OBJECTIVES:
To describe management of common physical problems that occur in patients with advanced cancer.

DATA SOURCES:
Research and review articles, book chapters, and published guidelines.

CONCLUSIONS:
Effective symptom control for patients with advanced cancer requires the coordinated efforts of a multidisciplinary team. Excellent palliation can be achieved in patients suffering from pain, as well as from gastrointestinal, respiratory, or dermatologic disorders.

IMPLICATIONS FOR NURSING PRACTICE:
Nursing is the cornerstone of effective palliative care. Through accurate assessments and expertise in delivering pharmacologic and nonpharmacologic treatments, nurses ensure optimal palliation of physical symptoms.

PROVIDING physical comfort is the cornerstone to the relief of suffering in cancer patients. Pain and a number of other distressing disorders occur frequently in this patient population and contribute significantly to patient discomfort. Satisfactory control of many of these problems can be achieved, and pain can be controlled in over 90% of patients. This article reviews pharmacologic and nonpharmacologic treatment strategies used to reverse the most common problems encountered by patients with cancer.

PAIN

Pain is usually classified as somatic, visceral, or neuropathic. Determining the type of pain can help elucidate its cause and indicate the type of pharmacologic therapy(ies) likely to be effective. A comprehensive pain assessment is required both to choose initial therapy and to measure its effectiveness. The oncology patients' experience of pain is often exacerbated by the psychosocial and spiritual stresses of their disease. In cancer patients, 62%-78% of pain is due to tumor involvement, 19%-25% is due to treatment of the cancer, and 3%-10% is due to an unrelated condition. Every effort should be made to eliminate the cause of the discomfort. However, while the cause is being determined, while the patient is receiving cancer-directed therapy, or when definitive therapy is no longer possible, the patient's symptoms can often be relieved.

Pharmacologic therapy is the mainstay of cancer pain relief; nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and adjuvant analgesics all have a role to play.
**Nonsteroidal Anti-inflammatory Drugs**

The World Health Organization analgesic ladder (Fig 1) indicates that NSAIDs are useful alone for mild pain, and, along with opioids, for moderate and severe pain. Nonsteroidal anti-inflammatory drugs inhibit prostaglandin synthesis; therefore, they both decrease pain intensity and minimize the inflammation associated with bone or tissue injury that is mediated by prostaglandins. Commonly used NSAIDs can be found in Table 1.

Both acetaminophen and aspirin have a "ceiling effect"; 1,000 mg is the ceiling dose for both agents. Patients will not get more pain relief from a dose of 1,500 mg of aspirin or acetaminophen than they will from a dose of 1,000 mg. In cancer patients, however, the NSAIDs aspirin, acetaminophen, and ibuprofen are rarely used alone. Instead, combination preparations that include one of these NSAIDs along with an opioid (especially oxycodone) are usually preferred for patients with mild to moderate somatic or visceral pain. Ketorolac, an NSAID, can be used alone, has the pain-relieving potency of an opioid and is indicated for patients with severe pain.

**Contraindications and side effects of NSAIDs.**

The NSAID-induced inhibition of prostaglandin synthesis can cause serious abnormalities in platelet and kidney function, in the gastrointestinal tract, and in the lungs. Patients receiving these agents are therefore at risk of developing bleeding, a variety of renal and gastrointestinal disorders, and asthma. Most NSAIDs are contraindicated in patients with low platelet counts or who are receiving anticoagulants. Prostaglandin inhibition is one of a number of mechanisms by which NSAIDs cause renal toxicity. Renal function therefore must be assessed during the first weeks of NSAID use, especially in elderly patients. Patients most likely to develop gastrointestinal bleeding are those older than 60 years; those with a history of previous ulcer disease, NSAID-induced bleeding, or cardiovascular disease; and those with concomitant use of steroids or anticoagulants or receiving multiple NSAIDs. Nonsteroidal anti-inflammatory drugs are also used with caution in asthmatic patients.

The side effects described above occur with therapeutic doses of NSAIDs. Patients who increase their dose of aspirin above 6,000 mg/d, however, often develop salicylate toxicity, manifested by tinnitus, ataxia, hyperventilation, delirium, and coma. Aspirin also can be "hidden" in a combination agent, and overdose can unwittingly occur. Acetaminophen excess from a similar increase in dose of combination medications can induce liver dysfunction, especially in patients who also ingest alcohol.

**Opioid Analgesics**

While NSAIDs are useful, opioids are needed to relieve the pain of the vast majority of cancer patients. General guidelines for the use of these agents can be found in Table 2.

Step 2 and 3 agents from the World Health Organization analgesic ladder (Fig 1) are listed in Table 3, along with recommended initial dosing, frequency of administration, adjustment for renal or hepatic failure, and available preparations. Be alert both to the differences between the oral and parenteral potency of the various agents and to the dosing equivalencies between agents. For example, 1.5 mg of parenteral hydromorphone is equivalent in potency to 7.5 mg orally, a fivefold difference. Dosing equivalent charts are readily available for reference.

**Codeine.** In cancer patients, using the step 2 agent codeine is problematic because it is nauseating, dysphoric, and ineffective in those patients who lack a specific hepatic enzyme that converts it to morphine or who are taking drugs that inhibit the enzyme's function, such as cimetidine.

**Oxycodone.** Oxycodone is listed both with the step 2 and step 3 agents because oxycodone is available both in a low-dose combination agent, effective only for moderate pain (step 2), and as pure oxycodone, for severe pain (step 3). Both short-acting oxycodone and a 12-hour continuous-release preparation are available.
**TABLE 1. Nonsteroidal Antiinflammatory Drugs**

<table>
<thead>
<tr>
<th>Chemical Class</th>
<th>Generic Name</th>
<th>Interval</th>
<th>Initial Dose*</th>
<th>Maximum 24-hr Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-aminophenol</td>
<td>Acetaminophen</td>
<td>Every 4-6 hr</td>
<td>650 mg</td>
<td>6,000 mg</td>
</tr>
<tr>
<td>Salicylates</td>
<td>Aspirin†</td>
<td>Every 4-6 hr</td>
<td>650 mg</td>
<td>6,000 mg</td>
</tr>
<tr>
<td></td>
<td>Choline magnesium salicylate</td>
<td>Every 12 hr</td>
<td>750-1,000 mg</td>
<td>4,500 mg</td>
</tr>
<tr>
<td></td>
<td>Salsalate</td>
<td>Every 12 hr</td>
<td>500-1,000 mg</td>
<td>4,000 mg</td>
</tr>
<tr>
<td></td>
<td>Diflunisal</td>
<td>Every 12 hr</td>
<td>500 mg</td>
<td>NA</td>
</tr>
<tr>
<td>Propionic acids</td>
<td>Ibuprofen</td>
<td>Every 6 hr</td>
<td>400 mg</td>
<td>4,200 mg</td>
</tr>
<tr>
<td></td>
<td>Fenoprofen</td>
<td>Every 6 hr</td>
<td>200 mg</td>
<td>3,200 mg</td>
</tr>
<tr>
<td></td>
<td>Ketoprofen</td>
<td>Every 6 hr</td>
<td>25 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td></td>
<td>Naproxen†</td>
<td>Every 12 hr</td>
<td>250 mg</td>
<td>1,500 mg</td>
</tr>
<tr>
<td></td>
<td>Flurbiprofen</td>
<td>Every 12 hr</td>
<td>100 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>Acetic acids</td>
<td>Indomethacin†</td>
<td>Every 8 hr</td>
<td>25 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td></td>
<td>Trolmetin</td>
<td>Every 8 hr</td>
<td>200 mg</td>
<td>2,000 mg</td>
</tr>
<tr>
<td></td>
<td>Di clofenac</td>
<td>Every 8 hr</td>
<td>25 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td></td>
<td>Sulindac</td>
<td>Every 12 hr</td>
<td>150 mg</td>
<td>400 mg</td>
</tr>
<tr>
<td>Ketorolac</td>
<td></td>
<td>30-60 mg IM load</td>
<td>150 mg d 1</td>
<td>120 mg day 2-7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(orally: 10 mg every 6 hr)</td>
<td>(orally: 40 mg)</td>
</tr>
</tbody>
</table>

*in the elderly and in patients with renal insufficiency, start at half to two thirds of these doses.
†Available in suppository form.

Abbreviations: IM, intramuscularly; NA, not available.

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**Morphine.** Morphine is available in both sustained-release and immediate-release preparations. Patients commonly receive both a sustained-release agent every 12 or 24 hours to control their baseline pain and a short-acting agent as needed every 2 hours to control unexpected exacerbations of pain. For those unable to swallow a pill, the drug pellets contained in the Kadian capsule (Zeneca, Wilmington, DE), if sprinkled on food or put in tube feedings with water, provide 24-hour relief.

**Meperidine.** Meperidine is not recommended for patients with cancer pain; its metabolite, normeperidine, often causes seizures.

**Transdermal fentanyl.** Transdermal fentanyl patches are composed of a drug reservoir lined on the bottom with a rate-limiting membrane, which itself is attached to a backing that adheres to the patient's skin. The lipophilic opioid fentanyl, in the patch's drug reservoir, diffuses into the fat in the skin and is absorbed into the blood stream. At least 12 hours are needed before there is enough fentanyl in the skin depot to establish an adequate blood level. By 14 to 20 hours, an effective plasma concentration is reached; steady state is reached by 48 hours, and in most patients is maintained for 72 hours. The patch is not the ideal choice for someone with acute, severe or excruciating pain because of this lag time; it is also problematic in febrile, medically unstable patients because drug absorption from the skin can increase, causing toxicity. If the patient develops an overdose, a low-dose naloxone drip may be needed for 12 to 24 hours or more to maintain respiration until the drug remaining in the skin reservoir (after the patch is removed) is metabolized.
TABLE 3. Commonly Used Opioids: Preparations Available6,39,40,43,44,49

<table>
<thead>
<tr>
<th>Initial Dose (mg)*</th>
<th>Name</th>
<th>Oral</th>
<th>IM/IV</th>
<th>Dose Interval (hr)</th>
<th>Dose Adjustments Needed</th>
<th>Preparations Available†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Morphine</td>
<td>30</td>
<td>10</td>
<td>3-4</td>
<td>Renal failure</td>
<td>IM/IV/SQ, IR, rectal, liquid, Liq Conc</td>
</tr>
<tr>
<td></td>
<td>Morphine, SR</td>
<td>60</td>
<td>NA</td>
<td>8-12</td>
<td>Renal/hepatic failure</td>
<td>SR</td>
</tr>
<tr>
<td></td>
<td>Morphine, SR</td>
<td>120</td>
<td>NA</td>
<td>24</td>
<td>Renal/hepatic failure</td>
<td>SR</td>
</tr>
<tr>
<td></td>
<td>Hydromorphone</td>
<td>6</td>
<td>1.5</td>
<td>3-4</td>
<td>Renal/hepatic failure</td>
<td>Combo</td>
</tr>
<tr>
<td></td>
<td>Oxydodone, combo</td>
<td>10</td>
<td>NA</td>
<td>3-4</td>
<td>Renal failure</td>
<td>IR, liquid</td>
</tr>
<tr>
<td></td>
<td>Oxydodone</td>
<td>20</td>
<td>NA</td>
<td>3-4</td>
<td>Renal failure</td>
<td>SR</td>
</tr>
<tr>
<td></td>
<td>Oxydodone, SR</td>
<td>60</td>
<td>NA</td>
<td>12</td>
<td>Renal/hepatic failure</td>
<td>Transdermal</td>
</tr>
<tr>
<td></td>
<td>Fentanyl</td>
<td>NA</td>
<td>50 µg/hr</td>
<td>72</td>
<td>Renal/hepatic failure</td>
<td>Oral transmucosal</td>
</tr>
<tr>
<td></td>
<td>Methadone</td>
<td>20</td>
<td>10</td>
<td>6-8</td>
<td>Renal/hepatic failure</td>
<td>IM/IV/SQ, IR, liquid</td>
</tr>
<tr>
<td></td>
<td>Levorphanol</td>
<td>4</td>
<td>2</td>
<td>6-8</td>
<td>Renal/hepatic failure</td>
<td>IM/IV, IR</td>
</tr>
<tr>
<td></td>
<td>Oxymorphine</td>
<td>NA</td>
<td>1</td>
<td>3-4</td>
<td>Renal failure</td>
<td>IM/IV/SQ, rectal</td>
</tr>
<tr>
<td></td>
<td>Demerol‡</td>
<td>N/R</td>
<td>100</td>
<td>3</td>
<td>Renal failure</td>
<td>IM/IV, IR</td>
</tr>
<tr>
<td></td>
<td>Tramadol‡</td>
<td>100</td>
<td>NA</td>
<td>4</td>
<td>Renal failure</td>
<td>IR</td>
</tr>
</tbody>
</table>

Abbreviations: IM, intramuscularly; IV, intravenously; SR, sustained release; NA, not available; N/R, not recommended.

*For patients weighing over 110 lb who have moderate to severe pain (from Agency for Health Care Policy and Research 94-0593: Management of Cancer Pain: Adults).
†IM/IV: parenteral, suitable for intravenous or intramuscular use; SQ: subcutaneous; IR: oral, immediately release; SR: oral, sustained release; Liq Conc: concentrated liquid solution; Combo: oral combination preparation with an NSAID (acetaminophen, aspirin, ibuprofen, etc).
‡Not recommended for use other than for a limited time (see text).
§Nonnarcotic, but binds to opioid receptors.

Oral transmucosal fentanyl citrate. Early reports demonstrate the safety and efficacy of a truly immediate-release form of pain relief: transmucosal fentanyl citrate in a palatable solid matrix.49 Two thirds of pain relief is achieved 15 minutes after initiation of the drug.

Rectal morphine. Administration of sustained-release morphine tablets into the rectal vault or into colostomies has not been approved by the Food and Drug Administration, but it has been extensively studied and found to be safe and effective.40

Subcutaneous/intravenous infusions. Some patients will not be able to tolerate oral medication and will not respond to fentanyl patches. Most of these will benefit from subcutaneous infusions3 of either morphine or hydromorphone. Subcutaneous methadone is not as well tolerated.50 Very high opioid doses can be delivered using hydromorphone preparations.51 Three milliliters per hour of this solution delivers 30 mg/hr of hydromorphone (the equivalent of 200 mg/hr of morphine). If necessary, intravenous infusions can be given through an implanted vascular access device already in place or via a peripherally inserted central venous catheter.52 Patient-controlled analgesia is available for both the intravenous and subcutaneous routes.53

Spinal opioids (epidural, subarachnoid). Spinal delivery of opioids produces pain relief because the exogenous opioids bind to receptors for natural opioids (enkephalins) that are already present in the spinal cord.54,55 Because they are being delivered locally, epidural opioids are effective at one tenth the systemic doses.56 Morphine is the agent most commonly used in epidural and intrathecal infusions, but fentanyl and its relatives also are used.57

Spinal opioids benefit those few patients with bilateral or midline pain below the umbilicus whose deep somatic or neuropathic pain syndrome is not responding to systemic opioids.58,59 They can be used alone or with anesthetics or α-adrenergic agents to improve their efficacy or minimize the opioid-induced side effects.59,60 Spinal opioids/anesthetics can be delivered via either temporary epidural catheters or permanent epidural or subarachnoid catheters.59,60 Patient-controlled epidural analgesia is available for either temporary or permanent infusions.62

Temporary catheters are used in some patients to enable them to regain sensitivity to lower doses...
of systemic opioids, but they also can be used to determine whether a patient will benefit from a permanent infusion. Patients with bilateral severe neuropathic pelvic pain from recurrent colorectal, bladder, or gynecologic cancers involving the lumbosacral and perineal nerve plexi, for example, have temporary catheter placement to determine whether the epidural route can provide effective pain relief.

Cancer patients, who usually are not opioid naive, rarely develop side effects from spinal infusions. If they do, small doses of naloxone can reverse them without eliminating analgesia. The most common complications of spinal infusions arise during implantation (bleeding, perforation of an abdominal or retroperitoneal viscus or lung, pump pocket seromas) or from the catheters themselves (they become dislodged, kink, tear, and cause epidural fibrosis and infection).

Adjuvant Analgesic Medications

Drugs that are used primarily for other indications can be analgesic as well. They are given orally, parenterally, or rectally, and are of particular value for patients with bone or neuropathic pain. Adjuvants useful for bone pain are listed in Table 4. Adjuvants useful for neuropathic pain are found in Table 5.

**Steroids.** Steroids are effective both in patients with malignant bone pain and in those with neuropathic pain, such as that caused by brain metastases, compression of the spinal cord, or infiltration of the brachial or lumbar plexus. They can be given epidurally, intravenously, or orally. Steroids alone have been shown to decrease the acute pain associated with herpes zoster infections, but there is no long-term benefit. Oral steroids also increase patients' appetites and sense of well-being, but results of controlled studies of their efficacy have been conflicting.

Side effects of steroids can be a problem. Misoprostol (200 µg two to three times per day) is often used to prevent peptic ulcers for patients receiving both steroids and NSAIDs. Oral and esophageal candidiasis can be treated either by low-dose ketoconazole (200 mg twice a day) or, for patients with the acquired immunodeficiency syndrome or those taking antacids, fluconazole (100 mg a day). Topical oral antifungals such as clotrimazole troches given three times a day help treat oral lesions but do not prevent esophageal candidiasis. Steroid-induced delirium responds to haloperidol (Table 6). Glucose intolerance is easily managed with insulin, but proximal muscle weakness can be refractory to therapy.

**Anticonvulsants.** Phenytoin, carbamazepine, and clonazepam are used in patients with neuropathic pain that is described as "sharp," "cutting," or "like an electric shock." Opioids alone can relieve this neuropathic pain, but high doses are often required and the side effects of these doses are often difficult to tolerate.

**Baclofen.** Baclofen is normally used to relax spastic limbs, but it also relieves trigeminal neuralgia pain. It therefore may help those patients with cancer of the head and neck who develop a neuropathic pain syndrome similar to that of trigeminal neuralgia.

**Antidepressants.** The tricyclic antidepressants are the best studied in patients with nonmalignant chronic pain, and they also are very useful for many cancer patients with continuous neuropathic pain, and lancinating neuropathic pain. The pain-relieving effects of these agents are independent of their ability to reverse depression and can appear much more quickly (in 4 to 7 days).

All antidepressants cause significant side effects: anticholinergic, sedation, orthostatic hypotension, and cardiac arrhythmias. Amitriptyline is therefore used with caution in the elderly, in

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamidronate</td>
<td>90-120 mg IV over 4 hr, every 3-6 wk</td>
<td>Effective for several months with repeated dosing</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>100-200 IU SQ twice daily</td>
<td>Often effective for weeks to a few months; can cause symptomatic hypocalemia</td>
</tr>
<tr>
<td>Strontium chloride (Sr 89)</td>
<td></td>
<td>Induces significant cytopenias; can be used only once</td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; SQ, subcutaneously.
Also see text and tables for discussions of NSAIDS (Table 1) and steroids (Table 5).
TABLE 5. Adjuvants for Neuropathic Pain3,64-66,70-73

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>Prednisone</td>
<td>40-60 mg in divided doses; taper to every other day as tolerated.</td>
<td>Add acyclovir for acute herpes zoster (see text)66. Side effects: gastrointestinal disorders, candidiasis, euphoria, depression, delirium, hyperglycemia.</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
<td>10-100 mg bolus; 6 mg orally/intravenously four times a day; taper as tolerated.</td>
<td>Cannot be given intramuscularly.</td>
</tr>
<tr>
<td>Anti-convulsants70</td>
<td>Phenytoin</td>
<td>1000 mg load; 200-300 mg every day.</td>
<td>Suspension available for rectal administration65. Do not exceed 1,200 mg/24 hr. Rarely used for neuropathic pain. Do not exceed 20 mg in 24 hr.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td>200 mg orally, at bedtime, increase every 3 days.</td>
<td>Used for tic-dolooreux-type pain. Target dose: 40-80 mg/24 hr.</td>
</tr>
<tr>
<td>Clonazepam</td>
<td></td>
<td>0.5 mg three times daily; increase by 0.5 mg every 3 days.</td>
<td></td>
</tr>
<tr>
<td>Baclofen71</td>
<td></td>
<td>5 mg three times a day; increase by 5 mg every 3 days.</td>
<td></td>
</tr>
<tr>
<td>Alpha-2 agonist73</td>
<td>Clonidine</td>
<td>0.1-0.3 mg patch.</td>
<td>Side effects: anticholinergic, sedation, cardiac arrhythmias, orthostatic hypotension. Amitriptyline: most sedating. Desipramine: least sedating, minimal cardiotoxicity; may need 150-300 mg for therapeutic effect. Nortriptyline: least orthostatic hypotension, minimal sedation.</td>
</tr>
<tr>
<td>Tricyclic</td>
<td>Amitriptyline, imipramine, doxepin, clomipramine, desipramine, nortriptyline</td>
<td>Begin at 10-25 mg orally, at bedtime; increase to therapeutic dose (50-150 mg in divided doses).</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines73</td>
<td>Alprazolam</td>
<td>0.25-2 mg orally three to four times a day.</td>
<td>May be given sublingually.</td>
</tr>
</tbody>
</table>

patients with a high risk of angle-closure glaucoma, or in patients with bladder outlet obstruction, arrhythmias, or other cardiac conduction problems.76 Imipramine, desipramine, and nortriptyline are less sedating and have fewer other side effects than amitriptyline,21 but their efficacy has been less well established. The benzodiazepine antidepressant, alprazolam, may relieve neuropathic pain,73 but fluoxetine does not.70

Opioid-Induced Side Effects and Management

Constipation. Constipation is the most common side effect of opioid therapy; it usually does not diminish with time. For a brief discussion of constipation, refer to the Gastrointestinal Problems section below.

Sedation. Sedation can be an important dose-limiting side effect in patients taking opioids and can make it difficult for a patient to achieve a satisfactory degree of pain control. Sedation is most prominent when the patient first begins taking opioids, it lessens within a few days, even if the dose is kept the same.74 Sustained-release preparations minimize sedation by providing a steady level of pain relief without excessive peak blood levels of opioid.46,75,76 If sedation persists beyond the first few weeks, another cause is usually sought (eg, an electrolyte imbalance, hypercalcemia, or other sedating medications).

If the opioid is responsible for the sedation, a different opioid may be substituted. If the sedation still persists, a psychostimulant such as methylphenidate may be added.77 Amphetamines have been shown to reduce the dose of opioid needed for pain relief by half, to reduce drowsiness, and to enhance mood.77 A list of effective psychostimulants and their usual starting doses is given in Table 7.

Respiratory depression. Respiratory depression is an unusual side effect of opioids given to treat cancer pain, so long as the opioid dose is titrated to the degree of pain and the patient's renal and hepatic function remain stable.21 Opioid
sensitivity leading to hypoventilation may occur in some hypothyroid patients, asthmatic patients, or patients with chronic obstructive pulmonary disease and patients taking sustained-release preparations can develop respiratory depression if the absorption or metabolism of the opioid suddenly changes. In all these conditions, the patient will appear sedated. If the patient is anxious or agitated, something other than opioid must be sought as a cause for the respiratory depression.

Laxatives, oral or intravenous motility agents, and enemas are used to help the patient rapidly eliminate remaining drug. If the patient is breath- ing normally, further opioid doses are withheld; if significant respiratory depression has occurred, a diluted solution of the opioid antagonist naloxone either as a slow intravenous "push" (1 mL [0.4 mg] naloxone in 10 mL normal saline) or a continuous infusion is indicated. The rate is adjusted to permit re-establishment of normal respirations but to not wake the patient suddenly. A severe withdrawal syndrome may occur if an undiluted injection of naloxone is administered.

**Delirium.** Delirium can be a frightening side effect both for the patients experiencing it and for their families. It manifests with hallucinations, paranoid ideation, disordered thinking and perception, delusions, and labile mood; patients may either appear withdrawn, lying in a fetal position, or agitated, exhibiting what is termed "psychomotor behavior." A number of organic problems cause delirium. Opioids alone are rarely responsible, but a number of other drugs are often implicated; these include psychostimulants, steroids, short-acting benzodiazepines, and combinations of drugs with anticholinergic side effects.

Treatment can begin while the cause is being sought. In some patients, lowering the opioid dose or stopping any other responsible agent will resolve the problem. Having a friend or family member sit with the patient, moving him to a well-known room, leaving the light on, and having a clock, a calendar, and favorite, familiar objects within sight may help the delirious patient. When these measures are not effective, pharmacologic therapy (usually haloperidol) is used (Table 6).

### GASTROINTESTINAL PROBLEMS

**Oral**

Oral discomfort in patients with cancer arises from poor oral hygiene, mucositis, candida infec-
tions, or dry mouth caused by mouth breathing, previous radiation therapy, or medications. General measures for oral comfort include presenting food at moderate temperatures; avoiding dry, acidic, or highly spiced foods; and minimizing alcohol and tobacco use.79-81

Oral hygiene should not be neglected. Patients should continue daily brushing using a soft-bristle brush, flossing (with unwaxed floss), and rinsing with an antibacterial mouth wash (that does not contain alcohol) or a solution of bicarbonate in water (eg, 1 tsp in a cup of water).81 They should be monitored closely for the development of mucositis, infection, and xerostomia, and treated promptly.82

Mucositis due to chemotherapy often responds to granulocyte colony-stimulating factor83; sucralfate also has been used to treat chemotherapy- and radiation therapy-induced mucositis, but trials are contradictory concerning its benefit.84,85 Capsaicin also may be of benefit.86 Patient-controlled analgesia may be needed for pain relief.

Candida infection presents as a burning tongue or pain when eating or swallowing; white plaques (which are easily wiped off, but bleed) along the sides of the tongue or cheeks, on the gums, or on the roof of the mouth; angular cheilitis; or, in denture wearers, red, edematous areas. Mucositis from candida can be effectively treated with fluconazole or topical antifungal agents, such as clotrimazole troches.79

Xerostomia should be addressed, as saliva is important to oral health. It is a lubricant, helps control plaque, protects teeth from dissolution and the mouth from bacterial, fungal, or viral infection, and enhances taste and the ability to swallow food.81 Mild xerostomia may respond to sugar-free sour lemon drops or other sugar-free hard candy. For those without cardiac contraindications, pilocarpine can be given an hour before meals; it is especially helpful for patients who have undergone radiation to the oral cavity or neck.87,88

In the last weeks of life, dry mouth may be caused by dehydration or opioids used to relieve pain. It is not necessary, however, to reverse the dehydration to relieve this symptom; in fact, no controlled studies have shown that rehydration is effective.81 Moistening the mouth with gauze soaked in ice water and offering sips of water, ice chips, or fruit-flavored ice pops are usually all that is needed.81

**Ascites**

Ascites occurs most often in patients with ovarian or breast cancer, but also occurs in patients with genitourinary, lung, and gastrointestinal cancers.89 For patients whose ascites are refractory to the usual diuretic measures (aldactone + oral furosemide) and who have 1 month or less to live, repeated paracentesis may be the most appropriate therapy.89 However, for those with a reasonable life expectancy, a peritoneal-venous shunt may provide prolonged symptomatic relief.90,91

**Constipation**

Increased water intake, increased activity, fiber therapies, or disodium disuccinyl docusate are usually ineffective for patients receiving opioids and may even exacerbate the problem.21,92 Daily laxatives are therefore indicated in any patient receiving opioid therapy.92,93 Agents that stimulate the myenteric nerve plexus and osmotic agents are the most effective.92,94 These are listed in Table 8. For an impaction, glycerine suppositories or olive oil enemas may be required.

**Diarrhea**

Diarrhea may be due to newly acquired lactose intolerance (eg, after chemotherapy), drug side effects, intermittent bowel obstruction, fecal impac-
Symptom control, sphincter incompetence, chronic radiation enteritis, infection, or products of rare neuroendocrine tumors, such as carcinoid.

Specific treatment, including octreotide, is often effective. Symptomatic treatment includes loperamide or tincture of opium and oral rehydration. To replace potassium, patients can be encouraged to eat bananas. To avoid exacerbating the diarrhea or inducing a recurrence immediately after it resolves, lactose-containing foods should be avoided. Similarly, highly spiced and fatty foods are discouraged. Potatoes, rice, and macaroni are usually well-tolerated.

**Nausea and Vomiting**

Nausea and vomiting are often amenable to therapy in patients with advanced cancer. Common etiologies in this population include pain, opioids, constipation, gastritis or gastric ulcer disease, gastric outlet or bowel obstruction, hypercalcemia, hypoadrenalinemia, hepatic or renal failure, or disease of the central nervous system. Frequent, small feedings of cold foods that have little odor, acupuncture, and hypnosis may alleviate the nausea. Pharmacologic therapies for nausea and vomiting and for bowel obstruction that cannot be treated surgically are reviewed in Table 9.

**Anorexia and Nutritional Replacement**

**Anorexia.** Anorexia is often distressing both to patients and to their family members because those who have prepared the food may feel that they, not the food, is what is being rejected. The patient should be evaluated for xerostomia and depression, as both are reversible causes of decreased appetite. In patients with advanced cancer, however, often no clear etiology is apparent. Symptomatic treatment includes enhancing the taste of favorite foods and paying careful attention to the patient’s likes and dislikes, such as avoiding foods with disturbing odors or tastes.

Unlike anabolic steroids, hydrazine sulfate, and cyproheptadine, the corticosteroids, megestrol acetate, and medroxyprogesterone acetate have been demonstrated to improve appetite in these patients and may prevent continued weight loss. With prolonged use, however, megestrol acetate may induce adrenal suppression, and the risk of adrenal insufficiency if the agent is stopped abruptly. Dronabinol has proved efficacious in reversing anorexia and weight loss in patients with AIDS, but has been less well studied in patients with advanced cancer.

**Parenteral/enteral feeding.** Parenteral or enteral feeding is most useful early in the course of the illness, while the patient is undergoing surgery, chemotherapy, or radiation therapy. It is more difficult to determine its benefit in the patient with advanced cancer. Parenteral nutrition does not lead to a marked increase in strength or energy in these patients. If they are hungry, but cannot eat, a feeding jejunostomy or gastrostomy may be indicated. Most, however, do not complain of hunger or thirst. Rather than asking them to undergo this invasive procedure, therefore, con-

<table>
<thead>
<tr>
<th>Etiology of nausea</th>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation of opioid therapy</td>
<td>Prochlorperazine</td>
<td>10 mg orally or 25 mg PR two or three times daily</td>
</tr>
<tr>
<td>Stimulation of chemoreceptor trigger zone</td>
<td>Haloperidol</td>
<td>1.5-5 mg orally three to four times daily; 2-10 mg IM two to three times daily</td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
<td>Prochlorperazine</td>
<td>10 mg orally or 25 mg PR two to three times daily</td>
</tr>
<tr>
<td>Vertigo</td>
<td>Methotrimeprazine</td>
<td>2-6.25 mg IM three times daily or 6-25 mg over 24 hr</td>
</tr>
<tr>
<td>Bowel obstruction*</td>
<td>Metoclopramide</td>
<td>10-20 mg two to four times daily or 1-3 mg/hr IV</td>
</tr>
<tr>
<td></td>
<td>Hycosine (scopolamine)</td>
<td>0.3 mg three times daily orally or SQ</td>
</tr>
<tr>
<td></td>
<td>Meclizine</td>
<td>50 mg orally three times daily or 25-50 mg IM</td>
</tr>
<tr>
<td></td>
<td>Octreotide</td>
<td>50-100 µg SQ two to three times daily or 300 µg over 24 hr SQ</td>
</tr>
<tr>
<td>Multiple causes, refractory</td>
<td>Ondansetron</td>
<td>4-8 mg orally two to three times daily</td>
</tr>
</tbody>
</table>

For nausea, initial steps should be (1) treat cause, if identified; (2) consider changing to a different opioid agent (see text); and (3) use adjuvants to decrease opioid dose.

*For symptomatic therapy when surgery is not possible.

Abbreviations: PR, per rectum; IM, intramuscularly; IV, intravenously; SQ, subcutaneously.
sider helping the family to understand why a feeding tube would not be of benefit.

**Respiratory Problems**

**Dyspnea**

Dyspnea is frightening to patients and their families; it creates significant problems in approximately 40% of these patients and occurs in as many as 70% at some time during their last 6 weeks of life. The most common etiologies are pulmonary or cardiac pathology, superior vena cava syndrome, ascites, and anemia. These are reversed when possible and appropriate.

For those with anxiety, relaxation techniques or formal hypnotic imagery may help. For those in an uncontrolled panic due to a perceived inability to breathe, midazolam, morphine (intravenous or by nebulizer), or chlorpromazine may be required.

Pleural effusions often can be symptomatically controlled with oxygen and/or morphine in sedentary patients. Drainage through a chest tube with instillation of a sclerosing agent may be required. In patients whose lung cannot be adequately drained or in whom the lung does not re-expand, and who have a reasonable life expectancy, open pleurodesis or a pleuroperitoneal shunt may be considered.

For the 25% of patients in whom no specific cause is identified, use of a fan blowing air softly onto the face or medications by nebulizer can be helpful. Nebulized morphine or hydromorphone often combined with dexamethasone are given every 4 hours as needed. The opioid dose is increased until dyspnea is relieved. If wheezing is present, albuterol can be added. The mixture is also given by a nebulizer using room air or oxygen at 5 to 6 L/min through an open face mask.

**Cough**

Cough, which is present in approximately 40% of patients with advanced cancer, is caused by postnasal drip, infection, heart failure, asthma/chronic obstructive pulmonary disease or esophageal reflux, angiotensin-converting enzyme inhibitors, obstruction of the airway, and disorders of swallowing. Nonspecific therapy includes oral opioids, sweet elixirs containing dextromethorphan, or one of the opioids used for mild pain; methadone syrup, if available, can be very effective. For more resistant coughs, higher doses of oral or nebulized opioids may be needed.

In addition, nebulized anesthetics can be given up to three times a day. For patients who cough from tenacious mucous, nebulized saline, albuterol, or terbutaline have been helpful; expectorants and mucolytics have not. Since ipatropium worsens this problem, it is discontinued when possible.

**Hiccups**

Hiccups are embarrassing and exhausting, and interfere with a patient's ability to eat, drink, and sleep. They are most commonly caused by gastric compression, injury to vagus or phrenic nerves, uremia, hyponatremia, hypocalcemia, benzodiazepines, barbiturates, intravenous corticosteroids, or, rarely, ear infections, pharyngitis, esophagitis, or pneumonia. If the underlying cause cannot be reversed, metoclopramide is usually effective. Chlorpromazine is also effective, but causes significant postural hypotension. Baeclfen and haloperidol are probably equally effective and safer in older patients. If none of these work and sedation is not a concern, methotrimeprazine or midazolam are often administered.

**Skin Problems**

**Fungating Lesions**

Fungating lesions from cancers growing out through the skin can cause a profound loss of self-esteem and lead to patient isolation. They occur in patients with primary skin cancers, cancers of the head and neck that are refractory to chemotherapy and radiation, metastatic breast cancer, renal cancer, and, rarely, other cancers. Surgery, chemotherapy, and radiation are all considered when the metastases first appear. Symptomatic treatment, however, is often needed. A number of skin care protocols are included in the literature. Important principles of care are listed in Table 10.

**Pressure Sores**

General treatment principles include prevent contamination and minimize shear forces, eliminate or control infection and debride (see Table 10), and protect the wound and promote healing. If infected or necrotic, use normal saline irrigation and enzymatic agents to remove eschar. Use hydrocolloid dressings and alginate dressings as indicated in Table 10.

**Pruritis**

Pain and pruritis is caused by dry skin, allergic reactions to drugs, uremia, obstructive liver
disease, skin involvement with cancer, or factors produced by the cancer, such as the pruritis found in Hodgkin’s disease. For pruritis from biliary obstruction, internal stenting or radiation to obstructing nodes in the porta hepatis often relieves the pruritis. If this is not possible, naloxone, ondansetron, methyltestosterone, or cholestipol powder are used.

Oral antihistamines are probably the best nonspecific relievers of pruritis, but they may cause excessive daytime sedation. The skin should be kept moist, the fingernails cut short, and all bath products that contain perfumes or deodorants avoided. The baths themselves should be lukewarm. Menthol-containing creams, calamine lotion, or a combination of calamine lotion and diphenhydramine can provide symptomatic relief.

NONPHARMACOLOGIC THERAPIES FOR SYMPTOM CONTROL

While they do not replace drug therapies, nonpharmacologic techniques are valuable adjuncts and can be effectively incorporated into symptom management strategies. Although these therapies are most commonly used to manage pain, they are also helpful adjuncts in controlling nausea, vomiting, and dyspnea. They require skilled practitioners. Because many of the techniques can be performed by properly trained lay persons, the practitioners often serve both as therapist and teacher.

Physical techniques include cutaneous interventions, such as heat and cold, massage, acupuncture/auriculotherapy, and transcutaneous electrical nerve stimulation, as well as positioning and exercise.

Cognitive-behavioral interventions are effective in ameliorating a wide range of symptoms, especially pain, anxiety, depression, mild delirium, anorexia, nausea, and dyspnea. Education and reassurance of patients and families relieves a great deal of fear and corrects potentially harmful misconceptions. Diversion of attention with music, videos, or visitors, progressive muscle relaxation and imagery, and hypnosis help patients to escape the problem or to think about it in alternative ways. Biofeedback teaches patients techniques to relieve their own pain by modifying certain physiologic functions. Music therapy offers diversion, distraction, and enhanced relaxation. Psychological counseling and cognitive behavioral training offer support, education, and help in developing coping skills, and diminishes the anxiety, depression, or delirium that may exacerbate the symptoms. Spiritual counseling relieves hidden concerns, reestablishes hope and meaning, and, in the terminal setting, enables patients to resolve issues that may prevent a peaceful death.

Of the cognitive-behavioral therapies, the efficacy of relaxation, hypnosis, and psychological counseling are well established. The physical transcutaneous electrical nerve stimulation technique has documented utility in nonmalignant pain syndromes, but its effectiveness has not been demonstrated in patients with cancer pain. In addition, there is much less data that support the efficacy of the other nonpharmacologic therapies in relieving cancer pain. Much of the data that are available, such as that on acupuncture and biofeedback, are contradictory. Alternative therapies have had increased attention and the reader is referred elsewhere for this discussion.

CONCLUSION

Patients with advanced cancer commonly experience a number of distressing physical symptoms that can interfere with their ability to achieve their final goals. Using a combination of pharmacologic and nonpharmacologic techniques, many of these problems can be ameliorated and, in
some cases, even resolved. A team approach can help ensure that all the patient's problems are identified and adequately managed. Hospice services provide such an approach with medical, nursing, psychosocial, and spiritual assessments and therapies to patients and their families, as well as bereavement care. 149,150

While a great deal has been learned about how to assess and manage a variety of distressing symp-

toms, much remains to be done. Standard, validated assessment tools for pain and other symptoms, such as the Memorial Symptom Assessment Scale,151 need to be adopted by health care systems and incorporated into routine monitoring and documentation. In addition, more research is needed to determine the best palliative interventions if we are to enable them to finish the work they wish to complete in their last days.

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