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Symptom Control in Palliative Care—Part III: Dyspnea and Delirium

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DYSPNEA

Dyspnea, defined as an uncomfortable awareness of breathing,[1] is a frequent symptom in patients with advanced illness and has been well documented to have prognostic value.[2] It is often described in terms of air hunger, suffocation, choking, or heavy breathing and is very distressing for family members. Caregivers consistently appear to overrate symptom scores of dyspnea, pain and constipation in cancer patients newly admitted to hospice.[3] In a sample of 49 patients admitted to a palliative care unit, physicians consistently underrated symptoms of dyspnea.[4] There are large variations in the reported prevalence of dyspnea in both cancer patients (21%–79%)[5–9] and in patients with acquired immune deficiency syndrome (AIDS) (11%–62%).[10–13] A comparison of patients with lung cancer and those with chronic lung disease revealed significantly more breathlessness during the last year of life in the latter group.[14] In patients with advanced cancer, dyspnea is more common in those with lung cancer or metastasis to lungs,[15] but it is also frequent in patients with no demonstrable lung involvement. Dyspnea as a lone symptom or in association with other parameters is a prognostic indicator of survival[16] and an independent predictor of the will to live.[17]

MECHANISMS

Dyspnea seems to occur most commonly when afferent input from peripheral receptors is enhanced or when cortical perception of respiratory work is excessive. Although effort and breathlessness are not the same, the sense of effort may be the predominant factor contributing to breathlessness when the respiratory muscles are fatigued or weakened[18] (as in cachexia). There are other clinical settings in which effort may play a lesser role.

Chemoreceptors

Peripheral and central chemoreceptors are stimulated by low P_{O_2} and high P_{CO_2} levels in the blood, which in turn stimulate the respiratory center, thereby increasing the respiratory rate and effort. The chemoreceptors also stimulate the cerebral cortex either directly[19] or indirectly[20] via stimulation of the respiratory center, which in turn leads to increased respiratory effort and stimulation of mechanoreceptors capable of stimulating cerebral cortex. The relative potency of hypoxia and hypercapnia in causing dyspnea remains uncertain.[21] In patients with chronic obstructive pulmonary disease (COPD), the administration of oxygen improves breathlessness,[22] in part because of an oxygen-induced decrease in exercise ventilation.[23] However, there also appears to be a direct effect that is independent of any change in ventilation.[22]

The mechanism of hypercapnia-induced dyspnea has changed from earlier concepts when it was thought that hypercapnia did not induce dyspnea directly, but only as a consequence of evoked changes in respiratory-muscle activity. More recent work has established that hypercapnia causes dyspnea independent of any associated reflex increase in respiratory-muscle activ-

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ity. Patients with COPD, neuromuscular disease, and other disorders associated with chronic hypercapnia and metabolic compensation may have little dyspnea at rest. It seems likely that the effects of carbon dioxide on dyspnea are mediated through changes in pH at the level of the central chemoreceptors, and on that basis one might expect acute and chronic (compensated) hypercapnia to differ markedly in the respiratory sensations they elicit.

Mechanoreceptors

Mechanoreceptors involved in breathing include those residing in the upper airway, lungs, chest wall, and respiratory muscles.

Upper-airway receptors

Several clinical observations have suggested that upper-airway and facial receptors may modify the sensation of dyspnea. Patients with COPD may experience an increase in exercise tolerance and improved dyspnea when they breathe cold air.[24] Patients may sometimes notice a decrease in the intensity of their dyspnea when sitting near a fan or open window. Studies of induced dyspnea in normal subjects indicate that receptors in the trigeminal-nerve distribution influence the intensity of dyspnea.[25,26] It is unclear whether the receptors responsible for the effect of airflow on dyspnea sense the mechanical effect of airflow or the temperature changes that accompany it.

Lung receptors

The lungs contain three main groups of receptors that transmit information to the central nervous system: (1) stretch receptors in the airways that respond to lung inflation and participate in the termination of inspiration; (2) irritant receptors in the airway epithelium that mediate bronchoconstriction in response to mechanical or chemical stimuli; and (3) J receptors or juxtapulmonary receptors located in the alveolar wall and blood vessels that respond to interstitial congestion.

Dynamic airway compression occurs in many patients with COPD and may contribute to their dyspnea. Breathing with pursed lips, a breathing strategy adopted spontaneously by some patients with COPD and learned by others (for example, during a pulmonary rehabilitation program), may derive its effect by altering the changes in transmural pressure along the airway. Presumably, receptors sensitive to the deformation of the airway or to changes in transmural pressure across the airway wall transmit the information that mediates the sensation of dyspnea.

Chest-wall receptors

Afferent information from receptors in the joints, tendons, and muscles of the chest wall play an important role in the mechanism of dyspnea. In normal subjects, hypercapnic tolerance increases when they are allowed to take larger breaths.[27,28]

Afferent mismatch

Clinical observation and studies have led to the general concept that dyspnea may result when there is a mismatch between outgoing motor signals to the respiratory muscles and incoming afferent information.[29,30] The brain "expects" a certain pattern of ventilation and associated afferent feedback, and deviations from this pattern cause or intensify the sensation of dyspnea.[18]

ASSESSMENT

Because dyspnea is a subjective symptom with multiple potential etiologies, objective findings such as tachypnea or oxygenation saturation levels may not adequately reflect the distress experienced by patients with dyspnea. The presencek and intensity of dyspnea should be assessed using validated assessment tools with numerical, verbal analogue or visual analogue scales. The intensity of dyspnea is included in several supportive care tools, such as the Support Team Assessment Schedule[31] and the Edmonton Symptom Assessment System.[32]

Additional assessment with blood tests (d-dimer, B-type Natriuretic Peptide (BNP), complete blood count [CBC], pulse oximeter) or radiologic tests (lower extremity ultrasound, chest radiograph, computed tomography [CT], angiogram) may be warranted if the benefits of the treatment envisaged outweigh the burdens.

MANAGEMENT

Treatment efforts should be aimed primarily at the patient's expression of dyspnea rather than at

objective findings, such as tachypnea or oxygen levels. This distinction is important because symptomatic treatments are directed toward the end point of relieving the symptom (dyspnea) and not the sign (tachypnea). Treatment approaches encompass treating the cause of dyspnea, management of symptoms, as well as managing psychosocial issues contributing to dyspnea. Table 1 lists the management of specific causes of dyspnea.

Symptomatic management of dyspnea includes oxygen therapy, drugs, and general measures of psychological support and counseling.

Pharmacologic

Oxygen. Long-term oxygen therapy has been shown to have beneficial effects on the outcome of patients with COPD and hypoxia, with improvement in survival, pulmonary hemodynamics, exercise capacity, neuropsychological function, and decreased sensation of dyspnea.[33] However, in the patient with advanced cancer for whom the goals of therapy are directed toward dyspnea control, the benefits of oxygen are not well established. In this population, dyspnea does not always correlate with the degree of hypoxemia. In a study of 100 patients with advanced cancer presenting with dyspnea, only 40% were found to be hypoxic.[34] Four randomized controlled crossover studies compared oxygen (4 or 5 L/min) versus air for relief of dyspnea in advanced cancer patients.[35–37] The first two studies showed that patients with advanced cancer who were hypoxemic on room air benefited from oxygen therapy. The third study, conducted on nonhypoxemic dyspneic patients with cancer, found no significant difference between oxygen and air in reducing the intensity of dyspnea or in increasing the distance walked during a 6-minute walk test. More studies are needed to investigate the role of oxygen therapy in individuals doing more strenuous activity and therefore experiencing more intense dyspnea or oxygen debt.

Opioids. Although the exact mode of action of opioids in dyspnea management is unknown, several mechanisms of action, both peripheral and central in origin, have been postulated. These may include depression of opioid receptors found in the lungs, spinal cord, and central respiratory centers. Opioids may diminish the ventilatory responses to hypoxia and hypercapnea. In addition, opioids help to decrease anxiety and the subjective sensation of dyspnea, without reducing respiratory rate or oxygen saturation.

Table 1. Treatment of Specific Causes and Symptoms of Dyspnea

Cachexia	*Pharmacologic and Non-Pharmacologic*
Cause of Dyspnea	**Possible Treatment**
Pleural Effusion	Thoracocentesis, chest tube, pleurodesis
Pulmonary Embolism	Anticoagulation
Pneumonia	Antibiotics, antivirals, or antifungals
Congestive Heart Failure	Diuretics, Ace inhibitors, B-blockers, digoxin Bronchodilators Corticosteroids (PO, IV)
COPD Exacerbation	Antibiotics NPPV O_2
Anemia	Blood Transfusion Erythropoetic Agents
Acites	Paracentesis
Superior Verna Cava Syndrome	Radiation Therapy High Dose Steroids
Carcinomatous Lymphangitis	Corticosteroids, Chemotherapy
Peridardial Effusion	Pericardiocentesis, Pericardial Window
Radiation Pneumonitis	Corticosteroids
Airway Obstruction	Stent; Later
Asthma	Bronchodilators; Steroids inhaled; PO, IV; O_2
Pneumothorax	Chest tube
MND (Motor neuron disease)	NPPV; O_2
Psychogenic	Anxiolytics

They also possibly cause venodilation of pulmonary vessels, thereby reducing preload to the heart.

Most of the studies using opioids in varying doses and routes of administration in dyspneic patients without cancer with COPD and interstitial lung diseases have found opioids to be beneficial in the management of dyspnea.[38–47] Although limited by the small number of patients, duration of study, and reliance on visual analog scales, these studies provide reassurance that opioids have benefits in relieving intractable dyspnea. More large-scale studies are needed to explore the role of opioids further in this setting. Caution should be exercised in opioid naïve COPD patients because of the risk of respiratory depression and hypercapnea. All published studies so far have found systemic opioids to be beneficial in relieving dyspnea in patients with advanced cancer.[48–53]

Opioid receptors are abundant in the lung, and it has been suggested that nebulized opioids might relieve dyspnea with minimal systemic effects. One recent placebo controlled crossover study compared nebulized morphine to systemic morphine.[54] In 11 patients with advanced cancer, both routes of morphine significantly reduced dyspnea within 30 minutes of administration. Although nebulized opioids have the potential advantages of ease of administration, rapidity in onset of action, and reduction of adverse effects because of low systemic bioavailabity, current evidence does not support their use for dyspnea management.[55–57]

Corticosteroids

Steroids are useful for managing dyspnea in patients with cancer who have carcinomatous lymphangitis, radiation pneumonitis, superior vena caval syndrome, or an inflammatory component to their dyspnea (as in asthma). In a study of patients with lung cancer, a large proportion had evidence of airflow obstruction, and bronchodilators provided significant relief of their dyspnea.[58] Corticosteroids benefit COPD exacerbations in the short term, however, long-term use is accompanied by significant side effects. There is some evidence of corticosteroid-induced negative functional and pathologic alterations in several muscle groups,[59] including those involved in breathing (such as the diaphragm). This finding may be of significance in patients who already have cachexia and muscle weakness. A double-blinded placebo-controlled randomized trial indicated that anabolic steroids may counteract the deleterious effects of systemic corticosteroids. Nandrolone[60] treatment restored respiratory muscle function and exercise capacity in moderate to severe COPD patients undergoing pulmonary rehabilitation.

Past trials of inhaled corticosteroids have measured the effect on progression of COPD and forced expiratory volume in 1 second (FEV_1) decline rather than clinical outcomes. A recent meta-analysis[61] suggested that inhaled corticosteroid trials of patients with a mean FEV_1 of less than 2 L (or $< 70\%$ of predicted) almost uniformly demonstrated a benefit of inhaled corticosteroids on exacerbations. Long acting β_2 agonists and tiotropium had similar efficacy and reduced exacerbation rates by 20%–25%. Whether a combination of these two classes of long acting bronchodilators would have an additive benefit is unknown. Combining a long-acting β_2 agonist with an inhaled corticosteroid resulted in an exacerbation reduction of 30%.

Benzodiazepines

There is no evidence to support the routine use of benzodiazepines in the management of dyspnea. They may have a limited role in dyspnea when anxiety is the predominant cause.[62]

Anticholinergics

Family members may misinterpret the gurgling sounds of accumulating secretions as dyspnea or choking in the patient who is approaching death.[63] Glycopyrrolate subcutaneously or intravenously every 4 hours as needed or transdermal scopolamine may be useful in this situation.

NONPHARMACOLOGIC MEASURES

A number of measures can be implemented for the support of both the patient and the family.

A nursing intervention study[64] in patients with lung cancer used strategies combining breathing control, activity pacing, relaxation techniques, and psychosocial support. After 8 weeks, those who received the intervention experienced improvements in breathlessness, performance status, and emotional state relative to control

patients. In patients who are mechanically ventilated long-term who have a difficult wean from the ventilator, biofeedback has shown some preliminary promise.[65] A randomized controlled trial is awaited.

Nutritional supplementation has demonstrated minimal benefit, but in a small trial of 45 stable, malnourished COPD patients, all showed an improvement in maximal inspiratory pressures when phosphate was administered. There was also a trend to improvement in visual analog measures of dyspnea.[66]

Noninvasive positive pressure ventilation (NPPV)[67] reduces the need for intubation, length of stay, mortality rate, and dyspnea[68] in selected patients with COPD exacerbations. Predictors of success include patient's level of cooperativeness, ability to protect the airway, severity of illness, and a good initial response within the first 1–2 hours of NPPV. Caution should be exercised not to add to patient discomfort, especially in the last few hours of life. Discomfort may be caused by the mask, nasal congestion, dryness, gastric insufflation, conjunctival irritation and insomnia. NPPV may also be used for palliation in patients with neuromuscular disorders. Continuous use of NPPV in patients with amyotrophic lateral sclerosis (ALS) appears to prolong survival and delay the need for tracheotomy.[69]

DELIRIUM

Delirium, one of the most frequent and serious complication in patients with advanced illness,[70,71] is a complex syndrome, with an acute onset and fluctuating course. It is not a disease, but a syndrome with multiple causes that result in protean neuropsychiatric symptoms that are common to other disorders, such as dementia, depression and psychosis. The clinical features of delirium are presented in Table 2. The essential core criteria are derived from the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (*DSM-IV*).[72] The emphasis in defining delirium has shifted from a multitude of symptoms to two essential components—disordered attention (arousal) and cognition, while continuing to recognize the importance of acute onset and organic etiology. Although delirium is frequently associated with behavioral manifestations such as agitation, this feature is not essential to its diagnosis. In contrast to delirium, dementia is primarily a disorder of cognition, with no alteration in arousal or attention. Table 3 outlines some of the important distinguishing features between delirium, dementia, depression, and psychosis.

The prevalence rates of delirium in advanced cancer patients admitted to acute hospitals or hospice have been found to be between 28%–48%,[73–75] and approximately 85%–90% of all patients experience delirium in the hours or days before death.[75–78] Variability in reported occurrence rates reflects the use of inconsistent diagnostic terminologies for delirium, sampling from different clinical settings or different stages in the clinical trajectory of illness.

Delirium is associated with increased morbidity and mortality rates.[79–81] In a study of advanced cancer patients, those with delirium had a median survival of 21 days, compared to 39 days in those without.[82] Also, in patients in the intensive care unit (ICU) who are mechanically ventilated, delirium is an independent predictor of a higher 6 month mortality.[83] The prevention of delirium in the patient with cancer has not been

Table 2. Clinical Symptoms Associated with Delirium

- Prodromal symptoms (restlessness, anxiety, irritability, sleep distrubance)
- Reduced attention (easy distractibility)
- Altered arousal
- Increased or decreased psychomotor activity
- Disturbance of sleep-wake cycle
- Affective symptoms (sadness, anger, emotional lability, euphoria)
- Altered perceptions (misperceptions, illusions, delusions, hallucinations
- Disorganized thinking
- Incoherent speech
- Disorientation to time, place or person
- Memory impairment
- Motor abnormalities (tremor, asterixis, myoclonus)
- Acute onset and fluctuation during the course of the day

TABLE 3. DISTINGUISHING FEATURES BETWEEN DELIRIUM, DEMENTIA, DEPRESSION, AND PSYCHOSIS

	Delirium	*Dementia*	*Depression*	*Psychosis*
Onset	Acute	Insidious	Vaiable	Variable
Course	Quick & Fluctuating	Slow and constantly progressive	Variation during the day	Variable
Reversibility	Sometimes	Non-reversible	Reversible	Variable
Level of consciousness & orientation	Disoriented	Lucid until the last stages	Generally normal	Intact, although the patient may be perplexed in the acute stage
Attention & memory	Poor short-term memory and constant inattention	Poor short-term memory, without inattention	Poor attention but intact memory	Poor attention but intact memory
Cognition	Focal cognitive failure	Global cognitive failure	Cognitive intact	Variable
Psychotic Symptoms	Frequent; psychotic ideation is brief and non-elaborated	Less frequent	Rare: psychotic ideation is complex and related to the mood of the patient	Frequent: psychotic symptoms are complex and often paranoid
EEG	Abnormalities in 80–90% (most frequent: generalized diffuse slowing	Abnormalities in 80–90% (most frequent: generalized diffuse slowing)	Normal	Normal
Evaluation and treatment	Requests medical attention as an emergency	Needs chronic therapy and adequate follow-up	May need rug therapy and psychotherapy	Needs psychiatric evaluation and treatment

Centeno C, Sanz A, Brudra E. Delirium in advanced cancer patients. *Palliative Medicine* 2004; 18:184–194.

systematically examined, but studies in elderly medical patients suggest that early identification of risk factors reduces the occurrence rate of delirium and the duration of episodes.[84]

MECHANISMS

The pathophysiologic mechanisms resulting in the clinical manifestations of delirium are not well defined.

The cholinergic hypothesis contends that delirium is mediated by a deficit of acetylcholine and/or a predominance of dopamine. Delirium can be induced by anticholinergic drugs and reversed by cholinergic agonists, such as physostigmine or neuroleptics. A deficiency of thiamine, hypoxia and hypoglycemia also reduces acetylcholine. A relative excess of dopamine would explain why antidopaminergic drugs, such as haloperidol, improve the symptoms of delirium. Other neurotransmitters that may be involved include serotonin and GABA (mainly in liver encephalopathy).

Cytokines (interleukin-1, interleukin-2, tumor necrosis factor, interferon) produced by the immune system, the cancer or its treatment may mediate central nervous system (CNS) effects, such as somnolence, agitation,[85] and cognitive failure. The clinical expression of all these proposed mechanisms is variable and unpredictable, since most patients experience a "mixed" delirium.

ASSESSMENT

Although delirium is one of the most frequent reasons for admission to palliative care units,[86] numerous studies have shown that the failure to recognize delirium is common.[87–92] When objective assessment of cognitive function was not performed in patients admitted to a palliative care unit, episodes of delirium went undetected by physicians and nurses in 23% and 20% of cases, respectively.[93] Delirium is often misdiagnosed as dementia or depression. One group reported that 41.5% of elderly patients referred to a psychiatry service because of depression were in fact delirious.[94] Poor recognition of delirium and misdiagnosis is associated with a number of factors as shown in Table 4.

The three subtypes of delirium are hyperactive, hypoactive and mixed, depending on the level of psychomotor activity and arousal disturbance.[95] In clinical practice, a delirious patient is often described as an "agitated patient" manifesting with uneasiness, repeated and constant limb movements, attempts to get up, undress, throw off bed covers, disconnect lines, etc. Disinhibition may manifest as constant repetition of a name or of a complaint about pain. These behaviors are often worse at night with sleep disturbances. Hyperactive delirium may also present with hallucinations, illusions, and other abnormal perceptions.[96] Almost half (47%) of hospice inpatients may experience hallucinations in the last 2 weeks of life.[97] Although hyperactive delirium is common, most cases of delirium appear to be hypoactive or of the mixed subtype.[98,99] Hypoactive delirium can be difficult to identify, because patients appear quiet and withdrawn and may give correct monosyllabic answers to simple questions. Further evaluation will usually reveal the inattention and disorganized thinking.

Assessment instruments

A history of the patient's baseline mental status prior to the onset of symptoms should be obtained from the family or caregivers. Factors[100] to consider when choosing an assessment instrument include: whether the tool is required mainly for screening (MMSE, CAM), or rating of severity (MDAS,DRS). Some instruments will address more than one goal. Other important considerations are time constraints, the level of expertise and training of the investigator (MMSE requires none), and constraints of the patient (for example, in the ICU).

Table 4. Factors Associated with Missed or Misdiagnosis of Delirium

• Inconsistencies in the terminology used to describe delirium
• Failure to conduct an objective test of cognition screening
• Presence of the hypoactive or hypoalert subtype, frequently diagnosed as depression
• Fluctuation in the intensity of symptoms with periods of apparent lucidity
• Delirium superimposed on dementia

Cognitive-impairment screening instrument. Because cognitive impairment is not specific to delirium, the MMSE should be limited to screening for cognitive failure. Other assessment instruments include the CCSE (Cognitive Capacity Screening Examination[101]) and SPMSQ (Short Portable Mental Status Questionnaire[102]). The MMSE is the most widely used cognitive screening instrument[103] and has been shown to have adequate test–retest (0.89) and interrater (0.82) reliability.[104] Although initially developed as a cognitive screening test for dementia, the MMSE has also been used for detecting patients with delirium or combined delirium and dementia.[105,106] The MMSE may not detect mild cases of cognitive failure and does not evaluate other major components of delirium, such as psychomotor agitation, hallucinations, or delusions.

While the MMSE is less sensitive and specific than the MDAS or the CAM, the latter tools require physicians or trained nurses to complete them. The MMSE can be administered by nurses, assistants or volunteers. A strategy of assessment at regular intervals encourages an early recognition of either cognitive failure or delirium.[75,107]

The Memorial Delirium-Assessment Scale. The MDAS may be used by a physician for diagnosis and rating of severity. It comprises a 10-item, 4-point delirium rating scale with a scoring range of 0–30. (The higher the score, the more severe the delirium.[108]) Earlier validation studies suggested a score of 13 as a cutoff point to diagnose delirium, but later studies in advanced cancer patients suggest a score of 7 will yield a sensitivity of 98% and specificity of 76%.[109] The items assess disturbance in arousal and level of consciousness, areas of cognitive functioning (memory, attention, orientation, and disturbances in thinking) and psychomotor activity.

Confusion Assessment Method (CAM). Based on *DSM-IV* criteria, the CAM can be administered quickly by a trained clinician as a 9-item scale or simplified algorithm. The algorithm requires the presence of an acute onset fluctuating course, inattention, and either disorganized thinking or altered level of consciousness. The importance of training and education was emphasized by a study showing underrecognition of delirium by nurses using the CAM.[110] Risk factors were hypoactive delirium, vision impairment, age 80 or older and dementia.[111] The CAM–ICU is easily administered in approximately 2 minutes[112] by a trained nurse in the ICU setting and displays high sensitivity (93%–100%) and specificity (98%–100%). In verbal nonintubated ICU patients, the standard CAM may be better at detecting subtle cases of delirium.[113]

Delirium Rating Scale. The DRS is a clinician rated scale that has high validity, sensitivity, specificity and interrater reliability.[114] It has been used for studies of treatment, outcome and at risk populations, and is ideal for longitudinal studies.

MANAGEMENT

Treatment should be aimed at the specific symptoms of delirium, and simultaneous efforts should be made to identify and treat underlying causes. Although delirium clearly has a recognized association with the dying phase, many episodes of delirium are reversible. In patients admitted to palliative care units, the delirium may be reversible through a suitable therapeutic approach in almost 50% of cases.[115–117] Other studies have similar results showing that therapeutic intervention can result in delirium reversal, or at least improvement, in 30% to 75% of episodes.[75,93,118–120] An episode of delirium is often best managed in hospital because aggressive investigation and treatment can be facilitated. Reversibility is more likely if the etiology of delirium is attributable to identifiable reasons such as drugs, dehydration, or metabolic abnormalities such as hypercalcemia. The response is less likely if there have been previous episodes or the delirium is related to hypoxic or global metabolic encephalopathy.[121]

Treatment of the cause

A physical examination should be done in order to identify infection, focal neurologic signs, urinary retention, and fecal impaction. Further evaluation through blood tests or imaging studies must be guided by the patient's prior wishes, his clinical condition, and the benefits and risks of any subsequent therapeutic intervention.

Drugs. Medications, especially opioids and other psychoactive drugs, contribute to delirium in the majority of cancer patients with altered mental status.[122] Patients with a history of drug or alcohol

abuse, somatization and incident or neuropathic pain may be especially at risk for dose escalation and side effects. A prospective study of 216 consecutive patients admitted to the ICU showed fentanyl and morphine were strongly related to the development of delirium regardless of the dosage.[123] Symptoms of opioid-induced toxicity include hallucinations, agitation, myoclonus, allodynia, hyperalgesia, and seizures. Interventions in the form of dose reduction, or typically opioid rotation in association with assisted hydration, allows for clearing of the offending opioids and their metabolites. Other nonessential drugs that may precipitate delirium should be discontinued or substituted. These include anticholinergics, benzodizepines, steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics (quinolones, cephalosporins), antiparkinsonian drugs, and some chemotherapeutic agents. An alcohol intake history is important to exclude states like alcohol intoxication, withdrawal or, rarely, Korsakoff psychosis or Wernicke's encephalopathy.[124] Vitamin replacement with folic acid and B_1, 3, and 12 may be required.

Elderly patients, especially those with cognitive impairment, may develop delirium as a result of poorly managed pain. In frail older adults, undertreatment of pain or avoiding opioids following hip fracture increased the risk for delirium.[125] A sample of 113 nursing home residents[126] showed that those with greater cognitive impairment received fewer analgesics than those with low cognitive impairment.

Infections. CNS infections such as meningitis and encephalitis should be considered. Often, a subtle delirium can point to an undetected infection in the urinary tract. Common sources of infection include venous access catheters, aspiration or community acquired pneumonia, and decubiti ulcers.

Dehydration. The adoption of a vigorous hydration stance in a palliative care unit in Canada was partly responsible for the diminished incidence of delirium.[127] Studies in patients with advanced cancer and in the elderly have found that hydration of these patient can prevent the development of delirium. Recently, a randomized, controlled double-blinded trial[128] determined the effects of parenteral hydration with 1000 mL/d versus 100 mL/d on four target symptoms (sedation, fatigue, hallucinations, and myoclonus). Eighty-three percent of the treatment group had improved myoclonus and sedation. These benefits may have resulted from the hydration *per se* or an increased elimination of active opioid metabolites because all patients were on opioids. The importance of double-blinded studies in symptom control was emphasized by the large placebo effect in this study (59% of patients in the placebo group perceived important overall symptomatic benefit after less than 36 hours).

Electrolyte and metabolic disturbances, such as severe hyponatremia or hypernatremia, are well known to cause altered mental status in patients. Hypercalcemia is extremely common in many cancers and can be treated with fluids and biphosphonates. Hypothyroism should be excluded in patients previously treated with radiation to the head and neck. Hepatic encephalopathy and kidney failure may also improve with targeted therapies.

CNS: Parenchymal brain mets and leptomeningeal disease may respond to radiation or chemotherapy and require imaging (magnetic resonance imaging [MRI] or CT) for diagnosis.

Symptom management

Antipsychotic drugs. Neuroleptic agents are the cornerstones of pharmacologic treatment. They are effective both in patients with a hyperactive or hypoactive delirium, and generally improve cognition.[129–131] Although both haloperidol and chlorpromazine have similar efficacy,[132] haloperidol remains the drug of choice because it has fewer active metabolites, limited anticholinergic effects, is less sedating, less hypotensive and can be administered by various routes.[133] Intravenous administration seems less likely to cause extra pyramidal side effects in patients with delirium.[134] An initial dosage of 1 mg every 6 hours intravenously and 1 mg every hour as needed is usually effective in treating agitation, paranoia and fear, but higher doses or even an infusion may be needed for intractable symptoms. Often, delirium in patients with advanced cancer requires more than a one drug treatment. In one small case series of 39 patients, haloperidol alone was effective in only 20% of cases.[135]

Atypical antipsychotics. New neuroleptics such as risperidone and olanzapine[136] are additional options. They have the advantage of fewer extrapyramidal adverse effects, few drug interac-

tions, and they can be administered once or twice daily. Disadvantages of atypical neuroleptics include their very high cost and parenteral formulations of these medications are not currently available. Risperidone has been shown to improve cognition in delirious patients,[137,138] and in a double blind trial[139] compared to haloperidol there were no significant differences in side effects or MDAS scores. A trial in the ICU of enteral olanzapine versus enteral haloperidol[140] for delirium demonstrated fewer extrapyramidal side effects in the olanzapine group. Risk factors[141] for a poor response to olanzapine in cancer patients with delirium include age greater than 70, history of dementia, CNS metastases, hypoxia, hypoactive delirium, and delirium of severe intensity (i.e., MDAS $>$ 23). Olanzapine may stimulate appetite, and like haloperidol, also has antiemetic properties.

Benzodiazepines. Benzodiazepines are first line treatment for delirium associated with seizures and alcohol withdrawal.[142] In the management of most patients with delirium, benzodiazepines are not helpful. In a study of hospitalized patients with AIDS,[143] lorazepam alone was ineffective and increased cognitive impairment. Occasionally, in patients with refractory severe agitation, deep sedation may be required. In these cases, midazolam can be used at a dose of 1 mg/hr intravenously and titrated up to 4 mg/hr according to the patient's response.

Counseling

Upset or ill-informed caregivers can exacerbate a patient's distress. Agitated behavior and cognitive failure is particularly distressing for family and caregivers.[144] Agitated behavior may be interpreted as a sign of suffering or pain. A study of patients who were able to recall their experience (53.5%) found delusions to be the most important predictor of distress ,and hypoactive delirium to be as distressing as hyperactive delirium. In a study of cancer patients with severe delirium and cognitive failure (MMSE = 0), patients were not been able to recall their increased expression of pain.[145] Discussions with family should include a simple explanation of delirium, its increased frequency in advanced illness, potential causes and varied clinical presentations, and the efforts being made to manage it. It may be necessary to demonstrate a decline in cognition to the family using simple tests such as the MMSE, if there are difficulties in accepting the diagnosis. Because symptoms of delirium are often not fully resolved at the time the patient is discharged from hospital, relatives play crucial roles in planning and monitoring care.

Supportive and environmental measures

Nonpharmacologic supportive measures in hospitalized elderly patients are successful in preventing delirium.[146] Adherence to these measures plays an important independent role in the effectiveness of this intervention strategy. Studies have not been done in the palliative care population, but similar measures would likely be of benefit. Patients who have recovered from delirium have reported that simple but firm communication, reality orientation, a visible clock, and the presence of a relative, all contribute to a heightened sense of control during delirium.[147]

Several environmental factors may be utilized in treating delirium, including simple measures such as a quiet and comfortable private room with ambient temperatures, adequate lighting, and a clearly visible sign providing the patient's location and date. Efforts should be made to decrease sources of excess noise and interruption by staff, equipment, and visitors. Recording vital signs may be minimized, especially at night, to ensure uninterrupted sleep. Ensure that patients have their glasses, hearing aids, and dentures, where appropriate. Communications should be clear and simple with no medical jargon. Give repeated verbal reminders of the day, time, location and identity of key individuals, including members of the treatment team and relatives. Involve family and caregivers and have familiar objects from the patient's home in the room to encourage security and orientation. Maintain activity levels and encourage self-care and participation in treatment plans. Physical therapists may help patients ambulate in the room and hallways, while nonambulatory patients should undergo range of motion exercises and position changes in bed.

CONCLUSION

Delirium is a clinical diagnosis and may go undetected by the physician unless regular assessment is performed using the screening and diag-

nostic tools described earlier. Its multifactorial nature and potential for reversibility should be recognized. Once the diagnosis is made, the therapeutic goals are to calm and reassure the patient and advise the family about the risk of aggressive or unusual behavior. In addition to treatment with neuroleptics, low-burden interventions such as a medication change or hydration must always be considered.

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