set-
ning for the dying patient with delirium is complex. For many
families, delirium seriously challenges the ability to grant a
loved one’s wish to die at home.

DEFINITIONS AND PREVALENCE
OF TERMINAL DELIRIUM

Dr H: Our inpatient hospice is a small facility with 6 beds. Pa-
tients tend to come there for [the] end of life, half of them from
our home program and half from local hospitals . . . [O]ne third
have relatively dramatic end-of-life delirium.

The Diagnostic and Statistical Manual of Mental Disorders
(Fourth Edition, Text Revision) diagnostic criteria define
delirium as a syndrome composed of disturbances of con-
sciousness, attention (ie, arousal), and cognition, with abrupt
onset and fluctuating course, and require that the distur-
bance be etiologically related to medical causes. Clinical fea-
tures can be quite varied (Box 1). Delirium is the most com-
mon neuropsychiatric disorder that terminally ill patients
face, with prevalence estimates ranging from rates as low
as 20% to 42% to rates as high as 52% to 88% among ter-
minally ill patients with cancer.5-7 Prospective studies con-
ducted in palliative care settings find that up to 42% of pa-
tients have delirium upon admission,3,5-7 and an additional
32% to 45% of patients develop delirium during the week
prior to death.3,7

Presentation and Subtypes of Delirium

Dr H: [Although] he had occasional periods of calling out, most
of the time he was sleeping. He did sip some fluid in the early
morning, but by the afternoon he was refusing any oral in-
take. He did all right during the night, but [the next day] he
awoke and was extremely restless. He was very angry and in-
Sitting on a bed and accusing them of stealing his jacket. He was trying
to climb out of bed.

Delirium is classified according to 3 clinical subtypes, based
on either motor or arousal disturbances: hypoactive, hy-
peractive, and mixed. The hypoactive (hypoalert, hypo-
aroused) subtype is characterized by psychomotor re-
 retardation, lethargy, sedation, and reduced awareness of
surroundings.6,8-12 Hypoactive delirium is often mistaken
for depression and is difficult to differentiate from seda-
tion due to opioids, or obtundation in the last days of life.12
The hyperactive (hyperalert, hyperaroused) subtype is more
commonly characterized by restlessness, agitation, hyper-
vigilance, hallucinations, and delusions.8-11 In the pallia-
tive care setting, hypoactive delirium is most common. One
meta-analysis found the mean prevalence of hypoactive de-
lirium to be 48% (range, 15%-71%),8 with 86% of delirium
being the hypoactive type in one study.6 Hyperactive de-
lirium occurs in 13% to 46% of patients in the palliative care
setting.8 Some studies suggest that the subtypes of de-
lirium may be related to different causes and may have dif-
ferent treatment responses.8,11-13 Hypoactive delirium has
generally been found to occur with hypoxia, metabolic dis-
turbances, and anticholinergic medications.8,11-13 Hyperac-
tive delirium is correlated with alcohol and drug with-
drawal, drug intoxication, or medication adverse effects.8,11-13
A randomized controlled trial of haloperidol and chlor-
promazine found that both drugs were equally effective in
hypoactive and hyperactive subtypes of delirium,14 whereas
an open label trial of olanzapine found poorer treatment re-
sponse with hypoactive delirium.9 Mortality is higher with
hypoactive than hyperactive delirium.14,15 Although agita-
tion was the initial focus of intervention for Mr L, he ex-

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hibited the “mixed” subtype of delirium, with periods of hypoaactivity and sedation, alternating with periods of hyperactivity and agitation.

**Assessment of Delirium**

In the palliative care setting, delirium is indicative of underlying medical problems, such as infections, electrolyte disturbances, organ failure, uncontrolled pain, and medication adverse effects and is often a preterminal event. Clinically, the diagnostic “gold standard” is the clinician’s assessment using the DSM-IV-TR criteria for delirium. Box 1 shows components of the bedside clinical examination to assist in the diagnosis of delirium.

In addition, several delirium screening and evaluation tools have been developed, including the Delirium Rating Scale-Revised 98, Confusion Assessment Method, Cognitive Test for Delirium, and Memorial Delirium Assessment Scale and are reviewed elsewhere. The Memorial Delirium Assessment Scale has been validated in inpatient palliative care settings with a sensitivity of 97% and a specificity of 95% at a cutoff score of 7.

**Box 1. Clinical Features of Delirium and Bedside Clinical Examination**

<table>
<thead>
<tr>
<th>Disturbance of Consciousness, Arousal, Awareness</th>
<th>Disorganized Thinking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask the patient to describe surroundings with eyes closed and ask, “What color is the wall?”</td>
<td>Ask patient an open-ended question, eg, “Describe your medical condition.”</td>
</tr>
<tr>
<td>Ask the patient, “Are you feeling 100% awake?” and if not, “How awake do you feel?”</td>
<td>Listen for rambling, incoherent speech or tangential and circumstantial thought process.</td>
</tr>
</tbody>
</table>

**Attention Disturbances**

Is the patient easily distracted by outside stimuli or overabsorbed in a task, such as picking at the bed sheet?

Test digit span, starting with 3, 4, then 5 digits forward, followed by 3, 4, then 5 digits backward.

**Disorientation**

Check for orientation to time, place, and person.

Test the limits of orientation, eg, year, month, date, day, and time.

Do not assume full orientation because patients know the year and the month.

**Cognitive Disturbances Including Memory Impairment, Executive Dysfunction, Aphasia, Paraphasia, Dysnomia, Apraxia, Agnosia**

Test registration and immediate recall (use different words for successive evaluations).

Test speech fluency, naming, reading, repetition, writing, comprehension.

Perform Clock Drawing Test.钟®

**Perceptual Disturbances (Illusions, Hallucinations)**

Ask specifically about hallucinations, eg, “Are you seeing or hearing strange things?”

Use nursing or family member reports to determine incidents of perceptual disturbances.

**Interference With Assessment and Management of Pain and Other Symptoms**

**Dtt H:** He slept on and off . . . He had 2 episodes [of] . . . moaning and calling out; those were assumed to be . . . pain and were treated with morphine. [When] he entered the dying phase, he was no longer verbally responsive; he had a minor response with movement, with occasional moaning for [which], he got “breakthrough” morphine.
In the medically ill, delirium can interfere significantly with the recognition and control of symptoms such as pain.\textsuperscript{24,26} Uncontrolled pain can cause agitation, as with Mr L; however, in the presence of a clear sensorium, delirium is an unlikely explanation. Patients with delirium use a significantly greater number of “breakthrough” doses of opioids at night compared with patients without delirium due to sleep-wakefulness cycle reversal.\textsuperscript{27} On the other hand, agitation due to delirium may be misinterpreted as uncontrolled pain, resulting in inappropriate escalation of opioids, potentially exacerbating delirium.\textsuperscript{25} Terminally ill hospice patients may have difficulty communicating their needs, with the degree of impairment related both to delirium and to opioid dosage.\textsuperscript{26} Some methods to improve assessment of pain in nonverbal palliative care patients are available.\textsuperscript{29}

**The Experience of Delirium for Patients**

Dr C: He [said] that he wanted to get out of bed, and try to urinate. I assisted him in sitting up and it was clear to me that he wasn’t going to be able to do it on his own. Then he insisted on standing up, and when he stood, he realized that he had weakness in his lower extremities from his metastases. He would forget that he had this weakness.

Delirium causes distress in patients, family members, clinicians, and staff, as illustrated by Mr L.\textsuperscript{30–33} In a study of 101 terminally ill cancer patients, Breitbart et al\textsuperscript{30} found that 54% of patients recalled their delirium experience after recovering from the episode. The more severe the episode, the less likely the patient was to recall it, but the presence of hallucinations and delusions made delirium more likely to be recalled (and to be reported as distressing). Distress related to the episode was rated by patients as a mean of 3.2 on a 0-to-4 scale (with 4 being most severe). Of note, patients with hypoactive delirium (ie, with few outward manifestations of discomfort or distress) were just as distressed as patients with hyperactive delirium. DiMartini and colleagues\textsuperscript{31} reported the development of posttraumatic stress disorder in patients who experienced hallucinations and delusions during delirium. These findings highlight the importance of treating the causes and controlling the symptoms of delirium in both hypoactive and hyperactive subtypes, using nonpharmacological and pharmacological interventions.

**The Experience of Delirium for Family Members, Clinicians, and Staff**

Ms S: The agitation involved him trying to get out of bed and leave the house. He was unable to walk by himself and he had no judgment, so [the partner] was constantly trying to keep him in bed.

Dr C: Along with the nursing assistant and the medical student [and me] . . . even with 3 of us, we couldn’t manage him.

In a study of caregiver distress related to delirium, Breitbart et al\textsuperscript{30} found that spouses or family caregivers rated their distress at 3.75 (on a 0-4 scale), and nurses, at 3.1, just below the average patient rating of 3.2. Two-thirds of 300 bereaved Japanese families who participated in a survey\textsuperscript{32} reported that delirium in their family members was highly distressing. Symptoms that caused the most distress included agitation and cognitive impairment. Caregivers of delirious terminally ill patients have been shown in 1 study to be 12 times more likely to develop an anxiety disorder than caregivers of nondelirious patients.\textsuperscript{33} Often, family members are unaware of the medical nature of delirium. Spouses may mistakenly believe that their partner has suddenly developed a psychiatric illness. Family members also describe a sense of “double bereavement”: they grieve the loss of meaningful connection because of the delirium and then grieve again when their loved one dies. It is important for the clinician to explain the medical nature of delirium, as well as potential treatment options (including palliative sedation).

**Etiologies and Diagnostic Work-up of Delirium**

The underlying etiologies of delirium are multiple, including infection, organ failure, medication adverse effects, and rarely, paraneoplastic syndromes, eg, malignant hypercalcemia.\textsuperscript{5,6,34–42} In the medical setting, the diagnostic workup typically includes an assessment of potentially reversible causes, eg, dehydration or medication, as well as those that are potentially irreversible, eg, sepsis or major organ failure. The clinician should obtain a detailed history from family and staff of the patient’s baseline mental status and verify the current fluctuating mental status. Physical examination should seek evidence of infection, dehydration, or organ (eg, liver, pulmonary, renal) failure.\textsuperscript{23,39,42} Medication adverse effects should be reviewed as a possible cause. Opioids, corticosteroids, benzodiazepines, and anticholinergics are commonly associated with delirium.\textsuperscript{23,34–37,39} Laboratory tests can identify metabolic abnormalities (eg, hypercalcemia, hyponatremia, hypoglycemia), hypoxia, or disseminated intravascular coagulation. In some instances, an electroencephalogram (to rule out seizures), brain imaging studies (to rule out brain metastases, intracranial bleeding, or ischemia), and lumbar puncture (to rule out leptomeningeal carcinomatosis or meningitis) may be appropriate.\textsuperscript{23,39,42} However, when confronted with delirium in the terminally ill or dying patient, the clinician must take an individualized and judicious approach to such testing, consistent with the goals of care. The appropriate extent of diagnostic evaluation in these patients is a matter of some debate.\textsuperscript{4–6,26}

Most palliative care physicians would undertake diagnostic studies only when a clinically suspected cause can be easily identified, with minimal use of invasive procedures and review of medications. An etiology is discovered in fewer than 50% of terminally ill patients with delirium.\textsuperscript{4} However, studies in patients with earlier stages of advanced cancer have demonstrated the potential utility of a thorough diagnostic assessment.\textsuperscript{38} In one study,\textsuperscript{38} 68% of delirious cancer patients experienced improved symptoms...
upon discovery of an etiology and institution of treatment, despite a 30-day mortality rate of 31%. Lawlor and colleagues explored the etiologic precipitants and potential reversibility of delirium in patients with advanced cancer admitted to a palliative care unit and found an overall reversibility rate of 49%. Delirium was more likely to reverse when dehydration could be corrected and when opioids or psychoactive medications were reduced or discontinued when possible. Irreversibility of delirium was associated with major organ failure and hypoxic encephalopathy. In a study of patients with advanced cancer admitted to hospice, the overall delirium reversibility rate was only 20% and the 30-day mortality rate was 83%. Reversibility of delirium was highly dependent on the etiology: hypercalcemia was judged reversible in 38%; medications in 37%; infection in 12%; and hepatic failure, hypoxia, disseminated intravascular coagulation, and dehydration each in less than 10%. Leonard and colleagues found a 27% recovery rate from delirium among patients in palliative care. Patients with irreversible delirium experienced greater disturbances of sleep and cognition. Mean (SD) time until death was 39.7 (69.8) days for 33 patients with reversible delirium vs 16.8 (10.0) days for 88 patients with irreversible delirium.

**Differential Diagnosis of Agitation and Delirium**

**Dr H:** In the differential diagnosis of agitation, the 2 most common ones are fecal impaction and bladder retention. Patients often come to us on opioids and lose track of bowel movements... and when they get a full bowel or full bladder, they get very agitated. Third, I would say, is unrelieved pain.

**Dr C:** We made sure that there weren’t any medical issues that we could change. First, I thought his pain wasn’t controlled. Second, I thought he was incredibly frustrated with the fact that his legs no longer worked.

Not all patients with agitation are delirious. The diagnosis is reserved for those who meet the diagnostic criteria and clinical syndrome described above. Patients may become agitated without delirium (ie, without disturbances of consciousness or cognition) for a variety of reasons. In addition to fecal impaction and urinary retention mentioned above, uncontrolled pain, medication-induced akathisia, panic attacks, or mania can cause agitation. It is often challenging to differentiate among delirium, dementia, and delirium superimposed on preexisting dementia. Delirium and dementia may both present with cognitive disturbances including disorientation, memory impairment, aphasia, apraxia, agnosia, and executive dysfunction. Impairments in judgment, abstract thinking, and disturbances in thought process are seen in both disorders. Delusions and hallucinations can be features of certain types of dementia (eg, Lewy body dementia). It is the abrupt onset, fluctuating course, and disturbances of consciousness or arousal that differentiates delirium from dementia. When delirium is superimposed on a preexisting dementia, diagnosis of delirium becomes even more challenging. Ordinarily, delirium, unlike dementia, is by definition reversible, although as noted, in terminally ill patients, delirium may be irreversible, either because the underlying cause cannot be corrected or because the patient dies before such efforts succeed.

When delirium presents with mood symptoms such as depression, apathy, euphoria, or irritability, these symptoms are not uncommonly attributed to major depressive disorder or bipolar disease, especially in patients with a past psychiatric or family history of these conditions. The hypoactive subtype of delirium is commonly misdiagnosed as depression. The hypoactive subtype of delirium is commonly misdiagnosed as depression (TABLE 1). On the other hand, symptoms such as severe anxiety and autonomic hyperactivity can lead the clinician to an erroneous diagnosis of panic disorder. Perceptual disturbances such as hallucinations and thought disturbances such as paranoid ideation can be misdiagnosed as schizophrenia (which is highly unlikely to present initially at ≥40 years). Acute onset, fluctuating course, disturbances of cognition, and consciousness, in the presence of 1 or more etiologic causes, are important in the diagnosis of delirium in terminally ill patients.

**Delirium as a Harbinger of Death**

**Ms S:** After discharge... the nurse at the facility [said] that he was agitated for 2 or 3 days, but [during] the last 2 days he was very peaceful.

Delirium in terminally ill patients is a reliable predictor of approaching death within days to weeks. In hospice patients with delirium range from 22% to 76%. On palliative care units and in hospice settings, delirium is often a predictor of impending death in patients with advanced cancer. Delirium presenting with hypoactive subtype, irreversible etiologies, and greater cognitive impairment is often associated with death within a period of days to weeks.

If advance care planning has not taken place before an episode of delirium in a terminally ill patient, it is often too late to do so. However, some patients with mild delirium can still participate in limited decisions such as naming a health care proxy (BOX 2).

**Goals of Care**

**Dr C:** We tried to determine what was causing his agitation. We started [regularly] scheduling his Haldol, and we had a sitter who knew him and would keep him oriented as to where he was and what was going on. It calmed him down. He did better with some sitters than with others.

**Ms S:** It’s not just the patient that we’re taking care of at the end of life, we’re taking care of the family... We tried to create an environment where [the partner] felt comforted that she was doing her best.
In the last days of life, the ideal goal of delirium management is a patient who is comfortable, not in pain, awake, alert, calm, cognitively intact, and able to communicate coherently with family and staff. Treatment of the symptoms of delirium should be initiated before, or in concert with, a diagnostic assessment of possible etiologies. When delirium is a consequence of the dying process, the goal of care may shift to providing comfort through the judicious use of sedatives, even at the expense of alertness.42

**Nonpharmacological Management**

Dr C: *The first thing I did was have the wrist restraints removed... and order a sitter... Sometimes just having a patient in a quiet place with no distractions, and allowing them to actually sleep, can help.* Turning the lights off, playing soothing music can help... finding... what will calm the patient down.

...we looked into other options for where he could be cared for. One of his options was inpatient hospice, which I think can be better at nonpharmacological management of agitation, particularly things like brushing people’s hair, orienting them, and sometimes massage.

Ms S: *We had him in the comfort care suite and tried to limit the number of people going in the room... He really responded to reassuring, quiet words and to someone holding his hand.*

Nonpharmacological and supportive therapies are important in patients with terminal delirium26,42 (Box 3). In nonpalliative care settings, there is evidence that nonpharmacological interventions used in these studies include oxygen delivery, fluid and electrolyte administration, ensuring bowel and bladder function, nutrition, mobilization, pain treatment, frequent orientation, use of visual and hearing aids, and environmental modifications to enhance a sense of familiarity.45,46,48-50 In the case of Mr L, measures to help reduce anxiety and disorientation included providing a quiet, well-lit room with familiar objects, favorite music, a clock and calendar, and family present.42 One-to-one nursing may be necessary for observation. When possible, physical restraints should be avoided42,47 because physical restraints in the treatment of delirium have been identified as an independent risk factor for its persistence at discharge.45 The American Psychiatric Association Task Force on the Psychiatric Uses of Seclusion and Restraint has developed guidelines for the appropriate use of restraints,42 as has the Joint Commission. Restraint orders should be used only when a patient represents a clear risk of harm to self and others and no less restrictive alternative is available. Restraint orders should be time-limited and the patient’s condition monitored closely.42

**Pharmacological Management**

Dr H: *The chief medication that we use is haloperidol. We can give it by various means, but typically give it by oral concentrate. If that’s not kicking in enough, we start to add on things.*

Dr C: *I talked to [Mr L’s partner] about the risks and benefits of medications... There are some concerns that atypical antipsychotics have a higher risk of death, but when you get to this point of caring for someone who is this difficult, most families, I’ve found, are more than willing to try anything that will help make the situation better.*

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**Table 1. Differentiating Hypoactive Delirium From Depression**

<table>
<thead>
<tr>
<th>Features</th>
<th>Hypoactive Delirium</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disturbance of arousal</td>
<td>Hyperaroused, hypaeralt, drowsy</td>
<td>Normal level of arousal, awake, and alert</td>
</tr>
<tr>
<td>Cognitive changes</td>
<td>Short-term memory loss, dysomia, impaired attention, decreased concentration, disorientation, agnosia, aphasia</td>
<td>Mild cognitive deficits may be present, primarily slowing of cognition, subjective problems with concentration</td>
</tr>
<tr>
<td>Temporal onset</td>
<td>Abrupt onset</td>
<td>Slow onset</td>
</tr>
<tr>
<td>Perceptual disturbances</td>
<td>Present in up to 75% of patients, visual hallucinations most common</td>
<td>Rarely present, only seen in depression with psychotic features, usually auditory hallucinations</td>
</tr>
<tr>
<td>Disturbance of thought content</td>
<td>Paranoic delusions often present</td>
<td>Guilt, worthlessness, hopelessness are common in depression</td>
</tr>
<tr>
<td>Mood symptoms</td>
<td>Patients may appear sad, depressed, irritable, mood is often labile, disorientation, due to delirium, can lead to expressions of desire for death or suicidal ideation</td>
<td>Patients frequently verbalize sad, depressed mood, suicidal ideation is common and related to thoughts of hopelessness, worthlessness, and guilt or burden</td>
</tr>
<tr>
<td>Psychomotor activity</td>
<td>Hyoactive, quiet, withdrawn, slowed</td>
<td>Usually hypoactive, withdrawn, or slowed, occasionally hyperactive and agitated</td>
</tr>
<tr>
<td>Family history</td>
<td>Not applicable</td>
<td>Family history of depression common</td>
</tr>
<tr>
<td>Past psychiatric history</td>
<td>Previous episodes of delirium may be present</td>
<td>Past episodes of depression not uncommon</td>
</tr>
<tr>
<td>Neurological examination</td>
<td>Asterixis, frontal release signs may be elicited</td>
<td>Usually normal examination</td>
</tr>
</tbody>
</table>

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Box 2. Statements That May Be Helpful to Clinicians in Guiding Patients and Families Through the Course and Treatment of Terminal Delirium

Prevalence and Nature of Delirium

“Delirium develops in almost all (up to 90%) patients during the last weeks of life.”

“Delirium presents with changes in behavior and thinking, but it is really a sign that multiple medical problems related to the underlying disease are interfering with the brain working normally.”

“Delirium is medical in nature; it does not mean that your loved one has now suddenly developed a new psychiatric illness or is having a ‘nervous breakdown.’”

The Experience of Delirium

“Delirium can be very distressing for patients, families, and hospital (hospice) staff.”

“Delirium can cause agitation or it can cause sedation and sleepiness, and it can be mistaken for depression.”

“Delirium can interfere with assessment of symptoms like pain.”

“Delirium can be effectively managed, resulting in less distress and better symptom control.”

“When you lose the ability to communicate with your loved one because of delirium, it is a terrible loss. It’s as if you’ve lost the essence of who they are, and your own grieving process may begin. That’s normal and it helps to anticipate that this might occur.”

Treatment of Delirium

“Would you prefer us to keep you sedated, sleepy, and comfortable, though unable to talk or eat and drink, or would you prefer us to keep you more awake, even at the expense of being confused and perhaps in some distress?”

“The goal of treating the symptoms of delirium is to have the patient awake, alert, coherent, and communicating meaningfully with the family and staff, if possible.”

“Using sedation to control symptoms at this stage of illness does not shorten survival, it merely provides better comfort.”

Delirium as a Harbinger of Death

“We may be running out of time to discuss important treatment preferences together, that is, while your loved one is still able to participate, even minimally, in decision making.”

“With the development of delirium at this stage of illness, it may be a good idea to bring to the hospital any family members who are far away and would want to be here if things took a turn for the worse.”

“Delirium, in patients with far advanced disease, is unfortunately often a predictor of death in the coming days to weeks.”

Treatment of antipsychotic or sedative medications is often essential to control the symptoms of delirium (TABLE 2, TABLE 3).”

“Typical” Antipsychotic Medications. No medications have been approved by the US Food and Drug Administration (FDA) for treatment of delirium. Haloperidol is the usual first-line antipsychotic medication for delirium in patients with advanced disease, due to its efficacy, relative safety, and versatility (eg, few anticholinergic effects, minimal cardiovascular adverse effects, lack of active metabolites, and availability in different routes of administration; Table 3). However, only 0.5% to 2% of hospitalized cancer patients receive haloperidol for symptoms of delirium, and only 17% of terminally ill patients receive any antipsychotic drugs for agitation or delirium. The American Psychiatric Association practice guidelines provide directions for the use of antipsychotics for treatment of delirium and growing evidence supports their use. In general, doses of haloperidol need not exceed 20 mg in a 24-hour period; however, some clinicians advocate higher doses in selected cases. The FDA has issued a warning about the risk of QTc prolongation and torsades de pointes on electrocardiogram with intravenous haloperidol; in nonterminal patients, QTc intervals should be monitored regularly. In severe agitation related to delirium, clinicians may add lorazepam to haloperidol. This combination may be more effective in rapidly sedating the agitated, delirious patient and may help minimize any extrapyramidal adverse effects of haloperidol.

Chlorpromazine can be used instead of haloperidol (with or without lorazepam) for severe agitation in terminally ill patients. It is important to monitor chlorpromazine’s anticholinergic and hypotensive adverse effects, particularly in elderly patients.

In a double-blind, randomized comparison trial of haloperidol, chlorpromazine, and lorazepam involving 30 patients, Breitbart and colleagues demonstrated that lorazepam alone, in doses up to 8 mg in a 12-hour period, was ineffective in the treatment of delirium, and in fact sometimes worsened it. This was the case with Mr L, whose delirium and agitation worsened after lorazepam alone. In contrast, both haloperidol and chlorpromazine, in low doses (approximately 2 mg of haloperidol equivalent per 24 hours), were effective in controlling the symptoms of delirium and in improving cognitive function in the first 24 hours of treatment. Both hyperactive as well as hypactive subtypes of delirium were equally responsive to treatment with haloperidol or chlorpromazine. A Cochrane review on drug therapy for delirium in terminally ill patients concluded that, based on this single study, haloperidol is the most suitable medication for the treat-
Atypical Antipsychotic Medications. Atypical antipsychotic agents (ie, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) are increasingly used due to decreased risk of extrapyramidal adverse effects.23 Another Cochrane review, comparing the efficacy and the incidence of adverse effects between haloperidol and atypical antipsychotics, concluded that, like haloperidol, selected newer atypical antipsychotics (risperidone, olanzapine) are effective in managing delirium.58 They found that haloperidol doses greater than 4.5 mg/d tended to result in increased rates of extrapyramidal symptoms compared with the atypical antipsychotics, but lower-dose haloperidol (ie, <3.5 mg/d) did not result in a greater frequency of extrapyramidal adverse effects.58 This Cochrane review found only 2 randomized controlled trials eligible to be included in the meta-analysis, limiting the power to detect a difference (n=199). However, the overall extrapyramidal adverse effects of the atypical antipsychotics risperidone and olanzapine did not differ significantly from haloperidol (odds ratio, 0.63; 95% confidence interval, 0.29-1.38; P=.25).53,54,58 Several authors have published their open-label experience with treating delirium and agitation with atypical antipsychotics, including olanzapine,9,59-61 risperidone,62-65 quetiapine,66,67 ziprasidone,73,74 and aripiprazole.75 Randomized controlled trials are needed to assess efficacy and tolerability of these other newer atypical antipsychotics for delirium in terminally ill patients. Clozapine should be avoided because of the risk of agranulocytosis.81

Risk of Death With Antipsychotic Medications. None of the atypical antipsychotics have FDA approval for treating delirium, and the FDA has issued a black box warning of increased risk of death when these antipsychotics are used to treat elderly patients with dementia-related psychoses. This warning was based on a meta-analysis by Schneider et al82 of 17 placebo-controlled trials involving patients with dementia. The risk of death in patients treated with atypical antipsychotic agents was 1.6 to 1.7 times greater than in those who received placebo. Most deaths were associated with cardiovascular disease or infection. A second, retrospective study of nearly 23,000 older patients found higher mortality rates associated with typical than with atypical antipsychotics—whether or not they had dementia.83 This finding led to an extension of the FDA warning to typical antipsychotics.84 Therefore, nonpharmacological efforts to reduce delirium are critical to reduce the need to use antipsychotic medications whenever possible.

Sedative Agents. The literature and clinical experience suggest that approximately 30% of dying patients with delirium do not have their symptoms adequately controlled by antipsychotic medications.5,23,85-88 In such cases, a reasonable choice is the use of sedative agents such as benzodiazepines (eg, midazolam, lorazepam), propofol, or opioids.86-89 In studies of the use of palliative sedation for symptom control, delirium was identified as the target symptom in up to 36% of cases.86,87 However, use of sedatives for management of delirium in dying patients raises issues regarding the patient’s decision making, the family’s anticipatory grief, and the clinician’s ethical concerns. Ideally, the option of palliative sedation for the control of symptoms such as delirium is discussed with the patient and family while the patient still has capacity to participate in

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Box 3. Nonpharmacological Management of Delirium*

Nonpharmacological Interventions

- Minimize the use of immobilizing catheters, intravenous lines, and physical restraints53-47
- Avoid immobility, early mobilization45-51
- Monitor nutrition48,49,51
- Provide visual and hearing aids47
- Monitor closely for dehydration47
- Control pain45
- Monitor fluid-electrolyte balance31
- Monitor bowel and bladder functioning31
- Review medications48,49,51
- Reorient communications with the patient45-47
- Place an orientation board, clock, or familiar objects (ie, family photographs) in patient rooms45-50

Encourage cognitively stimulating activities such as word puzzles9
- Facilitate sleep hygiene measures, including relaxation music or tapes at bedtime, warm drinks, and gentle massage42
- Minimize noise and interventions at bedtime, eg, by rescheduling medication times45-47,51

4 Level of Evidence Use of these nonpharmacological interventions in the prevention of delirium has been shown to reduce its incidence (level I).53,54,58 Use of these nonpharmacological interventions in the treatment of delirium has resulted in faster improvement of symptoms and of cognition scores without any effects on mortality or health related-quality of life outcomes (level I).45,46,48-52 However, all of the prevention and treatment trials with nonpharmacological interventions were conducted in general medical units or in postoperative patients and not in the palliative care setting. Some of the trials have allowed the use of antipsychotics and cholinesterase inhibitors when clinically indicated.48,49,51

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decision making. Fears that sedation will hasten death should be addressed.23,90 During palliative sedation, clinicians can periodically lighten the sedation to reassess delirium and to allow communication with family and staff, if possible.

Psychostimulants. Some clinicians have suggested that the hypoactive subtype of delirium may respond to psychostimulants such as methylphenidate, or combinations of antipsychotics and psychostimulants or antipsychotics and wakefulness agents such as modafinil.91-94 However, the published experience with psychostimulants in treating delirium is limited to case reports and 1 open-label study.92-94 The risks of precipitating agitation and exacerbating psychotic symptoms remain a concern.92-94

Cholinesterase Inhibitors. Impaired cholinergic function has been implicated as 1 of the final common pathways in the neuropathogenesis of delirium.10,95 Despite case reports of beneficial effects of donepezil and rivastigmine,96-98 a Cochrane review concluded that there is currently no evidence from controlled trials supporting use of cholinesterase inhibitors in the treatment of delirium.7

Controversies in the Pharmacological Treatment of Terminal Delirium. Clinicians are sometimes concerned that the use of sedating medications may hasten death via respiratory depression, hypotension, or even starvation. However, studies have found that the use of opioids and psychotropic agents in hospice and palliative care settings is associated with longer

### Table 2. Randomized Controlled Trials of the Treatment and Prevention of Delirium

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Dose and Duration, Mean (SD)</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of delirium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breitbart et al,14 1996</td>
<td>Double-blind RCT of terminally ill AIDS patients: 11, haloperidol; 13, chlorpromazine; and 6, lorazepam for treatment of delirium</td>
<td>1.4 (1.2) mg/d Haloperidol</td>
<td>DRS scores significantly improved in haloperidol and chlorpromazine groups ( P &lt; .05 )</td>
</tr>
<tr>
<td>Han and Kim,52 2004</td>
<td>Double-blind RCT of hospitalized patients: 12, haloperidol; 12, risperidone for the treatment of delirium</td>
<td>1.7 (0.84) mg/d Haloperidol</td>
<td>MDAS scores improved significantly in both groups, but no significant difference between groups</td>
</tr>
<tr>
<td>Hu et al,53 2004</td>
<td>Double-blind RCT of hospitalized patients: 75, olanzapine; 72, intramuscular haloperidol; and 29, oral placebo for the treatment of delirium</td>
<td>4.5 (4) mg/d Olanzapine</td>
<td>The improvement in DRS scores were significantly higher in the olanzapine (72%) and haloperidol (70%) groups vs placebo (29.7%) ( P &lt; .01 )</td>
</tr>
<tr>
<td>Prevention of delirium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalisvaart et al,55 2005</td>
<td>Double-blind RCT of patients undergoing hip replacement surgery: 212, haloperidol; 218, placebo for prevention of postoperative delirium</td>
<td>1.5 mg/d Haloperidol, starting 1-3 d preoperatively continued through 3 d postoperatively</td>
<td>Incidence of postoperative delirium did not differ between the haloperidol (15%) and placebo (16.5%) groups ( P &gt; .05 )</td>
</tr>
<tr>
<td>Liptzin et al,56 2005</td>
<td>Double-blind RCT of patients undergoing total joint replacement surgery: 40, donepezil; 40, placebo for the prevention of postoperative delirium</td>
<td>5 mg/d Donepezil or placebo for 14 d preoperatively followed by another 14 d postoperatively</td>
<td>No significant difference in the incidence of delirium between donepezil (20.5%) and placebo (17.1%) ( P = .17 )</td>
</tr>
<tr>
<td>Sampson et al,57 2007</td>
<td>Double-blind RCT of patients undergoing total hip replacement surgery: 19, donepezil; 14 placebo for the prevention of postoperative delirium</td>
<td>5 mg/d Donepezil or placebo for 4 d</td>
<td>No significant difference in the incidence of delirium ( P = .08 ) or in the length of hospital stay ( P = .09 ) between groups</td>
</tr>
</tbody>
</table>

Abbreviations: DRS, delirium rating scale; MDAS, Memorial Delirium Assessment Scale; RTC, randomized controlled trial.
rather than shorter survival. Antipsychotics or sedatives may rarely worsen a delirium by making the patient more confused or sedated. A review by Lo and Rubenfeld addressed the ethical concerns of palliative sedation.

### Table 3. Antipsychotic Medications in the Treatment of Delirium in Terminally Ill Patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>Level of Evidence</th>
<th>Dose Range</th>
<th>Available Route of Administration</th>
<th>Adverse Effects</th>
<th>Comments</th>
<th>Monthly Cost, US $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical antipsychotics</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Haloperidol</td>
<td>Level I&lt;sup&gt;14&lt;/sup&gt;</td>
<td>0.5-2 mg every 2 to 12 h</td>
<td>By mouth, intravenous, subcutaneous</td>
<td>Extrapyramidal effects can occur with doses &gt;4.5 mg/d&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Monitor QTc interval on ECG</td>
<td>Remains first-line therapy for terminal delirium</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Level I&lt;sup&gt;14&lt;/sup&gt;</td>
<td>12.5-50 mg every 4-6 h</td>
<td>By mouth, intravenous, intramuscular, subcutaneous, per rectum</td>
<td>More sedating and anticholinergic compared with haloperidol&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Monitor blood pressure for hypotension</td>
<td>Preferred in agitated patients due to its sedative effect</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Level II-&lt;sup&gt;3&lt;/sup&gt;,&lt;sup&gt;54&lt;/sup&gt;</td>
<td>2.5-5 mg every 12-24 h</td>
<td>By mouth&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Sedation is the main dose-limiting effect in short-term use&lt;sup&gt;15, 53, 61&lt;/sup&gt;</td>
<td>Older age, preexisting dementia, and hypoactive subtype of delirium are associated with poor response</td>
<td>202.43-654.99</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Level I&lt;sup&gt;1&lt;/sup&gt;,&lt;sup&gt;53, 62&lt;/sup&gt;-&lt;sup&gt;65&lt;/sup&gt;</td>
<td>0.25-1 mg every 12-24 h</td>
<td>By mouth&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Extrapyramidal adverse effects can occur with doses &gt;6 mg/d&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Orthostatic hypotension</td>
<td>Clinical experience suggests better results in patients with hypoactive delirium</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Level II-&lt;sup&gt;3&lt;/sup&gt;,&lt;sup&gt;67&lt;/sup&gt;</td>
<td>12.5-100 mg every 12-24 h</td>
<td>By mouth&lt;sup&gt;19, 60, 70&lt;/sup&gt;</td>
<td>Sedation, orthostatic hypotension&lt;sup&gt;31, 65, 72&lt;/sup&gt;</td>
<td>Preferred in patients with Parkinson disease or Lewy body dementia due to its lower risk of extrapyramidal adverse effects</td>
<td>137.08-594.00</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Level III&lt;sup&gt;52, 74&lt;/sup&gt;</td>
<td>10-40 mg every 12-24 h</td>
<td>By mouth&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Monitor QTc interval on ECG</td>
<td>Evidence is limited to case reports</td>
<td>Least preferred in the medically ill due to risk of QT prolongation vs other atypical antipsychotics&lt;sup&gt;60, 71&lt;/sup&gt;</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Level II-&lt;sup&gt;3&lt;/sup&gt;</td>
<td>5-30 mg every 24 h</td>
<td>By mouth&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Monitor for akathisia</td>
<td>Clinical experience suggests better results in hypoactive delirium</td>
<td>373.06-508.82</td>
</tr>
</tbody>
</table>

Abbreviation: ECG, electrocardiogram.

<sup>1</sup>Recommendations for pharmacological management of the symptoms of delirium are based on a comprehensive search of PubMed and the Cochrane Review databases, using the search terms delirium, treatment, terminal, and end-of-life from 1960 through September 2008, including all clinical trials, case series, and case studies.

<sup>2</sup>Based on levels of evidence.<sup>74</sup>

<sup>3</sup>Lower doses with slow titration are recommended in older patients and in patients with multiple medical comorbidities.

<sup>4</sup>Olanzapine, aripiprazole, and ziprasidone are available for intramuscular formulations; however, there are no case reports or studies on intramuscular use in management of delirious patients.

<sup>5</sup>There is a US Food and Drug Administration black box warning regarding the increased risk of mortality associated with use of antipsychotics in the treatment of behavioral disturbances and psychotic symptoms in dementia and a warning about an increased risk of QTc prolongation on ECG, predisposing to torsades de pointes, associated with use of intravenous haloperidol. Warnings should be discussed with the patient and families.

<sup>6</sup>The prices reflect approximate monthly costs for the given dose ranges.

<sup>7</sup>Olanzapine, risperidone, and aripiprazole are available in orally disintegrating tablets.
older patients include preexisting cognitive impairment, vi-
sual impairment, hearing impairment, sleep deprivation, im-
mobility, dehydration, and severe illness. Interventions di-
rected at constant orientation, correction of hearing and visual
impairment, reversal of dehydration, and early mobilization
appear to significantly reduce the number and duration of epi-
sodes of delirium in hospitalized older patients.103 These pre-
ventive interventions might be adapted to the needs of pa-
ients near the end of life, allowing families to work to actively
maintain patient comfort.42 In palliative care settings, when-
ever possible, clinicians should try to limit the number of med-
cations that are known to result in mental status changes and
use the minimum effective dose.

A Cochrane review of delirium prevention studies104 con-
cluded that the evidence on effectiveness of interventions to
prevent delirium is sparse.51,55-57,104 In non–palliative care
settings, antipsychotics have been studied for their poten-
tial role in prevention of delirium. In a randomized, placebo-
controlled, double-blind trial involving older patients un-
dergoing hip surgery, low-dose haloperidol prophylaxis was
not effective for the prevention of postoperative delirium.
However, it did reduce the severity and duration of deli-
rium.53 Whether such an approach would work with termi-

inally ill patients is uncertain. Two randomized placebo-
controlled prevention trials with donepezil among surgical
patients undergoing total joint replacement surgery failed
to show a difference in the incidence of delirium and the
duration of hospitalization.60,67 A randomized controlled trial
of proactive geriatric consultations—making recommenda-
tions for the type of measures detailed above—in a popu-
lation of patients undergoing surgery for hip fracture was
found to be the only effective intervention in reducing inci-
dence and severity of delirium.51

Setting

Dr C: This patient needed to be sent somewhere that had a 24-
hour RN that could assess the patient and a physician that could
visit the patient on a daily basis.

Ms S: We were trying to manage the symptoms and also get
him out of the hospital. [His partner] felt that he would never,
ever want to die in the hospital. . . . This was the first time that
we tried to transfer somebody with agitation. We had a lot of
concerns and anxiety about whether or not we were doing the
right thing.

The setting in which delirium and agitation are man-
aged deserves consideration. Ensuring safety is critical. Spe-
cialized training and constant observation may be required—
e.g., to prevent falls or to keep oxygen cannulas in place. It
is often not possible for delirious patients to be safely man-
aged by families at home. The physician may advise and re-
assure the family that the best and safest care may be pro-
vided in a dignified and respectful manner in an appropriate
institutional setting. Once this is done, family members be-
come more able to provide the love, comfort, and support
that is so essential during the dying process.

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Other Sources: For a list of relevant Web sites, see the article on the JAMA Web

Additional Contributions: We thank the patient for permission to publish his story.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Men-
tal Disorders. 4th ed, text revision. Washington, DC: American Psychiatric Asso-
ciation; 2000.


3. Pereira J, Hanson J, Bruera E. The frequency and clinical course of cognitive


5. Lawlor PG, Gagnon B, Mancini IL, et al. Occurrence, causes, and outcome of

6. Spiller KA, Keen JC. Hypoactive delirium: assessing the extent of the problem

spective study using daily screening, early diagnosis, and continuous monitoring.

8. Ross CA, Peyer CE, Shapiro I, Folstein MF. Delirium: phenomenologic and etio-

9. Breitbart W, Tremblay A, Gibson C. An open trial of olanzapine for the treat-
ment of delirium in hospitalized cancer patients. Psychosomatics. 2002;43(3):
175-182.

of 100 adult cases using standardised measures. Br J Psychiatry. 2007;
190:135-141.

11. Meagher DJ, O’Hanlon D, O’Mahony E, Casey PR, Trzepacz PT. Relation-
ship between symptoms and motoric subtype of delirium. J Neuropsychiatry Clin

12. Stagno D, Gibson C, Breitbart W. The delirium subtypes: a review of preva-
ience, phenomenology, pathophysiology, and treatment response. Palliat Sup-

13. Kielty DK, Jones RN, Bergmann MA, Marcantonio ER. Association between
psychomotor activity delirium subtypes and mortality among newly admitted post-

promazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients.


16. Smith MJ, Breitbart W, Platt M. A critique of instruments and methods to de-

17. Trzepacz PT. The Delirium Rating Scale: its use in consultation-liaison research.


19. Lawlor PG, Nekolaichuk C, Gagnon B, Mancini IL, Pereira J, Bruera ED. Clini-
cal utility, factor analysis, and further validation of the Memorial Delirium Assess-

20. Inouye SK, Vandyck C, Alessi C, Balkin S, Siegal AP, Horwitz RI. Clarifying
confusion: the confusion assessment method, a new method for the detection of

of a cognitive test for delirium in medical ICU patients. Psychosomatics. 1996;
37(6):533-546.

22. Adamis D, Morrison C, Treloar A, Macdonald AJ, Martin FC. The perfor-
mance of the Clock Drawing Test in elderly medical inpatients: does it have utility

23. Breitbart W, Friedlander M. Confusion/delirium. In: Bruera E, Higginson I,

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DELIRIUM AT THE END OF LIFE

Web Resources

THE AMERICAN PSYCHOSOCIAL ONCOLOGY SOCIETY (APOS)
http://www.apos-society.org/clinical/default.asp
The American Psychosocial Oncology Society Web site provides educational resources on the management of delirium in cancer.

THE INTERNATIONAL PSYCHO-ONCOLOGY SOCIETY (IPOS)
http://www.ipos-society.org/index.htm
The International Psycho-Oncology Society provides curriculum lectures on delirium for health care professionals.

THE AMERICAN ACADEMY OF HOSPICE AND PALLIATIVE MEDICINE (AAHPM)
http://www.aahpm.org
This site has several online resources, including a “Fast Facts” section, addressing delirium and many other topics pertinent to the care of terminally ill patients.

THE ACADEMY OF PSYCHOSOMATIC MEDICINE (APM)
http://www.apm.org
The Academy of Psychosomatic Medicine offers online courses on core topics of psychosomatic medicine, including delirium.