Delirium in Palliative Care

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ABSTRACT

Delirium is a common and often serious neuropsychiatric complication in palliative care settings, characterized by an abrupt onset of disturbances of consciousness, attention, cognition, and perception that fluctuate over the course of the day. Delirium, frequently the harbinger of impending death, is a sign of significant physiologic disturbance, usually involving multiple medical etiologies, including infection, major organ failure, electrolyte disturbances, and medication adverse effects. Delirium is associated with increased morbidity, causing distress in patients and caregivers, and is often the final challenge of palliative care management. Unfortunately, delirium is often under-recognized and untreated in the palliative care setting. Psychiatrists, primary care physicians, oncologists, and pain specialists must be able to diagnose delirium accurately, undertake appropriate assessment of etiologies, clarify the controversies regarding the goals of management, and understand the risks and benefits of the pharmacologic and nonpharmacologic interventions currently available for managing delirium.

INTRODUCTION

Delirium is a common neuropsychiatric complication in palliative care settings. The fluctuating clinical course and diverse phenomenology lead to under-recognition and under-treatment or mistreatment of delirium by clinicians. This article provides an overview of the incidence and prevalence as well as the main clinical features of delirium, including its subtypes, differential diagnosis, etiologies, and the reversibility of delirium in palliative care settings particularly among terminally ill. Pharmacologic and nonpharmacologic interventions, issues, and dilemmas common to the management of delirium in patients receiving palliative care are also summarized.

INCIDENCE AND PREVALENCE OF DELIRIUM

Delirium is highly prevalent in palliative care settings. The highest prevalence and incidence of delirium is reported in hospices among terminally ill patients. Postoperative patients as well as patients with cancer, AIDS, and advanced
illness are also at greater risk for delirium. The prevalence rates of delirium among terminally ill cancer patients have been found to range from 62% to 88%. Prospective studies conducted in inpatient palliative care units have found an occurrence rate of delirium ranging from 20% to 42% on admission and incident delirium developing during admission in 32% to 45%.

**CLINICAL FEATURES AND SUBTYPES OF DELIRIUM**

According to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition–Text Revision* the essential features of delirium are as follows: disturbance of consciousness with reduced ability to focus, sustain, or shift attention; change in cognition that is not better accounted for by a preexisting, established, or evolving dementia or development of a perceptual disturbance; development of the disturbance over a short period of time, usually hours to days, and fluctuation of symptoms during the course of the day; and evidence from the history, physical examination, or laboratory tests that the delirium is a direct physiologic consequence of a general medical condition, substance intoxication or withdrawal, use of a medication, or toxin exposure—or a combination of these factors.

The clinical features of delirium are numerous and include a variety of neuropsychiatric symptoms (Table 1). Main features of delirium include prodromal symptoms (e.g., anxiety, sleep disturbances, and irritability), rapidly fluctuating course, abrupt onset of symptoms, impaired attention, altered level of consciousness (arousal), increased or decreased psychomotor activity, disturbance of sleep-wake cycle, affective symptoms, perceptual disturbances, delusions, disorganized thinking and incoherent speech, disorientation, and memory impairment. Other cognitive domains can also be affected during the course of delirium, presenting as dysnomia, sensorimotor aphasia, or constructional apraxia. The *DSM-IV-TR* criteria for delirium does not address the prodromal or affective symptoms (i.e., depressed mood) of delirium, which might be more prominent in patients with delirium in palliative care settings and also associated with worse outcomes. Neurologic abnormalities may include tremors, asterixis, myoclonus, frontal release signs, and changes in muscle tone.

Two subtypes of delirium were described by Lipowski based on psychomotor behavior and level of arousal, including the hyperactive (or agitated or hyperalert) subtype and the hypoactive (or lethargic, hypoalert, or hypoaroused) subtype. A mixed subtype has since been proposed with alternating features of each. The hypoactive subtype is characterized by psychomotor retardation, lethargy, and reduced awareness of surroundings. In the palliative care setting, hypoactive delirium is most common and is frequently misdiagnosed as depression or severe fatigue. In a hospice setting, 29% of 100 acute admissions were found to have delirium; 86% of these had the hypoactive subtype. The hyperactive subtype is commonly characterized by restlessness, agitation, hypervigilance, hallucinations, and delusions. The hyperactive delirium is more easily recognized by clinicians.

There is evidence suggesting that the subtypes of delirium may be related to different causes and may have different treatment responses. Hypoactive delirium has most commonly been associated with hypoxia, metabolic disturbances, and hepatic encephalopathies and a higher mortality risk compared to the hyperactive subtype. Hyperactive delirium is correlated with alcohol and drug withdrawal or drug intoxication.

**ASSESSMENT OF DELIRIUM**

Clinically, the diagnostic gold standard for delirium is the clinician’s assessment utilizing the *DSM-IV-TR* criteria as outlined above. Several delirium screening and evaluation tools have been developed to maximize diagnostic precision and to assess delirium severity. A detailed review of these assessment tools is available elsewhere. Several examples of delirium assessment tools currently used in palliative care settings include the Memorial Delirium Assessment Scale, the Delirium Rating Scale-Revised 98, and the Confusion Assessment Method. Each of these scales have good reliability and validity.

<table>
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<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td>COMMON CLINICAL FEATURES OF DELIRIUM</td>
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<tr>
<td>Disturbance in level of alertness (consciousness) and arousal</td>
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<td>Attention disturbance</td>
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<td>Rapidly fluctuating course and abrupt onset of symptoms</td>
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<td>Increased or decreased psychomotor activity</td>
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<tr>
<td>Disturbance of sleep-wake cycle</td>
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<td>Mood symptoms</td>
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<td>Perceptual disturbances</td>
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<tr>
<td>Disorganized thinking</td>
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<td>Incoherent speech</td>
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<tr>
<td>Disorientation and memory impairment</td>
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<tr>
<td>Other cognitive impairments (e.g., dysgraphia, constructional apraxia, dysnomia)</td>
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</table>

ETIOLOGIES AND REVERSIBILITY OF DELIRIUM

Delirium can develop secondary to multiple etiologies, such as adverse effects of medications, electrolyte imbalance, dehydration, major organ failure, infection, paraneoplastic syndromes, and central nervous system malignancies. The diagnostic workup of delirium should include an assessment of potentially reversible causes of delirium. It is important to inquire about alcohol or other substance use disorders to be able to recognize and treat alcohol or other substance-induced withdrawal delirium. Medications that could contribute to delirium should be reviewed. Opioid analgesics, benzodiazepines, and anticholinergics are common causes of confusional states, particularly in the elderly and the terminally ill. Reducing the dose of opioids or switching to another opioid has been demonstrated to reverse delirium due to opioids. A screen of laboratory parameters will allow assessment of the possible role of metabolic abnormalities. In some cases, an electroencephalogram (to rule out seizures), brain imaging studies (to rule out brain metastases, or stroke), and lumbar puncture (to rule out meningitis) may be appropriate.

When assessing etiologies of delirium, an important challenge is the clinical differentiation of delirium as either a reversible phenomenon or an integral element of the dying process in terminally ill patients. When diagnostic information indicates a likely etiology, specific treatment may be able to reverse delirium. There is an ongoing debate as to the appropriate extent of diagnostic evaluation that should be pursued in a terminally ill patient with delirium. When confronted with delirium in a terminally ill patient, the clinician must take a more individualized and judicious approach, consistent with the goals of care.

In a study of terminally ill patients, an etiology was discovered in 43% of the patients with delirium, and 33% of the patients with delirium improved with treatment of the specific etiologies. Another study of advanced cancer patients found that in 68% of the cases delirium could be reversed despite a 31% rate of 30-day mortality. Among a group of advanced cancer patients with delirium admitted to a palliative care unit, the overall reversibility rate for delirium was reported as 49%. Reversibility of delirium was significantly associated with opioids, other psychoactive medications, and dehydration. In contrast, irreversibility of delirium was significantly associated with hypoxic encephalopathy, metabolic factors related to major organ failure, and refractory hypercalcemia. Leonard and colleagues found a 27% recovery rate from delirium among patients in palliative care. Patients with irreversible delirium experienced greater disturbances of sleep and cognition.

The reversibility of delirium depends on the interaction of the patient's predisposing factors to delirium (e.g., old age, underlying dementia, physical frailty), the precipitating etiologies, and any response to treatment. If a patient's predisposing factors are modifiable, then targeted interventions may reduce the risk of delirium upon exposure to a precipitant and increase the likelihood of response to treatment with restoration of cognitive functioning.

DIFFERENTIAL DIAGNOSIS OF DELIRIUM

Many of the clinical features of delirium can also be associated with other psychiatric disorders such as depression, mania, psychosis, and dementia.

When delirium presents with mood symptoms, these symptoms are frequently attributed to depression or mania, especially in patients with a past psychiatric or family history of these conditions. The hypoactive subtype of delirium is commonly misdiagnosed as depression. In distinguishing delirium from depression, an evaluation of the onset and temporal sequencing of depressive and cognitive symptoms is particularly helpful. The characteristic disturbance in level of arousal is present in delirium, while it is usually not a feature of depression. Similarly, a manic episode may share some features of delirium, particularly a hyperactive or mixed subtype of delirium. The temporal onset and course of symptoms, presence of a disturbance in level of arousal and cognition, and identification of a presumed medical etiology for delirium are helpful in differentiating these disorders. Symptoms such as severe anxiety and autonomic hyperactivity can lead the clinician to an erroneous diagnosis of panic disorder.

Delirium that is characterized by vivid hallucinations and delusions must be distinguished from a variety of psychotic disorders, such as schizophrenia. Delusions in delirium tend to be poorly organized and of abrupt onset. Hallucinations are more likely to be visual than auditory.

The most challenging differential diagnostic issue is whether the patient has delirium, dementia, or a delirium superimposed on a preexisting dementia. Both delirium and dementia are disorders of cognition. Delusions and hallucinations can be central features of certain types of dementia (e.g., dementia with Lewy bodies). The abrupt onset, fluctuating course, and disturbances of consciousness differentiate delirium from dementia. In delirium superimposed on an underlying dementia, differential diagnosis becomes even more challenging. Delirium, unlike dementia, is commonly reversible, although as noted previously, in terminally ill patients delirium may be irreversible. However, delirium represents a change from the patient's baseline cognitive functioning, even if the patient has dementia or other cognitive disturbances at baseline.

It is important to note that delirium can interfere dramatically with the recognition and control of pain in advanced cancer patients, particularly in the terminally ill. Agitation may be
misinterpreted as uncontrolled pain, resulting in inappropriate escalation of opioids. Accurate pain reporting depends on the ability to perceive the pain normally and to communicate the experience appropriately. Delirium may both impair the ability to perceive and report pain accurately in hospitalized adults. 

MANAGEMENT OF DELIRIUM

The standard approach to managing delirium in patients, even in those with advanced disease, includes a search for underlying causes, correction of those factors, and management of the symptoms of delirium. Delirium is associated with increased morbidity, causing distress in patients, family members, and staff. To minimize distress to patients and caregivers, treatment of the symptoms of delirium should be initiated before, or in concert with, a diagnostic assessment of the etiologies. In the terminally ill patient who develops delirium in the last days of life, the management of delirium is unique, presenting a number of dilemmas, and the desired clinical outcome may be significantly altered by the dying process. The desired and often achievable outcome is a patient who is awake, alert, comfortable, not in pain, cognitively intact, and communicating coherently. However, in some cases the goal of care in the terminally ill may shift to providing comfort through the judicious use of sedative agents, even at the expense of alertness.

Nonpharmacologic Interventions

Nonpharmacologic and supportive therapies play an essential role in the treatment of patients with delirium, especially in the terminally ill. There is evidence from studies in non-palliative care settings that nonpharmacologic interventions result in faster improvement of delirium and slower deterioration in cognition without any effect on mortality or health-related quality of life compared to usual care. Nonpharmacologic 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 (eg, quiet, well-lit room with familiar objects, a visible clock or calendar) to enhance a sense of familiarity.

Pharmacologic Interventions

Nonpharmacologic interventions and supportive measures alone are often not effective in controlling the symptoms of delirium. Symptomatic treatment with psychotrophic medications is required to control the symptoms of delirium. It is important to note that there are no Food and Drug Administration-approved medications for treatment of delirium.

Antipsychotics

American Psychiatric Association (APA) practice guidelines provide directions for the use of antipsychotics in the treatment of delirium and growing evidence supports their use (Table 2). Haloperidol is often the gold-standard medication for treatment of delirium, due to its efficacy and safety. The APA guidelines for treatment of delirium recommend use of low-dose haloperidol (ie, 1–2 mg PO every 4 hours PRN or .25–.5 mg PO every 4 hours for the elderly) as the treatment of choice in cases where medications are necessary. In general, doses of haloperidol need not exceed 20 mg in a 24-hour period; however, some clinicians advocate higher doses in selected cases. The FDA has issued a warning about the risk of QTc prolongation and torsades de pointes with intravenous haloperidol. Thus, monitoring QTc intervals daily among medically ill patients receiving intravenous haloperidol has become the standard clinical practice. In severe agitation related to delirium, lorazepam may be added to haloperidol. This combination may be more effective in rapidly sedating patients and may help minimize any extrapyramidal adverse effects of haloperidol.

Chlorpromazine is considered to be an effective alternative to haloperidol when increased sedation is required—especially in the intensive care unit setting where close blood pressure monitoring is feasible—and for severe agitation in terminally ill patients to decrease distress for the patient, family, and staff. It is important to monitor chlorpromazine’s anticholinergic and hypotensive side effects, particularly in elderly patients.

A Cochrane review on drug therapy for delirium in the terminally ill concluded that haloperidol was the most suitable medication for the treatment of patients with delirium near the end of life, with chlorpromazine being an acceptable alternative.

Atypical antipsychotics (ie, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) are increasingly used in the treatment of delirium in palliative care settings due to decreased risk of extrapyramidal adverse effects.

Several researchers have published their open-label experience with treating delirium and agitation with atypical antipsychotics, including olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole, mostly in non-palliative care settings. A comprehensive review of these studies is available elsewhere.

A Cochrane review comparing the efficacy and incidence of adverse effects between haloperidol and atypical antipsychotics concluded that, like haloperidol, selected newer atypical antipsychotics (risperidone, olanzapine) were effective in managing delirium. Both studies included in this Cochrane review were conducted in non-palliative care settings. Haloperidol doses >4.5 mg/day tended to
result in increased rates of extrapyramidal symptoms (EPS) compared with the atypical antipsychotics, but low-dose haloperidol (ie, <3.5 mg/day) did not result in a greater frequency of extrapyramidal adverse effects.

Important considerations in starting treatment with any antipsychotic for delirium may include EPS risk, sedation, anticholinergic side effects, cardiac arrhythmias, and possible drug-drug interactions. The FDA has issued a "black box" warning of increased risk of death associated with the use of typical and atypical antipsychotics in the treatment of elderly patients with dementia-related psychoses.68-70 A recent retrospective cohort study71 of Medicaid enrollees in Tennessee demonstrated an increased risk of serious ventricular arrhythmias and sudden cardiac death among users of both typical and atypical antipsychotics, which expands diagnostic categories and the age-group at risk.

**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.1,72-74 However, studies with psychostimulants in treating delirium are limited to case reports and one open-label study.72-74 The risks of precipitating agitation and exacerbating psychotic symptoms should be carefully evaluated when psychostimulants are considered in the treatment of delirium.72-74

**Cholinesterase Inhibitors**

Impaired cholinergic function has been implicated as one of the final common pathways in the neuropathogenesis of delirium.75 Despite case reports of beneficial effects of donepezil and rivastigmine, a Cochrane review76,77 concluded that there is currently no evidence from controlled trials supporting use of cholinesterase inhibitors in the treatment of delirium.

**Prevention of Delirium**

Several researchers studied both pharmacologic and nonpharmacologic interventions in the prevention of delirium among older patient populations, particularly in surgical settings.78-82 A Cochrane review82 of delirium prevention studies concluded that the evidence on effectiveness of any of these interventions to prevent delirium was sparse. The applicability of these interventions to the prevention of delirium in palliative care setting has not been studied.

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<th>TABLE 2</th>
<th>ANTIPSYCHOTIC MEDICATIONS IN THE TREATMENT OF DELIRIUM1</th>
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<tbody>
<tr>
<td><strong>Medication</strong></td>
<td><strong>Dose Range</strong></td>
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<tr>
<td><strong>Typical Antipsychotics</strong></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>12.5–50 mg every 4–6 hours</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.5–2 mg every 2–12 hours</td>
</tr>
<tr>
<td><strong>Atypical Antipsychotics</strong></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>5–30 mg every 24 hours</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5–5 mg every 12–24 hours</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>12.5–100 mg every 12–24 hours</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.25–1 mg every 12–24 hours</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>10–40 mg every 12–24 hours</td>
</tr>
</tbody>
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* Risperidone, olanzapine, and aripiprazole are available in the form of orally disintegrating tablets.

PO=by mouth; IV=intravenous; IM=intramuscular; SC=without food; PR=per rectum; EKG=electrocardiogram.

MANAGEMENT OF TERMINAL DELIRIUM

The use of antipsychotics and other pharmacologic agents in the management of delirium in the dying patient remains controversial. Management of delirium on a case-by-case basis seems wisest. Clinical experience in managing delirium in dying patients suggests that the use of antipsychotics in the management of agitation, delusions, and hallucinations is safe, effective, and often quite appropriate. The agitated, delirious dying patient should probably be given antipsychotics to help restore calm. A “wait-and-see” approach may be appropriate with some patients who have a lethargic or somnolent presentation of delirium or who are having frankly pleasant or comforting hallucinations. Such a wait-and-see approach must, however, be tempered by the knowledge that a hypoactive delirium may very quickly and unexpectedly become a hyperactive delirium that can threaten the serenity and safety of the patient, family, and staff.

Perhaps the most challenging clinical problem is management of the dying patient with a terminal delirium that is unresponsive to standard pharmacologic interventions. Approximately 30% of dying patients with delirium do not have their symptoms adequately controlled by antipsychotics. Sedative agents such as benzodiazepines (eg, lorazepam, midazolam), opioids, or propofol can be used alternatively in these cases. In studies of the use of palliative sedation for symptom control, delirium was identified as the target symptom in up to 36% of cases. Clinicians are often concerned that the use of sedating medications may hasten death via respiratory depression, hypotension, or even starvation. However, studies have shown that the use of opioids and psychotropic agents in hospice and palliative care settings is associated with longer rather than shorter survival. The clinician should consider the goals of care and communicate these goals to the staff, patients, and family members when treating delirium in the terminally ill. The clinician must weigh each of the issues when making decisions on how to best manage the terminally ill patient with delirium in a way that preserves and respects the dignity and values of that individual and family.

THE CONTRIBUTION OF DELIRIUM TO PROGNOSIS

Delirium in terminally ill patients is a relatively reliable predictor of approaching death in the coming days to weeks. The death rates among hospitalized elderly patients with delirium over the 3-month post-discharge period range from 22% to 76%, the wide range most likely reflecting the variability in underlying general medical conditions contributing to delirium in elderly patients. Several studies provide support that delirium reliably predicts impending death in patients with advanced cancer receiving palliative care; thus, recognizing an episode of delirium, in palliative care settings, is critically important in treatment planning and in advising family members on what to expect.

CONCLUSION

Psychiatrists commonly encounter delirium in palliative care settings as a major complication of medical illness and its treatments, particularly among the terminally ill. Proper assessment, diagnosis, and management of delirium are essential in improving quality of life and minimizing morbidity.

REFERENCES


