

Symptom Management and Supportive Care

Adjuvant Analgesics in Cancer Pain Management

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Identify the indications of adjuvant analgesics in the treatment of cancer pain.
2. Select an appropriate adjuvant analgesic for the treatment of pain in a specific cancer patient.
3. Know the dosing recommendations, side effects, and drug interactions of the most common adjuvant analgesics.

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ABSTRACT

Adjuvant analgesics are defined as drugs with a primary indication other than pain that have analgesic properties in some painful conditions. The group includes numerous drugs in diverse classes. Although the widespread use of these drugs as first-line agents in chronic nonmalignant pain syndromes suggests that the term “adjuvant” is a misnomer, they usually are combined with a less-than-satisfactory opioid regimen when administered for cancer pain. Some adjuvant analgesics are useful in several painful conditions and are described as multipurpose adjuvant analgesics (antidepressants,

corticosteroids, α_2 -adrenergic agonists, neuroleptics), whereas others are specific for neuropathic pain (anticonvulsants, local anesthetics, *N*-methyl-D-aspartate receptor antagonists), bone pain (calcitonin, bisphosphonates, radiopharmaceuticals), musculoskeletal pain (muscle relaxants), or pain from bowel obstruction (octreotide, anticholinergics). This article reviews the evidence supporting the use of each class of adjuvant analgesic for the treatment of pain in cancer patients and provides a comprehensive outline of dosing recommendations, side effects, and drug interactions. *The Oncologist* 2004;9:571-591

INTRODUCTION

Chronic pain is extremely prevalent among patients with cancer. Approximately one-third of patients have pain while undergoing active therapy for the disease, and more than three-quarters have pain during the last stages of illness [1, 2]. Fortunately, experience suggests that cancer pain can

be relieved in more than 70% of patients using a simple opioid-based regimen [3-5]. Different types of pain vary, however, in the extent to which they can be controlled with an opioid, and some characteristics may impart a relatively lesser degree of opioid responsiveness in some patients [5]. In such cases, a variety of strategies can be implemented to

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improve the balance between analgesia and side effects [5]. Among these strategies is the use of adjuvant analgesics.

The term ‘adjuvant analgesic’ describes any drug with a primary indication other than pain, but with analgesic properties in some painful conditions [6]. Although they can be used alone, they are usually coadministered with analgesics (acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], opioids) when treating cancer pain. The term ‘coanalgesic’ is sometimes used synonymously in this setting. Adjuvant analgesics are added to an opioid to enhance pain relief provided by the opioid, address pain that has not or has insufficiently responded, and allow the reduction of the opioid dose to reduce adverse effects [6].

Adjuvant analgesics often are administered as first-line drugs in the treatment of chronic nonmalignant pain. As a result, the term ‘adjuvant’ has become a misnomer, as use of these drugs has increased. In the cancer population, however, conventional practice has evolved to view opioids as first-line drugs, and adjuvant analgesics typically are considered after opioid therapy has been optimized [6]. To better assess response and reduce the risk of additive toxicity, it usually is best to initiate treatment with one drug at a time (Table 1).

TYPES OF ADJUVANT ANALGESICS

The adjuvant analgesics comprise a diverse group of medications with different primary indications. Based on conventional use, a category of nonspecific, multipurpose analgesics can be distinguished from those used for more specific indications, including neuropathic pain or bone pain (Table 2).

There are very few comparative trials, and the selection of the most appropriate adjuvant analgesic cannot be based on evidence of differential efficacies. Rather, selection of a category of drugs, or a specific drug, depends on a variety of factors gleaned from the comprehensive assessment of the patient [7]. This assessment should describe the pain, clarify its etiology (including its relationship to the underlying disease), and allow inferences about the predominating type of pain pathophysiology (e.g., nociceptive or neuropathic). It also should determine the impact of pain on function and quality of life and identify any relevant comorbidities [6-9]. In some cases, the type of pain suggests the value of one category of adjuvant analgesic over another; in others, the existence of another symptom concurrent with pain favors the use of a specific drug. For example, an antidepressant is preferred for a depressed patient, an anticonvulsant is preferred for a patient with a history of seizures, and a corticosteroid is preferred for a patient with anorexia. Careful monitoring of the concurrent symptom or comorbidity is necessary as the pain is treated; the secondary

Table 1. Using adjuvant analgesics in the management of cancer pain

1. Consider optimizing the opioid regimen before introducing an adjuvant analgesic.
2. Consider the burdens and potential benefits in comparison with other techniques used for pain that is poorly responsive to an opioid, including: A) opioid rotation, B) more aggressive side-effect management, C) a trial of spinal drug administration, and D) trials of varied nonpharmacologic approaches for pain control (e.g., nerve blocks, rehabilitative therapies, and psychological treatments).
3. Select the most appropriate adjuvant analgesic based on a comprehensive assessment of the patient, including inference about the predominating type of pain and associated factors (comorbidities) or symptoms.
4. Prescribe an adjuvant analgesic based on knowledge of its pharmacological characteristics, actions, approved indications, unapproved indications accepted in medical practice, likely side effects, potential serious adverse effects, and interactions with other drugs.
5. The adjuvant analgesics with the best risk:benefit ratios should be administered as first-line treatment.
6. Avoid initiating several adjuvant analgesics concurrently.
7. In most cases, initiate treatment with low doses and titrate gradually according to analgesic response and adverse effects.
8. Reassess the efficacy and tolerability of the therapeutic regimen on a regular basis, and taper or discontinue medications that do not provide additional pain relief.
9. Consider combination therapy with multiple adjuvant analgesics in selected patients.

condition may or may not respond, and additional treatments, such as an antidepressant selected specifically for the depression, may be needed.

Few adjuvant analgesics have been studied in cancer populations. To a large extent, therefore, drug selection, dosing, and monitoring approaches reflect extrapolation from the literature on nonmalignant pain.

Multipurpose Analgesics

Some adjuvant analgesics have been shown to have analgesic properties in diverse pain syndromes (Table 2). This suggests that they can be considered multipurpose analgesics.

Antidepressant Drugs

Tricyclic Antidepressants

The tricyclic antidepressants have been extensively studied, and there is compelling evidence for their analgesic properties in a variety of chronic nonmalignant pain conditions [10-12]. Both the tertiary amines—amitriptyline (Elavil®; Merck & Co.; Whitehouse Station, NJ), imipramine (Tofranil®; Mallinckrodt Inc.; St. Louis, MO), doxepin

Table 2. Adjuvant analgesics: major classes	
Drug class	Examples
Multipurpose analgesics	
Antidepressants	
Tricyclic antidepressants	amitriptyline (Elavil®)(tertiary amine) nortriptyline (Pamelor®), desipramine (Norpramin®); (secondary amines)
Selective serotonin reuptake inhibitors	paroxetine (Paxil®), citalopram (Celexa®)
Noradrenaline/serotonin reuptake inhibitors	venlafaxine (Effexor®)
Others	bupropion (Wellbutrin®)
Corticosteroids	dexamethasone (Decadron®), prednisone (Deltasone®; Orasone®)
α ₂ -adrenergic agonists	clonidine (Catapres®), tizanidine (Zanaflex®)
Neuroleptics	olanzapine (Zyprexa®)
For neuropathic pain	
Anticonvulsants	gabapentin (Neurontin®), topiramate (Topamax®), lamotrigine (Lamictal®), carbamazepine (Carbatrol®; Tegretol®), levetiracetam (Keppra®), oxcarbazepine (Trileptal®), pregabalin (Lyrica®), tiagabine (Gabitril®), zonisamide (Zonegran®), phenytoin (Dilantin®), valproic acid (Depakene®; Abbott Pharmaceuticals; Abbott Park, IL)
Local anesthetics	lidocaine (Xylocaine®; Lidoderm®), mexiletine (Mexitil®)
N-methyl-D-aspartate receptor antagonists	ketamine, dextromethorphan, memantine (Namenda®), amantadine (Symmetrel®)
Other	baclofen (Lioresal®) cannabinoids psychostimulant drugs: methylphenidate (Concerta®; Metadate CD®; Methylin®; Ritalin®), modafinil (Provigil®)
Topical drugs	lidocaine/prilocaine (EMLA®) lidocaine capsaicin
For bone pain	
Corticosteroids	dexamethasone, prednisone
Calcitonin (Miacalcin®)	
Bisphosphonates	pamidronate (Aredia®), zoledronic acid (Zometa®), clodronate
Radiopharmaceuticals	strontium ⁸⁹ , samarium ¹⁵³
For musculoskeletal pain	
Muscle relaxants	cyclobenzaprine (Flexeril®), orphenadrine (Norflex®), carisoprodol (Soma®), metaxalone (Skelaxin®), methocarbamol (Robaxin®)
Tizanidine (Zanaflex®)	
Baclofen (Lioresal®)	
Benzodiazepines	diazepam (Valium®), lorazepam (Ativan®; Wyeth Pharmaceuticals; Collegeville, PA), clonazepam (Klonopin®)
Adjuvants for pain from bowel obstruction	
Octreotide (Sandostatin®)	
Anticholinergics	hyoscine (scopolamine), glycopyrrolate (Robinul®)
Corticosteroids	

(Sinequan®; Pfizer Pharmaceuticals; New York, NY), and clomipramine (Anafranil®; Mallinckrodt Inc.)—and the secondary amines—nortriptyline (Pamelor®; Mallinckrodt Inc.) and desipramine (Norpramin®; Aventis Pharmaceuticals Inc.;

Bridgewater, NJ)—are analgesic. Although few clinical trials have specifically evaluated these drugs for cancer pain, partially controlled [13-15] and uncontrolled trials [16], as well as clinical experience, generally support their analgesic effects.

The use of the tricyclic antidepressants as analgesics in medically ill or elderly patients may be limited by the frequent occurrence of side effects [17, 18] (Table 4). Although

their most serious adverse effect, cardiotoxicity, is uncommon [18], patients who have significant heart disease (conduction disorders, arrhythmias, heart failure) should not be

Table 3. Dosing guidelines of adjuvant analgesics

Drug	Starting dose	Usual effective dose
Multipurpose Analgesics		
Antidepressants		
<i>Tricyclic antidepressants</i>		
Amitriptyline (Elavil®)	10-25 mg HS	50-150 mg HS
Nortriptyline (Pamelor®)	10-25 mg HS	50-150 mg HS
Desipramine (Norpramin®)	10-25 mg HS	50-150 mg HS
<i>Selective serotonin reuptake inhibitors</i>		
Paroxetine (Paxil®)	10-20 mg qd	20-40 mg qd
Citalopram (Celexa®)	10-20 mg qd	20-40 mg qd
<i>Noradrenaline/serotonin reuptake inhibitors</i>		
Venlafaxine (Effexor®)	37.5 mg qd	37.5-112.5 mg bid ^a
<i>Others</i>		
Bupropion (Wellbutrin®)	50-75 mg bid	75-150 mg bid
Corticosteroids		
Dexamethasone (Decadron®)	1-2 mg qd or bid	variable
Prednisone (Deltasone; Orasone®)	7.5-10 mg qd	variable
α₂-adrenergic agonists		
Clonidine (Catapres®/ Catapres®-TTS)	0.1 mg po qd 1/2 TTS-1 patch	variable 0.3 mg transdermal/day
Tizanidine (Zanaflex®)	2 mg HS	variable
Neuroleptics		
Olanzapine (Zyprexa®)	2.5 mg qd	unclear efficacy
Pimozide (Orap®; Gate Pharmaceuticals; Sellersville, PA)	1 mg qd	unclear efficacy
Adjuvants for Neuropathic Pain		
Anticonvulsants		
Gabapentin (Neurontin®)	100-300 mg HS	300-1,200 mg tid
Lamotrigine (Lamictal®)	25 mg qd	100-200 mg bid
Oxcarbazepine (Trileptal®)	75-150 mg bid	150-800 mg bid
Topiramate (Topamax®)	25 mg qd	100-200 mg bid
Pregabalin	150 mg qd	300-600 mg bid
Levetiracetam (Keppra®)	250-500 mg bid	500-1,500 mg bid
Tiagabine (Gabitril®)	4 mg HS	4-12 mg bid
Zonisamide (Zonegran®)	100 mg qd	100-200 mg bid
Carbamazepine (Carbatrol®; Tegretol®)	100-200 mg qd-bid	300-800 mg bid
Valproic acid (Depakene®)	250 mg tid	500-1,000 mg tid
Phenytoin (Dilantin®)	300 mg HS	100-150 mg tid
Local anesthetics		
Mexiletine (Mexitil®)	150 mg qd	100-300 mg tid
Lidocaine intravenous (Xylocaine®)	2 mg/kg over 30 minutes	2-5 mg/kg
Lidocaine topical (Lidoderm®)	1-3 patches 12 hours/24	

Table 3. Dosing guidelines of adjuvant analgesics (continued)		
Drug	Starting dose	Usual effective dose
N-methyl-D-aspartate receptor antagonists		
Ketamine	different regimen (see text)	
Dextromethorphan	15-20 mg tid	unclear
Amantadine (Symmetrel®)	100 mg qd	100-150 mg bid
Adjuvant analgesics for bone pain		
Corticosteroids		
Calcitonin (Miacalcin®)	1 IU/kg s.c. qd	200 IU intranasal qd
Bisphosphonates		
Pamidronate (Aredia®)	60 mg i.v. q month ^b	60-90 mg i.v. q month ^b
Zoledronic acid (Zometa®)	4 mg i.v. q 3 weeks	
Radiopharmaceuticals		
Adjuvant analgesics for musculoskeletal pain		
Muscle relaxants		
Cyclobenzaprine (Flexeril®)	5 mg tid	10-20 mg tid
Orphenadrine (Norflex®)	100 mg bid	100 mg bid
Carisoprodol (Soma®)	350 mg HS-tid	350 mg tid-qid
Metaxalone (Skelaxin®)	400 mg tid-qid	800 mg tid-qid
Methocarbamol (Robaxin®)	500 mg qid	500-750 mg qid
Tizanidine	2 mg HS	variable
Baclofen	5 mg tid	10-20 mg tid
Benzodiazepines		
Diazepam (Valium®)	1 mg bid	2-10 mg bid-qid
Lorazepam (Ativan®)	0.5-1 mg bid	1-2 mg bid-tid
Clonazepam (Klonopin®)	0.5 mg tid	1-2 mg tid
Adjuvant analgesics for pain from bowel obstruction		
Octreotide (Sandostatin®)	0.3 mg/day s.c. infusion	
Anticholinergics		
Hyoscine (scopolamine)	40 mg/day s.c. infusion	60 mg/day s.c. infusion
Glycopyrrolate (Robinul®)	0.1 mg s.c. or i.v. 3-4 times/day	0.2 mg s.c. or i.v. 3-4 times/day
Corticosteroids		
Dexamethasone (Decadron®)	4 mg bid	variable
Methylprednisolone (Solu-Medrol®)	10 mg tid	10-20 mg tid
Other adjuvant analgesics		
Baclofen (Lioresal®)	5 mg tid	10-20 mg tid
Cannabinoids		
Dronabinol (Marinol®)	2.5 mg bid	5-10 mg bid
Psychostimulants		
Methylphenidate (Metadate CD®, Methylin®, Ritalin®)	2.5 mg q a.m.	variable
Modafinil (Provigil®)	100 mg q a.m.	variable

^aThe extended-release formulation should be administered once daily.

^bPamidronate should be infused over 2-4 hours.

Abbreviations: qd = once a day; bid = twice a day; tid = three times a day; HS = every night; q = every; po = orally.

treated with a tricyclic. An electrocardiogram might be indicated before starting a tricyclic in a patient with an increased risk of cardiac disease (e.g., elderly, diabetic, or hypertensive). Given the risk of lethal cardiotoxicity encountered with an overdose, tricyclics also should be avoided in patients who are suicidal.

Tricyclic antidepressants are far more likely to cause orthostatic hypotension, and they must be used cautiously in patients at risk of orthostasis, such as the elderly and those with autonomic neuropathy. Tricyclics are also contraindicated in patients with a known history of a narrow anterior chamber of the eye or prior attacks of acute glaucoma. They should be used cautiously in those with cognitive impairment, or a high propensity for impairment, because of the risk of drug-induced confusion.

The secondary amine tricyclic antidepressants, desipramine and nortriptyline, are less anticholinergic and, therefore, better tolerated than the tertiary amines. Patients who are predisposed to side effects from the tricyclics, or who have distressing side effects during a trial of a tertiary amine drug, should, thus, be considered for a trial of desipramine or nortriptyline.

A favorable analgesic effect is usually observed within a week after achieving an effective dose of a tricyclic. Although a typically effective dose range has been observed (Table 3), there is large pharmacokinetic variability, and it can be useful to monitor plasma drug concentration to clarify the safety of dose escalation or to identify a concentration associated with a favorable effect.

Other Antidepressants

There is evidence from randomized controlled trials that several other antidepressants are analgesic. In aggregate, this evidence is far less than that which supports the efficacy of the tricyclic drugs [7]. Nonetheless, the nontricyclic compounds are generally safer and better tolerated. Accordingly, the nontricyclic antidepressants should be considered for patients who have not responded satisfactorily to tricyclics, have relative contraindications to tricyclics, or have experienced adverse effects during earlier treatment with a tricyclic antidepressant [7].

There are limited data supporting the analgesic efficacy of the selective serotonin reuptake inhibitors (SSRIs). Paroxetine (Paxil®; GlaxoSmithKline; Research Triangle Park, NC) and citalopram (Celexa®; Forest Laboratories, Inc.; New York, NY) are the only ones for which controlled studies have suggested benefit [19, 20]. No studies have been done on cancer pain. The main advantage of the SSRIs is their favorable side-effect profile [21].

Venlafaxine (Effexor®; Wyeth Pharmaceuticals; Collegeville, PA), a mixed reuptake inhibitor, has been shown to be

analgesic in several studies. Randomized controlled trials showed good pain relief for painful polyneuropathy [22] and for neuropathic pain following treatment of breast cancer [23]. Analgesic effects in neuropathic pain have also been suggested for a newer mixed reuptake inhibitor, duloxetine (Cymbalta™; Eli Lilly and Company; Indianapolis, IN). Bupropion (Wellbutrin®; GlaxoSmithKline; Research Triangle Park, NC), a noradrenergic compound, also is analgesic in neuropathic pain [24, 25] and often is activating. The latter effect can be particularly helpful in the hypoactive depressed, sedated, or fatigued patient often encountered in the cancer population [26].

In summary, there is substantial evidence that antidepressant drugs have analgesic effects in diverse types of chronic nonmalignant pain. There is limited evidence for analgesic effects in cancer pain. Given the established benefit of the antidepressants in patients with diverse types of neuropathic pain, the strongest indication for their use as an adjuvant analgesic in the cancer population occurs in the patient with neuropathic pain whose response to opioids has been inadequate. Early use of antidepressants as adjuvant analgesics is also justified when pain is accompanied by depression. In that situation, the clinical response of the depression should be evaluated carefully and the treatment adjusted if necessary. The sedating tricyclic antidepressants are often added when the patient complains of insomnia, the anxiolytic SSRIs can be useful in anxious patients, and bupropion can be considered in sedated or fatigued patients.

Corticosteroids

Corticosteroids possess analgesic properties for a variety of cancer pain syndromes, including bone pain, neuropathic pain from infiltration or compression of neural structures, headache due to increased intracranial pressure, arthralgia, and pain due to obstruction of a hollow viscus (e.g., bowel or ureter) or to organ capsule distention. Corticosteroids are also effective in managing pain and symptoms from metastatic spinal cord compression [27, 28] while awaiting more definitive treatment, if justified by the goals of care.

The relative risks and benefits of the various corticosteroids are unknown. Dexamethasone (Decadron®; Merck and Company, Inc.; West Point, PA) is often selected, a choice that gains theoretical support from the relatively low mineralocorticoid effects of this drug. Prednisone (Deltasone®; Pfizer Pharmaceuticals; New York, NY; Orasone®; Solvay Pharmaceuticals; Marietta, GA) and methylprednisolone (Medrol®; Pfizer Pharmaceuticals; New York, NY) can also be used.

On the basis of clinical experience, corticosteroids are usually administered either in a high- or a low-dose

regimen. A high-dose regimen (e.g., dexamethasone, 100 mg, followed initially by 96 mg/day in divided doses) has been used for patients who experience spinal cord compression or an acute episode of severe pain that cannot be promptly reduced with opioids [29]. The dose can be tapered over days or weeks after the initiation of other analgesic approaches (e.g., opioid therapy, radiation therapy).

A low-dose corticosteroid regimen (e.g., dexamethasone at a dose of 2-4 mg once or twice daily) can be used for patients with advanced cancer who continue to have pain despite optimal dosing of opioid drugs. In most cases, long-term therapy is then planned, and the dose should be tapered down to the lowest effective dose.

Corticosteroid drugs have several other indications. They can improve appetite, nausea, malaise, and overall quality of life [29-32]. Although the risk of adverse effects increases with both the dose and duration of therapy, long-term treatment with relatively low doses is generally well tolerated. Repeated assessments are required to ensure that benefits are sustained. Although steroids can be beneficial in patients with good prognoses for prolonged survival, as well as in patients with terminal illnesses, greater caution and monitoring for adverse effects are needed in the former group. Ineffective regimens should be tapered and discontinued and, if the therapy is beneficial, the lowest dose that yields the desired results should be sought.

Long-term corticosteroid therapy may increase the risk of peptic ulcer disease [33] and some clinicians may coadminister a gastroprotective drug (usually a proton pump inhibitor) in an effort to reduce this risk. Given the lack of evidence supporting this practice, however, many clinicians add a gastroprotective drug only if other important risk factors for peptic ulcer disease exist. The concurrent administration of an NSAID and a corticosteroid increases the risk of peptic ulcer disease substantially [34]; this combination is not desirable, and administration of a gastroprotective drug can be justified if it is used.

α₂-Adrenergic Agonists

Although clonidine (Catapres®; Boehringer Ingelheim Pharmaceuticals; Ridgefield, CT; Catapres-TTS®; Boehringer Ingelheim Pharmaceuticals; Ridgefield, CT) and tizanidine (Zanaflex®; Elan Pharmaceuticals) are α₂-adrenergic agonists and may be considered nonspecific multipurpose adjuvant analgesics, the supporting data are limited and the potential for side effects, most importantly somnolence and hypotension, is relatively great. For these reasons, trials of these drugs usually are considered after others have proved ineffective. Clonidine, administered either orally, transdermally, or intraspinally, has been studied in non-malignant neuropathic pain [35-37]. Fewer than one-fourth of patients are likely to respond to

systemic administration of clonidine [35], and side effects are a particular concern in the medically frail. Intraspinally clonidine has been shown to reduce pain (especially neuropathic pain) in patients with severe intractable cancer pain partly responding to opioids [38]. Consideration of this therapy requires referral to an interventional pain specialist.

Tizanidine is approved as an antispasticity agent. Although the evidence of the analgesic efficacy of tizanidine is limited to the treatment of myofascial pain syndrome [39, 40] and the prophylaxis of chronic daily headache [41], a favorable clinical experience supports its use as a multipurpose adjuvant analgesic. As it is more specific for the α₂-adrenergic receptor than clonidine, hypotension occurs less commonly.

Neuroleptics

The second-generation (atypical) agent olanzapine (Zyprexa®; Eli Lilly and Company; Indianapolis, IN) was reported to decrease pain intensity and opioid consumption, and improve cognitive function and anxiety, in a recent case series of cancer patients [42]. Apart from this limited observation, evidence that commercially available neuroleptic drugs have analgesic properties is very meager. Given their potential for side effects (Table 4) and potential risks (tardive dyskinesia, neuroleptic malignant syndrome), neuroleptics are not clinically used as adjuvant analgesics unless the primary indication of delirium or agitation is present, in which case the analgesic properties might provide better pain control and allow a decrease of opioid consumption, which might in turn be helpful in resolving the delirium [43]. Neuroleptics also sometimes tend to increase appetite, which may be desirable in some cancer patients.

Adjuvant Analgesics Specific for Neuropathic Pain

The term 'neuropathic pain' is applied to those pain syndromes for which the sustaining mechanisms are presumed to be related to aberrant somatosensory processes in the peripheral nervous system, central nervous system (CNS), or both [44]. Surveys have reported that up to 40%-50% of cancer pain can be categorized as exclusively or partly neuropathic [45, 46]. Neuropathic cancer pain syndromes can be related to the cancer or to therapeutic interventions (Table 5).

Role of Opioids in the Treatment of Neuropathic Pain

As noted previously, the focus on neuropathic pain as a target for adjuvant analgesics in the palliative care setting derives from the observation that pain of this type may be relatively less responsive to opioid drugs than other types of pain (e.g., nociceptive). It is important to emphasize, however, that this observation does not imply that these pains are "opioid resistant" or that the conventional role of opioid

Table 4. Adverse effects, prescribing precautions, and potential drug interactions with adjuvant analgesics

Drug	Adverse effects	Precautions	Selected potential drug interactions
Antidepressants			
<i>Tricyclics</i>	sedation, confusion, orthostatic hypotension, weight gain, tachycardia, arrhythmia, anticholinergic effects (dry mouth, blurred vision, urinary hesitancy)	caution in elderly and medically ill, cardiovascular disorders, or seizure history; contraindicated with narrow-angle glaucoma	MAOIs, SSRIs, anticholinergic agents, antiarrhythmics, clonidine, lithium, tramadol (Ultram [®] ; Ortho-McNeil Pharmaceutical Corp.; Raritan, NJ), agents that prolong QTc interval
SSRIs ^a	nausea, headache, diarrhea, insomnia, dizziness, tremor, sexual dysfunction	caution if seizure disorders	MAOIs, TCAs, bupropion, buspirone (BuSpar [®] ; Bristol-Meyers Squibb; Princeton, NJ), tramadol, warfarin (Coumadin [®] ; Bristol-Meyers Squibb; Princeton, NJ)
<i>Venlafaxine</i>	nausea, somnolence, hypertension, dry mouth, sexual dysfunction	caution if hypertension or seizure disorders	MAOIs, TCAs, SSRIs, tramadol
<i>Bupropion</i>	tachycardia, insomnia, agitation, tremor, headache, dry mouth	contraindicated with seizure history or MAOIs	MAOIs, TCAs, SSRIs, levodopa
Corticosteroids	hyperglycemia, increased appetite, weight gain, edema, cushingoid habitus, dyspepsia, delirium, insomnia, agitation	caution if hypertension, heart failure, peptic ulcer, diabetes, infection, thromboembolic disorders	NSAIDs, aspirin, aldesleukin (Proleukin [®] ; Chiron Therapeutics; Emeryville, CA), protease inhibitors
α_2 -adrenergic agonists	somnolence, dizziness, hypotension (usually orthostatic), dry mouth	caution in cardiovascular disorders; discontinue clonidine slowly to avoid rebound hypertension	antihypertensives
Neuroleptics	sedation, extrapyramidal symptoms, orthostatic hypotension, QTc prolongation, dry mouth	caution in cardiovascular disease, seizure history	antihypertensives, levodopa (Larodopa [®] ; Roche Laboratories, Inc.; Nutley, NJ), agents that prolong QTc interval
Psychostimulants	insomnia, anorexia, nervousness, hypertension, tachycardia, dry mouth	caution in cardiovascular disease, hypertension, hyperthyroidism, or seizure history	MAOIs, TCAs, antihypertensives, sympathomimetics ^b
Anticonvulsants ^c	somnolence, dizziness, headache, nervousness, tremor, fatigue, mood changes, confusion	increase dose gradually to improve tolerance; decrease dose gradually to avoid seizure ^f	other anticonvulsants that may alter CYP450 metabolism (Table 6) ^{c-e}
<i>gabapentin</i>	weight gain, edema		none
<i>oxcarbazepine</i>	hyponatremia, increased liver enzymes		
<i>lamotrigine</i>	serious rash (black box warning)	discontinue at first sign of rash	
Lidocaine	hypotension, lethargy, tremor, arrhythmia, cardiovascular collapse	caution with atrial fibrillation, heart block, heart failure	amiodarone (Cordarone [®] ; Wyeth Pharmaceuticals; Collegeville, PA; Pacerone [®] ; Upsher-Smith Laboratories; Minneapolis, MN), amprenavir (Agenerase [®] ; GlaxoSmithKline; Research Triangle Park, NC), ritonavir (Norvir [®] ; Abbott Pharmaceuticals; Abbott Park, IL), beta-blockers, phenytoin (Dilantin [®] , Parke-Davis; Morris Plains, NJ) agents that prolong QTc interval, other antiarrhythmics
NMDA receptor blockers			
<i>Ketamine</i>	hypertension, tachycardia, tremor, nystagmus, diplopia, airway resistance, myocardial depression	contraindicated with hypertension, heart failure, angina, aneurysms, cerebral trauma, recent myocardial infarction; caution with psychotic disorders, thyrotoxicosis, seizures	thyroid replacements
<i>Amantadine</i>	orthostatic hypotension, peripheral insomnia, agitation, confusion	caution in uncontrolled psychosis, or seizure history	anticholinergic agents
Baclofen	dizziness, somnolence, headache, confusion	caution in seizure history	TCAs, MAOIs

Table 4. Adverse effects, prescribing precautions, and potential drug interactions with adjuvant analgesics (continued)

Drug	Adverse effects	Precautions	Selected potential drug interactions
Calcitonin	facial flushing, nausea, diarrhea, anorexia, dizziness, polyuria, nasal irritation (nasal spray formulation)	contraindicated with hypersensitivity to salmon protein; monitor for allergic reaction	
Bisphosphonates	hypomagnesemia, hypocalcemia, hypokalemia, hypophosphatemia, nausea, diarrhea, constipation	contraindicated with severe renal impairment	

^aThere is a large variation in the potential drug interactions among the SSRIs due to the extent that each agent is metabolized by hepatic enzymes (Table 6).

^bModafinil may have additional drug interactions due to induction of CYP3A4 (Table 6).

^cGabapentin and levetiracetam are not metabolized by hepatic enzymes and therefore do not interact with the other anticonvulsants.

^dThere is a large variation in the potential drug interactions among the anticonvulsants due to the extent that each agent is metabolized by hepatic enzymes (Table 6).

^eThe side effects, precautions, and drug interactions common to the anticonvulsants as a class are listed. Other side effects, precautions, and drug interactions specific to a particular agent are further classified under that particular agent.

^fThe risk of seizure following the rapid discontinuation of an anticonvulsant in nonepileptic patients is unclear. However, as a few cases of withdrawal symptoms have been reported following the rapid discontinuation of gabapentin [145] and clinical experience has shown possible withdrawal seizures with other anticonvulsants, it might be safer to discontinue anticonvulsants gradually over 1-2 weeks.

Abbreviations: MAOIs = monoamine oxidase inhibitors; TCAs = tricyclic antidepressants.

Table 5. Classification of neuropathic cancer pain syndromes (adapted from *Portenoy* [146] and *Martin and Hagen* [147])

Syndromes	Examples
Tumor-related	
Painful peripheral mononeuropathies	rib metastases with intercostal nerve injury, lower trunk or leg pain with retroperitoneal masses
Painful polyneuropathies	paraneoplastic (e.g., small cell lung cancer), multiple vitamin deficiencies
Plexopathy	
Cervical	head and neck cancer with local extension, cervical lymph node metastases
Brachial	lymph node metastases from breast cancer or lymphoma, direct extension of Pancoast tumor
Lumbosacral	direct extension of colorectal cancer, cervical cancer, sarcoma, or lymphoma
Sacral	midline pelvic tumors
Radiculopathy	vertebral or leptomeningeal metastases, epidural mass
Epidural spinal cord compression	vertebral or epidural metastases
Cranial nerves neuralgias	base of skull or leptomeningeal metastases, head and neck cancers
Related to therapeutic interventions	
Postsurgical	postmastectomy, postradical neck dissection, postthoracotomy, postnephrectomy, postamputation (stump or phantom pain)
Postradiotherapy	myelopathy, radiation-induced fibrosis (neuropathy, plexopathy), radiation-induced second primary tumor
Postchemotherapy	peripheral neuropathy associated with vinca alkaloids, paclitaxel (Taxol®; Bristol Myers Squibb; Princeton, NJ), cytarabine
Intrathecal methotrexate	acute meningitic syndrome
Related to herpes zoster	
Preherpetic neuralgia	
Herpetic neuralgia	
Zoster sine herpette	
Postherpetic neuralgia	

drugs as first-line analgesics should be abandoned when pain is neuropathic [7]. Randomized controlled trials have established the potential efficacy of both morphine (MSir®; Purdue Pharmaceutical Products L.P.; Stamford, CT; MS-Contin®; Purdue Pharmaceutical Products L.P and oxycodone (OxyContin®; Purdue Pharmaceutical Products; Roxicodone®; Elan Pharmaceuticals; South San Francisco, CA) in nonmalignant neuropathic pain syndromes [47-51].

Anticonvulsant Drugs

There is good evidence that the anticonvulsant drugs are useful in the management of neuropathic pain [52-54]. The older drugs, which have been used for decades, are now complemented by a rapidly increasing number of newer agents (Tables 2 and 3).

An expanding role for the anticonvulsants began with the introduction of gabapentin (Neurontin®; Pfizer Pharmaceuticals; New York, NY). The analgesic efficacy of gabapentin has been established in several types of non-malignant neuropathic pain [55-60], and it is now widely used to treat cancer-related neuropathic pain [61, 62]. Due to its proven analgesic effect in several types of neuropathic pain, its good tolerability, and a rarity of drug-drug interactions, gabapentin is now recommended as a first-line agent for the treatment of neuropathic pain of diverse etiologies, especially in the medically ill population [7]. It should be initiated at a daily dose of 100-300 mg at bedtime and can be increased every 3 days. The usual maximum dose is 3,600 mg daily, but occasionally patients report benefits at higher doses. An adequate trial should include 1-2 weeks at the maximum-tolerated dose. The most common adverse effects are somnolence, dizziness, and unsteadiness. If titrated carefully, gabapentin is usually well tolerated, but in medically ill patients, somnolence can be a limiting factor [61].

Lamotrigine (Lamictal®; GlaxoSmithKline; Research Triangle Park, NC) was reported to relieve nonmalignant neuropathic pain in several randomized trials [63-66]. Its adverse effects (e.g., somnolence, dizziness, ataxia), however, require a slow titration and, although uncommon, the potential for severe rash and Stevens-Johnson syndrome poses some concerns. Oxcarbazepine (Trileptal®; Novartis Pharmaceuticals Corp.; East Hanover, NJ) is a metabolite of carbamazepine (Carbatrol®; Shire US Inc.; Florence, KY; Tegretol®; Novartis Pharmaceuticals Corp.) and has a similar spectrum of effects, with better tolerability. Although the current evidence is limited to a few case series and open-label trials, it appears promising [67]. Pregabalin (Pfizer Pharmaceuticals) is a new anticonvulsant with a mechanism identical to that of gabapentin and strong evidence of analgesic efficacy [68]; this drug will soon be avail-

able in the U.S. and other countries and will be specifically indicated for varied types of neuropathic pain. Topiramate (Topamax®; Ortho-McNeil Pharmaceutical Corp.; Raritan, NJ), tiagabine (Gabitril®; Cephalon, Inc.; West Chester, PA), and zonisamide (Zonegran®; Elan Pharmaceuticals; South San Francisco, CA) have some evidence of efficacy [52], and there is some favorable clinical experience with levetiracetam (Keppra®; UCB Pharma, Inc.; Atlanta, GA) [69, 70]. Like gabapentin and pregabalin, levetiracetam lacks any significant drug-drug interactions.

Among the older drugs, evidence of efficacy is best for carbamazepine and phenytoin (Dilantin®; Pfizer Pharmaceuticals; New York, NY), and both valproate (Depacon®; Abbott Pharmaceuticals; Abbott Park, IL) and clonazepam (Klonopin®; Roche Laboratories, Inc.; Nutley, NJ) have been widely used [52]. The classic indication for carbamazepine is trigeminal neuralgia [52], and the use of phenytoin in cancer pain has been described [71]. Due to their frequent side effects (sedation, dizziness, nausea, unsteadiness) and potential for drug-drug interactions, the use of these drugs has declined with the introduction of the newer analgesic anticonvulsants. In summary, selected anticonvulsant drugs may be effective for diverse types of neuropathic pain. Although earlier studies suggested that there might be a preferential role for these drugs in the treatment of neuropathic pain characterized by lancinating or paroxysmal components, this has not been confirmed in trials, and anticonvulsants are now routinely tried for any type of neuropathic pain. Among the anticonvulsants, gabapentin should be administered first due to its proven efficacy in different neuropathic pain syndromes and its good tolerability. Other newer anticonvulsants can be tried successively in patients who either have not responded satisfactorily to, have contraindications to, or have experienced adverse effects to gabapentin and other first-line adjuvant analgesics.

Oral and Parenteral Local Anesthetics

Local anesthetics have analgesic properties in neuropathic pain [6]. Due to their potential for serious side effects, they have been conventionally positioned as second-line therapies, reserved for the treatment of severe intractable or 'crescendo' neuropathic pain.

A brief intravenous infusion of lidocaine (Xylocaine®; AstraZeneca; Wayne, PA) has been shown to be effective in nonmalignant neuropathic pain [72, 73]. Despite negative results obtained in randomized controlled trials in neuropathic cancer pain [74, 75], clinical experience justifies considering its use. Brief infusions can be administered at varying doses within the range of 1-5 mg/kg infused over 20-30 minutes. In the medically frail patient, it is prudent to

start at the lower end of this range and provide repeated infusions at successively higher doses. A history of significant cardiac disease may relatively contraindicate this approach and should be evaluated before it is administered. An electrocardiogram should be done before starting the infusion or increasing the dose, and careful monitoring of vital signs is necessary during the period of the infusion and immediately thereafter.

Although prolonged relief of pain following a brief local anesthetic infusion may occur, relief usually is transitory. If lidocaine appears to be effective but pain recurs, long-term systemic local anesthetic therapy can be accomplished using an oral local anesthetic, typically mexiletine (Mexitil®; Boehringer Ingelheim Pharmaceuticals, Inc.; Ridgefield, CT). For rare patients with refractory neuropathic cancer pain who respond only to intravenous lidocaine infusion, long-term subcutaneous administration has been reported to provide sustained relief [76].

The predictive value of a brief lidocaine infusion for the subsequent effectiveness of an oral local anesthetic has not been established for pain. Many patients are treated from the start with an oral agent, such as mexiletine. Given the limited number of supportive studies, mexiletine and other oral local anesthetics are used as second-line agents for neuropathic pain that has not responded to trials of anticonvulsant or antidepressant analgesics. Controlled studies of mexiletine have demonstrated a relatively high rate of adverse effects (nausea, vomiting, tremor, dizziness, unsteadiness, and paresthesias) and discontinuation due to toxicity in almost one-half of patients [77].

N-methyl-D-Aspartate Receptor Blockers

Interactions at the *N*-methyl-D-aspartate (NMDA) receptor are involved in the development of CNS changes that may underlie chronic pain and modulate opioid mechanisms, specifically tolerance [78]. Antagonists at the NMDA receptor may offer another novel approach to the treatment of neuropathic pain in cancer patients.

At the present time, there are four commercially available NMDA receptor antagonists in the U.S.—the antitussive, dextromethorphan; the dissociative anesthetic, ketamine; the antiviral drug, amantadine (Symmetrel®; Endo Laboratories; Chadds Ford, PA); and a drug approved for the treatment of Alzheimer's disease, memantine (Namenda®; Forest Laboratories, Inc.; New York, NY). Most of these drugs have been shown to have analgesic effects in nonmalignant neuropathic pain [78].

Ketamine, administered by intravenous infusion or orally, is effective in relieving cancer pain [79-82] and reducing opioid requirements [83]. Clinicians who are experienced in the use of parenteral ketamine may, therefore,

consider this option in patients with refractory pain. The side-effect profile of ketamine (Table 4) can be daunting, however, particularly in the medically frail. Typically, ketamine therapy for pain has been initiated at low doses given subcutaneously or intravenously, such as a starting dose of 0.1-0.15 mg/kg by brief infusion or 0.1-0.15 mg/kg/hour by continuous infusion. The dose can be gradually escalated, with close monitoring of pain and side effects. For patients with refractory pain and limited life expectancies, long-term therapy can be maintained using continuous subcutaneous infusion or repeated subcutaneous injections. Oral administration also has been used, but experience is more limited with that approach. The ratio of doses needed to maintain effects when converting from parenteral to oral dosing is uncertain. Based on anecdotal data, some authors have suggested a 1:1 ratio [84], or an oral dose equivalent to 30%-40% of the parenteral dose [85]. It is also recommended to lower the opioid dose when starting ketamine [85].

In patients undergoing surgery for bone malignancy, dextromethorphan was shown to augment analgesia and lessen analgesic requirements [86]. Other studies and clinical experience have yielded mixed results. If prescribed, a prudent starting dose is 45-60 mg/day, which can be gradually escalated until favorable effects occur, side effects supervene, or a conventional maximal dose of 1 g is achieved.

Amantadine is a noncompetitive NMDA antagonist, and limited data suggest that it might reduce pain, allodynia, and hyperalgesia in chronic neuropathic pain [87, 88] and surgical neuropathic cancer pain [89]. Currently available data are, however, too meager to support recommending its use.

Memantine is an NMDA antagonist recently marketed in the U.S. for the treatment of Alzheimer's disease. Although it could theoretically possess some analgesic properties, controlled trials published so far have been disappointing [90, 91].

The d-isomer of the opioid methadone also blocks the NMDA receptor [92]. In the U.S., methadone is available as the racemic mixture, 50% of which is the d-isomer. The contribution of this nonopioid molecule to the analgesia produced by methadone is uncertain, but growing clinical experience with this drug suggests that it may play a role. There are no data, however, to support the conclusion that methadone is better than other opioids for the treatment of neuropathic pain.

New NMDA receptor antagonists are in development and may ultimately prove useful for a variety of medical indications. Advances in this area have occurred rapidly, and it is likely that the role of these agents in the management of pain will be much better defined within a few years.

Other Systemic Drugs

Other drugs also may be considered for trials of adjuvant analgesics. Some, such as baclofen (Lioresal[®]; Novartis Pharmaceuticals, Corp.), have a long history in clinical practice despite a paucity of studies. Others, such as the cannabinoids, are undergoing investigation now and are likely to have an expanded role in the future. In the population with cancer pain, most of these drugs are tried conventionally in the setting of refractory neuropathic pain.

Baclofen

Baclofen, an agonist at the gamma aminobutyric acid type B (GABAB) receptor, has established efficacy in trigeminal neuralgia [93] and is often considered for a trial in any type of neuropathic pain. The effective dose range is very wide (20 mg/day to >200 mg/day orally), and titration from a low initial dose is necessary. The possibility of a serious withdrawal syndrome on abrupt discontinuation must be avoided by a gradual dose taper.

Cannabinoids

Cannabinoids have antinociceptive effects in animal models and oral delta-9-tetrahydrocannabinol (dronabinol; Marinol[®]; Roxane Laboratories; Columbus, OH) has been shown to be effective in cancer pain [94]. Not all data are positive [95], and more studies on the various cannabinoids are needed.

Benzodiazepines

The evidence for analgesic effects from benzodiazepines is limited and conflicting, and overall provides little support for the conclusion that these drugs are analgesic for neuropathic pain [96, 97]. Nonetheless, a trial of clonazepam can still be justified in refractory neuropathic pain on the basis of anecdotal experience, especially in the case of the common coexistence of pain and anxiety.

Psychostimulants

There is substantial evidence that psychostimulant drugs dextroamphetamine (Dexedrine[®]; GlaxoSmithKline; Research Triangle Park, NC), methylphenidate (Metadate CD[®]; CellTech Pharmaceuticals; Rochester, NY; Methylin[®]; Mallinckrodt Inc.; St. Louis, MO; Ritalin[®]; Novartis Pharmaceuticals Corp.), and caffeine have analgesic effects [98]. Although pain is not considered a primary indication for these drugs, the potential for analgesic effects may influence the decision to recommend a trial. In cancer patients, methylphenidate can reduce opioid-induced somnolence, improve cognition, treat depression, and alleviate fatigue [99]. Treatment is typically begun at 2.5-5 mg in the morning and again at midday, if necessary, to keep the patient alert dur-

ing the day and not interfere with sleep at night. Doses are increased gradually until efficacy is established. Modafinil (Provigil[®]; Cephalon, Inc.), a newer psychostimulant with a unique mechanism, is also used to reduce opioid-induced somnolence in cancer patients [100]. It is usually started at 100 mg/day and then increased. Although there are currently no scientific data supporting its use to reduce opioid-induced sedation, atomoxetine (Strattera[®]; Eli Lilly and Company), a selective norepinephrine reuptake inhibitor approved for the treatment of attention-deficit/hyperactivity disorder [101], has been used successfully in clinical practice. The analgesic properties of modafinil and atomoxetine have not yet been studied.

Topical Analgesics

The development of a lidocaine 5% patch (Lidoderm[®]; Endo Laboratories; Chadds Ford, PA) has facilitated the topical application of local anesthetics. This formulation is approved in the U.S. for the treatment of postherpetic neuralgia [102], and clinical experience supports its use for other neuropathic pain conditions. There is minimal systemic absorption. The patch is usually applied 12 hours per day, but a few studies indicate a high level of safety with up to three patches for periods up to 24 hours [103]. An adequate trial may require several weeks of observation. The most frequently reported adverse event is mild to moderate skin redness, rash, or irritation at the patch application site.

EMLA[®] (AstraZeneca), an eutectic mixture of local anesthetics (prilocaine and lidocaine), can produce dense local cutaneous anesthesia, which can be useful to prevent pain from needle punctures. Although it may be applied to larger areas for the treatment of neuropathic pain, its use typically is limited by cost. Topical lidocaine may be tried in various concentrations (up to a compounded formulation of 10%) as an alternative.

Capsaicin is the ingredient in chili pepper that produces its pungent taste. When applied topically, it causes the depolarization of the nociceptors and release of substance P. Regular use eventually leads to depletion of substance P from the terminals of afferent C-fibers, potentially leading to decreased pain perception. In cancer patients, capsaicin cream (Zostrix[®]; Rodlen Laboratories; Vernon Hills, IL) has been shown to be effective in reducing neuropathic postsurgical pain (such as postmastectomy pain) [104]. There are two commercially available concentrations (0.025% and 0.075%), and an initial trial usually involves application of the higher concentration three to four times daily. A trial of several weeks is needed to adequately judge effects. Many patients experience severe burning pain after the first applications (related to the initial release of substance P), which

usually decreases gradually over a few days if the cream is applied regularly. Some patients tolerate the lower concentration cream better, or tolerate application only if preceded by a topical local anesthetic or ingestion of an analgesic.

Numerous anti-inflammatory drugs have been investigated for topical use in populations with neuropathic pain, and results have generally been mixed. These formulations have established effectiveness for musculoskeletal pains.

Adjuvant Analgesics Specific for Bone Pain

Bone pain is a common problem in the palliative care setting. Radiation therapy is usually considered when bone pain is focal and poorly controlled with an opioid, or is associated with a lesion that appears prone to fracture on radiographic examination. Multifocal bone pain may benefit from treatment with an NSAID or a corticosteroid. Other adjuvant analgesics that are potentially useful in this setting include calcitonin (Miacalcin®; Novartis Pharmaceuticals Corp.), bisphosphonate compounds, and selected radiopharmaceuticals.

Calcitonin

Calcitonin may have several pain-related indications in the palliative care setting, including pain from bone metastasis [105-107]. The most frequent routes of administration are subcutaneous and intranasal. If subcutaneous boluses are used, they should be preceded by skin testing with 1 IU to screen for hypersensitivity reactions, especially in patients with a history of reactions to salmon or seafood. The optimal dose is not known. A trial may be initiated at a relatively low dose, which then can be gradually increased if tolerated. The intranasal formulation avoids the need for subcutaneous injections, facilitating the use of this drug in home care. It is administered once daily, with an initial dose of 200 IU in one nostril, alternating nostrils every day. There are no data from which to judge the dose-response relationship for pain; escalation of the dose once or twice is reasonable if the first response is unfavorable. Apart from infrequent hypersensitivity reactions associated with subcutaneous injections, the main side effect is nausea. The likelihood and severity of this effect may be reduced by gradual escalation from a low starting dose. It usually subsides after a few days and is less frequent with the intranasal form. Periodic monitoring of calcium and phosphorus is prudent during treatment.

Bisphosphonates

Bisphosphonates are analogues of inorganic pyrophosphate that inhibit osteoclast activity and, consequently, reduce bone resorption in a variety of illnesses. The analgesic efficacy of these compounds, particularly pamidronate (Aredia®; Novartis Pharmaceuticals Corp.), has been well established.

Pamidronate has been extensively studied in populations with bone metastases [108]. Its analgesic effects have been shown in breast cancer [109-111] and multiple myeloma [112]. The dose usually recommended is 60-90 mg i.v. (infused over 2-4 hours) every 3-4 weeks [111]. There are dose-dependent effects, and a poor response at 60 mg can be followed by a trial of 90 or 120 mg. The reduction of skeletal morbidity (pathological fractures, need for bone radiation or surgery, spinal cord compression, hypercalcemia) described with the administration of pamidronate in multiple myeloma and breast cancer patients is another incentive to use it as an adjuvant [113-114]. Adverse effects, including hypocalcemia and a flu-like syndrome, are dose related and typically transitory. Nephrotoxicity occurs rarely, usually following relatively rapid infusions, and typically is transitory; the drug can be used in those with impaired renal function.

Zoledronic acid (Zometa®; Novartis Pharmaceuticals Corp.) is a new bisphosphonate that is approximately two to three times more potent than pamidronate. It has been shown to reduce pain and the occurrence of skeletal-related events in breast cancer [112, 115, 116], prostate cancer [117], and multiple myeloma [112], as well as a variety of solid tumors, including lung cancer [118]. It is effective in both osteoblastic and osteolytic lesions [116]. It is as effective as pamidronate [112, 116], and its use is more convenient, as it can be infused safely over 15 minutes at a dose of 4 mg every 3 weeks. The side effects are similar to those encountered with pamidronate, and the dose does not have to be adjusted in patients with mild-to-moderate renal failure [119].

Data on the analgesic effect of clodronate are conflicting, but it has been shown to be effective in prostate cancer and multiple myeloma [108]. The main advantage of clodronate over pamidronate is its good oral bioavailability, which avoids the need for i.v. administration. An oral dose of 1,600 mg daily seems to be optimal [108]. Clodronate is not available in the U.S.

Scarce data exist on the efficacy of the other newer bisphosphonates alendronate (Fosamax®; Merck and Company, Inc.; West Point, PA) and ibandronate (Boniva™; Hoffman-La Roche Inc.). These drugs, which are very potent, are likely to be analgesic.

Radiopharmaceuticals

Radionuclides that are absorbed at areas of high bone turnover have been evaluated as potential therapies for metastatic bone disease. Strontium-89 and samarium-153, which are commercially available in the U.S., may be effective as monotherapy or as an adjunct to conventional radiation therapy [120-124]. Given the potential for myelosuppression

associated with their use, these drugs usually are considered when pain is refractory to other modalities.

Adjuvant Analgesics Used for Musculoskeletal Pain

Pain that originates from injury to muscle or connective tissue is frequent in patients with cancer [125]. The efficacy of so-called muscle relaxants and other drugs commonly used for the treatment of musculoskeletal pain has not been evaluated in cancer patients.

The so-called muscle relaxants include drugs in a variety of classes, including antihistamines (e.g., orphenadrine; Norflex[®]; 3M Pharmaceuticals; St. Paul, MN [126, 127]), tricyclic compounds structurally similar to the tricyclic antidepressants (e.g., cyclobenzaprine; Flexeril[®]; McNeil Consumer and Specialty Pharmaceuticals; Fort Washington, PA [128, 129]), and others (e.g., carisoprodol; Soma[®]; Wallace Laboratories; Cranbury, NJ [130], metaxalone; Skelaxin[®]; King Pharmaceuticals; Bristol, TN [131], methocarbamol; Robaxin[®]; Schwarz Pharma; Milwaukee, WI [132]). Although these drugs can relieve musculoskeletal pain, these effects may not be specific, and there is no evidence that they relax skeletal muscle in the clinical setting. Although they have been shown to reduce musculoskeletal pains [129-133], their risk:benefit ratio relative to the NSAIDs or opioids is unknown [133]. The most common adverse effect is sedation, which can be additive to other centrally acting drugs, including opioids. Treatment should be initiated with relatively low initial doses. The potential for abstinence, as well as abuse by predisposed patients, warrants caution when discontinuing therapy or administering these drugs to those with a substance abuse history [127].

If a muscle spasm is present and is believed to be responsible for the pain, drugs with established effects on skeletal muscle should be tried in place of the muscle relaxants. These include diazepam (Valium[®]; Roche Laboratories, Inc.) or other benzodiazepines, the α_2 -adrenergic agonist tizanidine or the GABA_B agonist baclofen. Injections of botulinum toxin can be considered for refractory musculoskeletal pain related to muscle spasms [134], including those occurring after radiation therapy [135].

Adjuvant Analgesics Used for Pain Caused by Bowel Obstruction

The management of symptoms associated with malignant bowel obstruction may be challenging. If surgical decompression is not feasible, the need to control pain and other obstructive symptoms, including distension, nausea, and vomiting, becomes paramount. The use of opioids may be problematic due to dose-limiting toxicity (including gastrointestinal toxicity) or the intensity of breakthrough pain. Anecdotal reports suggest that anticholinergic drugs, the somatostatin analogue

octreotide (Sandostatin[®]; Novartis Pharmaceuticals Corp.), and corticosteroids may be useful adjuvant analgesics in this setting. The use of these drugs may also ameliorate non-painful symptoms and minimize the number of patients who must be considered for chronic drainage using nasogastric percutaneous catheters.

Octreotide

The somatostatin analogue octreotide inhibits the secretion of gastric, pancreatic, and intestinal secretions, and reduces gastrointestinal motility. These actions, which can occur more rapidly than similar effects produced by anticholinergic drugs [136], probably underlie the analgesia and other favorable outcomes that have been reported in case series [137] and one randomized trial [138] in patients with bowel obstruction. Octreotide has a good safety profile, and its considerable expense may be offset in some situations by the avoidance of gastrointestinal drainage procedures.

Anticholinergic Drugs

Anticholinergic drugs could theoretically relieve the symptoms of bowel obstruction by reducing propulsive and nonpropulsive gut motility and decreasing intraluminal secretions. Two small series demonstrated that a continuous infusion of hyoscine butylbromide (scopolamine) at a dose of 60 mg daily can control symptoms from nonoperable malignant bowel obstruction, including pain [137, 139]. Glycopyrrolate (Robinul[®]; First Horizon Pharmaceutical Corp.; Roswell, GA) has a pharmacological profile similar to that of hyoscine butylbromide, but may produce fewer side effects because of a relatively low penetration through the blood-brain barrier; this drug, however, has not been systematically evaluated in a population with symptomatic bowel obstruction.

Corticosteroids

The symptoms associated with bowel obstruction may improve with corticosteroid therapy. The mode of action is unclear, and the most effective drug, dose, and dosing regimen are unknown. Dexamethasone has been used in a dose range of 8-60 mg/day [140], and methylprednisolone has been administered in a dose range of 30-50 mg/day [31]. The potential for complications during long-term therapy, including an increased risk of bowel perforation [141, 142], may limit this approach to patients with short life expectancies.

COMBINATION OF ADJUVANT ANALGESICS

Specialists in pain management often undertake combination therapy with multiple analgesics, including two or more adjuvant analgesics, during the treatment of severe, refractory pain. The treatment of a patient with severe

cancer-related neuropathic pain, for example, ultimately may require the addition of an antidepressant, an anticonvulsant, and a lidocaine patch to an opioid regimen. In the setting of advanced disease, a corticosteroid also is commonly added. Combination therapy of this type, like that used to treat other disorders, such as epilepsy [143], must be undertaken cautiously. In most cases, drugs are added sequentially, starting with low initial doses. If meaningful analgesia is observed during dose titration, the dose is optimized and the drug is continued as another is tried. If therapy is ineffective because of side effects or the administration of a maximum safe dose without benefit, the drug should be discontinued (usually with a tapering of the dose). Although this approach to combination therapy has received very little study, one open-label trial reported that the addition of levetiracetam to gabapentin provided synergistic relief [70], and one small randomized controlled trial suggested that adding lamotrigine to phenytoin or carbamazepine was beneficial [63].

Data are insufficient to posit recommendations for preferred drug combinations, or the sequence in which various adjuvant analgesics should be tried. Unfortunately, drug selection during these trials is based on clinical judgment and is executed in a trial-and-error fashion. Some clinicians prefer to choose drugs in different classes, but there is no specific evidence to support this approach. In all cases, however, careful attention should be given to potential interactions between drugs during sequential trials.

DRUG INTERACTIONS

Cancer patients with pain often require multiple drugs, analgesic and otherwise, and are therefore at increased risk for drug-drug interactions. An understanding of the types of drug interactions can help a clinician anticipate and minimize risk.

Drug interactions can be classified as being either pharmacodynamic or pharmacokinetic. Pharmacodynamic interactions involve drug actions independent of pharmacokinetics and may relate to competition for the same receptor, or to additive or inhibitory effects on effects other than analgesia. For example, an opioid and a benzodiazepine both cause CNS depression, and their concomitant use can result in additive sedation without a change in the plasma concentrations of either drug.

In contrast, pharmacokinetic interactions imply that one drug interferes with the absorption, distribution, metabolism, or elimination of another, resulting in alterations in the concentration of one or both. Many pharmacokinetic drug interactions are mediated through the hepatic cytochrome P450 (CYP450) enzyme system, which is responsible for the metabolism of numerous drugs, including analgesics,

antidepressants, anticonvulsants, steroids, anticoagulants, chemotherapeutic agents, and others. Within the CYP450 system, drugs can be further classified as substrates, inducers, or inhibitors. Substrates are agents that are metabolized by a particular enzyme, while inducers and inhibitors increase or decrease, respectively, the metabolism of other agents that are substrates of the same enzyme. For example, carbamazepine, phenytoin, and methadone are well-known inducers of the 2D6 isoenzyme (CYP2D6) and can decrease serum levels of drugs that are substrates for that enzyme, such as amitriptyline, dextromethorphan, modafinil, and sertraline (Zoloft®; Pfizer Pharmaceuticals). Likewise, paroxetine is a well-known inhibitor of CYP2D6 and may lead to higher or toxic levels of drugs that are substrates for that enzyme.

Interpatient variability (e.g., age, genetics, disease state, race) can make it difficult to predict the extent to which a pharmacokinetic interaction will affect a specific patient. Genetic polymorphism exists most commonly with CYP2D6, leading to some patients being classified as poor metabolizers. In Caucasian populations, approximately 10% are poor metabolizers of substrates for CYP2D6. This may result in increased levels of a poorly metabolized parent compound, or decreased levels of an active metabolite. Codeine is metabolized to morphine via CYP2D6, for example, and it is reasonable to assume that as many as 10% of Caucasian patients may experience relatively reduced effectiveness from codeine as a result of genetically impaired metabolism. The same problem could arise if codeine is administered with a drug that inhibits CYP2D6.

Table 6 is a quick reference for potential drug interactions involving the CYP450 system. A further discussion of the CYP450 system and the interaction of medications can be found in *Bernard* [144].

CONCLUSIONS

The potential utility of adjuvant analgesics in the management of cancer pain has grown as new drug development, and translational research yields a firmer scientific foundation for the use of drugs in diverse classes. These drugs can be extremely important for those patients whose pain is only partially responsive to opioids. Some adjuvant analgesics possess analgesic properties in several types of pain, whereas others are specific for neuropathic, bone, musculoskeletal, or bowel obstruction-related pain.

Unfortunately, the use of adjuvant analgesics in cancer patients is still often guided solely by anecdotal experience or derived from data on nonmalignant pain. Future studies focused on the cancer population are needed to expand and improve the use of these drugs.

Table 6. Potential drug interactions for selected pharmacologic agents used in pain and cancer management^a

1A2	2C9	2C19	2D6		2E1	3A4	
Substrates							
Amitriptyline (Elavil [®])	Celecoxib (Celebrex [®] ; Pharmacia; New York, NY)	Amitriptyline	Amitriptyline	Methodone	Acetaminophen (Tylenol [®] ; McNeil Consumer Pharmaceuticals; Fort Washington, PA)	Alprazolam (Xanax [®] ; Pfizer Pharmaceuticals; New York, NY)	Imipramine
Clomipramine (Anafranil [®])	Ibuprofen	Citalopram (Celexa [®])	Bupropion (Wellbutrin [®])	Modafinil (Provigil [®])		Amitriptyline	Ketamine
Desipramine (Norpramin [®])	Phenytoin	Clomipramine	Clomipramine	Morphine		Bupropion	Lidocaine
Imipramine (Tofranil [®])	Tamoxifen (Nolvadex [®] ; AstraZeneca; Wayne, PA)	Imipramine	Clozapine (Clozaril [®] ; Novartis Pharmaceuticals Corp.; East Hanover, NJ)	Nortriptyline		Citalopram	Modafinil
Lidocaine (Xylocaine [®])	Topiramate (Topamax [®])	Topiramate	Clonazepam (Klonopin [®])	Olanzapine		Clozapine	Methodone
Nortriptyline (Pamelor [®])			Codeine	Oxycodone (OxyContin [®] ; Roxicodone [®])		Cyclosporin	Paclitaxel (Taxol [®])
Olanzapine (Zyprexa [®])			Desipramine	Paroxetine (Paxil [®])		Dexamethasone (Decadron [®])	Prednisone (Deltasone [®] ; Orasone [®])
Phenytoin (Dilantin [®])			Dextromethorphan	Sertraline (Zoloft [®])		Dextromethorphan	Sertraline
			Doxepin (Sinequan [®])	Tiagabine (Gabitril [®])		Etoposide (Etopophos [®] , VePesid [®] ; Bristol-Myers Squibb; Princeton, NJ)	Tamoxifen
			Fluoxetine (Prozac [®] , Sarafem [®] ; Eli Lilly and Company; Indianapolis, IN)	Tramadol (Ultram [®])		Fentanyl (Duragesic [®] ; Janssen Pharmaceutica Products, L.P.; Titusville, NJ)	Tiagabine
			Haloperidol	Venlafaxine (Effexor [®])		Fluoxetine	Venlafaxine
			Hydrocodone	Vinblastine (Velban [®] ; Eli Lilly and Company; Indianapolis, IN)		Ifosfamide (Ifex [®] ; Bristol-Myers Squibb; Princeton, NJ)	Vincristine (Oncovin [®] ; Eli Lilly and Company; Indianapolis, IN)
			Imipramine				
Inhibitors							
Citalopram	Fluoxetine	Citalopram (weak)	Citalopram (weak)			Cyclosporin	
Fluoxetine		Fluoxetine	Desipramine			Dexamethasone	
Mexiletine (Mexitil [®])		Modafinil	Fluoxetine			Dextromethorphan	

Table 6. Potential drug interactions for selected pharmacologic agents used in pain and cancer management^a (continued)

1A2	2C9	2C19	2D6	2E1	3A4
Paroxetine (weak)		Topiramate	Haloperidol Olanzapine (weak) Paroxetine Sertraline		Fluoxetine Paroxetine (weak) Sertraline Venlafaxine
Inducers					
Carbamazepine (Carbatrol [®] ; Tegretol [®])	Carbamazepine		Carbamazepine	Phenytoin	Carbamazepine
Phenytoin	Fluoxetine		Phenobarbital		Dexamethasone
Smoking			Phenytoin		Erythromycin Modafinil Phenobarbital Phenytoin

^aLess predictable drug interactions are those involving the CYP450 enzymes. Inhibitors of a particular enzyme may lead to higher or toxic levels of drugs that are substrates for that same enzyme. Inducers of a particular enzyme may lead to decreased or subtherapeutic levels of drugs that are substrates for that enzyme. There is much variation in the extent that this type of interaction occurs in individuals.

REFERENCES

- Portenoy RK, Miransky J, Thaler HT et al. Pain in ambulatory patients with lung or colon cancer: prevalence, characteristics, and effect. *Cancer* 1992;70:1616-1624.
- Coyle N, Adelhardt J, Foley KM et al. Character of terminal illness in the advanced cancer patient: pain and other symptoms during the last four weeks of life. *J Pain Symptom Manage* 1990;5:83-93.
- Hanks GW, Justins DM. Cancer pain: management. *Lancet* 1992;339:1031-1036.
- Grond S, Radbruch L, Meuser T et al. Assessment and treatment of neuropathic cancer pain following WHO guidelines. *Pain* 1999;79:15-20.
- Vielhaber A, Portenoy RK. Advances in cancer pain management. *Hematol Oncol Clin North Am* 2002;16:527-541.
- Lussier D, Portenoy RK. Adjuvant analgesics in pain management. In: Doyle D, Hanks G, Cherny N, et al., eds. *Oxford Textbook of Palliative Medicine, Third Edition*. Oxford, England: Oxford University Press, 2003:349-377.
- Dworkin RH, Backonja M, Rowbotham MC et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol* 2003;60:1524-1534.
- Cherny NI, Portenoy RK. Cancer pain: principles of assessment and syndromes. In: Wall PD, Melzack R, eds. *Textbook of Pain, Fourth Edition*. London: Churchill Livingstone, 1999:1017-1064.
- Gonzales GR, Elliott KJ, Portenoy RK et al. The impact of a comprehensive evaluation in the management of cancer pain. *Pain* 1991;47:141-144.
- Onghena P, Van Houdenhove B. Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. *Pain* 1992;49:205-219.
- Watson CP. The treatment of neuropathic pain: antidepressants and opioids. *Clin J Pain* 2000;16(suppl 2):S49-S55.
- Collins SL, Moore RA, McQuay HJ et al. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review. *J Pain Symptom Manage* 2000;20:449-458.
- Ventafriidda V, Bonezzi C, Caraceni A et al. Antidepressants for cancer pain and other painful syndromes with deafferentation component: comparison of amitriptyline and trazodone. *Ital J Neurol Sci* 1987;8:579-587.
- Walsh TD. Controlled study of imipramine and morphine in chronic pain due to advanced cancer. *Proc Am Soc Clin Oncol* 1986;5:237.
- Breivik H, Rennemo F. Clinical evaluation of combined treatment with methadone and psychotropic drugs in cancer patients. *Acta Anaesthesiol Scand Suppl* 1982;74:135-140.
- Magni G, Arsie D, De Leo D. Antidepressants in the treatment of cancer pain: a survey in Italy. *Pain* 1987;29:347-353.
- Preskorn SH, Irwin HA. Toxicity of tricyclic antidepressants—kinetics, mechanism, intervention: a review. *J Clin Psychiatry* 1982;43:151-156.
- Glassman AH, Bigger JT Jr. Cardiovascular effects of therapeutic doses of tricyclic antidepressants. A review. *Arch Gen Psychiatr* 1981;38:815-820.

- 19 Sindrup SH, Gram LF, Brosen K et al. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. *Pain* 1990;42:135-144.
- 20 Sindrup SH, Bjerre U, Dejsgaard A et al. The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy. *Clin Pharmacol Ther* 1992;52:547-552.
- 21 Masand PS, Gupta S. Selective serotonin-reuptake inhibitors: an update. *Harvard Rev Psychiatry* 1999;7:69-84.
- 22 Sindrup SH, Bach FW, Madsen C et al. Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. *Neurology* 2003;60:1284-1289.
- 23 Tasmuth T, Hartel B, Kalso E. Venlafaxine in neuropathic pain following treatment of breast cancer. *Eur J Pain* 2002;6:17-24.
- 24 Semenchuk MR, Davis B. Efficacy of sustained-release bupropion in neuropathic pain: an open-label study. *Clin J Pain* 2000;16:6-11.
- 25 Semenchuk MR, Sherman S, Davis B. Double-blind, randomized trial of bupropion SR for the treatment of neuropathic pain. *Neurology* 2001;57:1583-1588.
- 26 Settle EC Jr. Bupropion sustained release: side effect profile. *J Clin Psychiatry* 1998;59(suppl 4):S32-S36.
- 27 Greenberg HS, Kim JH, Posner JB. Epidural spinal cord compression from metastatic tumor: results with a new treatment protocol. *Ann Neurol* 1980;8:361-366.
- 28 Vecht CJ, Haaxma-Reiche H, van Putten WL et al. Initial bolus of conventional versus high-dose dexamethasone in metastatic spinal cord compression. *Neurology* 1989;39:1255-1257.
- 29 Ettinger AB, Portenoy RK. The use of corticosteroids in the treatment of symptoms associated with cancer. *J Pain Symptom Manage* 1988;3:99-103.
- 30 Watanabe S, Bruera E. Corticosteroids as adjuvant analgesics. *J Pain Symptom Manage* 1994;9:442-445.
- 31 Farr WC. The use of corticosteroids for symptom management in terminally ill patients. *Am J Hosp Care* 1990;7:41-46.
- 32 Mercadante S, Fulfaro F, Casuccio A. The use of corticosteroids in home palliative care. *Support Care Cancer* 2001;9:386-389.
- 33 Messer J, Reitman D, Sacks HS et al. Association of adreno-corticosteroid therapy and peptic-ulcer disease. *N Engl J Med* 1983;309:21-24.
- 34 Piper JM, Ray WA, Daugherty JR et al. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. *Ann Intern Med* 1991;114:735-740.
- 35 Byas-Smith MG, Max MB, Muir J et al. Transdermal clonidine compared to placebo in painful diabetic neuropathy using a two-stage 'enriched enrollment' design. *Pain* 1995;60:267-274.
- 36 Zeigler D, Lynch SA, Muir J et al. Transdermal clonidine versus placebo in painful diabetic neuropathy. *Pain* 1992;48:403-408.
- 37 Rauck RL, Eisenach JC, Jackson K et al. Epidural clonidine treatment for refractory reflex sympathetic dystrophy. *Anesthesiology* 1993;79:1163-1169; discussion 27A.
- 38 Eisenach JC, Du Pen S, Dubois M et al. Epidural clonidine analgesia for intractable cancer pain. *Pain* 1995;61:391-399.
- 39 Nadler SF, Malanga GA, Smith R et al. Open-label trial evaluating tizanidine for myofascial pain syndrome. Presented at the 10th World Congress on Pain, International Association for the Study of Pain, 2002.
- 40 Vallejo R, Santiago-Palma J, Barna S et al. Tizanidine for the treatment of chronic myofascial pain. Presented at the 10th World Congress on Pain, International Association for the Study of Pain, 2002.
- 41 Saper JR, Lake AE 3rd, Cantrell DT et al. Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. *Headache* 2002;42:470-482.
- 42 Khojainova N, Santiago-Palma J, Kornick C et al. Olanzapine in the management of cancer pain. *J Pain Symptom Manage* 2002;23:346-350.
- 43 Patt RB, Proper G, Reddy S. The neuroleptics as adjuvant analgesics. *J Pain Symptom Manage* 1994;9:446-453.
- 44 Portenoy RK, Forbes K, Lussier D et al. Difficult pain problems: an integrated approach. In: Doyle D, Hanks G, Cherny N et al., eds. *Oxford Textbook of Palliative Medicine, Third Edition*. Oxford, England: Oxford University Press, 2003:438-458.
- 45 Caraceni A, Portenoy RK. An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. *Pain* 1999;82:263-274.
- 46 Manfredi PL, Gonzales GR, Sady R et al. Neuropathic pain in patients with cancer. *J Palliat Care* 2003;19:115-118.
- 47 Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology* 2003;60:927-934.
- 48 Huse E, Larbig W, Flor H et al. The effect of opioids on phantom limb pain and cortical reorganization. *Pain* 2001;90:47-55.
- 49 Raja SN, Haythornthwaite JA, Pappagallo M et al. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology* 2002;59:1015-1021.
- 50 Rowbotham MC, Twilling L, Davies PS et al. Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl J Med* 2003;348:1223-1232.
- 51 Watson CPN, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. *Neurology* 1998;50:1837-1841.
- 52 Backonja MM. Anticonvulsants (antineuropathics) for neuropathic pain syndromes. *Clin J Pain* 2000;16(suppl 2):S67-S72.
- 53 Tremont-Lukats IW, Megeff C, Backonja MM. Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy. *Drugs* 2000;60:1029-1052.
- 54 Backonja MM. Use of anticonvulsants for treatment of neuropathic pain. *Neurology* 2002;59(suppl 2):S14-S17.
- 55 Morello CM, Leckband SG, Stoner CP et al. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. *Arch Intern Med* 1999;159:1931-1937.

- 56 Backonja M, Beydoun A, Edwards KR et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA* 1998;280:1831-1836.
- 57 Rowbotham M, Harden N, Stacey B et al. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA* 1998;280:1837-1842.
- 58 Dallocchio C, Buffa C, Mazzarello P et al. Gabapentin vs. amitriptyline in painful diabetic neuropathy: an open-label pilot study. *J Pain Symptom Manage* 2000;20:280-285.
- 59 Rice AS, Maton S. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. *Pain* 2001;94:215-224.
- 60 Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. *Clin Ther* 2003;25:81-104.
- 61 Oneschuk D, al-Shahri MZ. The pattern of gabapentin use in a tertiary palliative care unit. *J Palliat Care* 2003;19:185-187.
- 62 Caraceni A, Zecca E, Martini C et al. Gabapentin as an adjuvant to opioid analgesia for neuropathic cancer pain. *J Pain Symptom Manage* 1999;17:441-445.
- 63 Zakrzewska JM, Chaudhry Z, Nurmikko TJ et al. Lamotrigine (lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover trial. *Pain* 1997;73:223-230.
- 64 Simpson DM, Olney R, McArthur JC et al. A placebo-controlled trial of lamotrigine for painful HIV-associated neuropathy. *Neurology* 2000;54:2115-2119.
- 65 Vestergaard K, Andersen G, Gottrup H et al. Lamotrigine for central poststroke pain: a randomized controlled trial. *Neurology* 2001;56:184-190.
- 66 Simpson DM, McArthur JC, Olney D et al. Lamotrigine for HIV-associated painful sensory neuropathies: a placebo-controlled trial. *Neurology* 2003;60:1508-1514.
- 67 Carrazana E, Mikoshiba I. Rationale and evidence for the use of oxcarbazepine in neuropathic pain. *J Pain Symptom Manage* 2003;25(suppl 5):S31-S35.
- 68 Dworkin RH, Corbin AE, Young JP Jr et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology* 2003;60:1274-1283.
- 69 Price MJ. Levetiracetam in the treatment of neuropathic pain: three case studies. *Clin J Pain* 2004;20:33-36.
- 70 Ward S, Jenson M, Royall M et al. Gabapentin and levetiracetam in combination for the treatment of neuropathic pain. *J Pain* 2002;3(2 suppl 1):38.
- 71 Yajnik S, Singh GP, Singh G et al. Phenytoin as a coanalgesic in cancer pain. *J Pain Symptom Manage* 1992;7:209-213.
- 72 Attal N, Gaudé V, Brasseur L et al. Intravenous lidocaine in central pain: a double-blind, placebo-controlled, psychophysical study. *Neurology* 2000;54:564-574.
- 73 Rowbotham MC, Reisner-Keller LA, Fields HL. Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia. *Neurology* 1991;41:1024-1028.
- 74 Bruera E, Ripamonti C, Brenneis C et al. A randomized double-blind crossover trial of intravenous lidocaine in the treatment of neuropathic cancer pain. *J Pain Symptom Manage* 1992;7:138-140.
- 75 Ellemann K, Sjogren P, Banning AM et al. Trial of intravenous lidocaine on painful neuropathy in cancer patients. *Clin J Pain* 1989;5:291-294.
- 76 Brose WG, Cousins MJ. Subcutaneous lidocaine for treatment of neuropathic cancer pain. *Pain* 1991;45:145-148.
- 77 Campbell RW. Mexiletine. *New Engl J Med* 1987;316:29-34.
- 78 Parsons CG. NMDA receptors as targets for drug action in neuropathic pain. *Eur J Pharmacol* 2001;429:71-78.
- 79 Tarumi Y, Watanabe S, Bruera E et al. High-dose ketamine in the management of cancer-related neuropathic pain. *J Pain Symptom Manage* 2000;19:405-407.
- 80 Mercadante S, Arcuri E, Tirelli W et al. Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, crossover, double-dose study. *J Pain Symptom Manage* 2000;20:246-252.
- 81 Jackson K, Ashby M, Martin P et al. "Burst" ketamine for refractory cancer pain: an open-label audit of 39 patients. *J Pain Symptom Manage* 2001;22:834-842.
- 82 Kannan TR, Saxena A, Bhatnagar S et al. Oral ketamine as an adjuvant to oral morphine for neuropathic pain in cancer patients. *J Pain Symptom Manage* 2002;23:60-65.
- 83 Lauretti GR, Lima IC, Reis MP et al. Oral ketamine and transdermal nitroglycerin as analgesic adjuvants to oral morphine therapy for cancer pain management. *Anesthesiology* 1999;90:1528-1533.
- 84 Benitez-Rosario MA, Feria M, Salinas-Martin A et al. A retrospective comparison of the dose ratio between subcutaneous and oral ketamine. *J Pain Symptom Manage* 2003;25:400-402.
- 85 Fitzgibbon EJ, Hall P, Schroder C et al. Low dose ketamine as an analgesic adjuvant in difficult pain syndromes: a strategy for conversion from parenteral to oral ketamine. *J Pain Symptom Manage* 2002;23:165-170.
- 86 Weinbroum AA, Bender B, Bickels J et al. Preoperative and postoperative dextromethorphan provides sustained reduction in postoperative pain and patient-controlled epidural analgesia requirement: a randomized, placebo-controlled, double-blind study in lower-body bone malignancy-operated patients. *Cancer* 2003;97:2334-2340.
- 87 Eisenberg E, Pud D. Can patients with chronic neuropathic pain be cured by acute administration of the NMDA receptor antagonist amantadine? *Pain* 1998;74:337-339.
- 88 Amin P, Sturrock ND. A pilot study of the beneficial effects of amantadine in the treatment of painful diabetic peripheral neuropathy. *Diabet Med* 2003;20:114-118.
- 89 Pud D, Eisenberg E, Spitzer A et al. The NMDA receptor antagonist amantadine reduces surgical neuropathic pain in cancer patients: a double blind, randomized, placebo-controlled trial. *Pain* 1998;75:349-354.
- 90 Maier C, Dertwinkel R, Mansourian N et al. Efficacy of the NMDA-receptor antagonist memantine in patients with

- chronic phantom limb pain—results of a randomized double-blinded, placebo-controlled trial. *Pain* 2003;103:277-283.
- 91 Wiech K, Kiefer RT, Topfner S et al. A placebo-controlled randomized crossover trial of the *N*-methyl-D-aspartic acid receptor antagonist, memantine, in patients with chronic phantom limb pain. *Anesth Analg* 2004;98:408-413.
- 92 Davis AM, Inturrisi CE. d-methadone blocks morphine tolerance and *N*-methyl-D-aspartate-induced hyperalgesia. *J Pharmacol Exp Ther* 1999;289:1048-1053.
- 93 Fromm GH. Baclofen as an adjuvant analgesic. *J Pain Symptom Manage* 1994;9:500-509.
- 94 Noyes R Jr, Brunk SF, Avery DA et al. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clin Pharmacol Ther* 1975;18:84-89.
- 95 Campbell FA, Tramer MR, Carroll D et al. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *BMJ* 2001;323:13-16.
- 96 DelleMijn PL, Fields HL. Do benzodiazepines have a role in chronic pain management? *Pain* 1994;57:137-152.
- 97 Reddy S, Patt RB. The benzodiazepines as adjuvant analgesics. *J Pain Symptom Manage* 1994;9:510-514.
- 98 Dalal S, Melzack R. Potentiation of opioid analgesia by psychostimulant drugs: a review. *J Pain Symptom Manage* 1998;16:245-253.
- 99 Rozans M, Dreisbach A, Lertora JJ et al. Palliative uses of methylphenidate in patients with cancer: a review. *J Clin Oncol* 2002;20:335-339.
- 100 Webster L, Andrews M, Stoddard G. Modafinil treatment of opioid-induced sedation. *Pain Med* 2003;4:135-140.
- 101 Wernicke JF, Kratochvil CJ. Safety profile of atomoxetine in the treatment of children and adolescents with ADHD. *J Clin Psychiatry* 2002;63(suppl 12):50-55.
- 102 Galer BS, Rowbotham MC, Perander J et al. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain* 1999;80:533-538.
- 103 Gammaitoni AR, Davis MW. Pharmacokinetics and tolerability of lidocaine patch 5% with extended dosing. *Ann Pharmacother* 2002;36:236-240.
- 104 Ellison N, Loprinzi CL, Kugler J et al. Phase III placebo-controlled trial of capsaicin cream in the management of surgical neuropathic pain in cancer patients. *J Clin Oncol* 1997;15:2974-2980.
- 105 Szanto J, Ady N, Jozsef S. Pain killing with calcitonin nasal spray in patients with malignant tumors. *Oncology* 1992;49:180-182.
- 106 Hindley AC, Hill EB, Leyland MJ et al. A double-blind controlled trial of salmon calcitonin in pain due to malignancy. *Cancer Chemother Pharmacol* 1982;9:71-74.
- 107 Roth A, Kolaric K. Analgesic activity of calcitonin in patient with painful osteolytic metastases of breast cancer: results of a controlled randomized study. *Oncology* 1986;43:283-287.
- 108 Fulfaro F, Casuccio A, Ticozzi C et al. The role of bisphosphonates in the treatment of painful metastatic bone disease: a review of phase III trials. *Pain* 1998;78:157-169.
- 109 Lipton A, Glover D, Harvey H et al. Pamidronate in the treatment of bone metastases: results of 2 dose-ranging trials in patients with breast or prostate cancer. *Ann Oncol* 1994;5(suppl 7):S31-S35.
- 110 van Holten-Verzantvoort AT, Kroon HM, Bijvoet OL et al. Palliative pamidronate treatment in patients with bone metastases from breast cancer. *J Clin Oncol* 1993;11:491-498.
- 111 Glover D, Lipton A, Keller A et al. Intravenous pamidronate disodium treatment of bone metastases in patients with breast cancer. A dose-seeking study. *Cancer* 1994;74:2949-2955.
- 112 Rosen LS, Gordon D, Kaminski M et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer J* 2001;7:377-387.
- 113 Hortobagyi GN, Theriault RL, Porter L et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. *N Engl J Med* 1996;335:1785-1791.
- 114 Berenson JR, Lichtenstein A, Porter L et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. *N Engl J Med* 1996;334:488-493.
- 115 Berenson JR, Rosen LS, Howell A et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. *Cancer* 2001;91:1191-1200.
- 116 Lipton A, Small E, Saad F et al. The new bisphosphonate, Zometa (zoledronic acid), decreases skeletal complications in both osteolytic and osteoblastic lesions: a comparison to pamidronate. *Cancer Invest* 2002;20(suppl 2):45-54.
- 117 Saad F, Gleason DM, Murray R et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002;94:1458-1468.
- 118 Rosen LS. Efficacy and safety of zoledronic acid in the treatment of bone metastases associated with lung cancer and other solid tumors. *Semin Oncol* 2002;29(suppl 21):28-32.
- 119 Skerjanec A, Berenson J, Hsu C et al. The pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with varying degrees of renal function. *J Clin Pharmacol* 2003;43:154-162.
- 120 Lewington VJ, McEwan AJ, Ackery DM et al. A prospective, randomised double-blind cross-over study to examine the efficacy of strontium-89 in pain palliation in patients with advanced prostate cancer metastatic to bone. *Eur J Cancer* 1991;27:954-958.
- 121 Quilty PM, Kirk D, Bolger JJ et al. A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. *Radiother Oncol* 1994;31:33-40.
- 122 Anderson PM, Wiseman GA, Dispenzieri A et al. High-dose samarium-153 ethylene diamine tetramethylene phosphonate:

- low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. *J Clin Oncol* 2002;20:189-196.
- 123 Serafini AN, Houston SJ, Resche I et al. Palliation of pain associated with metastatic bone cancer using samarium-153 lexitronam: a double-blind placebo-controlled clinical trial. *J Clin Oncol* 1998;16:1574-1581.
- 124 Silberstein EB, Eugene L, Saenger SR. Painful osteoblastic metastases: the role of nuclear medicine. *Oncology (Huntingt)* 2001;15:157-163; discussion 167-170, 174.
- 125 Twycross RG, Fairfield S. Pain in far-advanced cancer. *Pain* 1982;14:303-310.
- 126 Batterman RC. Methodology of analgesic evaluation: experience with orphenadrine citrate compound. *Curr Ther Res Clin Exp* 1965;7:639-647.
- 127 Birkeland IW Jr, Clawson DK. Drug combinations with orphenadrine for pain relief associated with muscle spasm. *Clin Pharmacol Ther* 1968;9:639-646.
- 128 Bercel NA. Cyclobenzaprine in the treatment of skeletal muscle spasm in osteoarthritis of the cervical and lumbar spine. *Curr Ther Res Clin Exp* 1977;22:462-468.
- 129 Borenstein DG, Korn S. Efficacy of a low-dose regimen of cyclobenzaprine hydrochloride in acute skeletal muscle spasm: results of two placebo-controlled trials. *Clin Ther* 2003;25:1056-1073.
- 130 Vaeroy H, Abrahamsen A, Forre O et al. Treatment of fibromyalgia (fibrositis syndrome): a parallel double blind trial with carisoprodol, paracetamol and caffeine (Somadril comp) versus placebo. *Clin Rheumatol* 1989;8:245-250.
- 131 Diamond S. Double-blind study of metaxalone; use as skeletal-muscle relaxant. *JAMA* 1966;195:479-480.
- 132 Tisdale SA Jr, Ervin DK. A controlled study of methocarbamol (Robaxin) in acute painful musculoskeletal conditions. *Curr Ther Res Clin Exp* 1975;17:525-530.
- 133 Turturro MA, Frater CR, D'Amico FJ. Cyclobenzaprine with ibuprofen versus ibuprofen alone in acute myofascial strain: a randomized, double-blind clinical trial. *Ann Emerg Med* 2003;41:818-826.
- 134 Raj PP. Botulinum toxin therapy in pain management. *Anesthesiol Clin North America* 2003;21:715-731.
- 135 Van Daele DJ, Finnegan EM, Rodnitzky RL et al. Head and neck muscle spasm after radiotherapy: management with botulinum toxin A injection. *Arch Otolaryngol Head Neck Surg* 2002;128:956-959.
- 136 Mercadante S, Ripamonti C, Casuccio A et al. Comparison of octreotide and hyoscine butylbromide in controlling gastrointestinal symptoms due to malignant inoperable bowel obstruction. *Support Care Cancer* 2000;8:188-191.
- 137 Ripamonti C, Mercadante S, Groff L et al. Role of octreotide, scopolamine butylbromide, and hydration in symptom control of patients with inoperable bowel obstruction and nasogastric tubes: a prospective randomized trial. *J Pain Symptom Manage* 2000;19:23-34.
- 138 Mystakidou K, Tsilika E, Kalaidopoulou O et al. Comparison of octreotide administration vs conservative treatment in the management of inoperable bowel obstruction in patients with far advanced cancer: a randomized, double-blind, controlled clinical trial. *Anticancer Res* 2002;22:1187-1192.
- 139 De Conno F, Caraceni A, Zecca E et al. Continuous subcutaneous infusion of hyoscine butylbromide reduces secretions in patients with gastrointestinal obstruction. *J Pain Symptom Manage* 1991;6:484-486.
- 140 Fainsinger RL, Spachynski K, Hanson J et al. Symptom control in terminally ill patients with malignant bowel obstruction (MBO). *J Pain Symptom Manage* 1994;9:12-18.
- 141 Fadul CE, Lemann W, Thaler HT et al. Perforation of the gastrointestinal tract in patients receiving steroids for neurologic disease. *Neurology* 1988;38:348-352.
- 142 ReMine SG, McIlrath D. Bowel perforation in steroid-treated patients. *Ann Surg* 1980;192:581-586.
- 143 Nguyen DK, Spencer SS. Recent advances in the treatment of epilepsy. *Arch Neurol* 2003;60:929-935.
- 144 Bernard SA. The interaction of medications used in palliative care. *Hematol Oncol Clin North Am* 2002;16:641-655.
- 145 Norton JW. Gabapentin withdrawal syndrome. *Clin Neuropharmacol* 2001;24:245-246.
- 146 Portenoy RK. Pain syndromes in patients with cancer and HIV/AIDS. In : Portenoy RK, ed. *Contemporary Diagnosis and Management of Pain in Oncologic and AIDS Patients, Third Edition*. Newton, PA: Handbooks in Health Care Co., 2003:49-78.
- 147 Martin LA, Hagen NA. Neuropathic pain in cancer patients: mechanisms, syndromes, and clinical controversies. *J Pain Symptom Manage* 1997;14:99-117.