Three-Step Analgesic Ladder

For Management of

Cancer Pain 2006

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Key

ADH	=	antidiuretic hormone
bid	=	twice daily
BUN	=	blood urea nitrogen
CABG	=	coronary artery bypass graft
CBC	=	complete blood cell count
CNS	=	central nervous system
COX-2	=	cyclooxygenase-2
GI	=	gastrointestinal
IM	=	intramuscular
IU	=	international units
I.V.	=	intravenous
MAO	=	monoamine oxidase
NMDA	=	*N*-methyl-D-aspartate
NSAID	=	nonsteroidal anti-inflammatory drug
PCA	=	patient-controlled analgesia
PO	=	by mouth
PR	=	rectally
qd	=	once daily
SNRI	=	serotonin–norepinephrine reuptake inhibitor
SSRI	=	selective serotonin reuptake inhibitor
TCA	=	tricyclic antidepressant

Routes Of Administration

Although the oral and transdermal routes are preferred, alternative routes of administration will be required for a substantial number of patients at some point in their course.

Buccal: Supporting data meager (for oral suspensions, etc). Method currently unavailable and impractical.

Epidural: Repetitive bolus; continuous infusion.

Intracerebroventricular: Rarely indicated. Limited survey data available.

Intranasal: Available for butorphanol; not used in cancer pain management.

Intrathecal: Repetitive bolus; continuous infusion: Clearest indication is pain in lower body with poor relief and side effects from systemic opioids. Epidural catheter can be percutaneous (from lumbar region or tunneled to abdomen) or connected to subcutaneous portal, depending on patient's life expectancy. Intrathecal usually administered via implanted pump. Benefits of long-term intrathecal infusion in selected patients demonstrated in randomized trial (Smith TJ, et al. *J Clin Oncol*. 2002;20:4040-4049). Morphine, hydromorphone, fentanyl, and others in use, combined with local anesthetic or clonidine.

Intravenous: Repetitive bolus; continuous infusion; PCA (with or without infusion): Indicated if other routes are unavailable or not tolerated, or if patient has an indwelling I.V. access device.

Oral: Preferred route of administration for long-acting opioids in cancer pain management. Transdermal available for fentanyl.

Oral transmucosal: Available for fentanyl.

Rectal: Available for morphine, oxymorphone, and hydromorphone. Although few studies available, customarily used as if dose is equianalgesic to oral dose.

Subcutaneous: Repetitive bolus; continuous infusion; continuous infusion with PCA: Ambulatory infusion pumps permit outpatient continuous infusion. Can be accomplished with any parenteral drug. Drug mixtures to treat multiple symptoms and long-term hydration also feasible by this route.

Sublingual: Buprenorphine effective, and sublingual tablet available in the United States. Efficacy of morphine controversial.

Transdermal: Available for fentanyl.

INTRODUCTION

Cancer pain is extremely prevalent, occurring in more than three fourths of patients with advanced disease. Numerous studies have confirmed that the experience of unrelieved pain has potentially devastating effects on quality of life. The effective management of pain is a therapeutic imperative and central to the palliative care provided to all cancer patients. Pain continues to be undertreated, despite 2 decades that have witnessed the development of consensus-based guidelines for the management of cancer pain and intensive educational efforts on the part of professional societies, the philanthropic community, and industry. Undertreatment cannot be condoned, particularly in light of available evidence that pharmacotherapy with both opioid and nonopioid drugs can provide adequate relief to most patients. Although a multimodality strategy can augment pain relief, diminish the effect of pain that persists, and improve related outcomes, the mainstay approach to moderate or severe cancer pain continues to be opioid-based therapy. The "analgesic ladder," which was promulgated by the World Health Organization in the late 1980s, was the first guideline to codify an opioid-based treatment for cancer pain. Combined with straightforward dosing guidelines, it has had a significant effect on practice around the world. Although more recent guidelines emphasize the need for flexibility and the potential value of skipping steps and selecting specific drugs based on patient assessment, all continue to emphasize the value of opioids for moderate to severe chronic pain, the importance of dose individualization through a process of repeated titration, the use of analgesic polypharmacy in many cases, and the ongoing need to manage side effects to optimize the balance between pain relief and adverse drug effects.

Breakthrough Pain

Breakthrough pain (BTP) is a serious clinical problem, likely afflicting thousands of patients. Despite its seriousness, BTP is underappreciated by clinicians.

The terminology used to describe BTP—episodic pain in populations with chronic pain—has been widely debated, and various definitions have been created and published in the medical literature.[1] The broadest definition is probably the most useful: BTP is any transient and clinically significant pain that flares over baseline pain that is adequately controlled by any analgesic regimen.[1,4]

Epidemiology, Impact, and Characteristics

Studies of populations of patients with cancer pain have revealed that 50% to 90% of patients experience BTP.[2-7] In a survey of hospice patients without cancer, 63% had BTP.[8] A survey of patients with chronic noncancer pain identified a prevalence of 74% among patients taking opioid analgesics.[9] In the population of cancer patients, BTP is associated with a more severe pain syndrome,[3-5] reduced responsiveness to opioid therapy,[10,11] pain-related functional impairment and psychological distress,[5] and an increase in the economic burden for patients and the healthcare system.[12]

Although characteristics and location of a patient's

BTP are usually the same as those for the patient's baseline pain, there are notable differences in how BTP manifests between individuals.[1,3-9] The frequency of flares varies from fewer than 1 per day to many per hour; most patients experience approximately 3 flares per day. Most episodes are brief (<30 minutes), but on occasion a patient will experience BTP for hours. BTP can reach peak intensity over a period of minutes, but can also increase more gradually. BTP can appear without warning or be predictable, and predictable pain has a broad array of potential precipitants. One type of BTP, called *end of dose failure*, occurs at the end of a dosing interval. The etiologies and types of mechanisms underlying BTP are as variable as those of the baseline pain to which they usually relate.

The optimal management of BTP depends on a detailed assessment. If the information available does not allow a detailed understanding, further work-up with imaging studies or other tests should be considered.

Management of Breakthrough Pain

There have been few studies of BTP. A rational empiric approach includes three steps: 1) treatment of the etiology or precipitating causes, 2) optimization of the baseline analgesic regimen, and 3) trial of symptomatic interventions.

Treatment of the Etiology or Precipitating Causes

Primary therapy for the cause of the BTP, such as radiotherapy to a bony lesion, should be provided if it is feasible, does not subject the patient to excessive risk, has a reasonable likelihood of reducing the frequency or intensity of the pain, and is consistent with the goals of care. Cases of BTP that are precipitated by specific phenomena may be amenable to primary management of the precipitant. Examples include the treatment of cough-related pain with an antitussive and the treatment of suprapubic pain caused by bladder spasm with an anticholinergic drug.

Optimizing the Baseline Analgesic Regimen

Patients with end-of-dose failure may be helped by shortening the dosing interval or increasing the standing dose. Even those with BTP at other times may benefit, however, if the standing analgesic dose is increased.[13] An empiric increase in the regularly scheduled opioid dose to a level just below treatment-limiting side effects should be considered as a trial in all patients with BTP, even those with well-controlled baseline pain.

Trials of Symptomatic Interventions

The use of a *rescue dose*—a supplemental dose of an analgesic provided on an as-needed basis in combination with the regularly scheduled analgesic—is the most widely accepted approach for cancer-related BTP.[2] The rescue drug could be a nonopioid or an adjuvant analgesic such as ketamine,[14] but most experience has revolved around the use of opioids. Although opioid rescue dosing is being used for BTP associated with chronic noncancer pain, there are no published safety and

effectiveness data to date and the treatment should be used only if the assessment clearly suggests that benefits exceed risks.

There has been little systematic study of the opioid rescue dose. Some guidelines suggest that the rescue drug should be identical to the regularly scheduled opioid, but there is no evidence to support this recommendation. Although the typical BTP time course suggests that the ideal rescue drug should have a rapid onset of analgesia and a short duration of action, rescue dosing with a short-acting oral opioid drug has been widely used. There is presumably substantial variation in patient responses and studies are needed to better assess the impact of onset time for different populations with BTP.

Notwithstanding the latter observation, a rapid onset of analgesia does appear to be favored by those with BTP. Oral transmucosal fentanyl citrate (OTFC®) was developed on this basis. The development of OTFC® led to refined protocols for future clinical trials on BTP. Other formulations are in development for BTP, most attempting to replicate the concept of rapid onset via a transmucosally delivered lipophilic drug that was successfully commercialized in OTFC®.

Based on clinical experience, the appropriate dose of the rescue drug has been proposed to be approximately 5% to 15% of the total daily opioid dose. Controlled trials did not confirm this guideline for OTFC®[15,16] and dose titration from a low dose (200 mcg) is recommended in all cases. One study of morphine-treated patients indicated that 20% of the daily dose could be used safely.[17] Regardless of the starting dose, titration of the rescue drug based on the patient's response is an important principle.

The timing of the rescue dose is conventionally determined by the route of administration. Most guidelines suggest a minimum interval of 2 hours for oral administration and 15 to 60 minutes for parenteral and oral transmucosal administration.

If the rescue dose causes treatment-limiting side effects, various strategies may be considered in a manner identical to the approach to patients with a poor response to a regularly scheduled opioid regimen.[18] These include rotation of the rescue drug or the entire regimen to a different opioid, coadministration of a drug to treat the side effect, and coadministration of a pharmacologic or nonpharmacologic approach to reduce the opioid requirement.

The importance of the opioid rescue dose should not obscure the potential benefits of other approaches. For example, neuropathic BTP may respond to the administration of an adjuvant analgesic, usually an antidepressant or anticonvulsant.[13,19] Nonpharmacologic treatments are very helpful for some and include cognitive strategies (particularly if BTP is predictable), physical therapy or bracing, and various complementary treatments. Interventional approaches, such as injection therapies, neural blockade, and neuraxial analgesia, must be considered if BTP is refractory to other strategies.

1ST STEP Nonopioid Analgesics for mild to moderate pain

Patients who present with mild to moderate pain should be treated with a nonopioid analgesic. An adjuvant drug should be used if a specific indication for one exists. Adjuvant drugs include treatments for opioid side effects or other comorbid conditions and "adjuvant analgesics," which are drugs with primary indications other than pain that are analgesic in selected circumstances.

See Key, Routes of Administration, and Endnotes, page 40.

Generic Name	Half-Life, h (approx)	Dosing Schedule	Recommended Starting Dose, mg/d*	Maximum Recommended Dose, mg/d	Comments
***p*-Aminophenol derivative**					
Acetaminophen† (paracetamol)	2-4	q4-6h	2,600	4,000	Overdose causes hepatic toxicity. Minimally anti-inflammatory. May not be preferred as first-line analgesic or coanalgesic in patients with bone pain. Its lack of GI or platelet toxicity may be important in some cancer patients. When used at high doses, liver function tests should be done regularly.
COX-2–selective inhibitors					
Celecoxib†	11	q12h	200	600	Compared with other NSAIDs, COX-2 drugs are less toxic to GI tract and have no effect on platelets. Although expense is a concern, many clinicians now prefer the COX-2–selective drugs as first-line agents in medically frail or elderly patients who may be predisposed to GI toxicity or unable to tolerate GI hemorrhage, should it occur. Adverse cardiovascular effects that led to the withdrawal of rofecoxib and valdecoxib are now believed to be a COX-2 effect, which may be important not only in the COX-2–selective subclass of NSAIDs, but also in the nonselective COX-1/COX-2 subclass. In the US, the label for all NSAIDs now includes a boxed warning indicating that these drugs may increase the risk of thrombotic events. Although the risk is small, it should be assumed to be a class effect of NSAIDs generally.

See Key, Routes of Administration, and Endnotes, page 40.

Generic Name	Half-Life, h (approx)	Dosing Schedule	Recommended Starting Dose, mg/d*	Maximum Recommended Dose, mg/d	Comments
Salicylates§					
Aspirin†	3-12‖	q4-6h	2,600	6,000	Standard for comparison. May not be tolerated as well as some of the newer NSAIDs.
Choline magnesium trisalicylate†	9-17	q12h	1,500 × 1, then 1,000 q12h	4,000	Unlike other NSAIDs, choline magnesium trisalicylate and salsalate cause minimal GI toxicity and have no effect on platelet aggregation, despite potent anti-inflammatory effects. Although a better safety profile in cancer patients is not confirmed, may be preferred in some cancer patients on this basis.
Diflunisal†	8-12	q12h	1,000 × 1, then 500 q12h	1,500	Less GI toxicity than aspirin.
Salsalate	8-12	q12h	1,500 × 1, then 1,000 q12h	4,000	See comments for choline magnesium trisalicylate and endnote.
Propionic Acids§					
Fenoprofen†	2-3	q4-6h	800	3,200	See endnote.
Flurbiprofen	5-6	q8-12h	100	300	See endnote.
Ibuprofen†	1.8-2	q4-8h	1,200	3,200	Available over the counter. See endnote.
Ketoprofen†	2-3	q6-8h	150	300	Available over the counter.
Naproxen†	13	q12h	500	1,000	Available over the counter as tablets and as a suspension. Some studies show greater efficacy of higher doses, specifically 1,500 mg/d, with little to no increase in adverse effects; long-term efficacy of this dose and safety in a medically ill population are unknown. However, it should be used cautiously.

See Key, Routes of Administration, and Endnotes, page 40.

Generic Name	Half-Life, h (approx)	Dosing Schedule	Recommended Starting Dose, mg/d*	Maximum Recommended Dose, mg/d	Comments
Propionic Acids§					
Naproxen sodium†	13	q12h	550	1,100	Available over the counter. Some studies show greater efficacy of higher doses, specifically 1,650 mg/d, with little to no increase in adverse effects; long-term efficacy of this dose and safety in a medically ill population are unknown. However, it should be used cautiously.
Oxaprozin	42-50	q24h	600	1,800	Once-daily dosing may be advantageous in some patients.
Acetic Acids					
Diclofenac	2	q6h	150	200	Only immediate-release tablets are indicated for pain management.§
Etodolac†	7	q6-8h	600	1,200	See endnote.§
Indomethacin	4-5	q8-12h	75	200	Available in sustained-release and rectal formulations. Higher incidence of side effects, particularly GI and CNS, than with propionic acids.§
Ketorolac†	4-7	q6h	15-30 q6h I.V., IM 10 q6h PO	120 I.V., IM 40 PO	Parenteral formulation available. Use should be limited to treatment of acute pain; recommended maximum duration of treatment is 5 d.
Sulindac	7.8	q12h	300	400	See endnote.§
Tolmetin	2	q6-8h	600	1,800	See endnote.§
Naphthylalkanone					
Nabumetone	20-35	q24h	1,000	2,000	Studies in noncancer populations suggest relatively good safety profile. Once-daily dosing may be advantageous.§

See Key, Routes of Administration, and Endnotes, page 40.

Generic Name	Half-Life, h (approx)	Dosing Schedule	Recommended Starting Dose, mg/d*	Maximum Recommended Dose, mg/d	Comments
Oxicams§					
Meloxicam	15-20	q24h	7.5	15	COX-2 selective at lower doses.*
Piroxicam	50	q24h	20	40	Administration of 40 mg for >3 wk is associated with high incidence of peptic ulcer, especially in the elderly.
Fenamates§					
Meclofenamic acid†	1.3	q6-8h	150	400	See endnote.
Mefenamic acid†	2	q6h	500 × 1, then 250 q6h	1,000	Not recommended for use longer than 1 wk, and therefore not indicated in cancer pain therapy.
Pyrazole§					
Phenyl-butazone	50-100	q6-8h	300	400	Not a first-line drug because of risk for serious bone marrow toxicity. Not preferred for cancer pain therapy. If used, need CBC every 2 wk for 1 mo, then monthly, in addition to other monitoring.

2ND STEP Short-Acting Opioids for moderate pain

Patients who fail the 1st-step regimen or who present with moderate pain should be treated with an oral opioid for moderate pain as well as with a nonopioid analgesic and an adjuvant drug, if the clinician has evidence for the efficacy of the adjuvant. In current clinical practice, the 2nd step is applied flexibly; it may be skipped in lieu of treatment with a 3rd-step drug or primary treatment with an adjuvant analgesic in selected syndromes. In the treatment of continuous pain, analgesics should be given on a regular basis—"by the clock"—so that the next dose is given before the effect of the previous one wears off. These short-acting drugs are also used as "rescue" medications, given as needed for breakthrough pain during treatment with a long-acting opioid.

See Key, Routes of Administration, and Endnotes, page 40.

Generic Name	Dose[ll]	Half-Life, h	Peak Effect, h	Duration h	Toxicity	Comments
Morphine-Like Agonists						
Codeine	32-65	2-3	1.5-2	3-6	Same as morphine.	Usually combined with acetaminophen or an NSAID.
Dihydrocodeine	15-20	—	—	4-5	Same as morphine.	Only available combined with aspirin and caffeine.
Hydrocodone	—	4	0.5-1	4-6	Same as morphine.	Only available combined with acetaminophen, aspirin, or ibuprofen.
Meperidine (pethidine)	50	3-4	1-2	3-5	Same as morphine plus CNS excitation (eg, tremulousness, seizures) from accumulation of toxic metabolite, normeperidine; prolonged, high dosing and renal insufficiency predispose.	Contraindicated in patients using MAO inhibitors, in whom dangerous hyperthermic syndrome may develop.
Oxycodone	2.5	—	1	3-6	Same as morphine.	Considered a 2nd-step drug when combined with aspirin or acetaminophen. New combination product containing oxycodone and ibuprofen also will be useful.

See Key, Routes of Administration, and Endnotes, page 40.

Generic Name	Dose[ll]	Half-Life, h	Peak Effect, h	Duration h	Toxicity	Comments
Morphine-like agonists						
Propoxyphene HCl	65-130	12	2-2.5	3-6	Same as morphine plus seizures and cardiac toxicity with overdose.	Toxic metabolite, norpropoxyphene, accumulates with repetitive dosing but norpropoxyphene toxicity does not appear to represent a clinically significant problem at the doses typically used to treat pain (adults: 65 mg-130 mg q4h prn, up to 3 doses daily); often combined with acetaminophen or an NSAID.
Propoxyphene napsylate	100-200	12	2-2.5	3-6	Same as hydrochloride.	Same as propoxyphene HCl.
Agonist–antagonist						
Pentazocine	30	2-3	1.5-2	2-4	Same as morphine, with more risk for psychotomimetic effects and less risk for respiratory depression at high doses.	Can cause withdrawal symptoms in opioid-dependent patients; not recommended for cancer pain therapy.
Other						
Tramadol	—	6-7	2-3	4-6	Dizziness, nausea, constipation most common; seizure rare.	Mechanism: binds to μ-opioid receptor, weakly inhibits reuptake of norepinephrine and serotonin, enhances serotonin release; only 30% of analgesia is naloxone reversible; maximum recommended dose 400 mg/d (300 mg/d for patients aged ≥75 y); higher doses (eg, up to 600 mg/d) sometimes used. Seizure risk increases if coadministered with drugs that lower seizure threshold. Now also available with acetaminophen in a combination tablet.

3RD STEP Short and Long-Acting Opioids for moderate to severe pain

Patients who fail the 2nd-step regimen or who present with moderate to severe pain should be treated with an opioid indicated for such pain. The clinician should consider the addition of a nonopioid analgesic or an adjuvant drug. In the treatment of persistent pain, analgesics should be given on a regular basis—"by the clock"—so that the next dose is given before the effect of the previous one wears off.

Short-Acting

See Key, Routes of Administration, and Endnotes, page 40.

Generic Name	Dose[¶]	Half-Life, h	Peak Effect, h	Duration h	Toxicity	Comments
Morphine-Like Agonists						
Morphine	10 IM 20-60 PO**	3 2-4	0.5-1 1.5-2	6 4-7	Constipation, nausea, sedation most common; respiratory depression most serious; itch, dry mouth, urinary retention uncommon; sexual dysfunction possible; hypotension and inappropriate ADH secretion rare.	Standard of comparison for opioids. Multiple routes available (see Routes of Administration). Survey data indicate that a switch from immediate-release morphine to controlled-release morphine should be done at same milligram dose. Pharmacokinetics of newer extended-release formulation may suggest once-daily administration.
Hydromorphone	1.5 IM; 7.5 PO	2-3 —	0.5-1 1-2	4-5 4-5	Same as morphine.	Multiple routes available (see Routes of Administration). May become available as a modified-release formulation with a long duration of effect.
Meperidine (pethidine)	75 IM; 300 PO	3-4	0.5-1 1-2	2-4 3-6	Same as morphine + CNS excitation; contraindicated in those on MAO inhibitors.	Not preferred for cancer pain because of potential toxicity.

[¶]Dose that provides analgesia equivalent to 10 mg of IM morphine.

Short-Acting

See Key, Routes of Administration, and Endnotes, page 40.

Generic Name	Dose[¶]	Half-Life, h	Peak Effect, h	Duration h	Toxicity	Comments
Morphine-Like Agonists						
Oxycodone	20-30 PO	2-4	1	3-6	Same as morphine.	Available as a single agent and in combination with aspirin or acetaminophen; at higher doses used as a single agent for patients with severe pain or who have developed tolerance; no parenteral formulation.
Oxymorphone	1 IM; 10 PR	— —	0.5-1 1.5-3	3-6 4-6	Same as morphine.	No oral formulation. May become available as an oral formulation, including a modified-release formulation.
Agent Indicated for Breakthrough Pain In Patients With Cancer						
Oral transmucosal fentanyl citrate (OTFC®)	800 mcg PO	6	0.3-0.5	Related to blood levels of the drug	Same as morphine.	No relationship exists between effective OTFC® rescue dose and baseline opioid dose. Therefore, all patients should be started on a relatively low dose (200 mcg) and dose should be titrated to effect. This contrasts with guidelines recommending rescue opioid dosing at 5%-15% of total daily opioid dose.

[¶]Dose that provides analgesia equivalent to 10 mg of IM morphine.

Short-Acting

See Key, Routes of Administration, and Endnotes, page 40.

Generic Name	Dose[f]	Half-Life, h	Peak Effect, h	Duration h	Toxicity	Comments
Partial Agonist						
Buprenorphine	0.4 IM	2-5	0.5-1	6-8	Same as morphine, except less risk for respiratory depression at higher doses.	May cause withdrawal symptoms in opioid-dependent patients; has ceiling for analgesia and less abuse potential; sublingual tablets available in United States; may be useful in nondependent/nontolerant patients with cancer pain (ie, on the 2nd step of the analgesic ladder).
Mixed Agonists–Antagonists						
Butorphanol	2 IM	2-3	0.5-1	3-4	Same profile of effects as pentazocine, except for lower risk for psychotomimetic effects.	Agonist–antagonist. No oral formulation; may cause withdrawal in opioid dependent patients; not recommended for cancer pain therapy.
Nalbuphine	10 IM	4-6	0.5-1	3-6	Same as pentazocine, except for lower risk for psychotomimetic effects.	Agonist–antagonist. No oral formulation; may cause withdrawal symptoms in opioid-dependent patients; not recommended for cancer pain therapy.
Pentazocine	60 IM; 180 PO	2-3 —	0.5-1 1-2	3-6 3-6	Same as buprenorphine, except for greater risk for psychotomimetic effects.	Agonist–antagonist. Oral preparation combined with naloxone or acetaminophen in United States; may cause withdrawal symptoms in opioid-dependent patients; not recommended for cancer pain therapy.

Long-Acting

Morphine-Like Agonists						
Levorphanol	2 IM; 4 PO.	11-16	0.5-1	6-8	Same as morphine.	With long half-life, accumulation occurs after dose is begun or increased.

[f]Dose that provides analgesia equivalent to 10 mg of IM morphine.

Long-Acting

See Key, Routes of Administration, and Endnotes, page 40.

Generic Name	Dose¶	Half-Life, h	Peak Effect, h	Duration h	Toxicity	Comments
Morphine-like agonists						
Methadone	10 IM; 20 PO	15-150+	0.5-1.5	4-8	Same as morphine.	Available as a racemate; the D-isomer is an NMDA antagonist, which may account for unexpectedly high potency in some patients who are switched from another drug. This uncertainty about potency, together with concern about a long and variable half-life, necessitates caution in the use of this drug. When a patient is switched from another drug, the calculated equianalgesic dose should be reduced by 75% to 90%. Prolonged monitoring may be needed during dose titration. Multiple routes available.
Fentanyl transdermal system	25 mcg/h	17	24-72	72	Same as morphine.	Patches of different sizes can deliver 12, 25, 50, 75, or 100 mcg/h. Dosing interval is 48 to 72 h. Dose usually adjusted every 3 d if needed, and multiple patches may be used.
Modified-release morphine	20-60 PO**	2-3	3-4	8-24	Same as morphine.	Available formulations vary in duration of effect—from 8-12 h, to 12-24 h, to 24 h.
Modified-release oxycodone	20-30 PO	2-4	3-4	8-12	Same as morphine.	Available as a single agent and in combination with aspirin or acetaminophen; at higher doses used as a single agent for patients with severe pain or who have developed tolerance; no parenteral formulation.

¶Dose that provides analgesia equivalent to 10 mg of IM morphine.

Adjuvant Analgesics

Adjuvant analgesics comprise diverse classes of drugs that have other indications but also have analgesic properties in specific circumstances. These drugs should be used when the clinician has evidence of their utility.

See Key, Routes of Administration, and Endnotes, page 40.

Rationale for Use	Application	Examples	Dosing Schedule	Starting Dose, mg/d	Usual Daily Dose, mg/d	Comments
Anticonvulsants						
Extensive survey data and controlled trials support efficacy in neuropathic pain.	Neuropathic pain	Carbamazepine, gabapentin, lamotrigine, pregabalin	Variable	Variable	Variable	Gabapentin is now widely used, but many other anticonvulsants can be considered. Pregabalin, an anticonvulsant with a mechanism similar to that of gabapentin, was recently approved and has been studied extensively as an analgesic.
Other Sodium Channel Blockers						
Controlled studies in painful diabetic neuropathy.	Neuropathic pain	Mexiletine	q8h	450	600-900	
Antidepressants						
Proven analgesics in a variety of nonmalignant pain states.	Neuropathic pain; pain complicated by depression or insomnia	TCAs, SSRIs, SNRIs, others	Variable	Variable	Variable	Begin after opioid titrated. Evidence best for tricyclic drugs. Although minimal supporting data for serotonin-selective drugs, paroxetine has some support. Better support for mixed-mechanism drugs including duloxetine and venlafaxine.

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Rationale for Use	Application	Examples	Dosing Schedule	Starting Dose, mg/d	Usual Daily Dose, mg/d	Comments
Corticosteroids						
Extensive anecdotal experience in the treatment of pain and other symptoms confirmed by a single controlled study of methylprednisolone.	Pain from infiltration of neural structures; bone pain; pain in patients with far-advanced disease	Dexamethasone	q6-12h	Variable (eg, 10-20 mg × 1, then 4 mg q6h or less)	2-24	Higher doses used in epidural cord compression and various pain emergencies; lower doses suggested in other conditions. Dexamethasone may be preferred because of low mineralocorticoid effect, but others have been used (eg, prednisone).
Miscellaneous						
Controlled study in trigeminal neuralgia.	Neuropathic pain	Baclofen	q8h	15	30-120	
Controlled study and anecdotal reports.	Refractory bone pain and neuropathic pain	Calcitonin	q12h	200 IU	200-400 IU	
Controlled studies and anecdotal reports.	Refractory bone pain	Bisphosphonates (pamidronate)	Repeat monthly	60	—	
Controlled study.	Refractory bone pain	Strontium 89 Samarium 153	—	—	—	

See Key, Routes of Administration, and Endnotes, page 40.

Rationale for Use	Application	Examples	Dosing Schedule	Starting Dose, mg/d	Usual Daily Dose, mg/d	Comments
Miscellaneous						
Anecdotal reports.	Pain due to bowel obstruction	Anticholinergic drugs (eg, scopolamine and glycopyrrolate), octreotide	Variable	Variable	Variable	
Psychostimulants						
Clinical experience and controlled trials of dextroamphetamine in postoperative pain and methylphenidate in cancer pain.	Reversal of opioid-induced sedation	Methylphenidate; Dextroamphetamine	bid bid	5 5	10-40 10-40	

Endnotes

* Consider using lower than recommended starting dose in the elderly, in patients on multiple drugs, and in those with renal insufficiency (one half to two thirds recommended dose). Doses must be individualized. Low initial doses should be titrated upward if tolerated and clinical effect is inadequate. Doses can be increased in weekly increments. Studies of NSAIDs in the cancer population are meager; thus dosing guidelines are empiric.

† Although clinical experience suggests that any of the NSAIDs may be analgesic, pain is an approved indication only for those drugs noted.

‡ Half-life for aspirin increases with dose.

§ At relatively high doses, consider monitoring for adverse effects, eg, by checking for occult fecal blood or for changes in liver function tests, blood urea nitrogen and creatinine assessments, or urinalysis.

‖ Oral dose that provides analgesia equivalent to 650 mg of aspirin. Starting dose may be higher or lower, and dose titration is needed after therapy is begun.

¶ Dose that provides analgesia equivalent to 10 mg of IM morphine. The equianalgesic dose should not be interpreted as the starting, standard, or maximum dose, but rather as a guide; particularly useful in switching drugs or changing routes of administration. Depending on patient characteristics and prior opioid exposure, the starting dose can be lower or higher, and dose titration—either upward or downward—is repeatedly necessary in virtually all patients.

** Extensive survey data suggest that the relative potency of IM to PO morphine of 1:6 changes to 1:2 or 1:3 with long-term dosing.

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Notes