# Agitation and Delirium at the End of Life
## "We Couldn't Manage Him"

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**Delirium is the most common neuropsychiatric complication experienced by patients with advanced illness, occurring in up to 85% of patients in the last weeks of life. Using the case of Mr L, a 59-year-old man with metastatic lung cancer who developed an agitated delirium in the last week of life, we review the evaluation and management of delirium near the end of life. Although some studies have identified agitation as a central feature of delirium in 13% to 46% of patients, other studies have found up to 80% of patients near the end of life develop a hypoactive, nonagitated delirium. Both the agitated (hyperactive) and nonagitated (hypoactive) forms of delirium are harbingers of impending death and are associated with increased morbidity in patients who are terminally ill, causing distress for patients, family members, and staff. Delirium is a sign of significant physiological disturbance, usually involving multiple causes, including infection, organ failure, and medication adverse effects. Often these causes of delirium are not reversible in the dying patient, and this influences the outcomes of its management. Delirium can also significantly interfere with the recognition and control of other physical and psychological symptoms, such as pain. Unfortunately, delirium is often misdiagnosed or unrecognized and thus inappropriately treated or untreated in terminally ill patients. To manage delirium in terminally ill patients, clinicians must be able to diagnose it accurately, undertake appropriate assessment of underlying causes, and understand the benefits and risks of the available pharmacological and nonpharmacological interventions.**

*JAMA. 2008;300(24):2898-2910* www.jama.com

### 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

**See also Patient Page.**


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**Perspectives on Care at the Close of Life** is produced and edited at the University of California, San Francisco, by Stephen J. McPhee, MD, Michael W. Rabow, MD, and Steven Z. Pantilat, MD; Amy J. Markowitz, JD, is managing editor.
**Perspectives on Care at the Close of Life Section Editor:** Margaret A. Winker, MD, Deputy Editor.

control pain. Dexamethasone and insulin were discontinued, given that they were no longer contributing to his comfort and were potentially exacerbating his agitation. Lorazepam was discontinued due to its apparent paradoxical effect. Haloperidol was initiated on an "as needed" basis but resulted in only partial control of his agitation.

On hospital day 4, his haloperidol regimen was switched to every 4 hours. The palliative care team asked Ms P to bring in his favorite music, which seemed to calm him. Mr L's agitation improved and he was transferred to an inpatient hospice facility. Upon transfer, Mr L's regimen included the following medications: fentanyl patch, 37.5 µg/h every 72 hours; haloperidol, 2 mg intravenously every 6 hours; haloperidol, 0.5 mg intravenously or subcutaneously every 4 hours as needed for agitation; lorazepam, 0.5 to 2 mg intravenously every 3 hours as needed for insomnia or anxiety. Mr L was given intravenous haloperidol just before his ambulance transfer and morphine was ordered for administration during the transport. At the residential hospice facility, 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 Perspectives 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 partner . . . she was exhausted to the point of dropping.*

DR H: *[Delirium] is one of the things that people have difficulty 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 illustrated by the case of Mr L. In the palliative care setting, delirium is often the harbinger of impending death; it is distressing 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 setting 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. Patients 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)[1] diagnostic criteria define delirium as a syndrome composed of disturbances of consciousness, attention (ie, arousal), and cognition, with abrupt onset and fluctuating course, and require that the disturbance be etiologically related to medical causes. Clinical features can be quite varied (**BOX 1**). Delirium is the most common 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 terminally ill patients with cancer.[2-7] Prospective studies conducted in palliative care settings find that up to 42% of patients have delirium upon admission,[3,5-7] and an additional 32% to 45% of patients develop delirium during the week prior to death.[5-7]

### 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 intake. He did all right during the night, but [the next day] he awoke and was extremely restless. He was very angry and insisted on leaving. He was screaming at the nurses to fetch his jacket 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, hyperactive, and mixed. The *hypoactive* (hypoalert, hypoaroused) subtype is characterized by psychomotor retardation, lethargy, sedation, and reduced awareness of surroundings.[6,8-12] Hypoactive delirium is often mistaken for depression and is difficult to differentiate from sedation due to opioids, or obtundation in the last days of life.[12] The *hyperactive* (hyperalert, hyperaroused) subtype is more commonly characterized by restlessness, agitation, hypervigilance, hallucinations, and delusions.[8-11] In the palliative care setting, hypoactive delirium is most common. One meta-analysis found the mean prevalence of hypoactive delirium to be 48% (range, 15%-71%),[8] with 86% of delirium being the hypoactive type in one study.[6] Hyperactive delirium occurs in 13% to 46% of patients in the palliative care setting.[8] Some studies suggest that the subtypes of delirium may be related to different causes and may have different treatment responses.[8,11-13] Hypoactive delirium has generally been found to occur with hypoxia, metabolic disturbances, and anticholinergic medications.[8,11-13] Hyperactive delirium is correlated with alcohol and drug withdrawal, drug intoxication, or medication adverse effects.[8,11-13] A randomized controlled trial of haloperidol and chlorpromazine 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 response with hypoactive delirium.[9] Mortality is higher with hypoactive than hyperactive delirium.[14,15] Although agitation was the initial focus of intervention for Mr L, he ex-

**Box 1. Clinical Features of Delirium and Bedside Clinical Examination[a]**

**Disturbance of Consciousness, Arousal, Awareness**

Ask the patient to describe surroundings with eyes closed and ask, "What color is the wall?"

Ask the patient, "Are you feeling 100% awake?" and if not, "How awake do you feel?"

**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.[b]

**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.

**Disorganized Thinking**

Ask patient an open-ended question, eg, "Describe your medical condition."

Listen for rambling, incoherent speech or tangential and circumstantial thought process.

**Delusions**

Ask patient, "Are you feeling unsafe here?"

Find out from family or staff whether patient is acting in a paranoid, suspicious, hypervigilant, fearful, or hostile fashion.

**Psychomotor Disturbances**

Observe whether the patient is restless and agitated or slow and hypoactive.

Use observations of family, staff, or both to assess psychomotor activity over previous 24 hours.

**Sleep-Wakefulness Cycle Disturbances**

Determine from family, staff, or both whether the patient has been "awake most of the night, and asleep most of the day."

**Acute Onset, Fluctuating Course**

Staff and family are often the best informants. The clinical presentation can be abrupt in onset (eg, hours to days) and each of the symptoms of delirium can fluctuate over the course of a 24-hour period.

**Neurological Signs Consistent With Delirium, eg, Asterixis, Frontal Release Signs, Myoclonus**

These findings are supportive of delirium. An electroencephalogram can also be supportive of a delirium diagnosis (diffuse slowing) or can reveal seizure activity.

[a]Based on clinical experience assessing the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision)[1] components of delirium.
[b]Clock Drawing Test primarily assesses the severity of cognitive impairment. Despite its frequent use in the clinical setting, it has low utility in differentiating delirium from dementia when used alone.[22]

hibited the "mixed" subtype of delirium, with periods of hypoactivity 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,[8,12,15] and is often a preterminal event. Clinically, the diagnostic "gold standard" is the clinician's assessment using the *DSM-IV-TR* criteria[1] 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,[16-22] including the Delirium Rating Scale-Revised 98,[17] Confusion Assessment Method,[20] Cognitive Test for Delirium,[21] and Memorial Delirium Assessment Scale,[18,19] and are reviewed elsewhere.[16,23] 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.[18,19]

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

DR 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.[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.[27] On the other hand, agitation due to delirium may be misinterpreted as uncontrolled pain, resulting in inappropriate escalation of opioids, potentially exacerbating delirium.[25] Terminally ill hospice patients may have difficulty communicating their needs, with the degree of impairment related both to delirium and to opioid dosage.[28] Some methods to improve assessment of pain in nonverbal palliative care patients are available.[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.[30-33] In a study of 101 terminally ill cancer patients, Breitbart et al[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 manifestation of discomfort or distress) were just as distressed as patients with hyperactive delirium. DiMartini and colleagues[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[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[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.[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.[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.[23,39,42] Medication adverse effects should be reviewed as a possible cause. Opioids, corticosteroids, benzodiazepines, and anticholinergics are commonly associated with delirium.[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.[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.[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.[4] However, studies in patients with earlier stages of advanced cancer have demonstrated the potential utility of a thorough diagnostic assessment.[38] In one study,[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[5] 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%.[36] 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[15] 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.[15]

### 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.[39]

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.[39] 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.[23,39]

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.[23,39] The hypoactive subtype of delirium is commonly misdiagnosed as depression[40,41] (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).[39] 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.[4,5,38,39,42,43] In-hospital mortality rates among elderly patients with delirium range from 22% to 76%.[39,42,44] On palliative care units and in hospice settings, delirium is often a predictor of impending death in patients with advanced cancer.[4,5,43,44] Delirium presenting with hypoactive subtype, irreversible etiologies, and greater cognitive impairment is often associated with death within a period of days to weeks.[15,36,38]

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 delirium[26,42] (BOX 3). In nonpalliative care settings, there is evidence that nonpharmacological interventions to management may result in faster improvement in delirium and slower deterioration in cognition, although no effects on mortality or health-related quality of life compared with usual care.[45,46,48-50] 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 avoided[42,47] because physical restraints in the treatment of delirium have been identified as an independent risk factor for its persistence at discharge.[47] The American Psychiatric Association Task Force on the Psychiatric Uses of Seclusion and Restraint has developed guidelines for the appropriate use of restraints,[52] as has the Joint Commission. Restraints 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.[52]

### 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 such as lorazepam.*

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.*

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

| Features | Hypoactive Delirium | Depression |
|---|---|---|
| Disturbance of arousal | Hypoaroused, hypoalert, drowsy | Normal level of arousal, awake, and alert |
| Cognitive changes | Short-term memory loss, dysnomia, impaired attention, decreased concentration, disorientation, agnosia, aphasia | Mild cognitive deficits may be present, primarily slowing of cognition, subjective problems with concentration |
| Temporal onset | Abrupt onset | Slow onset |
| Perceptual disturbances | Present in up to 75% of patients<br>Visual hallucinations most common<br>Misperceptions and illusions are common | Rarely present<br>Only seen in depression with psychotic features<br>Usually auditory hallucinations |
| Disturbance of thought content | Paranoid delusions often present<br>Usually vague and not systematized | Guilt, worthlessness, hopelessness are common in depression<br>Delusions are rare, but sometimes present in severe depression with psychotic features |
| Mood symptoms | Patients may appear sad, depressed, irritable<br>Mood is often labile<br>Disinhibition, due to delirium, can lead to expressions of desire for death or suicidal ideation | Patients frequently verbalize sad, depressed mood<br>Suicidal ideation is common and related to thoughts of hopelessness, worthlessness, and guilt or burden |
| Psychomotor activity | Hypoactive, quiet, withdrawn<br>Slowed | Usually hypoactive, withdrawn, or slowed<br>Occasionally hyperactive and agitated |
| Family history | Not applicable | Family history of depression common |
| Past psychiatric history | Previous episodes of delirium may be present | Past episodes of depression not uncommon |
| Neurological examination | Asterixis, frontal release signs may be elicited | Usually normal examination |

**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 with 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).[39] However, only 0.5% to 2% of hospitalized cancer patients receive haloperidol for symptoms of delirium,[39,77] and only 17% of terminally ill patients receive any antipsychotic drugs for agitation or delirium.[23,39,77] The American Psychiatric Association practice guidelines provide directions for the use of antipsychotics for treatment of delirium[39] and growing evidence supports their use.[9,53,54,58-75] In general, doses of haloperidol need not exceed 20 mg in a 24-hour period; however, some clinicians advocate higher doses in selected cases.[78] 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.[79] 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.[80]

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.[39]

In a double-blind, randomized comparison trial of haloperidol, chlorpromazine, and lorazepam involving 30 patients, Breitbart and colleagues[14] 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.[14] Both hyperactive as well as hypoactive subtypes of delirium were equally responsive to treatment with haloperidol or chlorpromazine. A Cochrane review on drug therapy for delirium in terminally ill patients[72] concluded that, based on this single study,[14] haloperidol is the most suitable medication for the treat-

 

**Box 3. Nonpharmacological Management of Delirium[a]**

**Nonpharmacological Interventions**

Minimize the use of immobilizing catheters, intravenous lines, and physical restraints[45-47]

Avoid immobility, early mobilization[45-51]

Monitor nutrition[48,49,51]

Provide visual and hearing aids[47]

Monitor closely for dehydration[47]

Control pain[51]

Monitor fluid-electrolyte balance[51]

Monitor bowel and bladder functioning[51]

Review medications[48,49,51]

Reorient communications with the patient[45-47]

Place an orientation board, clock, or familiar objects (ie, family photographs) in patient rooms[45-50]

Encourage cognitively stimulating activities such as word puzzles[47]

Facilitate sleep hygiene measures, including relaxation music or tapes at bedtime, warm drinks, and gentle massage[47]

Minimize noise and interventions at bedtime, eg, by rescheduling medication times[45-47,51]

[a] **Level of Evidence** Use of these nonpharmacological interventions in the *prevention* of delirium has been shown to reduce its incidence (level I).[47,51] 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).[45,46,48-50] 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]

ment of patients with delirium near the end of life, with chlorpromazine an acceptable alternative.[72] However, the review also emphasized that, due to the small number of patients in the study,[14] evidence is insufficient to draw firm conclusions.[72]

**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 al[82] 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

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

| | Intervention | Dose and Duration, Mean (SD) | Results | Comments |
|---|---|---|---|---|
| Treatment of delirium | | | | |
| Breitbart et al,[14] 1996 | Double-blind RCT of terminally ill AIDS patients: 11, haloperidol; 13, chlorpromazine; and 6, lorazepam for treatment of delirium | 1.4 (1.2) mg/d Haloperidol<br>36 (18.4) mg/d Chlorpromazine<br>4.6 (4.7) mg/d Lorazepam<br>Used for up to 6 d | DRS scores significantly improved in haloperidol and chlorpromazine groups ($P < .05$)<br>No significant extrapyramidal symptoms observed | Lorazepam group was discontinued early due to worsening of delirium symptoms |
| Han and Kim,[53] 2004 | Double-blind RCT of hospitalized patients: 12, haloperidol; 12, risperidone for the treatment of delirium | 1.7 (0.84) mg/d Haloperidol<br>1 (0.4) mg/d Risperidone<br>Used for 7 d | MDAS scores improved significantly in both groups, but no significant difference between groups<br>No significant difference in adverse effects observed | Researchers were not able to provide tablets identical in appearance, which might have adversely affected the double-blind study design |
| Hu et al,[54] 2004 | Double-blind RCT of hospitalized patients: 75, olanzapine; 72, intramuscular haloperidol; and 29, oral placebo for the treatment of delirium | 4.5 (4) mg/d Olanzapine<br>7 (2.3) mg/d Haloperidol<br>Placebo<br>Used for 7 d | The improvement in DRS scores were significantly higher in the olanzapine (72%) and haloperidol (70%) groups vs placebo (29.7%) ($P < .01$)<br>Increased rates of extrapyramidal symptoms observed in the haloperidol group | Comparison of oral olanzapine and oral placebo with intramuscular haloperidol interferes with the double-blind study design |
| Prevention of delirium | | | | |
| Kalisvaart et al,[55] 2005 | Double-blind RCT of patients undergoing hip replacement surgery: 212, haloperidol; 218, placebo for prevention of postoperative delirium | 1.5 mg/d Haloperidol, starting 1-3 d preoperatively continued through 3 d postoperatively | Incidence of postoperative delirium did not differ between the haloperidol (15%) and placebo (16.5%) groups ($P > .05$)<br>Delirium duration and length of hospital stay were significantly lower in the haloperidol group ($P < .01$)<br>No significant adverse effects | Difficult to replicate a prevention trial using antipsychotics in the absence of well-established treatment data |
| Liptzin et al,[56] 2005 | Double-blind RCT of patients undergoing total joint replacement surgery: 40, donepezil; 40, placebo for the prevention of postoperative delirium | 5 mg/d Donepezil or placebo for 14 d preoperatively followed by another 14 d postoperatively | No significant difference in the incidence of delirium between donepezil (20.5%) and placebo (17.1%)<br>Donepezil was well tolerated | Difficult to replicate a prevention trial using anticholinesterase inhibitor in the absence of well-established treatment data |
| Sampson et al,[57] 2007 | Double-blind RCT of patients undergoing total hip replacement surgery: 19, donepezil; 14 placebo for the prevention of postoperative delirium | 5 mg/d Donepezil or placebo for 4 d | No significant difference in the incidence of delirium ($P = .08$) or in the length of hospital stay ($P = .09$) between groups<br>Donepezil was well tolerated | Researchers acknowledged that study had insufficient power to detect possible differences (95 patients per group would be needed) |

Abbreviations: DRS, delirium rating scale; MDAS, Memorial Delirium Assessment Scale; RTC, randomized controlled trial.

 

rather than shorter survival.[23,87,88,99-102] A review by Lo and Rubenfeld[90] addressed the ethical concerns of palliative sedation.

Antipsychotics or sedatives may rarely worsen a delirium by making the patient more confused or sedated.[23] Until more evidence becomes available, clinicians are advised to use low doses of antipsychotics for as brief a period as possible, especially in older patients. Nevertheless, clinical experience suggests that antipsychotics are both effective and appropriate in the management of agitation, paranoia, hallucinations, and altered sensorium. A wait-and-see approach may be appropriate with some patients who present with a lethargic or somnolent type of delirium or who are having comforting hallucinations. Such an approach must, however, be tempered by the knowledge that a lethargic or hypoactive delirium may very quickly and unexpectedly become an agitated or hyperactive delirium that can threaten the serenity and safety of the patient, family, and staff.[23]

## PREVENTION

DR H: *If you can treat it fast, you will be much better off. Also, you can let the family know what to look for, for example, [that] people who are restless and pulling at their clothes might be a sign that delirium is starting.*

Families, as well as all members of the medical team, should be educated as to the prodromal symptoms and signs of delirium. Inouye and colleagues[103] reported on a successful multicomponent intervention program to prevent delirium in hospitalized older patients. Predictive risk factors for delirium in

**Table 3.** Antipsychotic Medications in the Treatment of Delirium in Terminally Ill Patients[a]

| Medication | Level of Evidence[b] | Dose Range[c] | Available Route of Administration[d] | Adverse Effects[e] | Comments | Monthly Cost, US $[f] |
|---|---|---|---|---|---|---|
| Typical antipsychotics | | | | | | |
| Haloperidol | Level I[14] | 0.5-2 mg every 2 to 12 h | By mouth, intravenous, intramuscular, subcutaneous | Extrapyramidal effects can occur with doses >4.5 mg/d[58]<br>Monitor QTc interval on ECG | Remains first-line therapy for terminal delirium<br>May add lorazepam (0.5-1 mg every 2 to 4 h) for agitated patients | 14.99-124.07 |
| Chlorpromazine | Level I[14] | 12.5-50 mg every 4-6 h | By mouth, intravenous, intramuscular, subcutaneous, per rectum | More sedating and anticholinergic compared with haloperidol[14]<br>Monitor blood pressure for hypotension | Preferred in agitated patients due to its sedative effect | 16.99-26.99 |
| Atypical antipsychotics | | | | | | |
| Olanzapine | Level II-1[9,54,59-61] | 2.5-5 mg every 12-24 h | By mouth[g] | Sedation is the main dose-limiting effect in short-term use[9,54,59-61] | Older age, preexisting dementia, and hypoactive subtype of delirium are associated with poor response | 202.43-654.99 |
| Risperidone | Level II-1[53,62-65] | 0.25-1 mg every 12-24 h | By mouth[g] | Extrapyramidal adverse effects can occur with doses >6 mg/d[62-65];<br>Orthostatic hypotension | Clinical experience suggests better results in patients with hypoactive delirium | 113.20-331.37 |
| Quetiapine | Level II-3[66,67] | 12.5-100 mg every 12-24 h | By mouth | Sedation, orthostatic hypotension[54,68-72] | Preferred in patients with Parkinson disease or Lewy body dementia due to its lower risk of extrapyramidal adverse effects | 137.08-594.00 |
| Ziprasidone | Level III[73,74] | 10-40 mg every 12-24 h | By mouth | Monitor QTc interval on ECG | Evidence is limited to case reports<br>Least preferred in the medically ill due to risk of QT prolongation vs other atypical antipsychotics[68-71] | 361.86-435.20 |
| Aripiprazole | Level II-3[75] | 5-30 mg every 24 h | By mouth[g] | Monitor for akathisia | Clinical experience suggests better results in hypoactive delirium | 373.06-508.82 |

Abbreviation: ECG, electrocardiogram.
[a] 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*, *terminally ill*, and *end-of-life* from 1960 through September 2008, including all clinical trials, case series, and case studies.
[b] Based on levels of evidence.[76]
[c] Lower doses with slow titration are recommended in older patients and in patients with multiple medical comorbidities.
[d] 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.
[e] 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.
[f] The prices reflect approximate monthly costs for the given dose ranges.
[g] Olanzapine, risperidone, and aripiprazole are available in orally disintegrating tablets.

older patients include preexisting cognitive impairment, visual impairment, hearing impairment, sleep deprivation, immobility, dehydration, and severe illness. Interventions directed at constant orientation, correction of hearing and visual impairment, reversal of dehydration, and early mobilization appear to significantly reduce the number and duration of episodes of delirium in hospitalized older patients.[103] These preventive interventions might be adapted to the needs of patients near the end of life, allowing families to work to actively maintain patient comfort.[42] In palliative care settings, whenever possible, clinicians should try to limit the number of medications that are known to result in mental status changes and use the minimum effective dose.

A Cochrane review of delirium prevention studies[104] concluded 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 potential role in prevention of delirium. In a randomized, placebo-controlled, double-blind trial involving older patients undergoing hip surgery, low-dose haloperidol prophylaxis was not effective for the prevention of postoperative delirium. However, it did reduce the severity and duration of delirium.[55] Whether such an approach would work with terminally 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.[56,57] A randomized controlled trial of proactive geriatric consultations—making recommendations for the type of measures detailed above—in a population of patients undergoing surgery for hip fracture was found to be the only effective intervention in reducing incidence 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 managed deserves consideration. Ensuring safety is critical. Specialized training and constant observation may be required—eg, to prevent falls or to keep oxygen cannulas in place. It is often not possible for delirious patients to be safely managed by families at home. The physician may advise and reassure the family that the best and safest care may be provided in a dignified and respectful manner in an appropriate institutional setting. Once this is done, family members become more able to provide the love, comfort, and support that is so essential during the dying process.

**Financial Disclosures:** None reported.
**Funding/Support:** The Perspectives on Care at the Close of Life series is made possible by funding from the California HealthCare Foundation. Dr Breitbart's work is currently supported by grants from the Fetzer Institute and by grants RO1CA128187, 1R21 CA101767, RO1 CA10194, and RO1CA102201 from the US National Cancer Institute.
**Role of the Sponsor:** None of the funding agencies had a role in the preparation, review, or approval of the manuscript.
**Other Sources:** For a list of relevant Web sites, see the article on the *JAMA* Web site at http://www.jama.com.
**Additional Contributions:** We thank the patient for permission to publish his story.

**REFERENCES**

**1.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed, text revision. Washington, DC: American Psychiatric Association; 2000.
**2.** Massie MJ, Holland J, Glass E. Delirium in terminally ill cancer patients. *Am J Psychiatry*. 1983;140(8):1048-1050.
**3.** Pereira J, Hanson J, Bruera E. The frequency and clinical course of cognitive impairment in patients with terminal cancer. *Cancer*. 1997;79(4):835-842.
**4.** Bruera E, Miller L, McCallion J, Macmillan K, Krefting L, Hanson J. Cognitive failure in patients with terminal cancer: a prospective study. *J Pain Symptom Manage*. 1992;7(4):192-195.
**5.** Lawlor PG, Gagnon B, Mancini IL, et al. Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. *Arch Intern Med*. 2000;160(6):786-794.
**6.** Spiller JA, Keen JC. Hypoactive delirium: assessing the extent of the problem for inpatient specialist palliative care. *Palliat Med*. 2006;20(1):17-23.
**7.** Gagnon P, Charbonneau C, Allard P, et al. Delirium in terminal cancer: a prospective study using daily screening, early diagnosis, and continuous monitoring. *J Pain Symptom Manage*. 2000;19(6):412-426.
**8.** Ross CA, Peyser CE, Shapiro I, Folstein MF. Delirium: phenomenologic and etiologic subtypes. *Int Psychogeriatr*. 1991;3(2):135-147.
**9.** Breitbart W, Tremblay A, Gibson C. An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients. *Psychosomatics*. 2002;43(3):175-182.
**10.** Meagher DJ, Moran M, Raju B, et al. Phenomenology of delirium: assessment 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. Relationship between symptoms and motoric subtype of delirium. *J Neuropsychiatry Clin Neurosci*. 2000;12(1):51-56.
**12.** Stagno D, Gibson C, Breitbart W. The delirium subtypes: a review of prevalence, phenomenology, pathophysiology, and treatment response. *Palliat Support Care*. 2004;2(2):171-179.
**13.** Kiely DK, Jones RN, Bergmann MA, Marcantonio ER. Association between psychomotor activity delirium subtypes and mortality among newly admitted post-acute facility patients. *J Gerontol A Biol Sci Med Sci*. 2007;62(2):174-179.
**14.** Breitbart W, Marotta R, Platt M, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. *Am J Psychiatry*. 1996;153(2):231-237.
**15.** Leonard M, Raju B, Conroy M, et al. Reversibility of delirium in terminally ill patients and predictors of mortality. *Palliat Med*. 2008;22(7):848-854.
**16.** Smith MJ, Breitbart W, Platt M. A critique of instruments and methods to detect, diagnose, and rate delirium. *J Pain Symptom Manage*. 1995;10(1):35-77.
**17.** Trzepacz PT. The Delirium Rating Scale: its use in consultation-liaison research. *Psychosomatics*. 1999;40(3):193-204.
**18.** Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S. The Memorial Delirium Assessment Scale. *J Pain Symptom Manage*. 1997;13(3):128-137.
**19.** Lawlor PG, Nekolaichuk C, Gagnon B, Mancini IL, Pereira JL, Bruera ED. Clinical utility, factor analysis, and further validation of the Memorial Delirium Assessment Scale in patients with advanced cancer: assessing delirium in advanced cancer. *Cancer*. 2000;88(12):2859-2867.
**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 delirium. *Ann Intern Med*. 1990;113(12):941-948.
**21.** Hart RP, Levenson J, Sessler C, Best A, Schwartz S, Rutherford L. Validation 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 performance of the Clock Drawing Test in elderly medical inpatients: does it have utility in the identification of delirium? *J Geriatr Psychiatry Neurol*. 2005;18(3):129-133.
**23.** Breitbart W, Friedlander M. Confusion/delirium. In: Bruera E, Higginson I, Ripamonti C, von Gunten C, eds. *Palliative Medicine.* London, England: UK London Hodder Press; 2006:688-700.

 

**24.** Bruera E, Fainsinger RL, Miller MJ, Kuehn N. The assessment of pain intensity in patients with cognitive failure: a preliminary report. *J Pain Symptom Manage*. 1992;7(5):267-270.
**25.** Coyle N, Breitbart W, Weaver S, Portenoy R. Delirium as a contributing factor to "crescendo" pain: three case reports. *J Pain Symptom Manage*. 1994; 9(1):44-47.
**26.** Fainsinger R, Miller MJ, Bruera E, Hanson J, Maceachern T. Symptom control during the last week of life on a palliative care unit. *J Palliat Care*. 1991;7(1): 5-11.
**27.** Gagnon B, Lawlor PG, Mancini IL, Pereira JL, Hanson J, Bruera ED. The impact of delirium on the circadian distribution of breakthrough analgesia in advanced cancer patients. *J Pain Symptom Manage*. 2001;22(4):826-833.
**28.** Morita T, Tei Y, Inoue S. Impaired communication capacity and agitated delirium in the final week of terminally ill cancer patients: prevalence and identification of research focus. *J Pain Symptom Manage*. 2003;26(3):827-834.
**29.** Morrison RS, Meier DE, Fischberg D, et al. Improving the management of pain in hospitalized adults. *Arch Intern Med*. 2006;166(9):1033-1039.
**30.** Breitbart W, Gibson C, Tremblay A. The delirium experience: delirium recall and delirium related distress in hospitalized patients with cancer, their spouses /caregivers, and their nurses. *Psychosomatics*. 2002;43(3):183-194.
**31.** DiMartini A, Dew MA, Kormos R, McCurry K, Fontes P. Posttraumatic stress disorder caused by hallucinations and delusions experienced in delirium. *Psychosomatics*. 2007;48(5):436-439.
**32.** Morita T, Hirai K, Sakaguchi Y, Tsuneto S, Shima Y. Family-perceived distress from delirium-related symptoms of terminally ill cancer patients. *Psychosomatics*. 2004;45(2):107-113.
**33.** Buss MK, Vanderwerker LC, Inouye SK, Zhang B, Block SD, Prigerson HG. Associations between caregiver-perceived delirium in patients with cancer and generalized anxiety in their caregivers. *J Palliat Med*. 2007;10(5):1083-1092.
**34.** Bruera E, Macmillan K, Hanson J, MacDonald RN. The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. *Pain*. 1989; 39(1):13-16.
**35.** Gaudreau JD, Gagnon P, Harel F, Roy MA, Tremblay A. Psychoactive medications and risk of delirium in hospitalized cancer patients. *J Clin Oncol*. 2005; 23(27):6712-6718.
**36.** Morita T, Tei Y, Tsunoda J, Inoue S, Chihara S. Underlying pathologies and their associations with clinical features in terminal delirium of cancer patients. *J Pain Symptom Manage*. 2001;22(6):997-1006.
**37.** Stiefel FC, Breitbart WS, Holland JC. Corticosteroids in cancer: neuropsychiatric complications. *Cancer Invest*. 1989;7(5):479-491.
**38.** Fainsinger R, Bruera E. Treatment of delirium in a terminally ill patient. *J Pain Symptom Manage*. 1992;7(1):54-56.
**39.** American Psychiatric Association. Practice guidelines for the treatment of patients with delirium. *Am J Psychiatry*. 1999;156(5 suppl):1-20.
**40.** Nicholas LM, Lindsey BA. Delirium presenting with symptoms of depression. *Psychosomatics*. 1995;36(5):471-479.
**41.** de Rooij SE, Schuurmans MJ, van der Mast RC, Levi M. Clinical subtypes of delirium and their relevance for daily clinical practice: a systematic review. *Int J Geriatr Psychiatry*. 2005;20(7):609-615.
**42.** Casarett DJ, Inouye SK; American College of Physicians-American Society of Internal Medicine End-of-Life Care Consensus Panel. Diagnosis and management of delirium near the end of life. *Ann Intern Med*. 2001;135(1):32-40.
**43.** Morita T, Tsunoda J, Inoue S, Chihara S. Survival prediction of terminally ill cancer patients by clinical symptoms: development of a simple indicator. *Jpn J Clin Oncol*. 1999;29(3):156-159.
**44.** Maltoni M, Caraceni A, Brunelli C, et al; Steering Committee of the European Association for Palliative Care. Prognostic factors in advanced cancer patients: evidence-based clinical recommendations—a study by the Steering Committee of the European Association for Palliative Care. *J Clin Oncol*. 2005;23(25):6240-6248.
**45.** Cole MG, Primeau FJ, Bailey RF, et al. Systematic intervention for elderly inpatients with delirium: a randomized trial. *CMAJ*. 1994;151(7):965-970.
**46.** Cole MG, McCusker J, Bellavance F, et al. Systematic detection and multidisciplinary care of delirium in older medical inpatients: a randomized trial. *CMAJ*. 2002;167(7):753-759.
**47.** Inouye SK, Zhang Y, Jones RN, Kiely DK, Yang F, Marcantonio ER. Risk factors for delirium at discharge: development and validation of a predictive model. *Arch Intern Med*. 2007;167(13):1406-1413.
**48.** Pitkälä KH, Laurila JV, Strandberg TE, Tilvis RS. Multicomponent geriatric intervention for elderly inpatients with delirium: a randomized, controlled trial. *J Gerontol A Biol Sci Med Sci*. 2006;61(2):176-181.
**49.** Pitkala KH, Laurila JV, Strandberg TE, Kautiainen H, Sintonen H, Tilvis RS. Multicomponent geriatric intervention for elderly inpatients with delirium: effects on costs and health-related quality of life. *J Gerontol A Biol Sci Med Sci*. 2008; 63(1):56-61.
**50.** Milisen K, Lemiengre J, Braes T, Foreman MD. Multicomponent intervention strategies for managing delirium in hospitalized older people: systematic review. *J Adv Nurs*. 2005;52(1):79-90.
**51.** Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *J Am Geriatr Soc*. 2001;49(5):516-522.
**52.** Sadock BJ, Sadock VA. *Kaplan and Sadock's Synopsis of Psychiatry*. 9th ed. Philadelphia, PA: Lippincott Williams and Wilkins Press; 2003:1351-1365.
**53.** Han CS, Kim Y. A double-blind trial of risperidone and haloperidol for the treatment of delirium. *Psychosomatics*. 2004;45(4):297-301.
**54.** Hu H, Deng W, Yang H. A prospective random control study comparison of olanzapine and haloperidol in senile delirium. *Chongging Med J*. 2004;8:1234-1237.
**55.** Kalisvaart KJ, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. *J Am Geriatr Soc*. 2005;53(10):1658-1666.
**56.** Liptzin B, Laki A, Garb JL, Fingeroth R, Krushell R. Donepezil in the prevention and treatment of post-surgical delirium. *Am J Geriatr Psychiatry*. 2005; 13(12):1100-1106.
**57.** Sampson EL, Raven PR, Ndhlovu PN, et al. A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. *Int J Geriatr Psychiatry*. 2007;22(4):343-349.
**58.** Lonergan E, Britton AM, Luxenberg J, Wyller T. Antipsychotics for delirium. *Cochrane Database Syst Rev*. 2007;(2):CD005594.
**59.** Sipahimalani A, Massand P. Olanzapine in the treatment of delirium. *Psychosomatics*. 1998;39(5):422-430.
**60.** Kim KS, Pae CU, Chae JH, Bahk WM, Jun T. An open pilot trial of olanzapine for delirium in the Korean population. *Psychiatry Clin Neurosci*. 2001;55(5): 515-519.
**61.** Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting. *Intensive Care Med*. 2004;30 (3):444-449.
**62.** Liu CY, Juang Y, Liang H, Lin NC, Yeh EK. Efficacy of risperidone in treating the hyperactive symptoms of delirium. *Int Clin Psychopharmacol*. 2004;19 (3):165-168.
**63.** Horikawa N, Yamazaki T, Miyamoto K, et al. Treatment for delirium with risperidone: results of a prospective open trial with 10 patients. *Gen Hosp Psychiatry*. 2003;25(4):289-292.
**64.** Mittal D, Jimerson N, Neely E, et al. Risperidone in the treatment of delirium: results from a prospective open-label trial. *J Clin Psychiatry*. 2004;65(5):662-667.
**65.** Parellada E, Baeza I, de Pablo J, Martínez G. Risperidone in the treatment of patients with delirium. *J Clin Psychiatry*. 2004;65(3):348-353.
**66.** Schwartz TL, Masand PS. Treatment of delirium with quetiapine. *Prim Care Companion J Clin Psychiatry*. 2000;2(1):10-12.
**67.** Kim KY, Bader G, Kotlyar V, Gropper D. Treatment of delirium in older adults with quetiapine. *J Geriatr Psychiatry Neurol*. 2003;16(1):29-31.
**68.** Boettger S, Breitbart W. Atypical antipsychotics in the management of delirium: a review of the empirical literature. *Palliat Support Care*. 2005;3(3): 227-237.
**69.** Lacasse H, Perreault MM, Williamson DR. Systematic review of antipsychotics for the treatment of hospital-associated delirium in medically or surgically ill patients. *Ann Pharmacother*. 2006;40(11):1966-1973.
**70.** Michaud L, Bula C, Berney A, et al; Delirium Guidelines Development Group. Delirium: guidelines for general hospitals. *J Psychosom Res*. 2007;62(3):371-383.
**71.** Seitz DP, Gill SS, van Zyl LT. Antipsychotics in the treatment of delirium: a systematic review. *J Clin Psychiatry*. 2007;68(1):11-21.
**72.** Jackson KC, Lipman AG. Drug therapy for delirium in terminally ill patients. *Cochrane Database Syst Rev*. 2004;(2):CD004770.
**73.** Leso L, Schwartz T. Ziprasidone treatment of delirium. *Psychosomatics*. 2002; 43(1):61-62.
**74.** Young CC, Lujan E. Intravenous ziprasidone for the treatment of delirium in the intensive care unit. *Anesthesiology*. 2004;101(3):794-795.
**75.** Straker DA, Shapiro PA, Muskin PR. Aripiprazole in the treatment of delirium. *Psychosomatics*. 2006;47(5):385-391.
**76.** Canadian Task Force on the Periodic Health Examination. The periodic health examination, II: 1987 update. *CMAJ*. 1988;138(7):618-626.
**77.** Derogatis LR, Feldstein M, Morrow G, et al. A survey of psychotropic drug prescriptions in an oncology population. *Cancer*. 1979;44(5):1919-1929.
**78.** Fernandez F, Holmes V, Adams F, Kavanaugh J. Treatment of severe refractory agitation with a haloperidol drip. *J Clin Psychiatry*. 1988;49(6):239-241.
**79.** Information for healthcare professionals: haloperidol (marketed as Haldol, Haldol Decanoate and Haldol Lactate). US Food & Drug Administration Web page. http://www.fda.gov/CDER/DRUG/InfoSheets/HCP/haloperidol.htm. Accessed November 26, 2008.
**80.** Menza MA, Murray G, Holmes V, Rafuls WA. Controlled study of extrapyramidal reactions in the management of delirious medically ill patients: intravenous haloperidol versus intravenous haloperidol plus benzodiazepines. *Heart Lung*. 1988;17(3):238-241.

**81.** Clozaril [prescribing information]. East Hanover, NJ: Novartis; 2004. http://www.fda.gov/cder/foi/label/2005/019758s056lbl.pdf. Accessed November 26, 2008.
**82.** Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA*. 2005;294(15):1934-1943.
**83.** Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs atypical antipsychotic medications. *N Engl J Med*. 2005;353(22):2335-2341.
**84.** Information for healthcare professionals: antipsychotics. US Food & Drug Administration Web page. http://www.fda.gov/cder/drug/InfoSheets/HCP/antipsychotics_conventional.htm. Accessed November 26, 2008. .
**85.** Ventafridda V, Ripamonti C, DeConno F, Tamburini M, Cassileth BR. Symptom prevalence and control during cancer patients' last days of life. *J Palliat Care*. 1990;6(3):7-11.
**86.** Fainsinger RL, Waller A, Bercovici M, et al. A multicentre international study of sedation for uncontrolled symptoms in terminally ill patients. *Palliat Med*. 2000;14(4):257-265.
**87.** Rietjens JA, van Zuylen L, van Veluw H, van der Wijk L, van der Heide A, van der Rijt CC. Palliative sedation in a specialized unit for acute palliative care in a cancer hospital: comparing patients dying with and without palliative sedation. *J Pain Symptom Manage*. 2008;36(3):228-234.
**88.** Connor SR, Pyenson B, Fitch K, Spence C, Iwasaki K. Comparing hospice and nonhospice patient survival among patients who die within a three-year window. *J Pain Symptom Manage*. 2007;33(3):238-246.
**89.** Mercadante S, DeConno F, Ripamonti C. Propofol in terminal care. *J Pain Symptom Manage*. 1995;10(8):639-642.
**90.** Lo B, Rubenfeld G. Palliative sedation in dying patients: "we turn to it when everything else hasn't worked." *JAMA*. 2005;294(14):1810-1816.
**91.** Lawlor PG, Fainsinger RL, Bruera ED. Delirium at the end of life: critical issues in clinical practice and research. *JAMA*. 2000;284(19):2427-2429.
**92.** Gagnon B, Low G, Schreier G. Methylphenidate hydrochloride improves cognitive function in patients with advanced cancer and hypoactive delirium: a prospective clinical study. *J Psychiatry Neurosci*. 2005;30(2):100-107.
**93.** Keen JC, Brown D. Psychostimulants and delirium in patients receiving palliative care. *Palliat Support Care*. 2004;2(2):199-202.
**94.** Morita T, Otani H, Tsunoda J, Inoue S, Chihara S. Successful palliation of hypoactive delirium due to multi-organ failure by oral methylphenidate. *Support Care Cancer*. 2000;8(2):134-137.
**95.** Trzepacz PT. Update on the neuropathogenesis of delirium. *Dement Geriatr Cogn Disord*. 1999;10(5):330-334.
**96.** Mukadam N, Ritchie CW, Sampson EL. Cholinesterase inhibitors for delirium: what is the evidence? *Int Psychogeriatr*. 2008;20(2):209-218.
**97.** Overshott R, Karim S, Burns A. Cholinesterase inhibitors for delirium. *Cochrane Database Syst Rev*. 2008;(1):CD005317.
**98.** Kalisvaart CJ, Boelaarts L, de Jonghe JF, Hovinga IM, Kat MG. Successful treatment of three elderly patients suffering from prolonged delirium using the cholinesterase inhibitor rivastigmine. *Ned Tijdschr Geneeskd*. 2004;148(30):1501-1504.
**99.** Sykes N, Thorns A. Sedative use in the last week of life and the implications for end-of-life decision making. *Arch Intern Med*. 2003;163(3):341-344.
**100.** Morita T, Chinone Y, Ikenaga M, et al; Japan Pain, Palliative Medicine, Rehabilitation, and Psycho-Oncology Study Group. Efficacy and safety of palliative sedation therapy: a multicenter, prospective, observational study conducted on specialized palliative care units in Japan. *J Pain Symptom Manage*. 2005;30(4):320-328.
**101.** Bercovitch M, Adunsky A. Patterns of high-dose morphine use in a home-care hospice service: should we be afraid of it? *Cancer*. 2004;101(6):1473-1477.
**102.** Vitetta L, Kenner D, Sali A. Sedation and analgesia-prescribing patterns in terminally ill patients at the end of life. *Am J Hosp Palliat Care*. 2005;22(6):465-473.
**103.** Inouye SK, Bogardus ST Jr, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med*. 1999;340(9):669-766.
**104.** Siddiqi N, Stockdale R, Britton AM, Holmes J. Interventions for preventing delirium in hospitalised patients. *Cochrane Database Syst Rev*. 2007;(2):CD005563.

 

# 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.