A B S T R A C T

Well established guidelines exist for the relief of pain at the end of life. Opioids are useful in treating a variety of painful conditions, with morphine being the gold standard. By following established protocols, opioids may be adjusted or exchanged safely. Patients with severe pain often require sustained-release opioids coupled with immediate-release opioids for breakthrough pain relief. Tricyclic antidepressants, anticonvulsants, and corticosteroids are adjuvant medications that can be used to augment analgesics in many pain syndromes. Nonpharmacologic treatment, including social support, counseling, and pastoral care is an important part of palliative care.

Although pain is common in the palliative care population, nonpain symptoms substantially contribute to patient suffering. All patients benefit from a diagnostic approach aimed at identifying treatable causes of symptoms. Management should include both pharmacologic and nonpharmacologic measures. Treatment of nausea and vomiting should be prompt and prophylactic when possible. All patients taking opioids should receive a stool softener and stimulant laxative to prevent constipation. Anorexia requires a multimodal, multidisciplinary approach. Dyspnea responds well to a combination of ventilation, oxygen, and opioids and/or benzodiazepines. Delirium is usually multifactoral and, if treatable underlying causes cannot be identified, haloperidol can be helpful. In all patients, underlying depression and anxiety should be promptly identified and treated.


P atients receiving palliative care frequently suffer from both pain and nonpain symptoms that have serious negative consequences for quality of life. Symptoms can be related to a patient's primary illness or from the side effects of treatment. In some cases nonpain symptoms may be more disturbing than pain. Patients should be frequently assessed for medication side effects and common distressing symptoms. This article, the second of a 2-part series, will focus on the management of pain and common nonpain symptoms in palliative care.

Dr Whitecar is Associate Professor in the Department of Family Medicine at Wright State University in Dayton, Ohio; Associate Director of Dayton Community Family Practice Residency; and former director of Ohio's Integrated Hospice.

Ms Maxwell is Executive Director of the Center for Palliative Care, Department of Family Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania. She is a Project on Death in America Faculty Scholar, Open Society Institute.

Dr Douglass is Assistant Director, Family Practice Residency Program, Middlesex Hospital, Middletown, Connecticut; Assistant Professor of Family Medicine, University of Connecticut School of Medicine; Assistant Clinical Professor of Medicine, Yale University School of Medicine; and Chair of the Group on Palliative Care and Pain Management, Society of Teachers of Family Medicine.

Dr Whitecar receives research support from Endo Pharmaceuticals. Ms Maxwell and Dr Douglass report having no financial or advisory relationships with corporate organizations related to this activity.

Off-Label Product Discussion: The authors of this article include information on off-label use of topiramate and gabapentin; venlafaxine hydrochloride and mirtazapine; scopolamine hydrobromide; lorazepam; methylphenidate hydrochloride; and metoclopramide hydrochloride.

Correspondence to: Philip S. Whitecar, MD, 4428 Indian Ripple Road, Beavercreek, OH 45440. Email: philip.whitecar@wright.edu.
**Analgesics and Their Use**

The goals of care for patients at the end of life are to maximize comfort and functionality and to minimize side effects of treatment. Although diagnostic testing may be indicated to better identify the etiology of the pain, pain relief measures should be instituted even if the etiology is unclear. The pharmacologic management of pain has long been based upon the World Health Organization’s “analgesic ladder,” where the selection of an agent is dependent upon the severity and type of pain experienced. Patients with mild pain are started on nonopioid agents with or without the addition of adjuvant medications. Pain that is moderate in intensity often requires opioid in addition to nonopioid medications. Patients with advanced, progressive illness at the end of life usually require treatment with opioids.

Oral morphine has been the standard of care for more than 20 years. Recent advances include long-acting controlled-release preparations administered orally or transdermally. When more options available for pain control, the standard of care for managing pain is an individualized regimen consisting of opioids that can be combined with adjuvant therapy to achieve the best balance between pain relief and side effects.

**Titrating Upwards**

When choosing an opioid, agents that can be safely titrated upwards are preferred. The dose of an opioid that is combined with acetaminophen can be safely escalated, but such combinations have a ceiling because of potential acetaminophen toxicity. The American Geriatric Society’s (AGS) guidelines recommend no more than 3000 mg/24 hours of acetaminophen. Meperidine, and to a lesser extent morphine, have active metabolites that can accumulate and cause toxicity, including myoclonus and delirium, especially at high doses or in patients with reduced renal clearance.

Patients vary in the amount of analgesic they require; therefore, doses must be titrated until pain relief is achieved or intractable side effects occur. Responsiveness of an individual patient to a specific drug cannot be determined unless the dose is increased to treatment-limiting toxicity. There is no maximal or “correct” opioid dose. In opioid-naïve patients, start with a low dose and administer frequently. Once the patient is no longer opioid naïve, titration upward can involve using immediate- or sustained-relief medications.

When titrating opioids, the key principle is to increase the dose by a percentage of the current dose, with increases that range from 25% to 100%, based upon the patient’s pain rating score and clinical condition. Opioid dosage may be increased 50% to 100% in a 24-hour period for severe pain. Although smaller increases will be effective for moderate pain, increases of less than 25% are usually ineffective. Short-acting agents can be titrated every 2 hours, until either adequate analgesia is reached (usually defined as >50% reduction in pain) or side effects such as sedation are encountered.

**Sustained-Relief Opioids**

The dosage of sustained-release oral opioids can be escalated every 24 hours, whereas the dosages of transdermal fentanyl and methadone should not be increased more frequently than every 72 hours. Once stable, sustained-release opioids are more convenient and provide a steady state of drug to prevent the “peaks and valleys” associated with short-acting agents, which minimizes side effects and maximizes pain control.

When using sustained-release opioids, it is important to provide “breakthrough” pain medication. Ten percent of the daily total of the sustained-release opioid dose should be available every 4 hours for breakthrough pain. For those individuals taking high-dose opioids, who have severe breakthrough pain, transmucosal fentanyl may be used. It is important to remember to increase the “rescue” or short-acting, breakthrough dose as the baseline dose increases.

**Opioid Rotation**

Physicians should regularly reassess total daily opioid dose and adjust as necessary. Patients may respond to opioids unpredictably, so if a patient has a poor response to one opioid, switching to another and working through the class of opioids may be necessary to find a drug that the patient finds satisfactory.

When switching between opioids, calculate the equianalgesic dose, then decrease by 25% for severe pain or ≤50% in moderate pain to account for incomplete cross-tolerance among these drugs (Table 1). M ethadone has an extremely long half-life, up to 1 week, that complicates its use. While the conversion chart in Table 2 emphasizes decreasing ratios of methadone to morphine as the dose increases, the length of time a patient is taking methadone is also a factor. As a result, methadone, while inexpensive and effective, requires that the practitioner have experience with it for optimal effectiveness. Loss of the ability to swallow oral medications is common at the end of life. Providers should be familiar with alternate delivery routes (Table 3).
ADJUVANT MEDICATIONS IN PALLIATIVE CARE

Several adjuvant medications have been used to relieve pain, augment analgesics, or relieve associated symptoms (Table 4). Most of these medications will be discussed in the sections on neuropathic and bone pain. The following medications fill several niches in palliative care. Methylphenidate has been used to augment the analgesic effect of opioids, to make rapid improvements in depressive symptoms, attenuate somnolence, and perhaps improve cognitive function. A short course (20 days) of methylprednisolone has been found to augment analgesics, improve appetite and mood, and increase activity. Cannabinoids are no more effective than codeine for control of pain, and they have significant neurodepressant effects that limit their use.

NEUROPATHIC PAIN

Neuropathic pain is poorly tolerated by most people, and it is not very responsive to opioid therapy alone. Neuropathic pain may be peripheral due to direct nerve injury, often from trauma or cancer growth; it may also be of central origin, due to remodeling of the sensory pathway from chronic undertreated pain or to direct injury to spinal nerves. Several agents individually or in combination with opioids have been found to provide relief for both types of neuropathic pain. The lidocaine patch is effective for relieving peripheral neuropathic pain and has minimal side effects.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Single Dose Equivalent Parenteral</th>
<th>Daily Dose Equivalent Parenteral</th>
<th>Usual Starting Dose Parenteral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>5 mg</td>
<td>15 mg</td>
<td>30 mg (5 mg q4h)</td>
</tr>
<tr>
<td>Morphine SR</td>
<td>NA</td>
<td>NA</td>
<td>90 mg (15 mg q4h)</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>NA</td>
<td>10 mg</td>
<td>60 mg (10 mg q4h)</td>
</tr>
<tr>
<td>Oxycodone SR</td>
<td>NA</td>
<td>NA</td>
<td>60 mg (30 mg q12h)</td>
</tr>
<tr>
<td>Methadone</td>
<td>1.5 mg</td>
<td>5 mg</td>
<td>(See Table 2)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.75 mg</td>
<td>3.75 mg</td>
<td>1.5 mg q8h</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>NA</td>
<td>15 mg</td>
<td>90 mg (15 mg q4h)</td>
</tr>
<tr>
<td>Codeine with acetaminophen</td>
<td>NA</td>
<td>90 mg</td>
<td>(See Table 2)</td>
</tr>
<tr>
<td>Tramadol</td>
<td>NA</td>
<td>100 mg</td>
<td>540 mg (NR)</td>
</tr>
<tr>
<td>Meperidine</td>
<td>50 mg</td>
<td>150 mg (NR)</td>
<td>600 mg (NR)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>NA</td>
<td>NA</td>
<td>300 mg (50 mg q4h)</td>
</tr>
<tr>
<td>Fentanyl SR</td>
<td>NA</td>
<td>NA</td>
<td>900 mg (NR)</td>
</tr>
<tr>
<td>Meperidine</td>
<td>50 mg</td>
<td>150 mg (NR)</td>
<td>25 mg q4h</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>NA</td>
<td>NA</td>
<td>25 mcg/hr patch</td>
</tr>
</tbody>
</table>

Table 2. Methadone Conversion Chart

<table>
<thead>
<tr>
<th>Morphine Daily Equivalent (mg)</th>
<th>Morphine to Methadone Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>2 to 1</td>
</tr>
<tr>
<td>30-99</td>
<td>4 to 1</td>
</tr>
<tr>
<td>100-299</td>
<td>8 to 1</td>
</tr>
<tr>
<td>300-499</td>
<td>12 to 1</td>
</tr>
<tr>
<td>500-999</td>
<td>15 to 1</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>20 to 1</td>
</tr>
</tbody>
</table>
Anticonvulsants are effective treatments for all types of neuropathic pain.15 Because of the need for titration up to effective doses, they are often used in combination with analgesics. Gabapentin is commonly used for central neuropathic pain, because when the dosage is increased gradually the side effects are minimal.16 Topiramate, because it has several mechanisms of action, may be more effective than existing anticonvulsants, although its propensity for causing weight loss is common and troublesome.17 However, it has not been as well studied as older anticonvulsants. Older anticonvulsants are as effective as and less expensive than gabapentin, but they are associated with more side effects.

Tricyclic antidepressants are also useful for treating neuropathic pain.18 Their effectiveness is dose dependent, and careful titration is necessary to minimize side effects. Venlafaxine is effective for neuropathic pain, and it causes fewer side effects than the tricyclic antidepressants.19 Selective serotonin reuptake inhibitors (SSRIs) have not been found to relieve neuropathic pain.

**Bone Pain**

Bone pain is a distinct type of pain that is neurochemically different from inflammatory and neuropathic pain.20 Bone pain can be intermittent, though it often becomes chronic. It can be exacerbated by activities that are not ordinarily accompanied by pain, and is most common in breast and prostate cancer. Nonsteroidal anti-inflammatory drugs, because of their antiprostaglandin activity, are especially useful in bone pain. Corticosteroids are also helpful for this type of pain, especially when the pain is acute.

Opioids alone can be effective for relieving bone pain, but often combination therapy is required. Bisphosphonates are effective in about 50% of patients with bone cancer. They are particularly helpful for treating bone pain from multiple myeloma and other cancers.21 Strontium-89 and samarium-153 are helpful for multiple metastatic lesions that are osteoblastic on bone scan.22,23 Pain relief often lasts 4 months or more with minimal side effects. External beam radiation is very successful, with 70% of patients receiving some benefit and about 30% experiencing complete relief24; however, the effect can be temporary. One half of the patients will experience the return of pain, often as severe as it was initially.

**Adjuvant Therapy**

Several physical, environmental, psychologic, and invasive techniques are available to augment medications or for patients whose pain is unresponsive to medical treatment. There is some evidence of improvement in pain and function when physical modalities are used. Proven modalities include massage, osteopathic and chiropractic manipulation, acupuncture, and exercise.25 The evidence for transcutaneous electrical nerve stimulation and ultrasound is not as strong.25

### Table 3. Dosing Routes for Common Palliative Care Medications

<table>
<thead>
<tr>
<th>Route*</th>
<th>Medications</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sublingual</td>
<td>Immediate-release morphine, hydromorphone, and fentanyl</td>
<td>Patients with dysphagia or who need rapid pain relief</td>
</tr>
<tr>
<td>Rectal</td>
<td>Hydromorphone, morphine (immediate- and slow-release), and oxymorphone</td>
<td>Presence of upper GI lesions; often used as a bridge while changing to a different route</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Fentanyl</td>
<td>Useful for patients who need stable drug delivery, or oral route causes side effects</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Morphine, oxymorphone and hydromorphone</td>
<td>Useful when oral route not available; rapid; eliminates fluid overload of IV route, can be given as continuous drip</td>
</tr>
<tr>
<td>Intravenous</td>
<td>Morphine</td>
<td>Rapid; can deliver concentrated doses</td>
</tr>
<tr>
<td>Epidural/Intrathecal</td>
<td>Morphine, hydromorphone, and fentanyl</td>
<td>Severe pain unresponsive to or limited by side effects to medications delivered by other routes</td>
</tr>
</tbody>
</table>

*In general, doses given SC, IV, or IM are equivalent. Doses given orally or rectally are equivalent. IV = intravenous; SC = subcutaneous; IM = intramuscular.*
Relaxation techniques and guided imagery have been shown to improve the patient's sense of control and to decrease pain. Hypnosis can be useful in patients with event-specific pain. Aromatherapy improves patient scores on depression, anxiety, and quality-of-life instruments. Therapeutic touch has been noted to produce improvement in pain scores.

Palliative chemotherapy can provide pain relief in a variety of cancers. Ideally, such treatments are short courses of low-toxicity medications that are given orally. Palliative radiation therapy is best used for focal lesions such as bone metastasis, spinal cord compression, or dysphagia from esophageal cancer. Short-course, focused therapy can improve pain symptoms while minimizing side effects. It is important to clarify with the patient and family that these techniques are not to be confused with curative treatments. The goal of these often uncomfortable procedures is to lessen suffering. The person agreeing to them must be fully informed of the risks and benefits.

Invasive procedures, including neuromodulation, dorsal-root entry zone lesioning, cordotomy, radiofrequency lesioning, intrathecal delivery systems, and implantable pumps are all available for extreme cases of severe unrelieved pain.

Table 4. Common Adjuvant Agents

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medications</th>
<th>Starting Dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic pain</td>
<td>Antidepressants, tricyclic</td>
<td>Amitriptyline 10-50 mg qhs, imipramine 10-50 mg qhs, desipramine 25-50 mg qhs, doxepin 25-50 mg qhs, venlafaxine 37.5 mg qd, Gabapentin 100-300 mg qd, valproate 250 mg bid-tid, carbamazepine 200 mg bid-tid, topiramate 25 mg qd</td>
</tr>
<tr>
<td>Inflammation/Bone pain</td>
<td>Corticosteroids</td>
<td>Dexamethasone 2-8 mg bid, naproxen 250 mg bid, ibuprofen 400 mg tid, celecoxib 100 mg bid, rofecoxib 12.5 mg qd, valdecoxib 10 mg qd</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Benzodiazepines</td>
<td>Lorazepam 0.5 mg tid, diazepam 5 mg tid, alprazolam 0.25 mg bid, 7 mg bid, hydroxyzine 25 mg tid</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>Baclofen</td>
<td>5 mg tid, lorazepam 0.5 mg tid or diazepam 5 mg tid, cyclobenzaprine 10 mg qhs, tizanidine 4 mg qhs, metaxalone 800 mg qhs, methocarbamol 500 mg qhs</td>
</tr>
<tr>
<td>Generalized chronic pain</td>
<td>Antidepressants</td>
<td>Amitriptyline 10 mg tid, imipramine 10 mg tid, venlafaxine 37.5 mg qd, desipramine 25 mg qd, mirtazapine 15 mg qhs</td>
</tr>
<tr>
<td>Depression</td>
<td>Tricyclic antidepressants</td>
<td>Amitriptyline 10-50 mg qhs, imipramine 10-50 mg qhs, desipramine 25-50 mg qhs, doxepin 25-50 mg qhs, mirtazapine 15 mg qhs, venlafaxine 37.5 mg qd, sertraline 25 mg qd, fluoxetine 10 mg qd, citalopram 10 mg qd, paroxetine 10 mg qd</td>
</tr>
</tbody>
</table>

COX 2 = cyclo-oxygenase; CNS = central nervous system; SSRI = selective serotonin reuptake inhibitor.

* Not approved by the Food and Drug Administration for the use(s) presented in the article and this table.
pain that is expected to last several months. Each of these procedures is associated with procedural morbidity and considerable cost.

**MEDICATION SIDE EFFECTS**

Individualizing therapy is the best way to ensure that patients maintain a balance between symptom management and side effects. Some patients value comfort and function equally, requesting relief of pain and other symptoms with as little impact on their cognitive abilities and physical functioning as possible. Other patients are willing to compromise function for greater comfort. In either case, however, dissatisfaction with medication side effects is common. In one study, the 2 most frequently cited reasons for referral to a pain service among patients receiving analgesic therapy were continued uncontrolled chronic pain and excessive side effects without adequate pain relief.

**ASSESSMENT**

Assessment of side effects is a vital first step. Symptoms attributable to pain medications, especially in older patients and patients with advanced illness, may in fact be related to concurrent medical problems, other drugs, metabolic disturbances, or underlying disease progression. In addition, the occurrence and intensity of opioid-related side effects may not remain constant; patients’ responses to opioids can change over time, so monitoring and assessment of side effects must be ongoing.

**OLDER PATIENTS**

Particular attention should be paid to older patients. The therapeutic window that presents an appropriate balance between effectiveness and toxicity is much narrower in these patients. Those over 60 years of age have a 10% to 25% risk of adverse drug reactions. This risk is 2 to 3 times higher than that of patients younger than 30 years. This increased risk is due to a multitude of factors, including polypharmacy, compliance problems, comorbidities, and the physiologic changes that occur with aging. For this reason, the American Geriatric Society recommends starting with a lower dose and carefully titrating upwards in older patients.

**EVALUATION AND MANAGEMENT OF FATIGUE**

Fatigue is probably the most prevalent symptom in patients with advanced disease and is a particularly well-documented phenomenon in cancer patients. Fatigue and weakness have a direct impact upon quality of life and unlike in those who are not ill, they are not reversible with rest. Nevertheless, patients may be reluctant to discuss their fatigue, believing that there is little anyone can do about it. Caregivers often share this impression.

There are numerous possible etiologies for fatigue, including the underlying disease itself, anemia, secondary infections, metabolic abnormalities, medication side effects, malnutrition, chronic pain, and depression. When identifiable causes of fatigue can be found, they should be treated. Eliminating or reducing medications that exacerbate fatigue; correcting electrolyte abnormalities; and treating infection, pain, and emotional problems can be helpful. Due to their expense and inconvenience, using blood transfusions or erythropoietin to treat anemia in patients with end-stage disease should be based on evidence of quality-of-life outcomes such as improved stamina and less shortness of breath rather than improvements in hemoglobin levels only. Regrettfully, in many instances the underlying problem cannot be corrected, and general conservative measures should be tried. Patients need to pace their activities and modify their environments to reduce the disabling effect of fatigue. They should be encouraged to reorder their daily priorities and integrate planned rest periods into their days. On the other hand, frequent napping may contribute to insomnia in some patients.

Pharmacologic therapy may benefit some patients, although few studies have been conducted to evaluate which drugs effectively ameliorate fatigue. A recent study evaluated the use of the psychostimulant methylphenidate for the treatment of fatigue in cancer patients. Using a small amount (5 mg) on an as-needed basis (but not more than 4 times a day or more frequently than every 2 hours) resulted in a reduction in drowsiness, depression, and pain, as well as improved nighttime sleep. Corticosteroids have been demonstrated to improve patients’ overall sense of well-being and appetite and should be considered for some patients. Megestrol acetate trials have not specifically addressed fatigue but have demonstrated improvements in appetite, weight gain, and well-being in some patients. Lastly, having a professional caregiver acknowledge how difficult it is to live with fatigue is in itself therapeutic.

**PREVENTION AND TREATMENT OF NAUSEA AND VOMITING**

Nausea, and to a lesser extent vomiting, is a demoralizing complaint that occurs in more than
one half of terminal cancer patients; however, it can be controlled in most patients with appropriate therapy, even in the presence of a bowel obstruction. Nausea and vomiting are controlled by a midbrain vomiting center that receives input from sources that include the cerebral cortex (intracranial tumor, elevated intracranial pressure, pain, and anxiety); the gastrointestinal (GI) tract (drugs, constipation, distension, obstruction); the vestibular apparatus (vestibular disease and motion sickness); and the chemoreceptor trigger zone (CTZ) in the floor of the fourth ventricle (drugs, electrolyte imbalances, and metabolic causes). Although nausea is usually multifactorial, a clear definition of the specific contributing factors is helpful to the treating physician.

Treatment of nausea and vomiting should be prompt and prophylactic whenever possible, as conditioned reflexes develop quickly. Oral treatments are often effective, but a variety of parenteral routes are also available. The major categories of antinauseants are antihistamines, anticholinergics, corticosteroids, benzodiazepines, dopamine antagonists, and serotonin antagonists (Table 5).

Physicians often find selecting a specific treatment difficult and frequently resort to selecting an agent empirically. Whenever possible, however, specific treatments should be chosen that address the underlying cause of a patient’s symptoms. Cortical causes of nausea and vomiting typically respond best to treatment of underlying etiologies, such as corticosteroids for cerebral edema. Nausea originating in the GI tract typically responds to discontinuing the inciting medications and treating constipation or obstruction.

For the treatment of nausea and vomiting when mechanical obstruction is not present, promotility agents or dopamine antagonists may be considered. Vestibular apparatus disturbances respond well to antihistamines and anticholinergics. CTZ-mediated nausea responds best to discontinuing the offending drugs and treating the metabolic disturbances. Dopamine antagonists and serotonin antagonists are particularly effective. Nonpharmacologic approaches such as eating food at room temperature, limiting intake of clear liquids, avoiding foods with strong flavors or odors, providing fresh air and distraction, and learning relaxation techniques can all be helpful. Nasogastric intubation generally does not provide lasting relief and should be avoided except in patients anticipating surgery or with high obstructions that are unresponsive to medication.

Prevention and Treatment of Constipation

Constipation is highly distressing and it too occurs in more than one half of palliative care patients. Constipation is caused by disruption in 1 or more of the 4 major components required for a normal bowel movement: intestinal solids, water, motility, and lubrication. The most common cause of constipation in the patient receiving palliative care is opioid analgesics and other medications that impair bowel motility. Additional factors contributing to the high prevalence of constipation in this population are low intake of fluids and fiber, impaired mobility, and complicating medical conditions such as bowel obstructions.

The key to successful management is constant attention to prevention and early treatment. Since opioid-related constipation is dose-dependent and tolerance to this side effect does not develop, all patients receiving opioids should receive regularly scheduled doses of a stool softener and stimulant laxative. Bulk-forming agents such as psyllium should be avoided because of their tendency to form impactions when oral fluid intake decreases.

When constipation is already present, initial assessment should include a careful bowel history plus abdominal and rectal exams. If a hard impaction is present, it should be softened with a retention enema and then digitally removed. Premedication with a benzodiazepine is often helpful during this uncomfortable procedure. Soft

Table 5. Pharmacologic Therapy for Nausea and Vomiting

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug</th>
<th>Starting Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamines</td>
<td>Cyclizine</td>
<td>50 mg q6h PO</td>
</tr>
<tr>
<td></td>
<td>Diphenhydramine</td>
<td>25 mg qid PO, IM</td>
</tr>
<tr>
<td></td>
<td>Hydroxyzine</td>
<td>10-25 mg qid PO, IM</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Scopolamine</td>
<td>0.3-0.6 mg IM, SC, IV, or 1 patch</td>
</tr>
<tr>
<td></td>
<td>Hyoscyamine</td>
<td>0.125 mg qid PO</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Dexamethasone</td>
<td>5-10 mg qid PO, IV</td>
</tr>
<tr>
<td></td>
<td>Prednisone</td>
<td>5-10 mg qid PO</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Lorazepam</td>
<td>0.5 - 2.5 mg qid PO, IV</td>
</tr>
<tr>
<td></td>
<td>Diazepam</td>
<td>2-5 mg qid PO, IV, IM, PR</td>
</tr>
<tr>
<td>Dopamine antagonists</td>
<td>Prochlorperazine</td>
<td>10-25 mg qid PO, IV, PR</td>
</tr>
<tr>
<td></td>
<td>Haloperidol</td>
<td>0.5-1 mg PO, IM</td>
</tr>
<tr>
<td></td>
<td>Metoclopramide</td>
<td>5-10 mg qid PO, IM, IV</td>
</tr>
<tr>
<td>Serotonin antagonists</td>
<td>Ondansetron</td>
<td>8 mg bid IV, PO</td>
</tr>
<tr>
<td>Mixed antagonists</td>
<td>Olanzapine</td>
<td>2.5 mg q6h PO</td>
</tr>
</tbody>
</table>

PO = orally; IM = intramuscular; SC = subcutaneous; IV = intravenous; PR = by rectum

Prevention and Treatment of Constipation

Constipation is highly distressing and it too occurs in more than one half of palliative care patients. Constipation is caused by disruption in 1 or more of the 4 major components required for a normal bowel movement: intestinal solids, water, motility, and lubrication. The most common cause of constipation in the patient receiving palliative care is opioid analgesics and other medications that impair bowel motility. Additional factors contributing to the high prevalence of constipation in this population are low intake of fluids and fiber, impaired mobility, and complicating medical conditions such as bowel obstructions.

The key to successful management is constant attention to prevention and early treatment. Since opioid-related constipation is dose-dependent and tolerance to this side effect does not develop, all patients receiving opioids should receive regularly scheduled doses of a stool softener and stimulant laxative. Bulk-forming agents such as psyllium should be avoided because of their tendency to form impactions when oral fluid intake decreases.

When constipation is already present, initial assessment should include a careful bowel history plus abdominal and rectal exams. If a hard impaction is present, it should be softened with a retention enema and then digitally removed. Premedication with a benzodiazepine is often helpful during this uncomfortable procedure. Soft
impactions will often respond to bisacodyl suppositories or large volume enemas. Once the GI tract is moving freely, a regular prophylactic regimen as described above should be begun. Bowel obstructions are a contraindication to stimulant laxatives, as they may precipitate colic.

**Management of Anorexia and Cachexia**

Anorexia, a loss of appetite and reduced caloric intake, is another frequent and distressing symptom in patients with advanced cancer. Anorexia also occurs in patients with other advanced chronic illnesses associated with organ failure. Often, anorexia is accompanied by other troubling symptoms, such as weakness, chronic nausea, and psychological problems. In patients with cancer, anorexia is associated with reduced survival time. Cachexia, which may or may not accompany anorexia, is an involuntary weight loss of more than 10% of pre-morbid weight with associated lipolysis and loss of muscle and visceral protein. Cachexia is associated with profound weight loss and the related change in physical appearance that can be very upsetting to both the patient and the family.

Anorexia and cachexia are categorized based on etiology. In patients with cancer, primary anorexia and cachexia are a metabolic syndrome caused by the interaction between the immune system and the tumor, resulting in complex metabolic and neuroendocrine changes and the production of cytokines. As a result, body mass, particularly skeletal muscle and fat, are lost. Anorexia is thought to be a consequence of this catabolic process rather than the cause of the cachexia. This explains why aggressive feeding and total parenteral nutrition fail to improve the symptoms, clinical outcomes, or nutritional status of patients with cancer. Secondary anorexia and cachexia occur as a result of decreased oral intake due to impaired function of the GI tract with resultant nausea, vomiting, constipation, diarrhea, bowel obstruction, and/or malabsorption. Dry mouth, mucosal ulceration, taste alterations, and oral infections may contribute. Anorexia can also occur secondary to depression, anxiety, pain, or dyspnea.

Lack of desire to eat is a major quality-of-life issue for patients, rated even higher than lack of physical strength or loss of the ability to work. Not eating has social as well as physiologic consequences. Anorexia is a major source of distress for patients and their families. Eating is a major source of social interaction and family members often view not eating as tantamount to “giving up.” Patients often feel pressured to eat. This can be highly stressful for many patients, who feel they are letting their loved ones down. For this reason, giving an explanation to family members and devising practical solutions are as important as pharmacologic or other therapies. A comprehensive approach to allaying anxiety involves a family discussion and education.

The treatment of anorexia requires a multimodal, interdisciplinary approach because it is a syndrome with multiple causes and consequences. Whenever possible, underlying causes should be treated, including pain, depression, constipation, dehydration, oral infections or mucositis, and nausea/vomiting. A host of nonpharmacologic measures can be implemented, including providing small, frequent meals; serving meals at room temperature; removing unpleasant odors; providing companionship for meals; and relaxing any dietary restrictions.

Pharmacologic therapies include progestins, corticosteroids, and prokinetic agents. Short courses of methylprednisolone have been used to increase appetite without significant side effects, but their long-term effects have not been well studied. They have been recommended for those with a short life expectancy or as a means to stimulate appetite. Progestational agents, such as megestrol acetate, have been shown to improve weight gain, increase appetite, and improve a sense of well-being in patients with cancer and acquired immune deficiency syndrome. Dronabinol therapy has been reported to benefit patients, but utility is limited by patients’ inability to tolerate the central nervous system side effects. Metoclopramide is helpful for those with gastric stasis syndrome.

**Assessment and Management of Dyspnea**

Dyspnea, the subjective sensation of being unable to breathe, can be acute or chronic. It can seriously affect quality of life for patients with a terminal illness. People with comparable degrees of functional lung impairment may experience varying degrees of dyspnea. Objective signs, such as respiratory rate and pulse oximetry, many times do not match the patient’s perception of dyspnea or the perceived degree of functional limitation. For this reason, the severity of dyspnea can only be determined by the person experiencing it. Severe dyspnea is a medical emergency.

There are several primary causes of dyspnea including: existing disease (ie, chronic obstructive pulmonary disease [COPD]; asthma; neuromuscular disease; or congestive heart failure); acute
superimposed illness (ie, atelectasis, pneumonia, or pulmonary embolus); cancer-induced complications (ie, bronchial obstruction, pleural effusion, superior vena cava syndrome, or tumor growth); or other causes, such as anemia, uremia, ascites, anxiety, and depression.61

Treatment of dyspnea should address the underlying cause, taking into account life expectancy and the risk-benefit ratio of any proposed therapeutic interventions. In many cases the underlying cause may not be reversible and the symptom itself must be palliated. When therapy specific to the underlying disease process is unavailable or ineffective, nonpharmacologic and pharmacologic interventions may help.

Nonpharmacologic measures to alleviate dyspnea include allowing the patient a position of comfort (usually sitting up and forward), making sure the room is well ventilated, and providing reassurance. Oxygen therapy is frequently prescribed, although the benefit in patients who are not hypoxic is questionable.62,63 Other therapies, such as opioids, may be more effective. Oxygen in the home setting is expensive and may be cumbersome. A nasal cannula, even at high flow rates, is often better tolerated than a mask, especially in the terminal setting.

Patients receiving intravenous fluids or tube feedings often develop fluid overload at the end of life, which may contribute to dyspnea. Artificial hydration and nutrition should be eliminated or reduced. Other potentially helpful measures include the treatment of anemia with blood transfusion or erythropoietin, if indicated, and the humidification of the air for patients with distressing cough.

Effective pharmacologic interventions for dyspnea include opioids, corticosteroids, and benzodiazepines. Opioids are safe and effective. They decrease respiratory distress by altering the perception of breathlessness and decreasing the ventilatory response to hypoxia and hypercapnia.64 Early use of low-dose morphine or other opioids in patients with dyspnea is recommended to improve quality of life.65 The usual dose of morphine in the opioid naïve patient is 5 to 10 mg orally (preferred route) every 4 hours. Intravenous, subcutaneous, or intramuscular doses should be adjusted accordingly by using a 3:1 oral-to-parenteral ratio. The morphine dose can be titrated upwards by 30% to 50% daily until symptoms improve or sedation becomes problematic. Those with intermittent exertional symptoms may benefit from an “as-needed” approach, whereas those with persistent symp- stoms should receive scheduled doses. Nebulized morphine has been used for the relief of dyspnea with some success, but at this time there is no evidence to support its use in place of oral or parenteral dosing.64 Nebulized fentanyl citrate, which is highly lipophilic, was found to decrease dyspnea in one study.66

Benzodiazepines play an important role in providing relief of the anxiety that may contribute to shortness of breath, but they should be used as second-line therapy or in combination with opioids because, unlike opioids, they do not treat the dyspnea directly. Lorazepam is a quick-acting oral agent that is generally recommended as first-line therapy if an anxiolytic is indicated. Chlorpromazine is the drug of choice if sedation is needed to relieve severe dyspnea and agitation at the end of life. Lorazepam can be administered orally, sublingually, and parenterally. Patients with severe acute dyspnea should receive a 2- to 4-mg bolus with a 1- to 5-mg/hour constant infusion.67

Bronchodilators are useful in patients with COPD and in many patients with lung cancer.68 In patients with cancer, corticosteroids may alleviate dyspnea in cases that involve lymphangitic tumor spread or superior vena cava syndrome.59

Ethically, there is no justification for withholding symptom treatment with opioids or benzodiazepines from a dying patient out of fear of potential respiratory depression. There is no evidence that proper symptom management hastens dying.69 The use of opioids to relieve dyspnea is ethical as long as the intent is to relieve distress rather than to shorten life. The important role of opioids in reducing the distress associated with dyspnea should be made clear to family members so that this use of opioids is not confused with an act of euthanasia.

Patients who are actively dying may benefit from anticholinergic agents such as hyoscine hydrobromide (scopolamine) patches (0.4 mg), which act to help dry the secretions that accumulate as a result of respiratory muscle weakness and cause the distressing noise commonly known as “death rattle.”70 Suctioning is generally not indicated. It is usually not beneficial and may be uncomfortable for the patient.

**Concomitant Psychiatric Illnesses**

Between 33% and 50% of patients who require palliative care meet the diagnostic criteria for a psychiatric disorder, yet up to one half of these patients remain undiagnosed. The most common disorders are the dementias, anxiety, and depression.71
While many patients receiving palliative care have depressive symptoms, the diagnosis of depression is complicated by the overlap of depressive symptoms with the symptoms of cancer, severe pain, and chronic organ dysfunction. Recent research has shown that asking the patient who is receiving palliative care, “Are you depressed?” is an adequate screening tool for depression.\textsuperscript{72} Formal depression screening tools can be useful for detecting depression, but their effectiveness at the end of life is not well studied. Receiving counseling, pastoral care, improving social support, and alleviating physical distress may all attenuate depressive symptoms. Depression that significantly interferes with patient function is best treated with medication.

Tricyclic antidepressants have a history of being prescribed for depression and pain, with good evidence to support their use.\textsuperscript{73,74} Amitriptyline has long been used for this purpose and is well studied, but anticholinergic side effects are a problem in the elderly and debilitated. Desipramine and nortriptyline have been found to be as effective as amitriptyline for depression and relief of pain, and with fewer side effects. SSRIs have been shown to be very effective for depression, but there is only weak evidence to support their use for pain. Fluoxetine can aggravate existing insomnia, so a less stimulating SSRI is preferred. Mirtazapine, a new atypical antidepressant, may help with depression as well as insomnia and anorexia.\textsuperscript{75} Venlafaxine provides effective treatment for depression, serves as an adjunct for pain management, and may have fewer side effects than the tricyclic antidepressants.\textsuperscript{76}

Several other medications can be used to treat depression when the above medications are not well tolerated or found to be ineffective. Methylphenidate can induce rapid improvements in patients with depressive symptoms. It has also been useful for attenuating opioid-induced somnolence and improving cognitive function.\textsuperscript{77} Neuroleptics are occasionally used to treat severe anxiety or psychotic depression in patients receiving palliative care.

Anxiety is a common finding at the end of a person's life. It may be acute and event-specific or generalized and chronic. Physical, social, and/or spiritual distress may cause anxiety. Taking a careful history may help to prevent the unnecessary use of medication, and treatment should first be directed toward resolving the cause of distress. Hospice personnel, such as counselors and clergy may be particularly skilled at alleviating situational or event-specific anxiety. Patients experiencing generalized anxiety with moderate life expectancy can benefit from cognitive behavioral counseling. For those patients who may need prompter resolution of their anxiety, SSRIs have been used successfully; however, it may be 4 to 6 weeks before they become fully effective. Short-term use of benzodiazepines is warranted for acute anxiety, although physicians must balance the risks of cognitive decline and somnolence with anxiety relief. Benzodiazepines have also been found useful for improving pain symptoms during specific anxiety-producing events, but not in patients with chronic anxiety.\textsuperscript{78}

DELIRIUM

A change in mental status is a common neurologic symptom that is experienced by patients at or near the end of life.\textsuperscript{79} There is a high prevalence of delirium in patients with advanced illness. The delirium is associated with increased morbidity\textsuperscript{80} and is characterized by an acute change in cognition and the inability to maintain or shift attention properly; it also may be accompanied by auditory and visual hallucinations and disturbances in the sleep–wake cycle. Early symptoms of delirium often go unrecognized.\textsuperscript{81} While there is no tool that is specific for detecting delirium, the Mini Mental State Examination has been shown to identify patients who are suffering from delirium before agitation develops.\textsuperscript{81}

Clinicians should maintain a high index of suspicion for delirium in patients who are very ill. Patients can exhibit either hypoactive or hyperactive phases with behavior ranging from mild memory problems to severe agitation and psychosis.\textsuperscript{82} Hyperactive delirium is sometimes mistaken for pain, and hypoactive delirium may be mistaken for depression.\textsuperscript{83}

The causes of delirium are usually multifactorial. Potential causes include the direct effects of

---

**Bowel Regimen for Patients Receiving Chronic Opioid Therapy**

- Begin with a stool softener and gentle laxative
  - Senokot® [sennosides], 1 to 2 tablets 2 to 3 times/day
- If no bowel movement in 48 hours, ADD ONE:
  - Milk of Magnesia® [magnesium hydroxide]
  - Dulcolax® [bisacodyl] tablet, 5 mg 1 to 2 tablets
- If no bowel movement in 72 hours, TRY ONE:
  - Dulcolax® suppository, 10 mg
  - Magnesium citrate, 8 oz
  - Fleet® [sodium biphosphate and sodium phosphate] enema
  - Actulose for chronic constipation not responsive to above
disease on the central nervous system (ie, primary brain tumor or metastatic spread) or indirect effects, such as metabolic encephalopathy from organ failure, electrolyte imbalance, infection, hematologic abnormalities, dehydration, urinary retention, and medication side effects (especially with opioids).

Treatment of delirium in the dying patient is complex. The underlying cause should be treated when possible, especially if related to medication toxicity. Unfortunately, in the majority of cases the underlying cause is elusive, and when a distinct cause is found, it is often irreversible. Work-up may be limited by the setting (usually home or inpatient hospice) and diagnostic procedures may not be desirable when the focus of care is on comfort.

Nonpharmacologic measures to treat delirium include a quiet, well-lit room with familiar surroundings and objects, a visible clock or calendar, and the presence of family. One-to-one care may be necessary. If these interventions are not adequate, then neuroleptics are indicated.

The severity of symptoms and the patient's condition determine therapy. The choice of neuroleptic is largely based upon anecdote, because few controlled trials have been conducted in patients receiving palliative care. One controlled trial found that both chlorpromazine and haloperidol improved symptoms, whereas lorazepam caused confusion. Haloperidol is a potent dopamine blocker and is the drug of choice in the treatment of hyperactive delirium. Haloperidol is usually dosed at 1 to 2 mg orally or subcutaneously and repeated hourly until the patient has been calmed. Haloperidol in low doses is usually effective for treating agitation, paranoia, and fear. If more sedation is needed, thioridazine or chlorpromazine can be prescribed.

For patients who are very agitated, lorazepam 0.5 to 1 mg every 1 to 2 hours orally or IV may be given along with the haloperidol for rapid sedation; however, lorazepam may worsen delirium in some patients. Olanzapine, a serotonin antagonist and dopamine antagonist, is effective for treating agitation. It may augment pain relief and has fewer side effects than older agents. The usual starting dose is 5 mg daily. Other new agents have been used but are still investigational in this population.

Conclusions

Pain is almost universal in patients receiving palliative care, but by following existing guidelines, it can be alleviated or at least improved in the vast majority of patients. A number of distressing and often disabling nonpain symptoms occur in patients with advanced or terminal illness. Although this article addressed the most common symptoms, reference texts such as those edited by Doyle and Berger discuss the management for many others, such as insomnia and diarrhea. Using good communication, strong assessment skills, frequent monitoring, and current knowledge of available medications, physicians and other healthcare providers can successfully offer a patient comfort and hope throughout the illness and the dying process.

REFERENCES


END-OF-LIFE CARE

100

Vol. 4, No. 2 ■ February 2004