Management of specific symptom complexes in patients receiving palliative care

Education

Éducation

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Abstract

DURING THE PAST 10 YEARS THERE HAVE BEEN MAJOR CHANGES in the management of the most common symptoms of terminal cancer. Opioid agonists remain the mainstay in the management of cancer pain. Slow-release preparations are currently available for several of these agents. The increased use of opioids has led to the recognition of opioid-induced neurotoxic effects and to the development of effective adjuvant drugs and other strategies to counteract these side effects. A number of drugs are available for the management of symptoms of cachexia, including corticosteroids and progestational drugs. Prokinetic drugs, either alone or in combination with other agents such as corticosteroids, are highly effective in the treatment of chronic nausea. For patients with asthenia, it should first be determined whether there are any reversible causes; if not, corticosteroids and psychostimulants may diminish the symptoms. Haloperidol, other neuroleptics and benzodiazepines may be required to manage hyperactive delirium. Oxygen and opioids are effective in treating dyspnea, whereas there is limited evidence that benzodiazepines provide any relief of this symptom. More research on the assessment and management of these devastating clinical symptoms of cancer is badly needed.

Résumé

LE TRAITEMENT DES SYMPTÔMES LES PLUS COMMUNS DU CANCER en phase terminale a changé radicalement depuis 10 ans. Les opioïdes agonistes demeurent le principal moyen utilisé pour traiter la douleur causée par le cancer. Des préparations à libération lente sont actuellement disponibles pour plusieurs de ces agents. L'utilisation accrue des opioïdes a débouché sur la définition des effets neurotoxiques causés par les opioïdes et la mise au point d'adjuvants efficaces et d'autres stratégies pour contrer ces effets secondaires. Il existe des médicaments pour traiter les symptômes de cachexie, y compris des corticostéroïdes et des progestatifs. Les agents procinétiques, administrés seuls ou avec d'autres agents comme les corticostéroïdes, sont très efficaces pour traiter la nausée chronique. Dans le cas des patients asthéniques, il faudrait déterminer d'abord s'il y a des causes réversibles. Sinon, les corticostéroïdes et les psychostimulants peuvent atténuer les symptômes. Pour traiter le délire hyperactif, il peut être nécessaire d'administrer de l'halopéridol, d'autres neuroleptiques et des benzodiazépines. L'oxygène et les opioïdes traitent efficacement la dyspnée, tandis qu'il y a peu de données probantes qui démontrent que les benzodiazépines soulagent ce symptôme. Il est urgent d'effectuer d'autres recherches sur l'évaluation et le traitement de ces symptômes cliniques dévastateurs du cancer.

Most palliative care programs treat patients with terminal cancer and AIDS.[1] These patients experience a number of devastating physical and psychosocial symptoms before they die.[2] In recent years there have been major developments in both the assessment and management of these symptoms. The purpose of this paper is to summarize the approaches currently being used to manage some of the most common symptoms. Hypothetical cases are presented throughout to illustrate these approaches. Because of space constraints this article covers only symptoms associated with advanced cancer; how-

ever, most of the same principles apply to the care of patients with other terminal diseases.

Cancer pain

Approximately 80% of patients with cancer experience pain before they die.[3] In most of these patients (approximately 80%) the pain is associated with a tumour; however, it can also be related to treatment, or it may be unrelated to either the tumour or the treatment.[3] Despite a number of guidelines and excellent reviews on appropriate pain management,[3–5] many patients with cancer continue to experience considerable pain, and approximately half of them receive inadequate analgesia.[6–8]

Pharmacologic treatment based on the regular use of oral opioids is very effective in controlling pain in most patients,[2,3,5] but other agents are also available (Table 1). The World Health Organization "analgesic ladder" has been used in many regions of the world in the implementation of programs to control cancer pain.[5] According to this approach, patients with persistent pain are treated with nonopioid analgesics first, then mild opioids if the analgesics do not provide relief and finally strong opioids if necessary.

Nonopioid drugs, including acetaminophen and NSAIDs, are effective analgesics for patients with mild cancer pain and can be combined with opioids in the treatment of moderate to severe pain.[2–4] Acetaminophen does not affect platelet function and has no significant renal or gastrointestinal toxic effects; these factors make it easy to use alone or in combination with opioids. NSAIDs can reduce the renal elimination of opioid metabolites and therefore increase the frequency of opioid-induced neurotoxic effects.[9] A new generation of highly specific cyclo-oxygenase II NSAIDs may potentiate opioids with minimal toxic effects;[10] however, they are not yet available in Canada.

Table 1: Pharmacological agents for treating cancer pain

Drug	Route or indication
Nonopioid analgesics	
Acetaminophen	
NSAIDs	
Opioid analgesics	
Codeine	Oral (rapid and slow release)
Hydromorphone	Oral (rapid and slow release), subcutaneous
Morphine	Oral (rapid and slow release), slow-release suppository, subcutaneous
Oxycodone	Oral (rapid and slow release), subcutaneous
Fentanyl	Transdermal, subcutaneous
Methadone*	Oral, suppository
Adjuvant drugs	
Tricyclic antidepressants (e.g., SSRIs)	Neuropathic pain
Corticosteroids	Multiple indications
Anticonvulsants	Neuropathic pain
Bisphosphonates	Bone metastases
Oral local anesthetics	Neuropathic pain
Psychostimulants	Opioid sedation
Muscle relaxants	Muscle spasm

Note: SSRI = selective serotonin reuptake inhibitor.
*Doses should be determined cautiously by a specialist because of methadone's higher potency and lower cross-tolerance relative to other opioids.

Opioid agonists

Opioid agonists are the mainstay of therapy for chronic cancer pain. Morphine administered orally has been considered the drug of choice; however, other opioid agonists such as oxycodone and hydromorphone have similar pharmacokinetic and pharmacodynamic effects in cases of cancer pain.[3,4]

Slow-release preparations of codeine, oxycodone, hydromorphone and morphine, for oral administration every 12 hours, are available in Canada, and there is also a preparation of morphine to be taken orally every 24 hours. A slow-release preparation of fentanyl (applied transdermally every 3 days) is available in Canada, as is a slow-release suppository of morphine for use every 12 hours. All of these preparations are used to maintain pain relief in patients for whom the appropriate dose has been determined by means of rapid-release opioid analgesics.[11,12] Patients receiving slow-release opioids should be allowed to receive extra doses of rapid-release opioids intermittently for breakthrough pain.[4,11] These extra doses have traditionally been assumed to constitute approximately 10% of the daily opioid dose; however, researchers using fentanyl administered transmucosally found recently that the optimal extra dose may range from 5% to 20% of the regular daily dose.[13]

The most common side effects of opioids are sedation, nausea, constipation, respiratory depression and urine retention. Sedation and nausea frequently occur soon after the patient begins taking opioids, but these effects usually subside spontaneously and are rarely a cause for discon-

Case 1: Opioids for pain

A 70-year-old woman with multiple bone metastases from breast cancer is in severe pain. She is taking two 325-mg tablets of acetaminophen plus 30 mg of codeine 4 to 6 times a day with only minimal relief.

This regimen is discontinued, and she is given 5 mg of morphine orally every 4 hours around the clock and 2.5 mg hourly as needed. To prevent constipation she takes docusate and senna capsules twice a day, and to relieve nausea she takes 10 mg of metoclopramide orally as needed. Within 2 days her pain control improves, and she needs only 1 or 2 extra doses of morphine per day. To maintain the analgesic effects, her regular opioid is changed to 15 mg of slow-release morphine every 12 hours or 30 mg every morning.

tinuing treatment. If the sedative effect is so strong that it limits the dose a patient can tolerate and does not diminish when the dose is modified, a brief course of psychostimulants may permit the opioid dose to be increased or may decrease the sedative effects.[3]

There is no consistent evidence that one particular opioid agonist is associated with a lower prevalence or intensity of sedation, nausea or constipation than the others.[3,4] There is, however, a general consensus that some patients experience less severe side effects with one rather than another opioid agonist; thus, a change in the type of opioid may help in overcoming the side effects.

Because of concerted educational efforts about the undertreatment of cancer pain, patients now generally receive higher doses of opioids for longer periods of time. This has led to a greater number of serious neuropsychiatric side effects, including cognitive impairment, hallucinosis, myoclonus and grand mal seizures, hyperalgesia and severe sedation. These side effects are probably the result of a combination of the nonopioid effects, caused by the accumulation of excitatory active opioid metabolites, and the opioid effects of the parent compounds.[14] Animal and human studies have shown that some opioids can have significant neurotoxic effects.[14,15]

Patients who experience the well-established side effects of opioids or the more recently recognized ones may benefit from a change in the type of opioid administered. Several authors have described clinical improvement in patients who experienced side effects related to morphine toxicity after substitution of alternative agonists such as hydromorphone or oxycodone. If the toxic effects are still severe after most of the common agonists have been tested, second-line drugs such as methadone should be considered. Methadone is very inexpensive and has no active metabolites, but it does have a long and unpredictable half-life and a more poorly defined equianalgesic dose than other opioid agonists.[15] Methadone is more potent in patients who already have a tolerance to other opioid agonists,[15–17] so switching from other opioids to methadone should be done cautiously by a physician experienced in this area. Once the switch has been completed, determining the dose of methadone is no different from determining the dose of other opioid agonists.

Other measures can be taken to treat the acute, toxic effects of opioids, including reducing the dose, starting hydration to increase the elimination of hydrosoluble active metabolites and prescribing drugs such as midazolam (by continuous subcutaneous infusion) or haloperidol to manage agitation.[15]

Case 2: Managing the side effects of opioids

A 65-year-old man with advanced colon carcinoma has severe abdominal pain, and his dose of morphine has been increased several times recently. Over the previous 2 days progressive confusion, mild psychomotor agitation, tactile hallucinations and myoclonus have developed. Because of his confusion, his oral intake of morphine has decreased, and he appears mildly dehydrated. His behaviour has been interpreted as pain by his relatives, who have given him several extra doses of opioids over the previous 24 hours.

He is admitted to hospital. The morphine is discontinued, and he is given hydromorphone at a dose equal to approximately half that of the morphine. Subcutaneous hydration is started (500-mL boluses of two-thirds dextrose and one-third saline twice a day for 3 days). Other psychoactive drugs are discontinued, and he begins taking 2 mg of haloperidol every 6 to 8 hours for agitation and hallucinations. Within 3 days his cognition returns to normal, and his hallucinations and agitation disappear. The hydration and haloperidol are discontinued, and the patient is discharged from hospital.

Adjuvant drugs

Opioid analgesics are effective in reducing the intensity of pain in most patients; however, they may not completely control pain in some patients and may cause side effects in others. Therefore, adjuvant drugs are prescribed to increase the analgesic effects of the opioids and to decrease their toxic effects. Some of the most commonly used adjuvant drugs are listed in Table 1; however, a detailed description exceeds the scope of this paper. It is important to note that in addition to potentiating opioid-induced analgesia, adjuvant drugs can themselves cause side effects and can potentiate some of the side effects of opioids. Table 2 presents recommendations for preventing problems when adjuvant drugs are prescribed.

Cachexia–anorexia syndrome

Cachexia–anorexia syndrome is characterized by progressive weight loss, lipolysis, loss of visceral and skeletal protein mass and profound anorexia. Almost all patients with cancer or AIDS experience this devastating disorder before they die.[18,19] Weight loss decreases a patient's chance of survival, and patients with cachexia experience more complications after surgery, radiation therapy and chemotherapy. In addi-

Table 2: Recommendations for preventing problems when adjuvant drugs are used to treat cancer pain

Recognize that opioids are the first-line treatment for most types of cancer pain
Increase opioid dose if analgesic effects are inadequate (unless there are opioid-induced toxic effects)
If a decision is made to use an adjuvant drug, use an effective (high) dose
Add one adjuvant drug at a time to avoid combined or enhanced side effects
Define outcome measures at the start of treatment
Discontinue the adjuvant drug if ineffective
Always monitor levels of sedation and cognition

tion, cachexia reinforces the weakness associated with anorexia and chronic nausea and is a source of psychological distress for patients and their families.

Cachexia was previously thought to be the result of the increased energy demanded by the growing tumour mass. However, recent research[19] has demonstrated that it is primarily due to major metabolic abnormalities, such as profound lipolysis and loss of skeletal and visceral proteins, both of which are caused by immune mediators (e.g., tumour necrosis factor and interleukin-6), and tumour by-products (e.g., lipolytic hormone). This means that anorexia, an almost universal characteristic of cachexia, should be interpreted as the result of metabolic abnormalities rather than the main cause of cachexia.[19,20]

Unfortunately, studies of aggressive nutritional support, including enteral and parenteral feeding, generally have shown no significant improvement in patient survival or tumour shrinkage and only limited effects on the complications associated with surgery, radiotherapy and chemotherapy.[21] Since most of these studies did not assess patients' symptoms, it is not clear if intensive feeding has any symptomatic benefits. However, intensive feeding may be appropriate in certain situations, such as when patients are recovering from surgery and awaiting chemotherapy or when starvation in patients with extremely slow-growing tumours or bowel obstruction is caused by lack of food rather than metabolic abnormalities.

In recent years a number of drugs have been proven effective in relieving the symptoms of cachexia; some of these improve appetite. Table 3 describes new drugs for the management of cancer cachexia.

Corticosteroids

Several randomized placebo-controlled trials have demonstrated the effects of different types of corticosteroids on cachexia–anorexia.[20,22] All researchers have found that these drugs have a limited effect (lasting for up to 4 weeks) on symptoms such as appetite, food intake, sense of well-being and performance status. However, in none of the studies did the patients gain weight. Corticosteroids have also been found to relieve nausea and asthenia[23] and to control pain.[24] Because of their significant (albeit short-lasting) ability to relieve symptoms, these drugs can be used in patients who are not expected to live for long and in whom weight gain is not a likely outcome. The most effective type, dose and route of administration have not been established. These issues should be addressed in randomized controlled trials.

Table 3: New drugs for treating cachexia in patients with cancer

Drug	Mechanism of action
Pentoxifylline	Decreases tumour necrosis factor-α
$ß_2$-Adrenoceptor agents (e.g.,clenbuterol)	Decrease breakdown of muscle protein
Anabolic androgenic steroids	Enhance protein synthesis through androgen receptor
Melatonin	Decreases tumour necrosis factor-α; modulates cytokine
Thalidomide	Decreases tumour necrosis factor-α; modulates cytokine
Cannabinoids	Increase appetite at level of central nervous system
Omega-3 fatty acids	Decrease interleukin-6

Progestational drugs

A relation has been demonstrated between the dose of progestational drugs and effects on appetite, caloric intake, weight gain (mainly of fat) and sense of well-being. The optimal dose ranges from 480 to 800 mg per day, administered orally.[22] Recent studies involving terminally ill patients have shown that the improvement in symptoms (better appetite, less fatigue, greater sense of well-being) occurs even in the absence of significant weight gain.[25,26] If abruptly discontinued, both megestrol and medroxyprogesterone can induce thromboembolic phenomena, breakthrough vaginal bleeding, peripheral edema, hyperglycemia, hypertension, Cushing's syndrome, alopecia, adrenal suppression and adrenal insufficiency. However, in most clinical trials, the adverse effects rarely led patients to discontinue these drugs.[22,25,26] Unfortunately, the progestational drugs are expensive, which is a problem especially when high doses are needed.

Multimodal approach

Recent research[27] suggests that, in the future, it may be possible to treat patients with cancer cachexia with combined drug therapy that focuses simultaneously on the release of immune by-products, the rate of protein break-

Case 3: Treating cachexia–anorexia

A 62-year-old woman with metastatic lung cancer is admitted to a hospice with severe bone pain, anorexia and cachexia. She spends most of her time in bed because of profound asthenia and chronic nausea. She receives 25 mg of morphine and 10 mg of metoclopramide every 4 hours.

On admission to hospital, her morphine dose is increased by 30%, and 10 mg of dexamethasone is administered subcutaneously every 12 hours. Within 48 hours her pain, nausea, anorexia and asthenia are significantly lessened, and she reports an overall improvement in well-being. The dexamethasone is changed to an oral preparation, and the dose is progressively decreased to the lowest effective maintenance dose.

down in muscles and the effects on appetite. Treatment in these cases should be given to manage symptoms and improve quality of life, not simply to improve nutritional status, since, given the incurable nature of the underlying disease, cancer patients with cachexia usually survive only weeks or months.

Chronic nausea

Patients with terminal cancer frequently experience nausea for extended periods (often more than 4 weeks).[28] Some of the most frequent causes of nausea are presented in Fig. 1. These include autonomic dysfunction (frequent in patients with advanced cancer), gastroparesis and opioid analgesics, which can cause nausea by direct central effects, as well as by aggravating delayed gastric emptying, vestibular stimulation and constipation.[28]

Attempts should be made to determine the underlying cause of chronic nausea and steps taken to relieve it, for example by treating metabolic abnormalities, providing aggressive bowel care or treating brain metastases.

Table 4 lists the antiemetic drugs used to treat chronic nausea. In patients with no bowel obstruction, metoclopramide is highly effective because of its combination of central nervous system and gastric emptying effects.[29] Slow-release metoclopramide is more effective than the rapid-release formulation in controlling chronic nausea,[30] and dexamethasone and other corticosteroids can potentiate the antiemetic effects of metoclopramide.[28,29] When either metoclopramide or corticosteroids are contraindicated or when the bowel is obstructed, a number of centrally active agents such as haloperidol and dimenhydrinate can be administered. In patients with bowel obstruction, drugs that decrease the amount of gastrointestinal secretions and motility, such as octreotide, can help control nausea and vomiting.[31]

Chronic nausea is highly prevalent in and distressing to patients with terminal cancer. Unfortunately, while there has been significant research in the pharmacologic management of chemotherapy-induced emesis, chronic nausea has received little attention and therefore our understanding of the mechanisms and treatment of this complex and multicausal condition is limited.

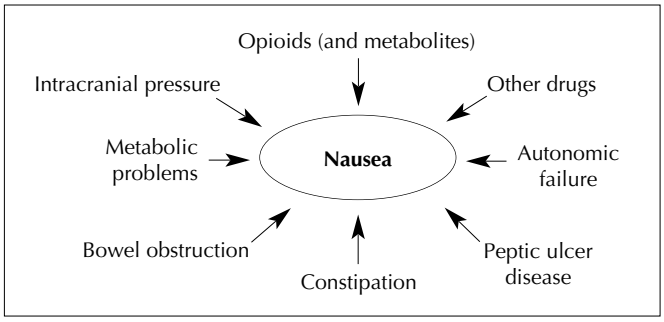

Fig. 1: Main causes of chronic nausea in patients with cancer.

Table 4: Drugs for treating chronic nausea in patients with cancer

Prokinetic agents
Metoclopramide
Domperidone
Cisapride
Corticosteroids
Dexamethasone
Methylprednisolone
5-Hydroxytryptamine$_3$ (5-HT$_3$) antagonist
Ondansetron
Granisetron
Agents to decrease gastrointestinal secretion and motility
Octreotide
Hyoscine butylbromide
Other drugs
Haloperidol
Dimenhydrinate
Prochlorperazine

Asthenia

Asthenia is characterized by profound tiredness occur-

Case 4: Treating nausea

A 55-year-old man with disseminated prostatic carcinoma complains of severe nausea. He is receiving 50 mg of morphine every 4 hours for pain due to bone metastases. Abdominal radiographs show no sign of bowel obstruction but do reveal a large accumulation of stool in the colon.

After an enema, the patient has 2 large bowel movements. He begins taking laxatives twice a day, including senna and docusate. He is given 10 mg of metoclopramide every 4 hours, with additional hourly 10-mg doses as needed for severe nausea. The opioid dose is reduced by 30% because of excellent pain control. Within 3 days, the patient's nausea is under control, and he is able to maintain an adequate intake of food and medication by mouth.

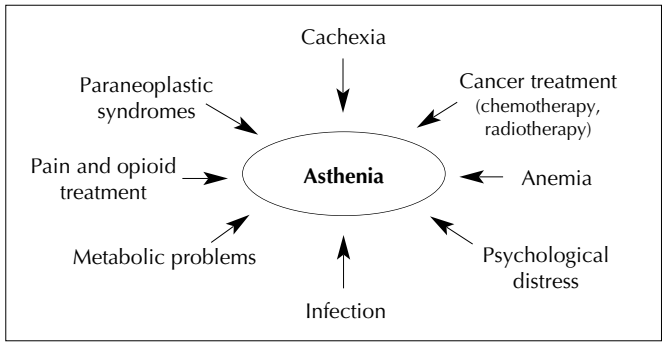

Fig. 2: Main causes of asthenia in patients with advanced cancer. Paraneoplastic syndromes include Eaton–Lambert syndrome, myasthenia and myositis.

ring after usual or minimal effort, accompanied by an unpleasant anticipatory sensation of generalized weakness. Asthenia is the most frequent symptom associated with advanced cancer.[23] The 3 main mechanisms associated with asthenia are direct tumour effects, tumour-induced by-products and accompanying factors, including anemia, paraneoplastic syndromes and chronic infection (Fig. 2).

The relation between asthenia and cachexia is complex. Most patients with advanced cancer experience symptoms of both simultaneously. However, some patients, such as those with early breast cancer or lymphoma, may experience severe asthenia with no malnutrition, whereas patients with conditions such as anorexia nervosa may experience severe malnutrition with no asthenia.

Fig. 3 presents a clinical approach to the management of asthenia. If specific causes can be identified, their correction will lead to a significant improvement. General nonpharmacologic measures such as adapting the activities of daily living, physiotherapy and occupational therapy will help match clinical function and symptom status with the expectations of patients and their families.[32]

Case 5: Managing asthenia

A 60-year-old woman with locally recurrent metastatic carcinoma of the lung reports severe tiredness and generalized weakness. During the previous 6 months she has lost 20 kg; she complains of severe loss of appetite but is not experiencing chronic nausea. A routine symptom assessment yields a score of 7 for depression on a 10-point visual analogue scale. The patient describes sadness, insomnia and anhedonia, which have lasted for approximately 3 weeks. Her blood count shows moderate anemia accompanied by postural hypotension and postural tachycardia.

A transfusion of 2 units of packed erythrocytes is administered. Megestrol is started at a dose of 160 mg 3 times a day to increase her appetite and relieve the symptoms of asthenia. The patient and her family receive counselling from the family physician and the home care nurse. Within 10 days, the patient feels that the symptoms of asthenia have diminished and her appetite has improved. Her depressive symptoms progressively lessen with expressive–supportive therapy.

Counselling may help patients in whom asthenia is an expression of an affective disorder, such as anxiety or depression.

General pharmacologic measures include corticosteroids and amphetamines. Corticosteroids have been found to decrease the symptoms of asthenia, either by inhibiting tumour-induced by-products or by inducing a central euphoriant effect.[23] Amphetamines have been found to antagonize opioid-induced sedation and fatigue,[13] and it has been suggested that they can also be used to manage hypoactive–hypoalert delirium and fatigue.[33]

Delirium

Delirium is the most frequent neuropsychiatric disorder in patients with advanced cancer, most of whom are in a delirious state when they die.[34] Despite its prevalence, the condition is underdiagnosed.[35] Patients with delirium experience combinations of cognitive failure, fluctuating levels of consciousness, changes in the sleep–wake cycle, psychomotor agitation, hallucinations, delusions and other perception abnormalities.[36] Delirium is often caused by a number of factors (Fig. 4). Although opioid toxicity is

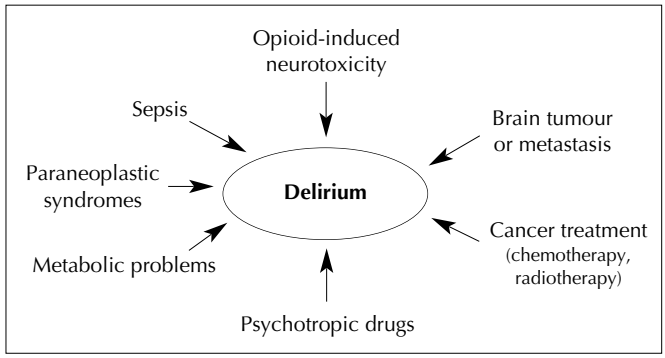

Fig. 4: Main causes of delirium in patients with advanced cancer. Metabolic problems causing delirium include increased calcium levels, reduced sodium levels and renal failure. Psychotropic drugs include tricyclic antidepressants and benzodiazepines.

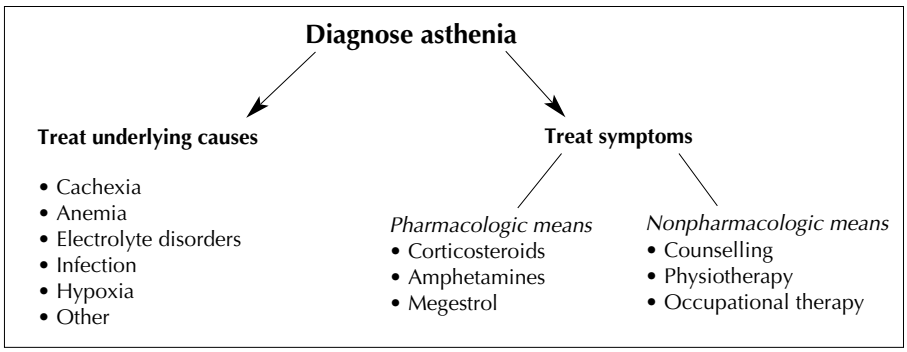

Fig. 3: Therapeutic approach to managing asthenia involves identifying and treating specific underlying causes, as well as treating specific symptoms by pharmacologic and nonpharmacologic means.

one of the most frequent causes,[14] others include infection, dehydration and metabolic abnormalities. Various drugs, such as benzodiazepines and drugs with a central anticholinergic effect, can cause or aggravate delirium. Fig. 5 presents the clinical approach to the treatment of delirium in patients with advanced cancer.

Approximately 30% of patients with cancer-related delirium experience a complete improvement in cognition after treatment.[36] The others usually continue in a state of hypoactive delirium or, if they were in a state of hyperactive or mixed delirium, become progressively hypoactive. A few patients remain in a state of chronic hyperactive or mixed delirium and require continuous psychotropic medication.

Haloperidol can be used to manage symptoms in patients experiencing forms of hyperactive delirium, including psychomotor agitation, delusions or hallucinations.[37] Haloperidol should be considered a temporary measure while other strategies are tested, such as changing the type of opioid, increasing hydration or managing metabolic or infectious complications. In most patients the hyperactive symptoms abate within 3 to 5 days. If no response is observed within 48 hours, other, more sedating neuroleptics such as methotrimeprazine should be tested.

Patients whose condition does not improve after at least 2 courses of neuroleptics may require aggressive sedation, for example, subcutaneous infusions of midazolam.[15] This highly liposoluble benzodiazepine is very potent and has a very short half-life, which allows the appropriate dose to be determined quickly. As with other neuroleptics, midazolam should be considered a short-term measure; other causes should be investigated (and treated) to determine if the delirium is reversible.

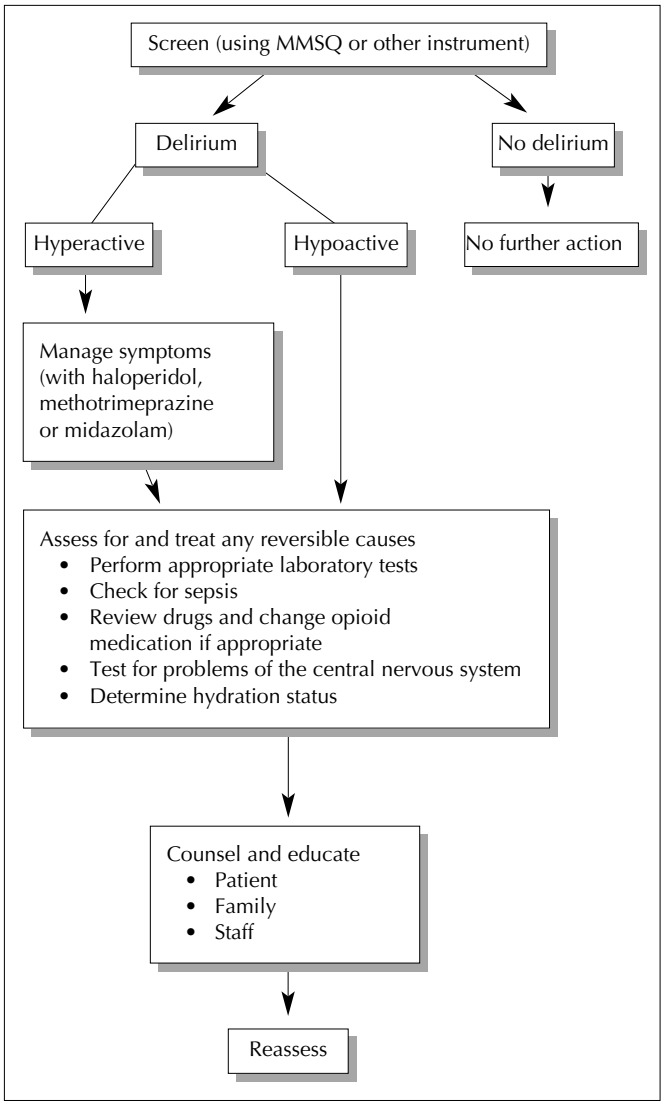

Fig. 5: Clinical approach to delirium in patients with advanced cancer. MMSQ = Mini-Mental State Questionnaire.

Dyspnea

Dyspnea has been defined as an uncomfortable awareness of breathing.[38] It is an unpleasant subjective sensation and cannot be measured by any physical abnormalities. Fig. 6 summarizes the mechanisms of dyspnea. Abnormalities in the blood gases (detected by the lung chemoreceptors) or stimulation of lung mechanoreceptors cause patients with cancer to experience dyspnea. A

Case 6: Treating delirium

A 75-year-old man with advanced renal cell carcinoma is admitted to a tertiary palliative care unit because of severe agitated delirium of recent onset. During the previous 4 days he has experienced confusion, psychomotor agitation, tactile and visual hallucinations and paranoid delusions. He receives acetaminophen 4 to 6 times a day for mild bone pain and 150 mg of amitryptyline every night for insomnia and mild depression.

He is admitted to hospital, appearing severely confused and agitated. His temperature is 38.5°C. When he does not urinate for more than 12 hours, a Foley catheter is inserted and 180 mL of concentrated, cloudy urine is obtained. Culture indicates a urinary tract infection; blood tests reveal severe hypercalcemia and dehydration.

The tricyclic antidepressant is discontinued. Hypodermoclysis (two-thirds dextrose, one-third normal saline) is started at a rate of 100 mL/h. Antibiotic therapy is started to treat the urinary tract infection. After 24 hours of rehydration, 1500 mg of clodronate in 1 L of normal saline is administered subcutaneously over 6 hours to treat the hypercalcemia. A 2-mg dose of haloperidol is administered subcutaneously every 6 hours, and 2-mg doses are administered every hour as needed to manage the patient's agitation.

Within 48 hours the patient's state of arousal and cognition have improved (as indicated by normal results for a Mini-Mental State Questionnaire). The haloperidol is discontinued, and he is given antibiotics and hydration by mouth. On day 7 after admission the patient is discharged to a hospice.

number of researchers have found great variability in the expression of dyspnea in patients with similar levels of functional abnormalities.[38] Therefore, the goal of treatment should be to improve the patient's subjective sensation rather than trying to modify any abnormality in blood gases or pulmonary function. The intensity of dyspnea can be easily assessed by means of verbal, numeric or visual analogue scales similar to those used to assess pain or nausea.

Fig. 7 presents the main causes of dyspnea in patients with cancer. Many of these conditions improve dramatically with treatment, for example, anticoagulants can be used to treat pulmonary embolism, antibiotics to treat pneumonia and blood transfusions to treat anemia. There are 3 main types of therapy used to manage the symptoms of dyspnea: oxygen therapy, drug therapy and counselling.

Oxygen

A number of randomized controlled trials involving patients with cancer and COPD have provided compelling evidence to support the use of oxygen for symptomatic treatment of hypoxemia. When the ability of oxygen to relieve symptoms in a given patient is in doubt, particularly when oxygen therapy may impede rapid discharge to home, an "*N* of 1" study can be conducted.[39] This type of study consists of multiple double-blind, crossover comparisons between oxygen and air and can usually be completed in less than 1 hour.

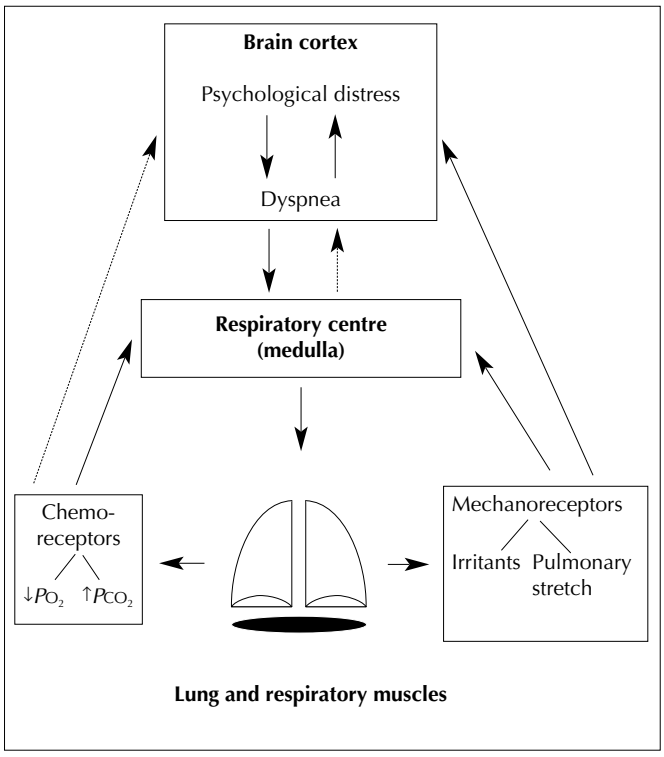

Fig. 6: Mechanisms of dyspnea in patients with cancer. Solid lines = demonstrated actions, broken lines = proposed actions. Chemoreceptors sense reduced partial pressure of oxygen (P_{O_2}) and increased partial pressure of carbon dioxide (P_{CO_2}). Mechanoreceptors sense irritants and pulmonary stretch.

Opioids

Several randomized controlled trials have found that systemic opioid therapy is beneficial for patients with cancer dyspnea.[38] However, the optimal type, dose and mode of administration have not yet been determined. In addition, the toxic effects of systemic opioid therapy for dyspnea are unclear. In one study, significant improvements in symptoms were associated with increases in partial pressure of carbon dioxide,[40] a marker of hyperventilation, but other studies have failed to detect any increase in these levels.[41]

In recent years, a number of authors have reported that different types and doses of nebulized opioids relieve the symptoms of dyspnea.[42] However, a recent randomized controlled trial showed no difference between nebulized morphine and placebo.[43]

Benzodiazepines

Benzodiazepines are commonly used to manage cancer-related dyspnea. However, 4 of the 5 randomized controlled trials of these agents found no significant benefit.[38] Benzodiazepines may be used when the dyspnea is considered to be a somatic manifestation of a panic disorder or when a patient has concurrent severe anxiety. Otherwise, opioids are probably more effective for the symptomatic management of dyspnea.

Other drugs

It has been suggested that corticosteroids are effective in the management of dyspnea associated with carcinomatous lymphangitis, and they are frequently used in the

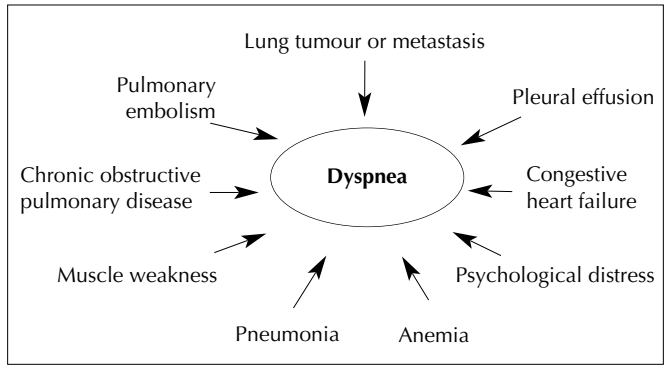

Fig. 7: Main causes of dyspnea in patients with advanced cancer.

management of superior vena cava syndrome.[38]

A large proportion of patients with cancer-related dyspnea have a history of smoking or COPD. In a recent study[44] almost half of 57 consecutive patients with lung cancer had evidence of airflow obstruction, and only 4 of these were receiving bronchodilators. The authors concluded that untreated airflow obstruction is common among patients with bronchial carcinoma and is strongly associated with breathlessness. These patients might benefit from simple bronchodilator treatment.

General support measures

Modifying activity level and using bathroom aids, portable oxygen and wheelchairs will increase the autonomy of patients with dyspnea. The risk of choking can elicit major psychological reactions from the patient and the family. It is therefore important to anticipate and prepare for the possibility of respiratory failure. Drugs for managing the symptoms of dyspnea should be made available and instruction for their administration provided.

Because dyspnea is frequently associated with tachypnea and the use of accessory respiratory muscles, patients may appear to be significantly dyspneic even when their symptoms are under control. It is important for relatives and staff members to assess dyspnea only by asking patients how short of breath they feel, rather than by estimating it on the basis of the degree of tachypnea or the use of respiratory muscles. It is not uncommon that patients with moderate to severe tachypnea will not complain of respiratory distress. In contrast, patients who are not tachypneic may report severe dyspnea. The goal should be to reduce the symptoms that contribute to the patient's sensation of dyspnea, rather than to relieve the objective variables that accompany this disorder.

Case 7: Managing dyspnea

A 45-year-old woman with advanced adenocarcinoma of the lung is admitted to a tertiary palliative care unit because of severe dyspnea. Chest radiography reveals a large pleural effusion on the right side and consolidation consistent with pneumonia on the left side. Her temperature is 38.5°C, and she complains of chest pain on the left side, cough and purulent sputum. Her oxygen saturation on room air is 82%.

Oxygen (3 L/min by nasal prongs) is started, which results in an increase in saturation, to 93%. Antibiotics are given to treat the pneumonia. A 5-mg dose of morphine is administered subcutaneously every 2 hours as needed for dyspnea. A pleural tapping drains 1500 mL of serous fluid.

Within 48 hours, the patient is afebrile, has normal oxygen saturation on room air and requires only occasional doses of morphine to relieve the dyspnea. She is discharged to a hospice, where she receives intermittent doses of morphine orally to manage the dyspnea.

Conclusion

During the past 10 years there have been major changes in the management of the most common symptoms of advanced cancer. A variety of new drugs have emerged to manage pain, cachexia and nausea, and the role of older drugs has also been better defined. There is more understanding of the complexity of these symptoms and the need for disciplined and multidimensional assessment and monitoring. However, the overall area of symptom assessment and management has received very limited attention from clinical researchers and granting agencies. Increased research into these highly prevalent and devastating clinical complications is badly needed.

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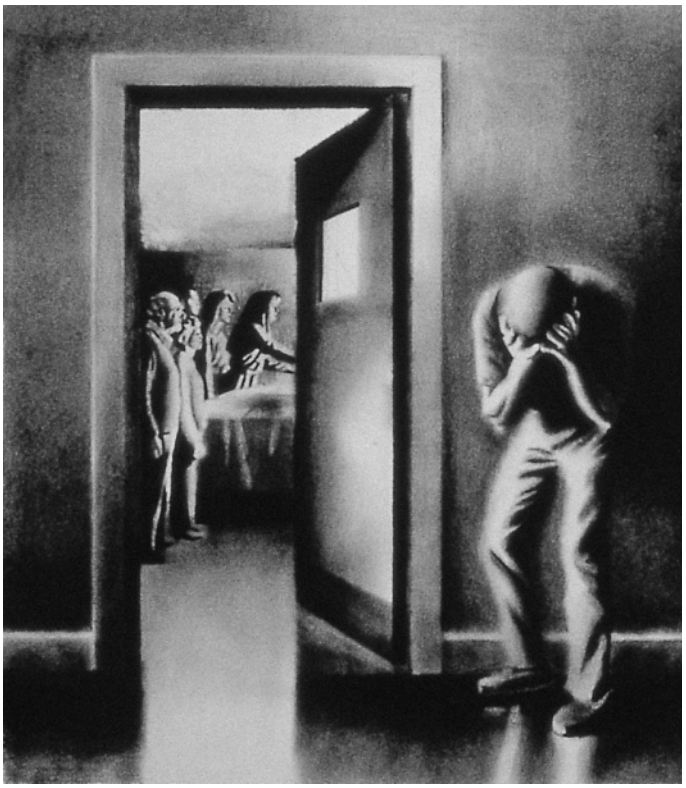

***A Friend's Story*, by Robert Pope (1990). Charcoal on paper, 36.4 × 31.6 cm.**

A Friend's Story

Over the course of my work in making images of cancer I have talked to and interviewed many dozens of cancer patients and their families. This image of public and private pain came out of a conversation with a friend. It is based on her description:

> Last year, my 41-year-old sister-in-law was diagnosed as having a malignant brain tumor. All members of my immediate large family flew home to Cape Breton from wherever they were living at the time — in my case, Toronto. I clearly remember the initial scene as everyone gathered around Donna's hospital bed. It had been a long time since we had all been in the same room together. Nobody knew what to say, either to Donna or to each other; in our collective state of shock, none of us knew what the appropriate reaction should be. So, in effect, we made it up as we went along.

She described to me how not everyone could fit inside the hospital room and how some of the family would have to wait in the hall. It was here, out of sight of the patient, that family members could allow their grief to be fully expressed.

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