Delirium is highly prevalent in cancer patients with advanced disease. Frequently a preterminal event, the condition is a sign of significant physiologic disturbance, typically involving multiple medical etiologies including infection, organ failure, adverse medication effects, and in rare situations, paraneoplastic syndromes. Unfortunately, delirium is frequently underrecognized or misdiagnosed and, therefore, inappropriately treated or untreated in terminally ill patients. The clinical features of delirium are numerous and encompass a variety of neuropsychiatric symptoms common to other psychiatric disorders. Three clinical subtypes of delirium, based on arousal disturbance and psychomotor behavior, have been described: hyperactive, hypoactive, and mixed. The differential diagnosis for delirium includes depression, mania, psychosis, and dementia. Numerous instruments have been developed to aid the clinician in rapidly screening for the disorder. Standard management requires an investigation of the etiologies, correction of the contributing factors, and management of symptoms. Symptomatic and supportive therapies, including numerous pharmacologic approaches, are important, but several aspects of the use of neuroleptics and other agents in the management of delirium in the dying patient remain controversial.

ABSTRACT: Delirium is highly prevalent in cancer patients with advanced disease. Frequently a preterminal event, the condition is a sign of significant physiologic disturbance, typically involving multiple medical etiologies including infection, organ failure, adverse medication effects, and in rare situations, paraneoplastic syndromes. Unfortunately, delirium is frequently underrecognized or misdiagnosed and, therefore, inappropriately treated or untreated in terminally ill patients. The clinical features of delirium are numerous and encompass a variety of neuropsychiatric symptoms common to other psychiatric disorders. Three clinical subtypes of delirium, based on arousal disturbance and psychomotor behavior, have been described: hyperactive, hypoactive, and mixed. The differential diagnosis for delirium includes depression, mania, psychosis, and dementia. Numerous instruments have been developed to aid the clinician in rapidly screening for the disorder. Standard management requires an investigation of the etiologies, correction of the contributing factors, and management of symptoms. Symptomatic and supportive therapies, including numerous pharmacologic approaches, are important, but several aspects of the use of neuroleptics and other agents in the management of delirium in the dying patient remain controversial.

Delirium in the Terminally Ill

Delirium is the most common and serious neuropsychiatric complication in cancer patients with advanced illness and has enormous relevance to symptom control and palliative care. The condition is highly prevalent in cancer patients with advanced disease, particularly in the last weeks of life, with prevalence rates ranging from 25% to 85%. Indeed, delirium is one of the most common mental disorders encountered in general hospital practice. An estimated 33% of hospitalized medically ill patients have serious cognitive impairments.

In a study of 334 hospitalized cancer patients evaluated by psychiatric consultation, 25% were diagnosed with delirium. In a smaller sampling of 13 terminal cancer patients, 85% were diagnosed with delirium. Pereira and coworkers identified the prevalence of cognitive impairment in cancer inpatients to be 44%, with the prevalence rising to 62.1% prior to death. Delirium has been described in up to 51% of postoperative patients. With increased numbers of elderly patients who are particularly susceptible, the incidence of delirium is rising. Studies of elderly patients admitted to medical wards estimate that 30% to 50% of patients age 70 years or older demonstrate symptoms of delirium at some point during their hospitalization. Elderly patients who develop delirium during a hospitalization have an estimated 22% to 76% chance of dying during that admission.
In the terminally ill, delirium is associated with increased morbidity, which causes distress in patients, family members, and staff.\[2,19,20\] In a recent study of terminally ill cancer patients, Breitbart and colleagues\[19\] discovered that 54% of patients recalled their delirium experience after resolution of their delirium. Factors predicting diminished recollection of the delirium experience included severe short-term memory impairment, severe delirium, and the presence of intense perceptual disturbances.

In the same study, distress related to the episode of delirium was rated by patients, spouses or caregivers, and nurses.\[19\] Distress was rated as severe by all three groups, with the spouse or caretaker group experiencing the most distress. A significant predictor of heightened spouse distress was a low Karnofsky performance status for the patient, indicating debilitation. The most significant factor predicting distress for patients was the presence of delusions. Patients with hypoactive delirium were as distressed as patients with hyperactive delirium (see Subtypes of Delirium, below). Delirium severity and intensity of perceptual disturbances also enhanced nurses’ distress. In the later stages of illness, delirium interferes dramatically with the recognition and control of other physical and psychological symptoms such as pain.\[21-23\]

A recent retrospective study of 284 hospice patients sought to identify factors that contribute to the impairment of communication capacity in terminally ill cancer patients.\[24\] The study demonstrated that communication capacity was frequently impaired in terminally ill cancer patients, and the degree of impairment significantly associated with higher doses of opioids. Patients who did not require high doses of opioids were able to retain complex and simple communication capacity longer than those who required high doses of opioids prior to death. Delirium was found in 20% of patients in this study, which emphasized the importance of further investigations to explore new strategies for maintaining communication capacity in this population.

Frequently a preterminal event, delirium is a sign of significant physiologic disturbance, typically involving multiple medical etiologies including infection, organ failure, adverse medication effects, and in rare situations, paraneoplastic syndromes.\[8,25-28\] Lawlor and colleagues\[29\] recently reported on their experience in the management of delirium in advanced cancer patients admitted to a palliative care unit. While only 42% of patients had delirium upon admission, "terminal" delirium was seen in 88% of patients at the time of death.

Unfortunately, delirium is frequently underrecognized or misdiagnosed, and therefore inappropriately treated or untreated in terminally ill patients. Impediments to progress in the recognition and treatment of delirium include confusion regarding terminology as well as lack of consistency in utilizing diagnostic classification systems. In addition, the signs and symptoms of delirium are diverse and frequently mistaken for other psychiatric disorders. Practitioners need to diagnose delirium accurately, undertake appropriate assessment of etiologies, and familiarize themselves with the benefits and risks of pharmacologic and nonpharmacologic interventions currently available to manage delirium in the terminally ill.

Assessment

The clinical features of delirium are numerous and encompass a variety of neuropsychiatric symptoms common to other psychiatric disorders, including depression, dementia, and psychosis.\[30\] Clinical features of delirium include prodromal symptoms (restlessness, anxiety, sleep disturbance, and irritability); rapidly fluctuating course; reduced attention (easily distractible); altered arousal; increased or decreased psychomotor activity; disturbance of the sleep-wake cycle; affective symptoms (emotional lability, sadness, anger, or euphoria); altered perceptions (misperceptions, illusions, poorly formed delusions, and hallucinations); disorganized thinking and incoherent speech; disorientation as to time, place, or person; and memory impairment (difficulty registering new material).

Neurologic abnormalities may be present during delirium, including cortical abnormalities (dysgraphia, constructional apraxia, dysnomic aphasia); motor abnormalities (tremor, asterixis, myoclonus, and reflex or tone changes); and electroencephalogram (EEG) abnormalities (typically global slowing). The protean nature of delirium, with its profound variability and fluctuation in clinical course, makes the condition more difficult to diagnose accurately and treat effectively. TABLE 1
Table 1 lists the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), criteria for delirium.[31] The essential defining features of delirium, based on DSM-IV criteria, have shifted from an extensive list of typical symptoms and abnormalities to a focus on the two essential concepts of disordered attention (arousal) and cognitive disturbance. The definition continues to recognize the importance of acute onset, fluctuating course, and organic etiology. Associated phenomena including altered psychomotor activity and behavior, perceptual disturbances, and delusions are not essential for the diagnosis of delirium. Delirium is now conceptualized primarily as “a disorder of arousal and cognition,”[32] in contrast to dementia, which is a disorder of cognition without an arousal disturbance. Disorder of the arousal system resulting in altered levels of consciousness and impaired attention is pathognomonic of delirium. This arousal disturbance is, in part, the basis for classifying delirium into several subtypes.

### Subtypes of Delirium

Three clinical subtypes of delirium, based on arousal disturbance and psychomotor behavior, have been described. These include the hyperactive subtype (hyperaroused, hyperalert, or agitated), the hypoactive subtype (hypoaroused, hypoalert, or lethargic), and a mixed subtype with alternating features of hyperactive and hypoactive delirium.[33,34] Research suggests that the hyperactive subtype is more frequently characterized by hallucinations, delusions, agitation, and disorientation, whereas the hypoactive subtype is characterized by confusion and sedation, and less frequently accompanied by hallucinations or delusions.[35]

In addition, there is evidence suggesting that the subtypes of delirium may result from specific etiologies, demonstrate unique pathophysiologies, and display differential responses to treatment.[36,37] An estimated 67% of cases of delirium are either the hypoactive or mixed subtype. The prototypical agitated delirium most familiar to clinicians actually occurs in a minority of cases.[33-35]

### Differential Diagnosis

Many of the clinical features and symptoms of delirium may be associated with other psychiatric disorders including depression, mania, psychosis, or dementia. A patient with delirium may exhibit mood disturbances such as anxiety, fear, depression, irritability, anger, euphoria, apathy, or mood lability.

- **Depression and Mania**—Delirium, particularly the hypoactive subtype, is often initially misdiagnosed as depression. Symptoms of major depression, including altered level of activity (hypoactivity), insomnia, impaired concentration, depressed mood, and suicidal ideation, may overlap with symptoms of delirium, making an accurate diagnosis more difficult. To differentiate delirium from depression, particularly in the context of advanced disease, an evaluation of the onset and temporal sequencing of depressive and cognitive symptoms is particularly helpful. Importantly, the degree of cognitive impairment in delirium is more severe, pervasive, and abrupt in onset than that associated with depression. Most notably, in delirium, a disturbance in arousal or consciousness is present. Arousal disturbance is not characteristic of depression. Similarly, a manic episode may share some features of delirium, particularly the hyperactive or mixed subtype. Again, the temporal onset and course of symptoms, as well as the presence of an arousal disturbance associated with cognitive impairment, assist in differentiating these disorders.

- **Psychosis**—Delirium characterized by vivid hallucinations and delusions must be distinguished from a variety of psychotic disorders. In delirium, psychotic symptoms occur in the context of a disturbance in consciousness or arousal associated with memory impairment and disorientation. These features are not present in other psychotic disorders. The delusions associated with delirium tend to be poorly organized and abrupt in onset. Visual and tactile hallucinations predominate in delirium, in contrast to the auditory hallucinations more characteristic of schizophrenia. Finally, the development of these psychotic symptoms in the context of advanced medical illness makes delirium a more likely diagnosis.

- **Dementia**—A common diagnostic task is to differentiate delirium from dementia or delirium superimposed upon a preexisting dementia. Both delirium and dementia are cognitive impairment disorders, sharing clinical features such as impaired memory, disordered thinking, limited judgment, and disorientation. However, the patient with dementia is alert without the disturbance of consciousness or arousal characteristic of delirium. The temporal onset of symptoms in dementia is subacute and chronically progressive, and the patient's sleepwake cycle is less disrupted. The most prominent disturbances in dementia include short- and long-term memory deficits, impaired
judgment, reduced capacity for abstract thinking, and alterations in higher cortical functions (aphasia and apraxia).

In contrast to dementia, delirium is typically conceptualized as a reversible process. Delirium is frequently reversible even in patients with advanced illness. However, delirium may not be reversible in the last 24 to 48 hours of life. This is most likely due to irreversible processes including multiple organ failure. Delirium occurring in these last days of life is sometimes referred to as "terminal" delirium in the palliative care literature.

### Tools for Assessing Delirium in Cancer Patients

**Delirium Screening/Diagnostic Scales**

Numerous scales or instruments have been developed to aid the clinician in rapidly screening for cognitive impairment disorders (dementia or delirium), or in establishing a diagnosis of delirium (see Table 2).[38-46] Such scales have been described, and their relative strengths and weaknesses reviewed elsewhere.[43,47] Perhaps most helpful to clinicians are the Mini-Mental State Examination (a cognitive impairment screening tool) and several delirium diagnostic and severity rating scales, including the Delirium Rating Scale, the Delirium Rating Scale-Revised-98, the Confusion Assessment Method, the Abbreviated Cognitive Test for Delirium, and the Memorial Delirium Assessment Scale. These tools are briefly described in the subsections below.

- **Mini-Mental State Examination**—The Mini-Mental State Examination (MMSE)[45] is useful in screening for cognitive failure but does not distinguish between delirium and dementia. The MMSE provides a quantitative assessment of the patient's cognitive performance and capacity, measuring the severity of cognitive impairment. It is most sensitive to cortical dementias such as Alzheimer's disease and less sensitive in detecting subcortical deficits such as those found in AIDS dementia. The MMSE assesses five general cognitive areas: orientation, registration, attention/calculation, delayed recall, and language. Traditionally, a score of 23 or less is considered indicative of cognitive impairment. However, a multitiered system is frequently utilized, with a score of 24-30 indicating no impairment, a score of 18-23 indicating mild impairment, and a score of 0-17 indicating severe impairment.

- **Delirium Rating Scale**—The Delirium Rating Scale (DRS), developed by Trzepacz and colleagues[47] is a 10-item clinician-rated symptom rating scale for diagnosing delirium. Based on DSM-III-R (third edition, revised) diagnostic criteria for delirium, the scale is designed to be used by the clinician to identify delirium and distinguish it reliably from dementia and other neuropsychiatric disorders. Each item is scored by choosing the best rating, which has a numerical weight designed to distinguish the phenomenologic characteristics of delirium. A score of 12 or greater is diagnostic of delirium.

- **Delirium Rating Scale-Revised 98**—A revision of the Delirium Rating Scale (DRS), the Delirium Rating Scale-Revised 98 (DRS-R-98) has 13 severity and 3 diagnostic items with descriptive anchors for each rating level. Although it was designed for phenomenologic and treatment research, the scale may be used clinically. Indeed, the DRS-R-98 is a valid, sensitive, and reliable instrument for the rating of delirium severity. It has advantages over the original DRS for repeated measures and phenomenologic studies due to its enhanced breadth of symptoms and separation into severity and
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diagnostic subscales.[48]

• **Confusion Assessment Method**— The Confusion Assessment Method (CAM)[49] is a nine-item delirium diagnostic scale utilizing the DSMIII-R criteria for delirium, which can be administered rapidly by a trained clinician. The CAM may be administered using a simplified diagnostic algorithm that includes only four items designed for rapid identification of delirium by nonpsychiatrists. The four-item algorithm requires an acute onset and a fluctuating course with inattention and either disorganized thinking or altered level of consciousness.

• **Abreviated Cognitive Test for Delirium**—Abreviated Cognitive Test for Delirium (CTD)[50] was recently developed as a tool to identify delirium in patients in the intensive care unit setting who have limited ability to communicate verbally. This brief tool utilizes visualization span and recognition memory of pictures. It reliably identifies delirium and discriminates delirium from dementia, depression, and schizophrenia. TABLE 3

<table>
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<tr>
<th>Items From the Memorial Delirium Assessment Scale (MDAS)</th>
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• **Memorial Delirium Assessment Scale**—Memorial Delirium Assessment Scale (MDAS) is a 10-item delirium assessment tool (see Table 3), validated among hospitalized inpatients with advanced cancer and AIDS.[39] The MDAS is both a good delirium diagnostic screening tool as well as a reliable tool for assessing delirium severity among patients with advanced disease. A cutoff score of 13 is diagnostic of delirium. The MDAS has advantages over other delirium tools in that it is both a diagnostic and a severity measure ideal for repeated assessments and for treatment intervention trials. Recently, Lawlor and colleagues[51] further examined the clinical utility and validation of the MDAS in a population of advanced cancer patients in a palliative care unit. The investigators demonstrated the usefulness of the MDAS in this select population. A cutoff score of 7 out of 30 yielded the highest sensitivity (98%) and specificity (76%) for a delirium diagnosis in this palliative care population.

**Management of Delirium in the Terminally Ill**

The standard approach to managing delirium in the medically ill, including patients with advanced disease, requires an investigation of the etiologies, correction of the contributing factors, and management of symptoms. The desired and frequently achievable outcome is a patient who is awake, alert, calm, cognitively intact, not psychotic, and able to communicate coherently with family and staff. In the terminally ill patient who develops delirium in the last days of life, the management of delirium is unique, presents a number of dilemmas, and may alter the desired clinical outcome.

**Assessment of Etiologies of Delirium**

Formulation of a differential diagnosis of the etiologies of delirium in a terminally ill or dying patient is useful. Controversy exists regarding the appropriate extent of diagnostic evaluation to be pursued in a dying patient with terminal delirium.[52,53] Most palliative care clinicians undertake diagnostic studies only if a clinically suspected etiology may be readily identified with minimal use of invasive procedures and effectively treated with simple interventions that minimize risk and limit distress to the patient. Diagnostic work-up in pursuit of an etiology for delirium may be limited by either practical constraints such as the setting (home, hospice) or the focus on patient comfort, so that unpleasant or painful diagnostic procedures are avoided. However, more often the etiology of terminal delirium is multifactorial or indeterminate. Bruera and colleagues[2] reported that an etiology is discovered in less than 50% of terminally ill patients with delirium. If a distinct cause is responsible for delirium in the terminally ill, it is frequently irreversible or difficult to treat. Studies in patients with earlier stages of advanced cancer, however, have demonstrated the potential utility of a thorough diagnostic assessment.[2,22] When such diagnostic information is available, a specific therapy may be able to reverse delirium. One study found that 68% of delirium in cancer patients could be improved, despite a 30-day mortality of
31%. Another study found that 33% of episodes of cognitive failure improved if an evaluation yielded a specific etiology.[2] In a prospective study of delirium in patients on a palliative care unit,[29] investigators reported that the etiology of delirium was multifactorial in the majority of cases. Despite the occurrence of delirium in 88% of dying patients in the last week of life, delirium was reversible in approximately 50% of cases. The causes of delirium most associated with reversibility included dehydration and psychoactive or opioid medications. Hypoxic and metabolic encephalopathies were less likely to be reversible in terminal delirium.

A diagnostic evaluation includes an assessment of potentially reversible causes of delirium. A full physical examination should examine for evidence of sepsis, dehydration, or major organ failure. Medications that contribute to delirium should be identified. A laboratory assessment identifies metabolic abnormalities including hypercalcemia, hypoxia, or disseminated intravascular coagulation that may cause delirium. Radiographic imaging studies of the brain and lumbar puncture for examination of cerebrospinal fluid may be appropriate in some instances. TABLE 4

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<th>Causes of Delirium in Patients With Advanced Disease</th>
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- **Potential Etiologies**—Delirium has multiple potential etiologies (Table 4). In patients with advanced cancer, delirium may be due either to direct effects on the central nervous system (CNS) or to indirect CNS effects of the disease or treatments (medications, electrolyte imbalance, major organ failure, infection, or vascular complications).[2,29]

Due to fragile physiologic functioning and the prescription of numerous medications, advanced cancer patients are more vulnerable to the development of delirium with routinely prescribed hypnotics. Narcotic analgesics including levorphanol (Levo-Dromoran), morphine, and meperidine are common causes of delirium in the elderly and terminally ill. Chemotherapeutic agents known to cause delirium include methotrexate, fluorouracil, vincristine, vinblastine, bleomycin, carmustine (BiCNU, Gliadel), cisplatin, asparaginase (Elspar), procarbazine (Matulane), ifosfamide (Ifex), and glucocorticosteroids[ 8,23,27,55-60]; as well as the immunotherapeutic agents interleukin-2 and interferon.

Most patients receiving chemotherapeutic agents will not develop prominent central nervous system effects unless dexamethasone or prednisone is included in the regimen. The spectrum of disturbances related to steroids includes anxiety, mood lability, major affective disorders (mania or depression), cognitive impairment (reversible dementia), and delirium (steroid psychosis). The incidence of steroid-induced disorders ranges from 3% to 57% in noncancer populations, with increased prevalence at higher doses. Symptoms typically develop within the first 2 weeks of administration but may occur at any time, with any dose, and even during the tapering phase.[22] These disorders are frequently rapidly reversible upon dose reduction or discontinuation.[22]

**Nonpharmacologic Interventions**

In addition to identifying and correcting the etiologies of delirium, symptomatic and supportive therapies are important.[3,4,20,53] In fact, symptomatic and supportive treatment may be the only interventions in a dying patient. Maintaining fluid and electrolyte balance, providing nutrition, supplementing vitamins, reducing anxiety and disorientation, and continuing comforting, reassuring interactions with family members may be helpful. Providing structure, routine, and familiarity will reduce anxiety and disorientation. Ensuring that the patient has a quiet, well-lit room with familiar objects, a visible clock or calendar, and the presence of family will provide comfort. Judicious use of physical restraints or one-to-one nursing observation may be appropriate, beneficial, and necessary.
Inouye and colleagues[61] reported on a successful multicomponent intervention program to prevent delirium in hospitalized older patients. They focused on a set of risk factors that were highly predictive of delirium in the elderly, including preexisting cognitive impairment, visual impairment, hearing impairment, sleep deprivation, immobility, dehydration, and severe illness. Interventions directed at constant reorientation, correction of hearing and visual impairment, reversal of dehydration, and early mobilization appeared to significantly reduce the number and duration of episodes of delirium in hospitalized older patients. The applicability of these interventions and the likelihood that they would prevent delirium in the terminally ill, particularly in the last days of life, is minimal.

Pharmacologic Interventions

Supportive techniques alone are frequently ineffective in managing symptoms of delirium, and symptomatic treatment with neuroleptics or sedative medications may be necessary (Table 5). Neuroleptic drugs (dopamine-blocking drugs) such as haloperidol, are utilized frequently as antiemetics in the medical setting. However, only 0.5% to 2% of hospitalized cancer patients, for instance, receive haloperidol for the management of delirium.[62,63] In terminally ill populations, as few as 17% receive an antipsychotic for agitation, despite an estimated prevalence of delirium ranging from 25% in hospitalized cancer patients to 85% in the terminally ill.[64,65]

**Neuroleptics**—Haloperidol, a neuroleptic with potent dopamine blockade, is frequently used in the treatment of delirium in patients with advanced disease.[65-73] Haloperidol in low doses (1 to 3 mg/d) is usually effective in targeting agitation, paranoia, and hallucinations. Haloperidol, 0.5 to 1.0 mg (po, IV, IM, SC), may be administered with repeated doses every 45 to 60 minutes titrated upward to relieve target symptoms.[52,74] An intravenous route facilitates rapid onset of action. If intravenous access is unavailable, an intramuscular or subcutaneous route of administration may be used and switched to oral administration when possible.

The majority of delirious patients can be managed with oral haloperidol. Parenteral doses are approximately twice as potent as oral doses. Many palliative care practitioners deliver haloperidol by the subcutaneous route.[21,75] A low dose of neuroleptic is typically sufficient to treat delirium in elderly, terminally ill patients. In general, doses need not exceed 20 mg of haloperidol in a 24-hour period. There are clinicians who advocate high doses (up to 250 mg of haloperidol intravenously over 24 hours) in selected cases.[69]

A common strategy in the management of delirium is the addition of parenteral lorazepam to a regimen of haloperidol.[76,77] Lorazepam (0.5 to 1.0 mg every 1 to 2 hours orally or intravenously), administered with haloperidol may provide effective sedation for the agitated delirious patient and minimize extrapyramidal side effects associated with haloperidol.[77] An alternative strategy is to switch from haloperidol to a more sedating neuroleptic such as chlorpromazine.

In a double-blind, randomized comparison trial of haloperidol, chlorpromazine, and lorazepam, 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. Lorazepam used alone exacerbated delirium and increased cognitive impairment.[1] Both haloperidol and chlorpromazine administered in low doses (haloperidol at 2 mg or its equivalent every 24 hours), were highly effective in managing symptoms of delirium (significant improvement in DRS scores) and improving cognitive function (significant
improvement in MMSE scores). In addition, both haloperidol and chlorpromazine significantly improved symptoms of delirium in both subtypes, ie, hypoactive and hyperactive.[1] Methotrimeprazine, a phenothiazine neuroleptic with properties similar to chlorpromazine, is often utilized parenterally (intravenously or by subcutaneous infusion) to control confusion and agitation in terminal delirium.[78] Doses range from 12.5 to 50 mg every 4 to 8 hours up to 300 mg/24 hours for the majority of patients. Hypotension and excessive sedation are potential limitations of this drug. Methotrimeprazine has the advantage of analgesic properties, equipotent to morphine, through nonopioid mechanisms.[78]

- **Atypical Neuroleptics**—Several new, atypical, antipsychotic agents with less risk of extrapyramidal side effects are currently available and include such agents as clozapine, risperidone (Risperdal), and olanzapine (Zyprexa).[79-83] Risperidone demonstrated usefulness in the treatment of dementia and psychosis in AIDS patients at doses of 1 to 6 mg/d, suggesting safe use in patients with delirium.[82] A limited number of published studies have addressed the use of these agents in the treatment of delirium.[80-83] In a recent doubleblind comparative delirium intervention study assessing the efficacy of haloperidol vs risperidone, Han and Kim demonstrated in a small sample of 24 patients that there was no significant difference in clinical efficacy or response rate.[84] Breitbart and colleagues[80] published a large (N = 82) open trial of olanzapine for the treatment of delirium in hospitalized patients with advanced cancer, and the drug proved highly effective. Delirium resolved in 76% of patients, without incidence of extrapyramidal side effects. Several factors were found to be significantly associated with poorer response to olanzapine, including age over 70, history of dementia, and the hypoactive subtype of delirium. The average starting dose was 2.5 to 5 mg and patients were given up to 20 mg daily. Sedation was the most common side effect. Many palliative care clinicians use risperidone (eg, 0.5-1 mg twice daily) and olanzapine (2.5-20 mg/d in divided doses) in the management of delirium in terminally ill patients, particularly those who have demonstrated intolerance to extrapyramidal side effects of the typical neuroleptics.[85] A current limitation on the use of atypical neuroleptics is the lack of availability in parenteral formulations.

While neuroleptics are most effective in reducing agitation, clearing the sensorium, and improving cognition in the delirious patient, this outcome may not be possible in delirium that complicates the last days of life. Processes causing delirium may be persistent and irreversible during the active dying phase. Ventafridda et al[86] and Fainsinger et al[23] reported that 10% to 20% of terminally ill patients experience delirium that necessitates management by sedation, resulting in significantly reduced arousal and decreased level of consciousness. The goal of treatment with midazolam, propofol (Diprivan), or methotrimeprazine is quiet sedation. Midazolam, administered by subcutaneous or intravenous infusion in doses ranging from 30 to 100 mg over 24 hours may be effectively used to control agitation related to delirium in the terminal stages.[87] Propofol, a short-acting anesthetic agent, has also been utilized primarily as a sedating agent for the control of agitated patients with terminal delirium. In several case reports, propofol has been used in terminal care with an intravenous loading dose of 20 mg followed by a continuous infusion at initial doses ranging from 10 to 70 mg/h, with titration upward to a maximum of 400 mg/h over a period of hours to days, to control severely agitated patients.[88,89] Propofol has the advantage of more readily titrated sedation and more rapid recovery by tapering the rate of infusion.[88]

**Controversies in the Management of Terminal Delirium**
Several aspects of the use of neuroleptics and other pharmacologic agents in the management of delirium in the dying patient remain controversial. Some clinicians contend that pharmacologic interventions with neuroleptics or benzodiazepines are inappropriate for delirium in the dying patient. Clinicians may hesitate to intervene, as they view delirium as an integral component of the dying process. In particular, some palliative care clinicians consider dying patients' hallucinations and delusions involving communication with predeceased relatives welcoming them to heaven as an important event in the transition from life to death. Given that some patients experience hallucinations and delusions as pleasant and comforting, clinicians may doubt the appropriateness of pharmacologic intervention or the necessity of perceived aggressive treatment in the actively dying patient. Moreover, parenteral neuroleptics or sedatives may mistakenly be avoided secondary to exaggerated fears of hastening death through hypotension or respiratory depression. Many clinicians are unnecessarily pessimistic about the possibility of effective results of neuroleptics in the symptomatic relief of terminal delirium. Some practitioners argue that as the underlying pathophysiologic process is irreversible, no improvement will be expected in the patient's mental status. Others are concerned that neuroleptics or sedatives may exacerbate delirium by further...
confusion or sedation. Clinical experience in terminal delirium suggests that the use of neuroleptics in the management of agitation, paranoia, hallucinations, and altered sensorium is safe, effective, and frequently appropriate.[76] Management of delirium on a case-by-case basis is wisest. An agitated, delirious dying patient should receive neuroleptics to restore calm. A "wait-and-see" approach, prior to intervening with neuroleptics, may be appropriate for patients who are lethargic, somnolent, or experiencing pleasant, comforting hallucinations. That said, such a wait-and-see approach must recognize that a lethargic or hypoactive delirium may rapidly and unexpectedly transform into an agitated or hyperactive delirium that threatens the serenity and safety of the patient, family, and staff.

Recent evidence suggests that neuroleptics effectively reduce the symptoms of delirium in both hyperactive and hypoactive subtypes of delirium.[1] Neuroleptics improve the arousal disturbance and cognitive function in patients with hypoactive delirium. Some clinicians suggest that the hypoactive delirium subtype responds to psychostimulants or combinations of neuroleptics and psychostimulants.[54]

- **Need for Sedation**—Perhaps the most challenging clinical problem is management of the dying patient with a terminal delirium that is unresponsive to standard neuroleptics, whose symptoms can only be controlled by sedation to the point of a significantly decreased level of consciousness. Before undertaking interventions such as midazolam or propofol infusions, in which the goal is a calm, comfortable, but sedated, unresponsive patient, the clinician must first take several steps. The clinician must have a discussion with the family (and the patient if he or she appears to have the capacity during lucid moments) to elicit concerns and wishes for the type of care that best honors a desire to provide comfort and symptom control during the dying process. The clinician should describe the optimal achievable goals of therapy as they currently exist. Family members should be informed that the goal of sedation is to provide comfort and symptom control, not to hasten death. They should also be told to anticipate that sedation may result in a premature sense of loss and that they may feel their loved one is in some sort of limbo state, not yet dead, but no longer alive in the vital sense.

The distress and confusion that family members can experience during such a period may be ameliorated by including the family in the decision-making process and emphasizing the shared goals of care. Sedation in such patients is not always complete or irreversible. Some patients have periods of wakefulness despite sedation, and many clinicians will periodically lighten sedation to reassess the patient's condition. Ultimately, the clinician must always keep in mind the goals of care and communicate these goals to the staff, patients, and family members. The clinician must consider these issues in the management of the dying patient who presents with delirium in such a way that preserves and respects the dignity and values of that individual and family.

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