Administration of opioids to alleviate moderate to severe acute pain and chronic cancer pain is an established management process. However, advancements in clinical pharmacologic research have shown that opioids are also effective in chronic noncancerous pain. Many patients properly treated for prolonged periods with opioids develop tolerance and subsequently, physical dependence. This process is not necessarily harmful to the patient and will not cause the patient to develop an addiction (properly defined as psychologic dependence).

For many patients who have been on opioid therapy for months or years, analgesic effectiveness tragically becomes less. In addition, opioid-induced constipation can be severe and cause pain; patients do not develop tolerance to this adverse reaction. Therefore, such issues become a management problem and require additional intervention.

Currently, many different classes of drugs can serve as effective adjuncts to opioids for treatment of pain. Adding adjunctive medication to opioid therapy improves pain management primarily by nonopioid mechanisms of action. Clinical outcomes of such combinations include greater analgesia and attenuation of opioid-induced adverse reactions such as nausea and vomiting, constipation, sedation, and respiratory depression. Adjuncts include acetaminophen, antiarrhythmics, anticonvulsants, antidepressants, antipsychotics, baclofen, benzodiazepines, capsaicin, calcium channel blockers, clonidine hydrochloride, central nervous system stimulants, corticosteroids, local anesthetics, N-methyl-D-aspartate receptor antagonists, nonsteroidal antiinflammatory drugs, pentoxifylline, and scopolamine.

Some adjuncts (eg, acetaminophen) are routinely used today, whereas others (eg, nifedipine [calcium channel blocker]) are used on a limited basis but have great potential for more widespread application.

All professionals (eg, nurses, pharmacists, physicians, physicians’ assistants, social workers, members of the clergy) involved in treating patients with unresolved pain recognize this to be an extraordinary and delicate time. It is when patients are likely to request physicians to provide some method to accelerate their death. Thus, inadequate analgesia can become a suicidogen, ie, any factor that causes a patient to want to commit suicide. Incorporation of adjuncts to opioid therapy can serve to lessen pain and improve quality of life for a suffering patient.

(Key words: adjunctive medications, analgesia, cancer pain, noncancerous pain, pain management)
Checklist

- Acetaminophen (Tylenol)
- α₂-Agonist
  - Clonidine hydrochloride (Catapres)
- Antiarrhythmic
  - Mexiletine (Mexitil)
- Anticonvulsants
  - Carbamazepine (Tegretol)
  - Gabapentin (Neurontin)
  - Lamotrigine (Lamictal)
  - Phenytoin (Dilantin)
  - Topiramate (Topamax)
- Antidepressants
  - Tricyclic antidepressants
    - amitriptyline hydrochloride (Elavil, Etrafon, Limbitrol)
    - clomipramine (Anafranil)
    - desipramine hydrochloride (Norpramin)
    - nortriptyline
- Antipsychotic (neuroleptic)
  - Methotrimeprazine (Levoprome)
- Antispastic agent
  - Baclofen (Lioresal)
- Antispasmodic agent
  - N-butyl scopolamine
- Benzodiazepines
  - Alprazolam (Xanax)
  - Midazolam hydrochloride (Versed)
- Calcium channel blockers
  - Diltiazem hydrochloride (Cardizem)
  - Nifedipine (Adalat; Procardia)
  - Nimodipine (Nimotop)
  - Verapamil hydrochloride (Calan, Isoptin, Verelan)
- Central nervous system stimulants
  - Caffeine
  - Methylphenidate (Ritalin)
- Corticosteroids
  - Betamethasone (Celestone)
  - Dexamethasone (Decadron)
  - Methyprednisolone (Medrol)
- Hemorrhologic agent
  - Pentoxifylline (Trental)
- Local anesthetics
  - Lidocaine (intravenous infusion)
  - Lidocaine hydrochloride jelly (Anestacon)
  - Lidocaine patch 5% (Lidoderm)
- NMDA receptor antagonists
  - Dextromethorphan
    - Fixed combination with morphine (MorphiDex)
- Nonsteroidal anti-inflammatory drugs
  - Aspirin (acetylsalicylic acid)
  - COX-2 inhibitors
    - celecoxib (Celebrex)
    - rofecoxib (Vioxx)
    - valdecoxib (Bextra)
  - Ibuprofen (Advil, Motrin, Nuprin)
  - Indomethacin (Indocin)
    - (Should not be used for extended periods)
  - Ketorolac tromethamine (Toradol)
    - (Should not be used for extended periods)
  - Naproxen (Aleve, Anaprox, Naprosyn)
- Topical irritant
  - Capsaicin (Zostrix)

Figure 2. Adverse reactions that may be attenuated by use of adjuncts to opioids as a result of enabling reduction of opioid dosage.

- selective reversible inhibition of cyclooxygenase or COX-2 inhibitors such as celecoxib, rofecoxib—there are fewer agents in this group, but the number increases yearly.

Although routine use in relatively simple cases of pain is accepted, use of NSAIDs in more extensive procedures is also beneficial. In this latter regard, clinical studies have shown that giving indomethacin via suppository in combination with (1) spinal morphine reduced requests for analgesic medications after cesarean delivery, and (2) patient-controlled analgesia (PCA) morphine decreased use of this opioid after cardiac surgery. Because of potentially severe adverse reactions such as GI bleeding, some NSAIDs should not be used for extended periods (eg, indomethacin, ketorolac tromethamine); another agent, piroxicam, is not recommended as an adjunct because the half-life of approximately 50 hours makes daily adjustments—which are often necessary in pain management—a difficult process. There are, of course, patients who should not receive NSAIDs, such as those with gastric ulceration. However, a thorough evaluation to rule out more definitively such contraindications could serve to identify more candidates for this therapy.

Another factor that interferes with use of these adjuncts is that some patients view over-the-counter NSAIDs as less effective because a physician’s prescription is not required. Clinical studies, however, clearly indicate the pharmacologic efficacy of such medications in many conditions; for example, the reduction in cardiovascular morbidity and mortality with low doses of aspirin. Health professionals...
involved in managing pain should spend extra time to counsel appropriate patients regarding NSAID use; significant gains in analgesia could occur.

- **Acetaminophen**—Acetaminophen is a widely used analgesic, effective alone or in combination with various opioids (eg, Percocet). Although debate exists over the degree of anti-inflammatory properties, it is clearly inferior to NSAIDs in this regard. Therefore, when inflammation is a significant component of a patient’s pain, an appropriate NSAID could be added to acetaminophen therapy. Additional monitoring should be instituted for patients who use alcohol and/or present with any degree of hepatic dysfunction.

- **Antidepressants**—Morphine analgesia can be enhanced by concomitant administration of tricyclic antidepressants (TCAs) such as amitriptyline hydrochloride, clomipramine, and desipramine hydrochloride as shown in several early preclinical studies.3,4 Subsequent human investigations confirmed this facilitative effect with other opioids. In the immediate 24 hours after elective cesarean section, amitriptyline hydrochloride, 25 mg administered intramuscularly, reduced the use of meperidine.5 During the 72 hours after elective cholecystectomy, patients receiving amitriptyline for 3 days after surgery used lower doses of various opioids, including morphine.6 In patients with cancer, TCAs are beneficial analgesic agents, especially in the presence of neuropathic pain.7 More recent investigations demonstrated that TCAs (eg, amitriptyline and nortriptyline) are effective in treatment of polyneuropathy in diabetic and nondiabetic patients8 and postherpetic neuralgia (PHN).9 Novel methods of successfully using amitriptyline for analgesia include combining it with electrotherapy for pain reduction in diabetic peripheral neuropathy,10 and preparing a transdermal gel form for a patient with severe inflammatory bowel disease who could not take drugs orally.11

That TCAs can provide analgesia within 24 hours of administration indicates that such effects are not related to any antidepressant action because this latter effect requires more than 1 week of daily administration. If after 7 days of daily administration, improvement in analgesia is not observed, the antidepressant should be withdrawn and other agents considered.

Possible mechanisms by which TCAs produce pain relief include blocking reuptake of serotonin at presynaptic membranes within central neurons involved in biologic analgesia; serotonin is a major neurotransmitter in these pain-suppression systems, and the increase in synaptic levels may augment these systems. Acute blockade of norepinephrine at related presynaptic membranes may also be a factor. Another important action may be TCA-induced stabilization of nerve membranes; this action may be of particular importance in neuropathic pain where a local anesthetic-like action is effective.

Results from recent clinical studies regarding selective serotonin reuptake inhibitors are varied and do not, at present, support routine administration of these agents in therapeutic approaches to pain management.

- **Topical irritant**—Substance P is a major neurotransmitter of pain signals from peripheral sites to the central nervous system (CNS). Capsaicin promotes depletion of substance P from local terminals of peripheral sensory neurons in the affected region, thus decreasing conduction in type C fibers and producing local anesthesia. Topical application has been shown to be effective in reducing postmastectomy pain12 and chronic neuropathic pain,13 including that associated with diabetic neuropathy,14 however, this agent failed to relieve pain in peripheral neuropathy associated with the human immunodeficiency virus (HIV).15 Recently, a patient with multitrauma in whom a complex regional pain syndrome type I developed in his left forearm experienced good analgesia after topical application of capsaicin.16 Pretreatment with EMLA (eutectic mixture of local anesthetics: lidocaine, 2.5% plus prilocaine, 2.5%) can decrease the initial burning and hyperalgesia that occurs with locally applied capsaicin.17

Patients must be directed to use gloves when applying capsaicin; this product is a powerful irritant and getting even an extremely small amount in the eye could result in excessive and prolonged production of tears that may require emergency intervention.

- **Calcium channel blockers**—Drugs classified as calcium channel blockers reduce the activity of cardiac cells (prolong recovery time after depolarization); this action decreases the rate and strength of cardiac muscle contractions, which, in turn, lessen the need for oxygen and reduce attacks of angina. Calcium ion movement into cells (presynaptic membrane) is also required for release of most neurotransmitters. Because substance P is a neurotransmitter, it is possible that a calcium channel blocker could reduce its release and thus provide some degree of analgesia. Sublingual nifedipine, 10 mg, given in combination with epidural morphine enhanced postoperative analgesia compared with morphine alone; those in thegroup receiving nifedipine had substantial hypotension that was successfully treated by rehydration.18

In a limited investigation in 23 patients with cancer taking morphine daily for prolonged periods (from 21 to 780 days), daily administration of nimodipine (Nimotop), 120 mg, resulted in use of lower doses of oral morphine in 16 of them; three patients on intrathecal morphine therapy also required lower amounts of morphine.19 In a larger double-blind, placebo-controlled study in 54 patients with cancer,20 adding nimodipine reduced the use of morphine and appeared to slow the development of tolerance. In contrast, Hasegawa and Zacny21 found that diltiazem hydrochloride, nimodipine, and verapamil hydrochloride had no effect on morphine analgesia when pain was experimentally induced (eg, cold pressor) pain. Inasmuch as this study was conducted with healthy volunteers, it may not have significance when compared with disorder-induced pain in patients.

- **α2-Agonist**—Several years ago, an 11-year-old boy with severe burns (second and third degree over 78% of his body) was receiving large amounts of morphine and having significant adverse GI, respiratory, and psychological reactions; the addition of low-dose intravenous clonidine hydrochloride resulted in a substantial decrease in morphine dosage with an associated reduction in opioid-induced side effects.22
Clonidine has been used more widely to improve postoperative analgesia. In a study of 200 patients who underwent major abdominal surgery, giving clonidine intravenously with morphine produced greater analgesia in men and in patients younger than 65 years old compared with morphine alone. More recent investigations showed that intra-articular (IA) clonidine plus morphine decreased pain and analgesic use and increased the duration of analgesia after knee surgery compared with IA morphine alone; similar benefits were observed in treatment of neuropathic pain after spinal injury with intrathecal clonidine plus morphine compared with either agent alone.

There are, however, several studies that reported that extradural, transdermal, or oral clonidine did not enhance morphine analgesia in patients undergoing meniscectomy, elective hysterectomy, or radical prostatectomy, respectively.

Local anesthetics—By blocking sodium channels, local anesthetics reduce neuronal hyperexcitability; these drugs have been used for decades to provide local analgesia in dental and more extensive surgical procedures. An ever-present danger of systemically active formulations is systemic absorption of a local anesthetic, which can cause seizures. In a controlled investigation, patients with PHN received an intravenous lidocaine infusion of either 1 mg per kilogram of body weight (mg/kg) or 5 mg/kg over 2 hours; pain and allodynia were reduced with both treatments, but plasma levels of lidocaine in some patients in the group receiving the higher dose were in the cardiotoxic range.

Several investigations indicate that topical application of lidocaine appears to be a particularly effective treatment for PHN. In 1995, Rowbotham et al conducted a placebo-controlled randomized acute study in PHN using a 5% lidocaine gel placed directly on painful skin areas; patients had pain relief with no systemic side effects, and plasma levels of lidocaine did not go above 600 ng/mL (antiarrhythmic activity occurs at 1000 ng/mL and higher). In a second similar study, Rowbotham et al used a lidocaine patch; significant analgesia was produced at the site of application for up to 12 hours, and blood levels of lidocaine were lower than with the gel, i.e., no higher than 104 ng/mL. Galer et al, using a vehicle-controlled cross-over design, examined the effectiveness of a lidocaine patch for 28 days in 32 patients with PHN; effective analgesia was obtained with no significant adverse reactions. An open-label, nonrandomized investigation used the topical lidocaine patch in 332 patients with PHN; no serious adverse reactions occurred, and approximately 75% of patients obtained pain relief. In a limited study, Devers and Galer reported good analgesia for approximately 6 weeks of using the topical lidocaine patch in 13 of 16 patients with refractory peripheral neuropathic pain from various conditions such as postmastectomy and postthoracotomy pain and diabetic polyneuropathy. A mild skin rash localized to the site of application is the most common adverse reaction associated with the lidocaine patch.

Therefore, results from these investigations indicate that the lidocaine patch is an efficacious, easy-to-use product for providing analgesia in PHN and it may have utility in other conditions associated with neuropathic pain.

Anticonvulsants—By blocking sodium channels, anticonvulsants such as carbamazepine, lamotrigine, phenytoin, and topiramate reduce neuronal hyperexcitability and have been successfully used to treat pain in cases in which opioids have little or no efficacy, such as trigeminal neuralgia and diabetic neuropathy. One possible reason is that an increase in density of sodium channels may occur after a patient recovers from nerve damage; support for this possibility is derived from a preclinical study. In a limited report on two patients with diabetic neuropathy or atypical facial neuralgia, lamotrigine in daily doses of 50 mg and 400 mg daily, respectively, provided pain relief when other drugs (eg, NSAIDs, opioids) did not. Eisenberg et al randomized administered placebo or lamotrigine to 59 patients with diabetic neuropathy and found this anticonvulsant to be effective in relief of pain. Gabapentin also produces analgesia in diabetic peripheral neuropathy and PHN; the mechanism of this action is not established but may be related to an effect on calcium channels.

Antiarrhythmics—Based on the fact that damaged nerves exhibit increased electrical excitability, the possibility exists that antiarrhythmic drugs, which suppress abnormal electrical cardiac activity, may also provide effective therapy for pain associated with peripheral neuropathy. However, these medications are not widely effective treatment for arrhythmias and often produce adverse reactions. Therefore, their use in pain management appears to be limited.

Kieburz et al used mexiletine and amitriptyline in a randomized double-blind study of pain in HIV; neither agent provided significant pain relief.

N-methyl-D-aspartate receptor antagonists—Tissue injury can activate N-methyl-D-aspartate (NMDA) receptors, which subsequently facilitate development of peripheral hyperalgesia (greater pain than normally expected) and central sensitization (“windup”) to painful stimuli. Some clinical investigations have reported efficacy in pain reduction with two NMDA-receptor antagonists, dextromethorphan and ketamine.

In patients with terminal cancer pain, intrathecal ketamine enhanced the effectiveness of intrathecal morphine, epidural ketamine increased the duration of epidural morphine, and intravenous ketamine improved oral morphine analgesia; subcutaneous ketamine was shown to improve analgesia and decrease tolerance to morphine in three case studies. More recently, oral ketamine increased pain relief in cancer patients with intractable neuropathic pain who were also taking maximally tolerated amounts of morphine, valproate, amitriptyline, or a combination of these medications.

With respect to dextromethorphan (DM), several studies show an inherent analgesic effect as well as a positive interaction with morphine. In diabetic neuropathy and PHN, Nelson et al started patients on DM at 120 mg orally and titrated over 4 weeks until side effects became intolerable (sedation or dizziness) or a total daily dose of 960 mg was reached (mean dosage was 381 mg/d in
the group with diabetic neuropathy; 439 mg/d, in the group with PHN); a decrease of 24% in pain was seen in the group with diabetic neuropathy, but there was no such effect in PHN. Katz\textsuperscript{50} evaluated the efficacy of a fixed combination of morphine and DM on chronic pain (17% of patients had cancer); this product decreased tolerance to morphine and allowed patients to use 50% less morphine. In knee surgery, patients who received 200 mg of DM every 8 hours used less morphine for their postoperative pain compared with those who were given placebo.\textsuperscript{51}

- **Central nervous system stimulants**—Sedation, a major problem in pain management, is often produced by opioids in the early stages of administration until tolerance develops and also when an opioid-tolerant patient is switched to a higher dose; similarly, this adverse reaction is associated with many adjuncts (eg, gabapentin). To counteract sedation, a CNS stimulant can be added to therapy. Analgesia will not be reduced; in fact, the opposite is likely to occur, ie, enhancement of pain relief.\textsuperscript{52} Caffeine is one such agent and may require only that a patient switch from drinking tea to coffee. If a more powerful effect is required, methylphenidate would be a better choice than amphetamine; this latter drug is more likely to produce anorexia and elevated blood pressure than the former.

- **Antispasmodic agents**—Opioids increase tone of the GI tract, which can lead to pain, and patients do not develop tolerance to this adverse reaction. In a limited study involving patients who underwent tubal ligation and vaginoplasty, N\textsubscript{-}butyl scopolamine, an anticholinergic antispasmodic agent, was added to the general anesthetic regimen 20 to 30 minutes before closure; this agent provided relief of postoperative visceral pain.\textsuperscript{53}

- **Antispastic agents**—Intrathecal administration of baclofen, which activates \(\gamma\)-aminobutyric acid (GABA) receptors (specifically GABA-B sites), reduces central pain in patients with spinal lesions. Gordon et al\textsuperscript{54} reported that baclofen enhanced morphine analgesia in patients undergoing oral surgery.

- **Hemorrheologic agents**—Pentoxifylline increases blood flow and tissue oxygenation by decreasing blood viscosity, increasing flexibility of erythrocytes, and possibly by reducing platelet activity. Although not considered a usual adjunct, pentoxifylline can reduce muscle pain and rest pain associated with intermittent claudication;\textsuperscript{55} this agent should be considered in such patients before opioids are administered.

- **Corticosteroids**—Because of the ability of reducing inflammation (inhibit prostaglandin production), edema (decrease in capillary permeability), and neuronal excitability (probable direct effect on cell membranes), corticosteroids can be used to treat back pain due to spinal cord compression and headache from brain mets (both related to edema), bone pain, and neuropathic pain. Betamethasone, dexamethasone, and methylprednisolone are among the most commonly used; they may also improve appetite and decrease nausea. In a large study on patients with PHN, intrathecal methylprednisolone given once per week for 4 weeks reduced pain; there was also a 70% decrease in use of the NSAID diclofenac.\textsuperscript{56} More recently, intrathecal administration of betamethasone in three patients with advanced pelvic or perineal cancer produced analgesia that was rapid (within 10 minutes) and sustained (5 or more days) with concomitant improvement in activity, appetite, and sleep.\textsuperscript{57}

Corticosteroids are very powerful drugs with substantial efficacy but can produce significant adverse reactions. Those that may occur within the first day to 2 weeks of administration include hypertension, hyperglycemia, immunosuppression (eg, increased incidence of candidiasis), GI ulceration, and psychiatric disorders (affective disorders, psychosis, cognitive impairment). Although of limited concern in terminally ill patients, toxicity occurring during prolonged administration include Cushing’s disease, proximal myopathy, osteoporosis, and, rarely, aseptic necrosis of bone.

- **Antipsychotics (neuroleptics)**—A review of the effectiveness of antipsychotics in pain management indicates that only methotrimeprazine has been shown to have analgesic activity.\textsuperscript{58} An investigation on emergency room patients with migraine demonstrated that intramuscular methotrimeprazine was as effective as intramuscular meperidine in producing pain relief.\textsuperscript{59} Although these agents are useful in reducing nausea, agitation, and psychological stress—factors known to increase pain sensitivity—it is also possible that they may increase sensitivity to pain. Adverse reactions associated with antipsychotics include drowsiness, orthostatic hypotension, pain at injection site, extrapyramidal reactions, tardive dyskinesia, cardiotoxicity, and agranulocytosis.

- **Benzodiazepines**—As routine preoperative medications, benzodiazepines are given for antianxiety effects; induction of general anesthesia is easier with a relaxed patient. However, there is also evidence showing that benzodiazepines provide some degree of pain relief. An early investigation showed that alprazolam produced substantial analgesia in patients with cancer who had malignancies and an associated causalgic pain syndrome.\textsuperscript{60} A study on healthy subjects given mildly painful electrical shocks found that alprazolam lowered not only anxiety ratings, but also pain scores.\textsuperscript{61} Patients who received an oral narcotic plus a benzodiazepine before undergoing bone marrow aspirate and biopsy had less pain than usual for this type of procedure.\textsuperscript{62} When midazolam hydrochloride was added to continuous epidural infusion of bupivacaine for treatment of pain after gastrectomy or cholecystectomy, more analgesia was produced compared with bupivacaine alone.\textsuperscript{63} A possible explanation for benzodiazepine-induced analgesia was reported in a recent in vitro study showing that these agents directly activate opioid receptors of the \(\kappa\) subtype.\textsuperscript{64}

**Comment**

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References


