

Pharmacist perspective on extended release analgesics for persistent pain

Jeffrey Fudin, Bill H. McCarberg, Gavril Pasternak, Leslie N. Schechter, Sidney H. Schnoll, and Stephen D. Lande

Abstract

Objective: To provide an overview of the key patient- and drug-related issues relevant to the use of extended release (ER) versus immediate release (IR) analgesics and the variables that must be taken into consideration when selecting a specific type of ER analgesic to optimize treatment, such as efficacy, dosing, safety, drug–drug and drug–disease interactions, and abuse and diversion issues.

Data sources: Published articles identified through bibliographies from gathered articles.

Study selection: By the authors.

Data extraction: By the authors.

Data synthesis: Persistent pain is a prevalent condition experienced by about 25% of Americans that continues to spur the use of prescription analgesic medications. ER analgesic formulations have been introduced that may offer several advantages over IR formulations, such as reduced “pill” burden, improved convenience and adherence, and around-the-clock pain relief. ER analgesics offer more consistent steady-state plasma levels without the more pronounced peaks and troughs associated with short-acting formulations, leading to reduced adverse events. In this article, the formulations of ER analgesics and the practical considerations, therapy options, and potential issues associated with them are discussed. In addition, several brief case studies are presented to highlight some of the clinical scenarios in which specific types of ER analgesics may offer greater benefit with less risk than other analgesics.

Conclusion: Pharmacists are uniquely positioned to assess patients’ response to therapy with and susceptibility to risk from ER analgesics and to counsel patients on the differences between specific analgesic classes and products.

Keywords: Analgesic, nonsteroidal anti-inflammatory, opioid, pain, pain management.

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Chronic pain—pain that persists beyond the normal healing period and disrupts sleep and normal daily activities—remains a prevalent condition that drives the use of OTC and prescription analgesic use.¹ Indeed, persistent noncancer pain, specifically musculoskeletal pain, is the chief symptom that triggers new visits to primary care physicians.² The American Pain Foundation estimates that about 25% of all Americans experience persistent pain, and about 10% take prescription

medication to manage it.³

In 2006, prescription analgesics accounted for 7.2% (almost 266 million) of all prescriptions dispensed (about 3.7 billion) in all pharmacy settings and for 7.7% of all prescriptions dispensed in the community pharmacy sector. Extended release (ER) prescription analgesics accounted for 7.0% (about 181 million) of all prescription analgesics dispensed in 2006 and 6.2% of all prescription analgesics dispensed in the community pharmacy sector. The annual percentage

growth rate in volume of ER analgesics has increased during the period 2003 to 2006, from 9.3% in 2003 to 11.4% in 2006. During 2003 to 2006, the annual percentage growth rate in volume of all analgesics increased from 4.0% to 5.7%. As a result, for pharmacists, analgesics, and increasingly ER analgesics, are among the most commonly dispensed prescriptions.⁴

Indeed, community pharmacists are at the forefront of balancing analgesic drug efficacy with risks across an array

of drug classes and patient groups. Pharmacists can play a central role in improving the management of persistent pain by counseling patients on the appropriate use of OTC and prescription analgesics and by consulting with prescribers when a prescription analgesic treatment appears inadequate or inappropriate, or when potential drug interaction issues arise. In addition, pharmacists can monitor for potential aberrant medication-taking behaviors indicating opioid analgesic abuse or diversion. In these roles, the pharmacist can act as a gatekeeper, assessing whether a prescribed analgesic prescription serves a useful and legitimate medical purpose through the life of the prescription.⁵ To perform these tasks, however, pharmacists require sufficient, up-to-date knowledge on pain management and newer analgesic formulations that have entered the market. Toward that end, the main purpose of this review is to provide an overview of the key patient- and drug-related issues relevant to the use of ER versus immediate release (IR) analgesics and the variables that must be taken into consideration when selecting a specific type of ER analgesic to optimize treatment.

ER analgesic formulations

Rationale

For many patients with persistent pain, ER analgesics can offer important advantages over short-acting formulations. The potential benefits of ER over IR analgesic formulations include improved convenience and adherence secondary to reduced “pill” burden and improved sleep secondary to reduced nighttime pain.^{6,7} Sustained pain relief is a primary goal in the management of persistent pain, and the use of ER formulations provides the best opportunity to achieve around-the-clock analgesia, with short-acting analgesics used to titrate to effective dose

and manage breakthrough pain.⁷

Further, more consistent steady-state plasma levels with long-acting formulations, without the more pronounced peaks and troughs associated with short-acting formulations, predict a reduction in troublesome adverse events such as nausea and somnolence. However, whether long-acting formulations yield consistently improved tolerability remains a controversial issue.⁸ Moreover, persistent pain has been directly linked to sleep disturbances, highlighting the importance of effective 24-hour analgesia as a step in improving patients’ quality of life and restoring normal daily function.⁹ The use of ER analgesics that require administration every 8 to 72 hours has shifted patients’ focus from pain and pain management to family, work, and daily activities.⁷

A number of prescription ER opioids and ER NSAIDs are currently available for the treatment of persistent pain.

NSAIDs

NSAIDs available in ER formulations are displayed in Table 1. Other NSAIDs—celecoxib (Celebrex—GD Searle), meloxicam (Mobic—Boehringer Ingelheim), and piroxicam (Feldene—Pfizer)—are indicated for once-daily dosing by virtue of their long half-lives. However, piroxicam is often not recommended for use in older patients, who may be more sensitive to its adverse effects.

All NSAIDs display efficacy in relieving pain and inflammation, and selective COX-2 inhibitors, such as celecoxib, demonstrate efficacy in persistent pain comparable to nonselective agents.^{10,11}

Certain patients may respond to one NSAID and not another. There are no data that would predict which patients will respond well to one NSAID versus another. Thus, an inadequate response to one NSAID does not preclude a response to another NSAID. If the response to an

NSAID is inadequate, factors such as the nature and extent of pain as well as patient adherence should be considered. Generally, less frequent dosing, as with ER formulations, bolsters adherence.¹² In addition, if an NSAID in one structural class (such as ibuprofen, a propionic acid derivative) is not effective, changing to another structural class (such as sulindac, an acetic acid derivative) may be beneficial. Overall, clinical studies show that the ER, once-daily NSAIDs are as effective as their IR counterparts or other IR NSAIDs, with comparable incidences of adverse effects.^{13,18}

Opioids

Opioid analgesics can activate three different classes of receptors—mu, kappa, and delta. While some short-acting opioids act at the kappa receptor, all of the long-acting opioids and opioids with ER formulations, with the exception of tramadol, exert their effects only through mu receptor activation. Some opioids, such as methadone and levorphanol (Levo-Dromoran—Valeant), may provide up to 8 hours of analgesia because of their long half-lives, while others are long-acting because they were designed as ER formulations (Table 2). In contrast to conventional opioid analgesics, tramadol, a unique, centrally acting, synthetic analgesic, displays a relatively modest affinity for mu opioid receptors—10 times less than codeine and 6,000 times less than that of morphine.¹⁹ In addition to its modest opioid activity, tramadol inhibits the reuptake of norepinephrine and serotonin, and, together, these complementary actions account for its analgesic activity.²⁰ Because tramadol has both opioid and nonopioid mechanisms of action, it is considered a mixed- or dual-action analgesic.

Morphine, oxycodone, and oxycodone are, in their IR formulations, effective short-acting agents that require frequent administration to achieve around-the-clock analgesia and are thus ideal candidates for developing ER formulations. Since fentanyl displays significant first-pass effect, it is administered in transdermal formulations to achieve long-duration analgesia. In addition, short-acting tramadol, because of its dual action or mixed mechanism of action, is well tolerated against both nociceptive and neuropathic pain, supporting an ER formulation to provide consistent 24-hour analgesia.²⁸⁻³⁰ In

Table 1. Extended release NSAIDs marketed in the United States

Brand name	Generic name
Voltaren XR	Diclofenac
Lodine XL	Etodolac
Indocin SR	Indomethacin
Naprelan	Naproxen
Oruvail	Ketoprofen

the treatment of persistent, noncancer pain, systematic reviews of the literature suggest that long-acting oral opioids alleviate both nociceptive and neuropathic pain, although clinical trials report substantial individual variations in response.³¹

The superior effectiveness, effect on quality of life, and adherence associated with ER versus IR analgesic formulations in the treatment of persistent cancer pain have been demonstrated. In a randomized study of 83 patients with chronic cancer pain, patients receiving controlled release (CR) morphine demonstrated a significant decrease in pain distress over time and significantly lower pain intensity, better adjustment to disease and treatment, improved strength and perception of quality of life, and better adherence than patients receiving short-acting opioids. Patients receiving

the short-acting opioids had significantly better outcomes in the areas of nausea and constipation, which may be a result of the higher rates of adherence and achievement of a steady analgesic state in the CR morphine group.³²

ER analgesic formulations have also been associated with improvements in physical function and sleep. In a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel group study of patients with persistent osteoarthritis, 124 patients who received tramadol ER (in doses up to 400 mg per day) demonstrated a significantly greater improvement in a number of endpoints than 122 patients who received placebo, including measures on the Arthritis Pain Intensity Visual Analog Scale and the Western Ontario and McMaster University Arthritis pain, physical function, and stiffness subscales.³²

Patients on tramadol ER also showed significantly greater improvements than those receiving placebo on various parameters of the Chronic Pain Sleep Inventory, including trouble falling asleep, awakened by pain during the night or in the morning, and overall quality of sleep. Additionally, the discontinuation rate because of lack of treatment was significantly lower in the tramadol ER versus the placebo group.³²

Although ER analgesics appear to have a favorable effect on physical function, sleep, and adherence, additional research is needed to determine whether ER analgesics of any therapeutic class are indeed superior to IR treatments on these parameters. Currently, the evidence from the larger body of clinical studies and systematic reviews is insufficient to conclude that ER opioids are superior to IR opioids in terms of pain

Table 2. Characteristics of extended release opioid analgesics marketed in the United States^a

Generic names	Brand names	Dosing frequency	Formulation	Time to steady state	Strengths	Mechanism of action
Fentanyl	Duragesic	72 hours	Patch	Varies depending on skin permeability and fentanyl clearance	12.5, 25, 50, 75, 100 µg/h	Mu agonist
Morphine sulfate	Avinza	24 hours	Capsule: IR and ER beads	2–3 days	30, 60, 90, 120 mg	Mu agonist
	Kadian	12 or 24 hours	Capsule: polymer-coated pellets	2 days	20, 30, 50, 60, 100 mg	Mu agonist
	Oramorph	8–12 hours	Tablet	1–2 days	15, 30, 60, 100 mg	Mu agonist
	MS Contin	8–12 hours	Tablet	1 days	15, 30, 60, 100, 200 mg	Mu agonist
Oxycodone HCl	OxyContin	12 hours	Tablet	1–1.5 days	10, 20, 40, 80 mg	Mu agonist
	Opana ER	12 hours	Tablet	3 days	5, 10, 20, 40 mg	Mu agonist
Tramadol	Ultram ER	24 hours	Tablet	4 days	100, 200, 300 mg	Mu agonist and serotonin and norepinephrine reuptake inhibition

^a Data derived from products' respective package inserts.^{21–27}

reduction and functional improvement or to support the use of one long-acting opioid over another.³³⁻³⁶

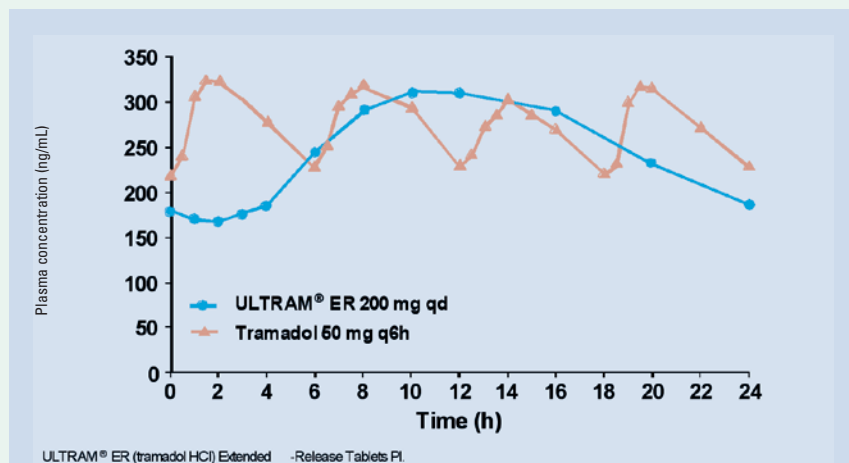
It should be noted, however, that clinical trials comparing ER and IR analgesic formulations may represent a setting that is significantly different from the real-world setting typically encountered by clinicians.³⁷ For instance, the intensive subject monitoring in clinical trials ensures adherence so that the efficacy and tolerability of the intervention, when ideally administered, can be accurately assessed. By contrast, in the real-world clinical setting, adherence is an unpredictable variable, and failure to achieve consistent adherence with the daily treatment regimen can clearly undermine long-term efficacy. Therefore, future research comparing ER and IR analgesics should be conducted in naturalistic settings to better assess the effects of these formulations on the various aforementioned parameters. In real-world settings, ER analgesic formulations should offer an advantage because reduced dosing frequency can boost adherence, and, in turn, sustain long-term efficacy in the management of persistent pain.¹²

Practical considerations

Dosing

NSAIDs induce dose-dependent analgesic effects characterized by a minimum effective dose and a ceiling dose.³⁸ Since NSAIDs are associated with substantial individual variability in minimum effective, toxic, and ceiling doses, titration from a low starting dose appears most appropriate. Further, NSAIDs appear most effective in pain secondary to inflammation and bone pain, and less effective in neuropathic pain.

Although opioid blood concentrations are not directly predictive of analgesic response, increasing the dose of strong opioids like morphine yields greater analgesia without a ceiling effect; the dose ceiling is determined largely by the emergence of adverse effects.³⁹ However, some opioid analgesics, including codeine and tramadol, do have ceiling effects.⁴⁰ According to the American Pain Society, the choice of an opioid analgesic should be based on the clinician's experience with the opioid and on patient-related factors such as age and previous experience with opioid treatment.⁴¹ Wide variations in pain percep-



ULTRAM® ER (tramadol HCl) Extended Release Tablets PI

Figure 1. Mean steady-state tramadol concentrations on day 8 after administration of Ultram ER once daily and tramadol every 6 hours

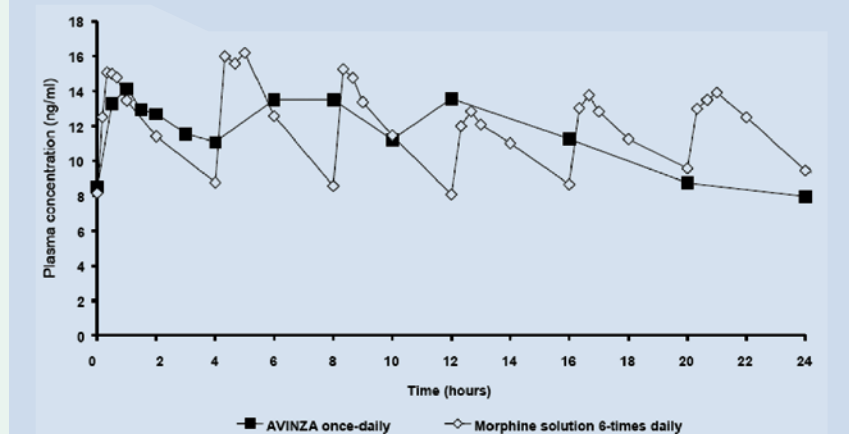


Figure 2. Mean steady-state morphine concentrations following once daily administration of Avinza capsules or 6-times daily administration of morphine solution

tion and response to certain analgesic therapies, possibly secondary to genetic polymorphism, comorbid conditions, concomitant medications, or tolerance, have fostered the use of opioid rotation (replacing one drug with equianalgesic doses of another) to achieve a satisfactory clinical response in patients with an inadequate response to one opioid analgesic.⁸ In addition, some patients with at least moderate pain may require more frequent dosing of ER opioids than recommended by the drug's manufacturer. The results of a recent prospective observational study that included adult outpatients receiving opioid treatment for chronic, nonmalignant pain revealed that more frequent dosing than recommended was required by 91%, 86%, and 50% of the patients treated with oxycodone ER, morphine ER, and the fentanyl patch, respectively.⁴²

At the initiation of opioid therapy, the dosage and frequency should be based on the intensity of the patient's pain, comorbidities, concomitant therapies, and previous opioid exposure.⁸ Short-acting opioids may be preferable at the initiation of therapy because these agents are easier to titrate; however, they result in rapid rises and falls in plasma opioid levels with long-term use. Consequently, after a stable, effective dose with a minimal need for rescue medication has been achieved with short-acting opioids, it is often preferable to convert to an ER formulation of the same opioid.

Alternatively, long-acting opioids, such as Avinza (morphine sulfate—King), OxyContin (oxycodone—Purdue), and Ultram ER (tramadol—Ortho-McNeil) are indicated and can be used in the initiation of analgesic therapy.^{22,25,27} In two separate studies—one in patients

Table 3. Potentially serious safety issues with currently marketed analgesics

Body system	Analgesic class			
	NSAID		Opioid	
	Nonspecific	COX-2 specific	Mu agonist	Mixed
Gastrointestinal	Perforations, obstructions, bleeding ⁴⁴	GI discomfort, bleeding, ulceration, and perforation of stomach, large and small intestine. However, decreased risk for upper GI tract complications and symptomatic GI ulcers versus nonspecific NSAIDs ^{44,45}	Nausea, constipation ²³	Nausea, vomiting ²⁸
Cardiovascular	Myocardial infarction, heart failure ⁴⁵⁻⁴⁸	Myocardial infarction, stroke, hypertension ^{45-47,49}	None	None
Central nervous system	None	None	Cognitive impairment, somnolence, reduced respiratory drive ^{50,51}	seizure risk, somnolence ²⁸
Hematologic	platelet aggregation ⁴²	Anemia ⁴⁹	None	None
Renal/hepatic	Renal pathology ⁵²	Long-term administration can cause renal papillary necrosis and other renal injury ⁴⁹	None	None

with chronic low back pain and the other in patients with chronic cancer pain—the percentage of patients achieving stable analgesia, the time to stable pain control, and the degree of pain control achieved was not significantly different between patients receiving ER and IR oxycodone.³⁶ Additionally, pain relief was achieved with a minimum dose titration of either ER or IR oxycodone in both trials. The authors concluded that oral ER oxycodone can be used as readily as the IR formulation for titration to stable pain control in patients with moderate to severe chronic cancer or noncancer pain.³⁶

Adverse effects

When compared with IR analgesic formulations, ER formulations display smoother steady-state drug plasma

concentrations, with notable absence of sharp peaks and troughs (Figures 1 and 2), a pharmacokinetic characteristic that may, in principle, predict a diminished risk for adverse events such as nausea, agitation, and somnolence.⁸ Studies have drawn different conclusions as to whether ER or IR formulations have the better adverse event profile; however, in general clinical practice, as opposed to a controlled trial setting, the convenience of longer-acting formulations may result in improved patient adherence, fewer dosing errors, and less-frequent adverse events.⁸

However, whether ER analgesics reduce the risk for adverse events remains a controversial issue. Because of the paucity of clinical data demonstrating differences in adverse effect liability

between ER and IR analgesics, a conservative approach to treatment would assume that ER and IR analgesic formulations confer a similar risk for adverse effects with long-term use in persistent pain. Thus, when choosing one ER analgesic over another, a consideration of the safety data for their respective IR formulations provides a reasonable portrayal of the adverse effects that could be expected with the ER formulation. The potential for serious adverse effects with the different analgesic classes with ER formulations varies considerably (Table 3).

NSAIDs

Gastrointestinal effects

NSAID use heightens the risk for adverse gastrointestinal (GI) events

almost threefold, with the highest risk in subjects over the age of 60.⁵² Moreover, among older patients (≥ 65 years), nonaspirin NSAID use elevates the risk for gastric ulcer fourfold.⁵³ The identification of *Helicobacter pylori* as a trigger for the development of peptic ulcer raises the possibility of a synergistic relationship between the presence of *H. pylori* infection and NSAID use.⁵⁴

In terms of GI tolerability, selective COX-2 inhibitors can offer short-term, modest benefits over nonselective agents in patients not taking concomitant aspirin. In the 6-month, Celecoxib Long-Term Arthritis Safety Study (CLASS), 8,059 subjects with osteoarthritis were randomized to either high-dose celecoxib therapy (400 mg twice daily) or to treatment with ibuprofen or diclofenac.⁴³ Low-dose aspirin use (≤ 325 mg/day) was permitted. In all celecoxib-treated subjects, the combined endpoint of annualized risk for upper GI tract complications (perforation, obstruction, or bleeding) plus symptomatic GI ulcers was significantly reduced with the use of celecoxib therapy, but not GI tract complications alone.

In subjects not taking aspirin, the combined endpoint, as well as the risk for upper GI tract complications, were significantly reduced, while in subjects taking aspirin, neither of these parameters was significantly reduced. For NSAIDs, the spotlight is now focusing on cardiovascular risks in addition to GI tract complications.

Cardiovascular effects

The results of a meta-analysis of 50 clinical trials suggest that nonselective NSAIDs can elevate blood pressure by 5 mm Hg and interfere with the actions of certain antihypertensive agents, such as beta-blockers, perhaps elevating the risk of cardiovascular mortality.⁵⁵ However, a recent meta-analysis of patient data derived from studies in osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, low back pain, and Alzheimer's disease suggested that the risk for the combined endpoint of nonfatal myocardial infarction (MI), nonfatal stroke, and cardiovascular death was statistically similar for celecoxib, nonselective NSAIDs, or placebo.⁵⁶ In this analysis, the dose

of celecoxib, the use of aspirin, or the presence of cardiovascular risk factors did not influence the results. These findings stand in sharp contrast to the findings of other clinical studies that show all NSAIDs—selective and nonselective—elevate the risk for cardiovascular adverse events, including at least a 40% increase in the risk for MI.^{44–46} Further, the use of nonaspirin NSAIDs has been linked to a twofold increase in the risk for hospitalization for congestive heart failure in older patients with a history of cardiovascular disease.⁴⁷ In this analysis, the risk for congestive heart failure increased as NSAID dose increased, and with the use of long-half-life formulations.

Renovascular effects

NSAIDs, both selective and nonselective, have been associated with the potential for renovascular adverse events.⁵⁷ In conditions associated with intravascular volume depletion or renal hypoperfusion, NSAID interference with COX-2 activity can hinder renal blood flow and glomerular filtration rate. In addition, the use of high-dose NSAIDs

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in patients with frequent urinary tract infections may enhance the risk for analgesic nephropathy, a condition characterized by slow, progressive renal failure.⁵⁸ NSAID use has also been associated with acute nephritis, hematuria, proteinuria, and occasional nephrotic syndrome.⁵¹

Hematologic effects

All nonselective NSAIDs diminish platelet aggregation by reversibly inhibiting COX-1. Platelet aggregation inhibition endures as long as therapeutic plasma concentrations are present; thus, with long-acting or ER NSAID formulations this effect would be continuous during therapy.⁴¹

Renal effects

NSAIDs can induce renal insufficiency by decreasing the synthesis of renal vasodilator prostaglandins yielding interstitial nephritis, impaired renal secretions, and enhanced tubular water and sodium reabsorption.⁴¹ The risk factors for NSAID-related acute renal failure include the presence of congestive heart failure, chronic renal insufficiency, cirrhosis with ascites, systemic lupus erythematosus, intravascular volume depletion, significant atherosclerotic disease in older patients, and multiple myeloma. Additionally, the risk for renal toxicity in older patients is sharply increased in the presence of diabetes and/or the concomitant use of ACE inhibitors.⁵⁹

Opioids

Overall adverse events

Sedation, constipation, nausea, vomiting, pruritis, and respiratory depression are the hallmark adverse effects associated with opioid therapy.⁴¹ However, these adverse effects may escape recognition unless the patient is queried directly by a health care professional. Often, the common adverse events secondary to long-term opioid treatment can be dampened or averted by lowering the opioid dose, changing drug formulations, or using a different opioid analgesic.²⁰ For instance, fentanyl and oxymorphone trigger minimal histamine release and are thus associated with a lower risk for pruritis compared with other opioid analgesics.⁴¹ Additionally, many of the opioid-related adverse effects usually subside or diminish over time, and the dose can be titrated without the risk of the original adverse effect.⁶⁰

A meta-analysis that included data

Table 4. Common drug interactions involving NSAIDs

Medication	Potential effect
Beta blocker	Antihypertensive action
ACE inhibitor	Impaired renal function
Statin	NSAID metabolism
Antihistamine (H ₂)	NSAID toxicity; NSAID efficacy
Corticosteroid	NSAID efficacy
Furosemide	NSAID toxicity
Sulfonylurea	Possible hypoglycemic effect
Benzodiazepine	Delayed NSAID absorption
Nifedipine	Nifedipine efficacy
Anticoagulant	Bleeding risk
Thiazides	Diuretic efficacy; hyponatremia
Tricyclic antidepressant	Tricyclic antidepressant toxicity

Adapted with permission from reference 71.

from 34 mostly short-term trials examined the incidence of common adverse events associated with opioids typically used for the management of moderate noncancer pain.⁵⁹ A total of 4,212 patients contributed data related to opioid adverse events; just over half received tramadol or tramadol plus acetaminophen, while a third received codeine plus acetaminophen, dextropropoxyphene plus acetaminophen, or morphine. Across these trials, about half the subjects experienced at least one treatment-emergent adverse event—the most prevalent was dry mouth (25%), followed by nausea (21%), constipation (15%), dizziness (14%), drowsiness or somnolence (14%), pruritus (13%), and vomiting (10%).

Central nervous system effects

At high doses or in patients with renal impairment, opioid-related neurotoxicity may manifest as cognitive impairment, hallucinations, delirium, generalized myoclonus, hyperalgesia and/or allodynia.⁴⁹ Further, in patients with persistent nonmalignant pain, daily opioid doses equivalent to morphine 60 mg (median) have been associated with impairments in measures of vigilance/attention, psychomotor speed, and working memory.⁶¹ Sedation typically emerges at the initiation of opioid therapy or with dose increases.⁶²

For all opioids, equianalgesic doses

yield similar reductions in respiratory drive.⁴⁹ However, pure mu opioid agonists, such as oxycodone and morphine, are seldom associated with significant respiratory depression when taken chronically as monotherapy in non-high risk patients. Although rare in patients receiving chronic opioid therapy for persistent pain, respiratory depression is more likely in opioid-naïve patients who require high opioid doses for severe pain.⁴⁰

According to the tramadol labeling, seizures have been reported in patients receiving this agent within the recommended dosage range, and the risk for seizures is heightened when tramadol is taken concomitantly with selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, other tricyclic compounds (e.g., cyclobenzaprine), or opioids. Tramadol may increase this risk in patients with, or at risk for, seizure disorders.²⁷ However, a postmarketing surveillance case control study of 10,916 patients who had taken tramadol during a 22-month period was conducted to estimate the risk of seizures associated with tramadol, which was generally prescribed for musculoskeletal disorders in a dose of 50 mg three to four times daily.⁴⁰ The study found 11 patients who had definite seizures and 6 who had possible seizures. Within 90 days prior to a seizure, no patient took only tramadol, 8 used opiates, 5 took both tramadol and

Table 5. Common interactions involving opioid analgesics

Medication	Potential effect
Tricyclic antidepressants	Inhibition of morphine glucuronidation leading to blood levels
MAO inhibitors and SSRIs	Risk for adverse events
Diuretics	Diuretic efficacy
Methadone and morphine	Metabolism of desipramine, yielding toxicity
Quinine	Conversion of codeine to morphine, yielding efficacy
Metoclopramide	Early peak plasma levels with controlled-release formulations
Erythromycin	Opioid effects
Rifampin	Opioid effects
CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine)	Tramadol levels Hydrocodone/codeine analgesia
CYP2D6 substrates (e.g., debrisoquin, dextromethorphan, metoprolol)	Tramadol levels
Central nervous system depressants	Risk for profound sedation or coma
Muscle relaxants	Risk for respiratory depression

Adapted from reference 21. Abbreviations used: CYP, cytochrome P450; MAO, monoamine oxidase; SSRI, selective serotonin reuptake inhibitor.

opiates, 3 received other analgesics and 1 took no analgesics. In the 30-day window prior to the onset of a seizure, only one patient took tramadol alone. The authors concluded that the use of tramadol alone as prescribed for patients in the study rarely causes seizures.⁴⁰

Multimodal therapy

The utility of multimodal therapy—combining analgesics with different mechanisms of action—has gained wide recognition in recent years.⁸ Prudent multimodal analgesic therapy offers the opportunity to improve efficacy and safety when compared with equi-analgesic doses of the individual agents.⁶³

Combinations of acetaminophen with a weak opioid agent have gained wide acceptance in the management of persistent pain. A substantial percentage of patients treated with oral morphine (10% to 30%) fail to achieve adequate analgesia because of excessive adverse effects, inadequate efficacy, or combination of both factors.⁶⁴ For these patients, the use of a multimodal regimen, such as adding an NSAID to the opioid regimen, can enhance analgesia in certain patients and is opioid-sparing—reducing the required opioid dosage by as much as 14% to 50%—thereby lowering the risk for adverse events and delaying

the development of tolerance and hyperalgesia.^{8,65} However, use of a combination product requires careful monitoring of the cumulative dose of the nonopioid (i.e., acetaminophen or NSAID) to avoid toxicity.

Another example of combination analgesia is tramadol plus acetaminophen, which offers complementary pharmacokinetic and pharmacodynamic actions, and the results of studies in animals suggest that this combination provides genuine synergistic analgesic efficacy.⁶³ In a study of patients with subacute back pain, tramadol 37.5 mg plus paracetamol 325 mg (acetaminophen) demonstrated a significant decrease in the incidence of adverse events, including nausea, vomiting, vertigo, and constipation, when compared to tramadol 50 mg alone.⁶³

Breakthrough pain

Multimodal therapy is also used to manage breakthrough pain, commonly defined as an abrupt, short-lived, and intense exacerbation of pain observed in patients with otherwise stable persistent pain. Breakthrough pain is common in patients with chronic pain associated with various diseases, including cancer, with a reported incidence ranging from 16% to 95%.⁶⁶ Results of a telephone

survey conducted with 228 patients with diverse types of chronic noncancer pain indicated that breakthrough pain is highly prevalent and varied in opioid-treated patients. Even though all patients had controlled baseline pain, 74% experienced severe to excruciating breakthrough pain.^{66,67} An important principle related to the use of ER analgesics is that breakthrough medication—in an immediate release formulation—should be made available during the extended dosing intervals.⁶⁸

While multimodal therapy may enhance the risk for adverse events from drug–drug interactions, combined therapy may allow for smaller therapeutic doses of each individual agent; thus, care must be taken when choosing analgesic combinations.

Drug interactions NSAIDs

Because of extensive plasma-protein binding, NSAIDs interact with commonly used drugs such as warfarin, digoxin, oral antidiabetics, and antihypertensives, especially ACE inhibitors and diuretics.⁶⁹ NSAIDs can decrease the efficacy of diuretics, beta-blockers, and ACE inhibitors.⁷⁰ Celecoxib undergoes extensive hepatic metabolism, specifically by the CYP2C9, 2C19, and

Table 6. Disorders that potentially interact with extended-release analgesics

Disorder	Analgesic class			
	NSAID		Opioid	
	Nonspecific	COX-2 specific	Mu agonist	Mixed
Renal disease	Renal toxicity ^{51,81}	Not recommended for use in patients with advanced renal disease because no information available about such use ^{48,82}	Opioid plasma concentrations ^{23,83}	Rate and extent of tramadol excretion ^{28,84}
Hepatic disease	ALT or AST ⁵¹	Not recommended for use in patients with severe hepatic impairment. Reduce dosage by 50% in patients with moderate impairment ^{48,82}	Opioid plasma concentrations ^{23,83}	Exposure with increasing hepatic impairment severity ^{28,84}
Pancreatic/biliary disease	None	None	Spasm of sphincter of Oddi and amylase levels ^{23,83}	None
Heart disease	Risk for MI ^{51,81}	Risk of MI and stroke in patients with known CV disease or risk factors. Worsening of preexisting hypertension ^{48,82}	Peripheral vasodilation may yield hypotension ²³	None
Seizure disorder	None	None	None	Seizure risk ^{28,84}
Head injury	None	None	Head injury may exacerbate respiratory depressant effects ^{23,83}	Head injury may exacerbate respiratory depressant effects ^{28,84}
GI disorders	Perforation, ulceration, and bleeding ^{51,81}	Risk for GI bleed in patients with history of peptic ulcer disease and/or GI bleeding ^{48,82}	Contraindicated in patients with paralytic ileus ^{23,83}	None
COPD	None	None	Yes: airway resistance and respiratory drive ²³	None
Asthma	Yes: patients with aspirin-sensitive asthma ^{51,81}	Yes: do not use in patients with aspirin-sensitive asthma. Use with caution in preexisting asthma ⁴⁸	Yes: contraindicated in acute or severe bronchial asthma ^{23,83}	None

Abbreviations used: ALT, alanine aminotransferase; AST, aspartase aminotransferase; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; GI, gastrointestinal; MI, myocardial infarction.

2D6 isoenzymes, yielding possible drug interactions with fluconazole, tricyclic antidepressants, SSRIs, and beta-adrenergic antagonists.⁶⁹ A retrospective chart review of a large emergency department

population (1,355 patients) identified the common potential NSAID interactions at the time of triage, before emergency room treatment.⁷¹ Of the 32 potential drug-drug interactions reported, 12 (38%)

involved NSAIDs, the most frequent drug category implicated (Table 4).

In older patients NSAIDs interact with ACE inhibitors, angiotensin receptor blockers (ARBs), and diuretics and

can trigger loss of blood pressure control, cardiac failure, and, in hypovolemic conditions such as dehydration, renal failure.⁷² These interactions can occur with all patients but may have a more pronounced effect in older patients, who seem to be more sensitive to the adverse effects of NSAIDs than younger patients.⁷³

Opioids

Most opioids are metabolized by oxidation and/or glucuronidation,⁷⁴ while fentanyl, methadone, and levorphanol also undergo significant 3A4 metabolism.^{21,75} Tramadol undergoes significant metabolism by CYP3A4 and 2D6. Both codeine and tramadol are converted to mu agonists by CYP2D6; thus, patients taking medications that block CYP2D6 such as fluoxetine, paroxetine, and amitriptyline or who are poor CYP2D6 metabolizers (10% of population) may fail to achieve analgesia with either agent.^{76,77} For tramadol, postmarketing surveillance has revealed rare reports of digoxin toxicity and alteration in the effect of warfarin, including elevation of prothrombin times.²⁷ Oxycodone does not inhibit

any of the major CYP450 isoforms, and clinical drug interaction studies show no induction of CYP2C9 or CYP3A4 activity, suggesting minimal risk for drug–drug interactions stemming from the induction or inhibition of hepatic enzymes.^{26,78} Generally, opioids can interact with several commonly prescribed drugs or drug classes, affecting the activity of the opioid or the coadministered drug (Table 5).

Drug–disease interactions

The analgesic classes that include ER formulations vary considerably in their risk for exacerbating certain disease states or having their pharmacology altered by commonly encountered disorders (Table 6). For instance, in patients with heart disease, NSAIDs can result in poorer outcomes because these agents have been associated with elevations in blood pressure and a heightened risk for MI.⁷⁹ Although the opioids appear free of serious cardiovascular effects, they can worsen symptoms of chronic obstructive pulmonary disease, and tramadol can elevate seizure risk in susceptible individu-

als. Because of these varying risks, the pharmacist faces an ongoing challenge in untangling which ER analgesic therapy would be most appropriate based on an individual patient's disease profile.

Age

In older patients, defined as individuals at least 65 years of age, persistent pain represents a common problem, with a prevalence of up to 50% in community-dwelling individuals.⁸⁴ Although pharmacotherapy is the most common treatment option for pain management in older patients, the choice of analgesic is complicated by the fact that many older patients have impaired hepatic and renal function, achlorhydria, as well as reductions in serum albumin levels and higher fat-to-lean body mass ratios.⁷⁰ In addition, older patients often display increased sensitivity to centrally active drugs, including opioid analgesics. In older patients, alterations in the pharmacodynamics and pharmacokinetics of certain analgesics result in differences in efficacy, sensitivity, and toxicity, when compared with younger patients. In



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fact, 3% to 10% of all hospitalizations in older patients result from adverse drug reactions.⁸⁵

Older patients are clearly more sensitive to NSAID-related GI toxicity. In long-term care facilities, nearly a quarter of older residents use NSAIDs, and, as a result, they experience a five- to sixfold increase in the risk for serious gastrointestinal events, when compared with the non-institutionalized older patients.⁶⁹ The use of adjunctive treatment, such as misoprostol or proton pump inhibitors can ameliorate the gastric toxicity associated with NSAIDs, but may be of limited use in older patient populations because these agents are expensive and associated with drug interactions. The doses required for significant misoprostol NSAID-induced GI protection are 200 mcg four times daily; this dose is often associated with GI cramping and diarrhea.⁸⁶ In addition, the cardiovascular adverse effects, such as increased arterial blood pressure, associated with long-term NSAID therapy may be of particular concern in older patients. Although generally mild, NSAID-related renal adverse effects, such as weight gain and edema, affect 3% to 5% of older patients. In addition, NSAIDs can trigger or contribute to acute renal failure in some older patients, especially in the presence of preexisting renal abnormalities.⁶⁹ In fact, older male patients who use NSAIDs on a regular basis display a twofold increase in the risk for chronic renal disease.

Moreover, in older patients, careful monitoring is required for potentially serious opioid adverse events, especially neurological, gastrointestinal, and cognitive-behavioral effects, as well as respiratory depression. Mild sedation and transient cognitive impairment are common at the initiation of opioid therapy in older patients; these events usually do not require dosage reduction, but rather patient reassurance that they will resolve after a few days.⁷⁶ Also, poor pain control in older patients can result in cognitive impairment independently of opioid use. Older patients with chronic obstructive pulmonary disease or sleep apnea may be at increased risk for opioid-related respiratory depression.⁸⁵ Because long-acting opioids require less frequent dosing and are associated with less breakthrough pain, they are

preferred in older patients, once stable opioid doses have been established with short-acting formulations.^{76,85}

Tramadol may represent an option for older patients who are at high risk for NSAID adverse effects but are reluctant to move on to more traditional opioid analgesics.⁷⁰ Tramadol is generally well tolerated in older patients; however, because this drug has been associated with dizziness and seizures, it should be used with caution, especially in those patients taking concomitant medications that elevate serotonin levels.

Abuse/diversion issues

The treatment of persistent pain with opioid analgesics remains inextricably entwined with patient and prescriber concerns related to potential abuse and dependence.⁸⁷ In a presentation to Congress in 2005, DEA recognized that the misuse of prescription opioids has become an increasingly widespread and serious problem in the United States.⁸⁸ DEA posited that the introduction of a new generation of high-dose ER opioid medications has markedly increased the risk for abuse and diversion. Despite established efficacy in the management of persistent pain, these agents contain increased amounts of potent and pure active ingredients that magnify their attractiveness to potential abusers. Typical abusers of high-dose ER opioids included young males with a history of opioid or alcohol abuse.^{89,90} Sees et al. have shown that nonmedical users of ER oxycodone demonstrate high rates of nonmedical use of other opioids and illicit drugs.⁹¹

Because of their high potential for abuse and diversion, all of the conventional opioids with ER formulations—morphine, oxymorphone, oxycodone, and fentanyl—are Schedule II, which provides the maximum amount of control possible under the Controlled Substances Act for a marketed prescription drug. The abuse potential and regulatory burden associated with Schedule II opioids impose clear barriers to their use in persistent pain. In one California survey, only 35% of the primary care physicians were willing to prescribe Schedule II opioids for around-the-clock analgesia, primarily because of concerns about physical dependence, tolerance, and addiction.⁹⁰ Other physician surveys suggest that more than half of

physicians reduce opioid dose, prescription quantity, or number of refills, or choose a less-potent, lower-scheduled opioid because of regulatory concerns.⁹³ Moreover, in New York City only 50% of the pharmacies citywide and 25% of the pharmacies in nonwhite neighborhoods stock adequate supplies of Schedule II opioid medications to treat severe pain.⁹⁴ The pharmacists cited five primary reasons for opioid analgesic understocking: disposal regulations, illicit use, fraud, low demand, and fear of theft.

In contrast, tramadol is the only unscheduled analgesic with opioid agonist properties.²⁰ The approval of tramadol in 1995 as an unscheduled drug was contingent upon the development of a proactive surveillance program overseen by an independent steering committee. Survey data for the first 3 years following introduction of the drug showed that the reported rate of abuse was low, stabilizing at a rate of less than 1 case per 100,000 patients;⁹⁵ and a follow-up study covering the period from 2001 to 2002 suggests the risk for abuse and diversion remains low.⁹⁶ In addition, the abuse liability of tramadol, NSAIDs, and hydrocodone-containing analgesics was evaluated in a 12-month randomized study in subjects with chronic noncancer pain.⁹⁷ The study used an “abuse index” algorithm to identify subjects displaying evidence of drug abuse—increasing dose without physician approval, use for purposes other than prescribed, inability to stop use, and withdrawal. The percentages of subjects per group who scored positive at least once over the 12-month follow-up were as follows: NSAID 2.5%, tramadol 2.7%, and hydrocodone 4.9%. When multiple algorithm hits were used to assess persistence, abuse rates were as follows: NSAIDs 0.5%, tramadol 0.7%, and hydrocodone 1.2%. These results indicate that the relative abuse of hydrocodone was significantly higher than either tramadol or NSAIDs ($P < 0.01$).

Case studies

This series of cases highlights some of the therapeutic dilemmas faced by prescribers when considering the use of ER analgesic formulations, along with possible treatment resolutions.

Case 1

Sally is a 56-year-old patient with moderate, persistent pain secondary to osteo-

arthritis of the hips and knees. This painful condition has persisted for 2 years. Her physician had prescribed NSAIDs that provide meaningful, but incomplete, pain relief, with twice-daily dosing. She admitted to not taking her medication as often as prescribed. After 3 months' treatment with NSAIDs, she developed an NSAID-related stomach ulcer. What alternative analgesic therapy could be considered?

Because she experienced NSAID-related GI toxicity, either a mu or a mixed opioid would represent a medically prudent option. Since her pain is persistent, an ER formulation would offer convenient dosing, and reduced "pill" burden may improve her ability to adhere to the prescribed regimen.

Case 2

A 40-year-old patient with mild to moderate, persistent low back pain, John has used OTC acetaminophen and short-acting NSAIDs, which reduced some of his pain since he initiated treatment 1 year ago. Yet because of persistent nocturnal pain flare-ups, which he described as at least moderate in intensity, John's

sleep is regularly disrupted. To maintain sleep, he has been consuming 1 or 2 ounces of alcohol before retiring, a strategy that has proved to be less than effective.

This patient would be an ideal candidate for an ER or long-acting analgesic, because of his clear need for around-the-clock analgesia. Because his pain is typically mild or moderate in intensity, analgesic options may include long-acting NSAIDs or ER tramadol.

Case 3

Steve is a 72-year-old patient with diabetic neuropathy, hypertension, coronary artery disease, moderate renal failure, and a history of dehydration and acute bronchial asthma. Over the last 2 years, he has experienced widespread osteo-arthritis that results in diffuse moderate to severe, persistent pain throughout the day. He is taking multiple medications, including an ACE inhibitor for hypertension, which have become increasingly difficult to manage. Steve is treated with prescription NSAIDs, which he supplements with acetaminophen when needed for break-

through pain.

Because Steve presents with cardiovascular disease, the use of NSAIDs may increase his risk for cardiovascular events, such as an MI. In addition, combining an NSAID with an ACE inhibitor, especially in a hypovolemic patient, elevates the risk for renal failure. Steve also has a history of bronchial asthma, a contraindication for the use of a strong opioid because of an increased risk for respiratory depression. For this patient, an agent such as ER tramadol may be a suitable option. Tramadol has demonstrated efficacy against neuropathic pain states, and the patient's persistent pain warrants an ER formulation.

Case 4

Judy is a 67-year-old patient with escalating pain secondary to breast cancer with bony metastases. Her pain, which has persisted for 6 months, often reaches severe levels and has worsened progressively over the last 2 months. She also takes carbamazepine for epilepsy and fluoxetine for depression.

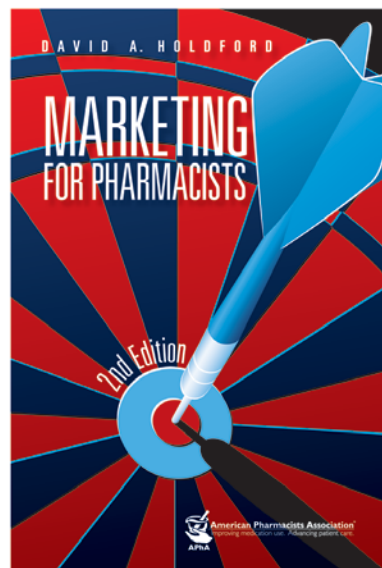
Because her pain can be severe

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and persistent, Judy is a candidate for ER opioid analgesic therapy. Moreover, unlike NSAIDs, opioids do not display ceiling analgesic effects, an important consideration in a patient with escalating pain. Tramadol would increase the risk for seizures in this patient because of her history of epilepsy and use of an SSRI. Further, tramadol is not indicated for severe pain and carbamazepine would increase tramadol metabolism, diminishing its analgesic activity. In this patient, a strong ER opioid may be the most appropriate alternative.

Conclusions

ER analgesics have demonstrated efficacy in treating persistent pain. Additionally, ER analgesics exhibit smoother steady-state drug plasma concentrations than their IR counterparts, which may be predictive of a decreased risk for adverse events. The literature suggests that ER analgesics can improve physical function and sleep. However, results from the larger body of clinical studies and analyses from systematic reviews make it difficult to conclude that ER analgesics are superior to IR analgesics in terms of efficacy, functional improvement, enhancement of sleep, or adverse event profiles. The need exists for additional research to affirm the benefits of ER versus IR analgesic formulations. Such research should be conducted in naturalistic settings to assess the performance and adverse events of these formulations in the manner in which they are used in clinical practice.

All analgesics—regardless of their mechanisms of action or formulations—are associated with risks. NSAIDs increase the risk for adverse gastrointestinal and cardiovascular events and have been associated with deleterious renovascular and renal effects. Additionally, nonselective NSAIDs decrease platelet aggregation. Opioids can cause sedation, pruritus, constipation, nausea, vomiting, itching, and respiratory depression, and are associated with increased risk of abuse and diversion. Tramadol can also cause dizziness, pruritus, nausea, vomiting, constipation, drowsiness, and seizures.

The challenge from the pharmacist's perspective is to balance the benefits and risks of the various analgesics and their different formulations in the individual patient. Therefore, it is critical that the

pharmacist have sufficient knowledge to evaluate the benefits and risks of currently available analgesic medications and their various formulations, so that they may provide the best counsel and support for each patient.

In summary, pharmacists are uniquely positioned to assess pain patients' response to therapy and susceptibility to risk and, in turn, to further best practices in the management of persistent pain.

References

1. Pain: Current understanding of assessment, management, and treatments; NPC and JCAHO collaborative project monograph. Accessed at www.npcnow.org/resources/PDFs/painmonograph.pdf on January 3, 2007.
2. Fleischer AB, Jr., Gardner EF, Feldman SR. Are patients' chief complaints generally specific to one organ system? *Am J Manag Care.* 2001;7:299-305.
3. The American Pain Foundation, Pain Facts. Accessed at www.painfoundation.org/page.asp?file=Library/PainSurveys.htm on January 2, 2007.
4. IMS Data: Analgesic Volume and Sales, 2002 to 2006.
5. Doucette W, Mays-Holland T, Memmott H, Lipman A. Cancer pain management: pharmacist knowledge and practices. *J Pharm Care Pain Symptom Control.* 1997;5:17-31.
6. Sloan P, Babul N. Extended-release opioids for the management of chronic non-malignant pain. *Expert Opin Drug Deliv.* 2006;3:489-97.
7. Vallerand AH. The use of long-acting opioids in chronic pain management. *Nurs Clin North Am.* 2003;38:435-45.
8. Sinatra R. Opioid analgesics in primary care: challenges and new advances in the management of noncancer pain. *J Am Board Fam Med.* 2006;19:165-77.
9. Marin R, Cyhan T, Miklos W. Sleep disturbance in patients with chronic low back pain. *Am J Phys Med Rehabil.* 2006;85:430-35.
10. Cannon GW, Breedveld FC. Efficacy of cyclooxygenase-2-specific inhibitors. *Am J Med.* 2001;110 Suppl 3A:6S-12S.
11. Kivitz AJ, Moskowitz RW, Woods E, et al. Comparative efficacy and safety of celecoxib and naproxen in the treatment of osteoarthritis of the hip. *J Int Med Res.* 2001;29:467-79.
12. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther.* 2001;23:1296-1310.
13. Porzio F. Meta-analysis of three double-blind comparative trials with sustained-release etodolac in the treatment of osteoarthritis of the knee. *Rheumatol Int.* 1993;13 Suppl:19S-24S.
14. Morley KD, Bernstein RM, Hughes GR, et al. A comparative trial of a controlled-release formulation of ketoprofen ('Oruvail') and a conventional capsule formulation of ketoprofen ('Orudis') in patients with osteoarthritis of the hip. *Curr Med Res Opin.* 1984;9:28-34.
15. Rhymer AR, Hart CB, Daurio C. A double-blind trial comparing indomethacin sustained release capsules (Indocid-R) with indomethacin capsules in patients with rheumatoid arthritis. *Rheumatol Rehabil.* 1982;21:101-06.

16. Hersh EV, Levin LM, Cooper SA, et al. Conventional and extended-release etodolac for postsurgical dental pain. *Clin Ther.* 1999;21:1333-42.
17. Clinical evaluation of a new controlled-release formulation of naproxen in osteoarthritis and rheumatoid arthritis. Canadian Multicentre Study Group. *Curr Med Res Opin.* 1988;11:16-27.
18. Kelly JG, Kinney CD, Devane JG, et al. Pharmacokinetic properties and clinical efficacy of once-daily sustained-release naproxen. *Eur J Clin Pharmacol.* 1989;36:383-88.
19. Raffa RB, Friderichs E, Reimann W, et al. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *J Pharmacol Exp Ther.* 1992;260:275-85.
20. Trescott AM, Boswell MV, Atluri SL, et al. Opioid guidelines in the management of chronic non-cancer pain. *Pain Physician.* 2006;9:1-39.
21. Duragesic (fentanyl transdermal system) package insert. Janssen. May 2003.
22. Avinza (morphine sulfate extended-release capsules) package insert. February 2003.
23. Oramorph SR (morphine sulfate sustained-release tablets) package insert. AAI Pharma. May 2001.
24. MS Contin (morphine sulfate controlled-release tablets) package insert. Purdue Frederick. January 2003.
25. Oxycontin (oxycodone HCl controlled-release tablets) Package Insert. Purdue Pharma. July 2003.
26. Opana ER (oxymorphone HCl) package insert. Endo Pharmaceuticals. 2006.
27. Ultram ER (tramadol HCl) package insert. PriCara. 2005.
28. Sindrup SH, Madsen C, Brosen K, Jensen TS. The effect of tramadol in painful polyneuropathy in relation to serum drug and metabolite levels. *Clin Pharmacol Ther.* 1999;66:636-41.
29. Boureau F, Legallier P, Kabir-Ahmadi M. Tramadol in post-herpetic neuralgia: a randomized, double-blind, placebo-controlled trial. *Pain.* 2003;104:323-31.
30. Schnitzer TJ, Gray WL, Paster RZ, Kamin M. Efficacy of tramadol in treatment of chronic low back pain. *J Rheumatol.* 2000;27:772-78.
31. Chou R, Clark E, Helfand M. Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review. *J Pain Symptom Manage.* 2003;26:1026-48.
32. Ferrell B, Wisdom C, Wenzl C, Brown J. Effects of controlled-released morphine on quality of life for cancer pain. *Oncol Nurs Forum.* 1989;16:521-26.
33. Klepstad P, Kaasa S, Jystad A, et al. Immediate- or sustained-release morphine for dose finding during start of morphine to cancer patients: a randomized, double-blind trial. *Pain.* 2003;101:193-98.
34. Caldwell JR, Hale ME, Boyd RE, et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal anti-inflammatory drugs: a double-blind, randomized, multicenter, placebo-controlled trial. *J Rheumatol.* 1999;26:862-69.
35. Wong JO, Chiu GL, Tsao CJ, Chang CL. Comparison of oral controlled-release morphine with transdermal fentanyl in terminal cancer pain. *Acta Anaesthesiol Sin.* 1997;35:25-32.
36. Salzman RT, Roberts MS, Wild J, et al. Can a controlled-release oral-dose form of oxycodone be used as readily as an immediate-release form for the purpose of titrating to stable pain control? *J Pain Symptom Manage.* 1999;18:271-79.

37. Godwin M, Ruhland L, Casson I, et al. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. Accessed at www.biomedcentral.com/1417-2288/3/28 on February 8, 2007. *BMC Medical Research Methodology*. 2003;3:28.
38. Lesage P, Portenoy RK. Trends in Cancer Pain Management. *Cancer Control*. 1999;6:136-45.
39. Amabile CM, Bowman BJ. Overview of oral modified-release opioid products for the management of chronic pain. *Ann Pharmacother*. 2006;40:1327-35.
40. Jick H, Derby LE, Vasilakis C, Fife D. The risk of seizures associated with tramadol. *Pharmacotherapy*. 1998;18:607-11.
41. Principles of analgesic use in the treatment of acute pain and cancer pain; 5th Edition. Glenview, Ill.: American Pain Society; 2003.
42. Gallagher RM, Welz-Bosna M, Gammaitoni A. Assessment of dosing frequency of sustained-release opioid preparations in patients with chronic nonmalignant pain. *Pain Med*. 2007;8:71-4.
43. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA* 2000;284:1247-55.
44. Helin-Salmivaara A, Virtanen A, Vesalainen R, et al. NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case-control study from Finland. *Eur Heart J*. 2006;27:1657-63.
45. Kearney PM, Baigent C, Godwin J, et al. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ*. 2006;332:1302-08.
46. Caldwell B, Aldington S, Weatherall M, et al. Risk of cardiovascular events and celecoxib: a systematic review and meta-analysis. *J R Soc Med*. 2006;99:132-40.
47. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem. *Arch Intern Med*. 2000;160:777-84.
48. Celebrex (celecoxib capsules) package insert. Pfizer, Inc. February, 2007.
49. National Cancer Institute; Pain, adverse effects of opioids. Accessed at www.nci.nih.gov/cancertopics/pdq/supportivecare/pain/HealthProfessional/page3#Section_169 on January 3, 2007.
50. White C. Drug-induced respiratory depression. Accessed at www.uspharmacist.com/oldformat.asp?url=newlook/files/Feat/ACF2ECE.cfm&pub_id=8&article_id=17 on January 3, 2007. *U.S. Pharmacist* 2006:1-8.
51. Anaprox (naproxen sodium) package insert. Roche Laboratories, 2007.
52. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. *Ann Intern Med*. 1991;115:787-96.
53. Griffin MR, Piper JM, Daugherty JR, et al. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. *Ann Intern Med*. 1991;114:257-63.
54. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. *N Engl J Med*. 1999;340:1888-99.
55. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Ann Intern Med*. 1994;121:289-300.
56. White WB, West CR, Borer JS, et al. Risk of cardiovascular events in patients receiving celecoxib: a meta-analysis of randomized clinical trials. *Am J Cardiol*. 2007;99:91-8.
57. Cheng HF, Harris RC. Cyclooxygenases, the kidney, and hypertension. *Hypertension*. 2004;43:525-30.
58. Munir MA, Enany N, Zhang JM. Nonopioid analgesics. *Med Clin North Am*. 2007;91:97-111.
59. Meldon SW, Woolard RH, Ma OJ, eds. *Geriatric Emergency Medicine*. New York: McGraw-Hill;2003:240.
60. Thompson AR, Ray JB. The importance of opioid tolerance: a therapeutic paradox. *J Am Coll Surg*. 2003;196:321-24.
61. Sjogren P, Thomsen AB, Olsen AK. Impaired neuropsychological performance in chronic nonmalignant pain patients receiving long-term oral opioid therapy. *J Pain Symptom Manage*. 2000;19:100-08.
62. Swegle JM, Logemann C. Management of common opioid-induced adverse effects. *Am Fam Physician*. 2006;74:1347-54.
63. Schug SA. Combination analgesia in 2005—a rational approach: focus on paracetamol-tramadol. *Clin Rheumatol*. 2006;25 Suppl 1:16-21.
64. Cherny N, Ripamonti C, Pereira J, et al. Strategies to manage the adverse effects of oral morphine: an evidence-based report. *J Clin Oncol*. 2001;19:2542-54.
65. Mercadante S. The use of anti-inflammatory drugs in cancer pain. *Cancer Treat Rev*. 2001;27:51-61.
66. Payne R. Recognition and diagnosis of breakthrough pain. *Pain Med*. 2007;8 Suppl 1:S3-7.
67. Portenoy RK, Bennett DS, Rauck R, et al. Prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain. *J Pain*. 2006;7:83-591.
68. Wall and Melzack's Textbook of Pain. Accessed at www.textbookofpain.com/content/bookcontent.cfm?ID=HC072004&searchterms=breakthrough%20pain&framesource=search&RestrictTo=P072008#P072008 on February 22, 2007.
69. Nikolaus T, Zeyfang A. Pharmacological treatments for persistent non-malignant pain in older persons. *Drugs Aging*. 2004;21:19-41.
70. Barkin RL, Barkin SJ, Barkin DS. Perception, assessment, treatment, and management of pain in the elderly. *Clin Geriatr Med*. 2005;21:465-90.
71. Goldstein J, Jaradeh I, Hawar P, Stair T. ED drug-drug interactions: frequency & type, potential & actual, triage & discharge. *Internet J Emerg Intensive Care Med*. 2005;8.
72. Savage R. Cyclo-oxygenase-2 inhibitors: when should they be used in the elderly? *Drugs Aging*. 2005;22:185-200.
73. Evans JM, MacDonald TM. Tolerability of topical NSAIDs in the elderly? Do they really convey a safety advantage? *Drugs Aging*. 1996;9:101-08.
74. Volles DF, McGory R. Pharmacokinetic considerations. *Crit Care Clin*. 1999;15:55-75.
75. Oda Y, Kharasch ED. Metabolism of methadone and levo-alpha-acetylmethadol (LAAM) by human intestinal cytochrome P450 3A4 (CYP3A4): potential contribution of intestinal metabolism to presystemic clearance and bioactivation. *J Pharmacol Exp Ther*. 2001;298:1021-32.
76. Davis MP, Srivastava M. Demographics, assessment and management of pain in the elderly. *Drugs Aging*. 2003;20:23-57.
77. Armstrong SC, Cozza KL. Pharmacokinetic drug interactions of morphine, codeine, and their derivatives: theory and clinical reality, part I. *Psychosomatics*. 2003;44:167-71.
78. Adams M, Pieniaszek HJ, Jr., Gammaitoni AR, Ahdieh H. Oxymorphone extended release does not affect CYP2C9 or CYP3A4 metabolic pathways. *J Clin Pharmacol*. 2005;45:337-45.
79. Johnsen SP, Larsson H, Tarone RE, et al. Risk of hospitalization for myocardial infarction among users of rofecoxib, celecoxib, and other NSAIDs: a population-based case-control study. *Arch Intern Med* 2005;165:978-84.
80. Advil (ibuprofen tablets) package insert. Wyeth Consumer Healthcare. 2007.
81. Arcoxia (etoricoxib) package insert. Merck & Co., Inc. January 2006.
82. Kadian (morphine sulfate extended-release capsules) package insert. Alpharma Branded Products Division Inc. October 2006.
83. Talwin (pentazocine) package insert. sanofi-aventis U.S. LLC. September 2006.
84. AGS Panel on Persistent Pain in Older Persons. The management of persistent pain in older persons. *J Am Geriatr Soc*. 2002;50: S205-24.
85. Otis J, McGeehey B. Managing pain in the elderly. *Clinical Geriatrics*. 2000;8:1-8.
86. Cytotec (misoprostol tablets) package insert. G.D. Searle & Co. September 2006.
87. Joranson DE, Ryan KM, Gilson AM, Dahl JL. Trends in medical use and abuse of opioid analgesics. *JAMA*. 2000;283:1710-14.
88. Rannazzisi J. DEA congressional testimony before the Committee on Government Reform Subcommittee on Regulatory Affairs (2005). Accessed at www.dea.gov/pubs/cngtrtest/ct091305.html on January 3, 2007.
89. Hays LR. A profile of OxyContin addiction. *J Addict Dis*. 2004;23:1-9.
90. Potter JS, Hennessy G, Borrow JA, Greenfield SF, Weiss RD. Substance use histories in patients seeking treatment for controlled-release oxycodone dependence. *Drug Alcohol Depend*. 2004;76:213-15.
91. Sees KL, Di Marino ME, Ruediger NK, et al. Non-medical use of OxyContin tablets in the United States. *J Pain Palliat Care Pharmacother*. 2005;19:13-23.
92. Potter M, Schafer S, Gonzalez-Mendez E, et al. Opioids for chronic nonmalignant pain. Accessed at www.jfponline.com/pages.asp?AID=2155 on February 12, 2007. *Family Practice*. 2001;50.
93. Joranson DE. Regulatory influence on pain management: real or imagined? *J Pharm Care in Pain and Symptom Control*. 1993;1:113-18.
94. Morrison RS, Wallenstein S, Natale DK, et al. "We don't carry that"—failure of pharmacies in predominantly nonwhite neighborhoods to stock opioid analgesics. *N Engl J Med*. 2000;342:1023-26.
95. Cicero TJ, Adams EH, Geller A, et al. A post-marketing surveillance program to monitor Ultram (tramadol hydrochloride) abuse in the United States. *Drug Alcohol Depend*. 1999;57:7-22.
96. Inciardi JA, Cicero TJ, Munoz A, et al. The Division of Ultram, Ultracet, and generic tramadol HCL. *J Addict Dis*. 2006;25:53-8.
97. Adams EH, Breiner S, Cicero TJ, et al. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. *J Pain Symptom Manage*. 2006;31:465-76.