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OPTIMIZING CHRONIC PAIN MANAGEMENT: INTEGRATING PHARMACOKINETICS AND PHARMACODYNAMICS

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PriCara
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TARGET AUDIENCE

This activity has been developed for community pharmacists who have expressed an interest in enhancing their knowledge and understanding of available pharmacotherapies for chronic pain.

STATEMENT OF NEED

Chronic pain is prevalent in nearly 25% of the US population, yet it continues to be undertreated and mismanaged. Surveys show that more than 40% of patients with chronic pain and nearly 60% of patients with severe pain failed to achieve adequate pain relief. The systematic undertreatment of pain represents a public health crisis in this country. Although all health care professionals must have knowledge of the tools used to help treat pain, pharmacists have a particularly significant role because they are highly visible and accessible members of the health care team. Their role in the health care system makes them invaluable in monitoring pharmacotherapy and the education of patients and health care providers. Optimal management of chronic pain necessitates that pharmacists understand the magnitude of chronic pain in the United States and the treatment barriers that must be surmounted to ensure effective care. Because analgesic agents vary widely in their pharmacodynamic and pharmacokinetic properties, the pharmacist must be knowledgeable about a drug's pharmacokinetics and formulation in order to support monitoring an analgesic regimen that can control pain while minimizing the side effects and interactions with any concurrent medication as well as instituting any formulation substitutions.

Pharmacists play a critical role in patient access to medications and patient safety. The number of available medications and formulations grows every year. Analgesic agents vary widely in their potency as well as side-effect profiles. Furthermore, pain management plans typically include treating comorbid illnesses and disability. Pharmacists serve as the "gatekeepers" who must determine whether dispensing a prescription order will alleviate pain without compromising safety. Pharmacists are in a privileged position to gather data regarding adverse responses to prescribed medication or incidents of medication mishaps. By informing clinicians of possible adverse effects or drug interactions, they have a critical role in a patient's overall health as well as the chain of drug distribution to the patient. Pharmacists who lack knowledge about pain management could be a weak link if they make decisions that break the chain of distribution of valid prescriptions for analgesics, thereby contributing to the epidemic of the undertreatment of pain. Communication between patients, clinicians, and pharmacists is an important factor in the pain management process; the best therapeutic outcomes may be obtained through an alliance among these individuals.

LEARNING OBJECTIVES

- Describe the vital role of the community pharmacist in the management of patients' chronic pain
- Discuss the prevalence and consequences of the undertreatment of chronic pain
- Explain the concept and intent of "rational polypharmacy" and the relevance of pharmacokinetics/pharmacodynamics to this concept
- Compare and contrast the characteristics and appropriate clinical applications of the various drugs available to treat chronic pain
- Describe the influence of pharmacokinetic/pharmacodynamic properties on formulation substitution

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OPTIMIZING CHRONIC PAIN MANAGEMENT: INTEGRATING PHARMACOKINETICS AND PHARMACODYNAMICS

"The pharmacist is not just a conduit for dispensing prescription medications but is as important as any other member of the treatment team." – Bill McCarberg, MD

INTRODUCTION

For the many people in the United States who live with chronic noncancer pain, one of the most important health care professionals, and the one who may be most consistently in contact with patients, is the community pharmacist. Thus, it is important that community pharmacists understand the impact of chronic pain, the rationales behind specific treatment choices, and the principles of managing pain. Armed with this knowledge, they can fully realize their role as pivotal components of a multidisciplinary care team for patients with chronic noncancer pain.

Chronic Pain Is a Pervasive Condition

Several groups have developed similar but varying definitions of chronic pain. The National Institute of Neurological Disorders and Stroke defines it as pain that persists for weeks, months, or years, either following an initial injury that has resolved, or because of an ongoing illness such as arthritis, or with no evident cause.[1] An estimated 75 million Americans suffer from chronic pain.[2] Nearly half of adults with pain responding to the National Health and Nutrition Examination Survey (NHANES) for the years 1999 to 2002 reported that their pain had lasted for a year or more (**Figure 1**).[3] Of this group of respondents, 36.5% were between 20 and 44 years of age, 43.7% were between 45 and 64 years of age, and 57.3% were at least 65 years of age. Examples of types and locations of chronic noncancer pain are shown in **Table 1**.[4,5] The majority of respondents to the NHANES reported back pain (10%), followed by leg or foot pain (7%) and arm/hand pain and headache (4% each). Although most patients' pain can be attributed to a specific cause, some chronic noncancer pain may have no identified etiology.[4,5]

The available treatments for chronic noncancer pain vary widely, comprising nonopioid analgesics (both over-the-counter [OTC] and prescription), opioid analgesics, adjuvant analgesia (medications with other indications that are also effective in treating some types of pain), and complementary or alternative medicine (CAM). The differences between treatments, as discussed below, exist not only between classes but also between individual drugs within a class and between different formulations of individual drugs. Additionally, the effects of drugs vary between patients. Many patients with chronic pain have other comorbid conditions, particularly as they grow older. For most patients with chronic pain, polypharmacy is the rule, and familiarity with the concept of "rational polypharmacy" is essential for everyone involved in their care.[6,7]

Role of the Community Pharmacist

Unfortunately, chronic pain is often undertreated and/or treated inappropriately, with potentially devastating ramifications for patients. Community pharmacists have an opportunity to contribute substantially to ensuring that this does not occur. Frequently the health care professionals most in contact with patients, community pharmacists may be the only members of the care team with a comprehensive picture of all of a patient's comorbid conditions and treatments. Community pharmacists are in the best position to counsel patients regarding potential interactions between prescription medications, OTC drugs,[8,9] and CAM such as herbal supplements. They are often the health care providers whose advice regarding medications is most trusted. Therefore, they are in a position to optimize patients' use of medications by educating and reassuring them about multiple aspects of their treatment.[8,10]

Patients should be reassured that some initial side effects of medications will diminish or become tolerable with time. Community pharmacists should explain that the consequences of not taking these medications are likely to outweigh their potential adverse effects. They can explain to patients that intermittent use of some analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs), is not harmful. They also can

Figure 1. Duration of Pain, US Adults ≥20 Years of Age[3]

Table 1. Types of Chronic Noncancer Pain[4,5]

Type of Pain	Comments
Abdominal pain	eg, irritable bowel syndrome, pancreatitis, peptic ulcer
Acute injury that has evolved	Untreated acute pain often evolves into chronic pain
Central pain	eg, spinal cord injury, stroke, multiple sclerosis
Complex regional pain syndrome	Types I and II
Fibromyalgia	
Headache	Actually intermittent but considered chronic because of frequent occurrence
Low back pain	Back pain most prevalent in NHANES 1999-2002 (N=10,271)
Myofascial pain	May occur absent a known injury or disease
Neuralgia	eg, postherpetic, trigeminal
Osteoarthritis	Legs, feet, arms, hands most frequent sites of pain after back in NHANES 1999-2002
Peripheral neuropathy	May occur absent a known injury or disease
Phantom limb pain	
Sickle cell disease	Actually intermittent but considered chronic because of frequent occurrence
Unexplained	No discernable cause: the pain is the disease

NHANES, National Health and Nutrition Examination Survey.

Table 2. Effect of Chronic Pain on Patients' Activities[2]

Activity	Affected by Pain
Enjoying time with significant other	71%
Sports	62%
Ability to care for oneself	61%
Yard work	60%
Frequency of sexual activity	59%
Participation in social activities	55%
Walking	54%
Household chores	50%
Falling asleep	~50%
Quality of spousal relationship	48%
Lifting heavy objects	47%
Extended sitting	43%
Shopping	41%
Staying asleep	>40%

forewarn patients about some potential effects of medication, such as diminished libido, so that patients will not be surprised if these adverse events occur. Additionally, community pharmacists can help patients prevent some likely side effects. For example, because constipation is the most common adverse effect of long-term opioid use and one to which tolerance rarely develops, it may be prudent to advise patients to increase their fiber and fluid intake and/or offer prophylactic therapy with senna, with or without a stool softener.[11]

Another important topic about which community pharmacists can counsel patients is appropriate storage of their medications. The 2005 National Survey on Drug Use and Health found that 53% of young adults (aged 18 to 25 years) who reported nonmedical use of prescription pain relievers stated that they were given the drugs by friends or relatives.[12] In the same year, 62% of adolescents responding to a survey by the Partnership for a Drug-Free America stated that prescription pain relievers were readily available to them in their parents' medicine cabinets.[13] Community pharmacists should advise patients to store their medications securely and dispose of them safely when the drugs are no longer needed.

Community pharmacists are the gatekeepers for patient safety. As such, they should be proactive in asking patients about all the medications they are taking, including OTC and CAM, keeping in mind the potential interactions of these therapies.[14] They should keep patient treatment and health profiles up-to-date so that they are in a position to raise a red flag regarding possible drug-drug, drug-supplement, or drug-disease interactions. They may be the best source of information for prescribers regarding comprehensive patient profiles; open communication between community pharmacist and patient, as well as between community pharmacist and prescriber(s), is the optimal situation.[10] That said, community pharmacists can explain to patients the risks in seeing multiple prescribers and the safeguard provided, if that cannot be avoided, by not going to multiple pharmacies with their prescriptions or for OTC medications. Armed with up-to-date, complete patient profiles and open lines of communication, community pharmacists can exercise their prerogatives regarding drug substitution judiciously and counsel patients effectively.

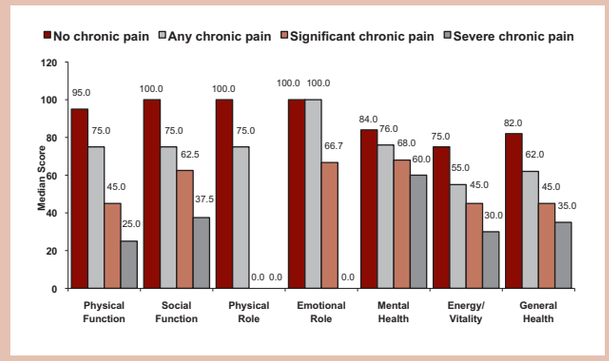
IMPORTANCE OF APPROPRIATE MANAGEMENT OF CHRONIC PAIN

Appropriate management of a patient's chronic noncancer pain can break the cycle of pain and profoundly improve patient quality of life.

Impact of Chronic Pain

Chronic pain affects all aspects of patients' lives and profoundly impacts their quality of life. Numerous studies have reported that patients' general sense of well-being is diminished by chronic pain, as are their sleep and their ability to perform activities of daily living. Vitality is reduced by chronic pain, and psychological symptoms such as depression and anxiety are common.[15,16] These effects extend beyond simple functioning to the activities that contribute most to quality of life, such as participation in social activities, sports, and hobbies. Perhaps most important, chronic pain affects patients' personal relationships. As shown in **Table 2**, patients report being less able to participate in social and community activities.[2] They tend to have fewer close friendships, and their relationships—including sexual—with their partners suffer, in part because they are afraid of being a burden to their loved ones. Smith and colleagues surveyed more than 3600 general-practice patients in Scotland.[17] Slightly more than half reported having chronic pain. **Figure 2** illustrates the profound impact of chronic pain on these patients' sense of health, as reflected in their scores on the Short Form-36 general health questionnaire. Chronic pain also interfered substantially with patients' daily activities.

Figure 2. Effect of Chronic Pain on Short Form-36 Scores[17]



Chronic pain has indirect costs for individuals and society. Stewart and colleagues conducted a survey of almost 30,000 US workers, of whom more than half reported having common, typically chronic pain conditions (headaches, arthritis, back pain, or unspecified musculoskeletal pain).[18] They found that although the number of days workers were absent from work because of pain was low, the amount of lost productive time while at work was 4 times that amount. The estimated cost of pain-related absence from and lost productive time at work was $61.2 billion per year, which did not account for costs such as hiring and training replacement workers or the disruption of coworkers' productivity.[18] In the study by Smith and colleagues, 61% of those with severe chronic pain were unable to work because of illness or disability, as were 20%, 13%, and 1% of those with significant, any, and no chronic pain, respectively.[17]

The direct costs of chronic pain are also difficult to estimate, because chronic pain exists in such a variety of forms. One estimate is that health care expenditures are about 60% higher for patients with chronic back pain than for individuals without back pain. Another estimate is that health care for patients with chronic pain may exceed the costs of treating patients with cancer, AIDS, and coronary artery disease together. Finally, the average annual costs to patients with chronic pain, excluding the costs of surgical procedures, have been estimated to range from $12,900 to $18,883.[19]

"Everything has a risk, but pain has a risk too. Patients need to be counseled not to underestimate how their quality of life is affected by pain." – Bill McCarberg, MD

Undertreatment of Chronic Pain

Perhaps the most common reason for undertreatment of pain is the discrepancy between patient and physician perceptions of pain severity. Absent reliable objective measures of pain, clinicians must rely on their patients' descriptions. Numerous studies have revealed that physicians underestimate the severity of their patients' pain, sometimes because of cultural differences, sometimes because patients are experiencing a type of pain (such as musculoskeletal pain) that is hard to describe, and sometimes for no apparent reason. The primary rule in pain assessment, "pain is what a patient says it is," is not always easy to remember.[8,20]

Patients sometimes are reluctant to take medications, either because of a belief that they should be stoic, because of a fear of adverse effects, or because of a fear of addiction. In some cases, physicians are equally reluctant to prescribe analgesia because of a fear of adverse effects, addiction potential, or potential for misuse or diversion of drugs.[2,7,15,20]

Unrelieved pain can result in a self-perpetuating cycle of inactivity, withdrawal, and escalating pain. In addition to the psychological symptoms of depression, anxiety, fear, and anger, undertreated pain can affect physical functioning, as shown in **Table 3**.[4]

Acute pain that is not relieved in a timely manner can evolve into a chronic pain syndrome. This evolution occurs as the neural pathways undergo (neuroplastic) changes that lead to hypersensitivity to pain signals. The neurotransmitter glutamate is released; glutamate activates ***N***-methyl-D-aspartate receptors, the ones most involved in chronic pain (**Figure 3**).[21] This results in disinhibition of dorsal horn neurons (***windup***), which then mount painful responses to normally innocuous input (***allodynia***) or exaggerated responses to less-noxious stimuli (***hyperalgesia***). Another neurotransmitter, substance P, stimulates the release of inflammatory and vasodilating agents such as histamine and nitric oxide, which in turn causes ***neurogenic inflammation***. This causes pain reactions to be triggered by signaling mechanisms in the central nervous system even after external stimuli are removed (***central sensitization***).[21,22]

Once a cycle of chronic pain is established, it becomes self-perpetuating unless it is broken. Therefore, patients need to understand the balance between the potential adverse effects of medications and the highly likely adverse effects of not managing their pain.

Rational Polypharmacy

Polypharmacy can be defined as the use of multiple medications to treat the same condition, the use of multiple drugs from the same class, or the use of multiple drugs with the same or similar mechanisms of action to treat different conditions.[23] Rational polypharmacy combines medications to achieve optimal pain relief with minimal toxicity. The purposes of rational polypharmacy can be summarized as follows[6,24]:

- To facilitate the use of lower doses of one or both drugs
  - To minimize adverse effects
  - To increase adherence
  - To be opioid sparing
- To maintain analgesic efficacy (eg, combining short-acting and long-acting agents for sustained pain relief)
  - To prevent breakthrough pain
- To increase efficacy by using 2 drugs with different mechanisms of action
  - To augment the effect of one agent with another (additive)
  - To potentiate the action of one agent with another (synergistic)
- To target different but associated symptoms (eg, pain and fatigue or pain and depression)
- To target different locations of the disease process (eg, peripheral and central pain; see **Figure 4, page 4**[25,26])

Achieving rational polypharmacy requires awareness of possible drug-drug interactions. The majority of drugs, including opioids, are metabolized by enzymes in the cytochrome P (CYP)-450 system. The CYP3A4 isoform accounts for the metabolism of about half of all marketed drugs. The extent to which drugs are metabolized varies between patients as levels of CYP isoforms vary. This between-individual variation can be affected by genetic and other factors, such as age, ethnicity, diet, alcohol and tobacco use, and chronic illness.[27,28]

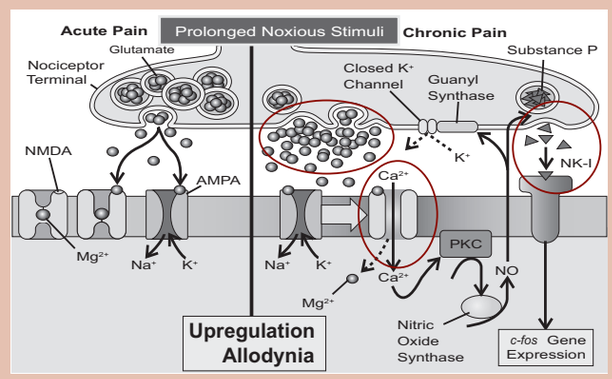
Drugs that are metabolized by an isoform are substrates of that isoform. Drugs that stimulate the synthesis of an isoform (inducers) enhance its metabolizing action and can thereby reduce plasma levels of substrates for that isoform, whereas inhibitors compete for the binding sites of an isoform, which may reduce metabolism of a substrate and, thus, increase plasma levels of that drug.[27,29] **Table 4, page 4,** shows the CYP-related status of selected agents commonly used in analgesia.[28-32]

Table 3. Physiologic Consequences of Unrelieved Pain[4]

System	Response to Pain	Examples of Manifestations
Cardiovascular	Increased heart rate Increase vascular resistance Increased blood pressure	Angina, myocardial infarction, deep vein thrombosis
Endocrine	Altered hormone release with metabolic disturbance	Weight loss, fever, shock
Gastrointestinal	Decreased rate of gastric emptying Decreased intestinal motility	Constipation, anorexia, ileus
Genitourinary	Abnormal hormone release	Decreased urine output, hypertension (fluid retention), electrolyte disturbance
Immune	Impaired function	Infection
Musculoskeletal	Muscle spasm Impaired muscle mobility/function	Immobility, weakness, fatigue
Respiratory	Decreased air flow	Atelectasis, pneumonia

Adapted with permission from National Pharmaceutical Council, Joint Commission on Accreditation of Healthcare Organizations. http://d.scribd.com/docs/1qeor4k1bd6nmb8g71hj.pdf. Accessed January 9, 2009.

Figure 3. Evolution From Acute to Chronic Pain[21]

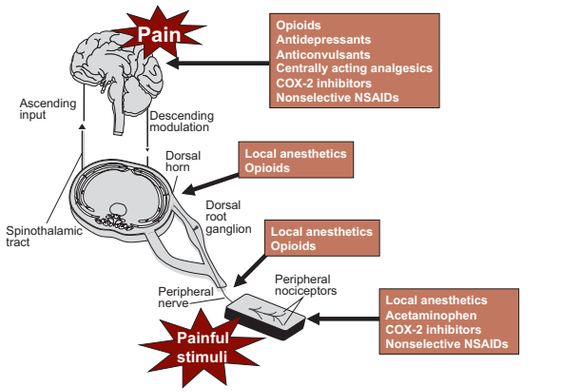


Incoming pain signals trigger the release of glutamate into the synaptic cleft between nociceptors and dorsal horn nerve cells. In acute pain (left panel), glutamate activates AMPA receptors on Na^+, K^+ channels. With prolonged activation, the polarization of the membrane changes; the Mg^{2+} plug in the Ca^{2+} channels is removed, and NMDA receptors in the channel complex are primed for glutamate activation. In chronic pain (right panel), increasing release of glutamate (circled in red) activates these primed channel complexes, permitting Ca^{2+} influx into the cell (circled in red), which activates protein kinase C, the enzyme needed for activation of NO synthase and production of NO. NO diffuses through the dorsal nerve cell membrane and synaptic cleft into the nociceptor and stimulates guanyl synthase–induced closure of K^+ channels. Since endorphins and enkephalins inhibit pain by opening these channels, closure induces opiate resistance. NO also stimulates the release of substance P, which, by binding to NK-1 receptors in the dorsal horn membrane (circled in red), triggers *c-fos* gene expression and promotes plasticity changes including neural remodeling and hypersensitization.

NMDA, *N*-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid; NK, neurokinin; PKC, protein kinase C; NO, nitric oxide.

Adapted with permission from Brookoff D. *Hosp Pract (Minneap).* 2000;35(7):45-52;59.

Figure 4. Rational Polypharmacy: Multiple Mechanisms and Sites of Action[25,26]



COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug.
Adapted with permission from Kehlet H, Dahl JB. *Anesth Analg*. 1993;77(5):1048-1056.

Rational polypharmacy is common practice in other chronic conditions, such as diabetes.[23,24] Its practice in chronic pain management can be as important and beneficial as in any other chronic condition, even if the consequences of uncontrolled pain are not as apparent as, for example, an amputation in diabetes. It only remains rational, however, if all of a patient's medications are known to the practitioners involved in the patient's care, especially the community pharmacist. Unfortunately, several factors may impede successful achievement of rational polypharmacy. A large survey found that a majority (78%) of Americans with pain take OTC drugs.[7] In another study, 43% of patients with pain reported using CAM.[14] If patients do not inform their prescribers or pharmacists of this use, drug-drug interactions may not be preventable. It is also not uncommon for patients to see multiple prescribers who may not be aware of all the medications a particular patient is taking. Again, if patients do not offer this information or if they are not questioned about this possibility, the result may well be "irrational" polypharmacy, which poses a significant risk of harm to the patient.[8,24] The community pharmacist may be in the best position to prevent that from happening.

AVAILABLE TREATMENTS FOR CHRONIC NONCANCER PAIN

Nonpharmacologic Measures

The majority of patients with pain likely use some form of nonpharmacologic therapy in addition to any pharmacologic treatment they are receiving. In one large survey of patients with pain, 76% of respondents (82% in suburban areas, 77% in urban settings, and 58% in rural areas) indicated that they used CAM, and 28% took herbal supplements.[33] The most frequently used supplements were glucosamine and chondroitin. Respondents less than 45 years of age used substantially more CAM than did older respondents. The most frequently used forms of CAM were heat and/or ice; exercise, stretching, and yoga; chiropractic treatment; massage; and relaxation techniques. Unfortunately, 31% of respondents had not informed their medical practitioners that they were using CAM.[33] When CAM takes the form of herbal supplements, this could result in "irrational" polypharmacy.

Additional nonpharmacologic treatment options include acupuncture, biofeedback, counseling, hypnosis, reflexology, weight control, smoking cessation, music therapy, and meditation,[34] none of which would interfere with pharmacologic treatment.

Nonopioid Analgesia

Nonopioid analgesia is considered first-line treatment for mild to moderate pain. Because some nonopioid analgesics are available OTC as well as in prescription combinations with other drugs, it is important for community pharmacists to ask patients about their OTC drug use.

Acetaminophen

Acetaminophen is available OTC and in combination with some opioids. Its mechanism of action involves central (but not peripheral) inhibition of prostaglandin. Acetaminophen is not anti-inflammatory, but it can be effective in mild pain. Although acetaminophen has a low side-effect profile with standard intermittent use, long-term and/or high-dosage use can result in hepatotoxicity. Thus, the daily dose should not exceed 4 g.[24,35] Acetaminophen is associated with some cardiovascular risk, but this is dose related. In a large study by Chan and colleagues, frequent and prolonged use of both acetaminophen and nonselective NSAIDs—but not brief, intermittent, or low-dosage use—was associated with increased cardiovascular risk, whereas aspirin was observed to have a protective effect against stroke.[36]

Table 4. Analgesia and CYP Enzymes[28-32]

Agent	Substrate of CYP Isoform	Inhibitor of CYP Isoform	Inducer of CYP Isoform
Anticonvulsants			
Carbamazepine	3A		3A, 2C19
Phenytoin	2C9, 3A		3A, 1A2
Antidepressants			
Amitriptyline	2D6, 3A, 1A2		
Bupropion	2B6	2D6	
Desipramine	2D6		
Duloxetine	1A2, 2D6	1A2, 2D6	1A2
Fluoxetine	2D6	2D6, 3A, 2C19	
Imipramine	2D6, 3A, 1A2, 2C19		
Nortriptyline	2D6		
Paroxetine	2D6	2D6, 3A	
Venlafaxine	2D6	2D6	
Nonopioids			
Acetaminophen	3A4, 2E1, 2A6, 2C9, 1A2, 2D6	3A4	
Celecoxib	2C9, 3A4	2D6, 2C8	
Ibuprofen	2C9, 2C19	2C9	
Naproxen	2C9, 1A2		
Opioids			
Buprenorphine	3A4	1A2, 2A6, 2C19	
Codeine	3A4, 2D6	2D6	
Fentanyl	3A4	3A4	
Hydrocodone	2D6		
Meperidine	2B6, 2C19, 3A4		
Morphine	2D6		
Oxycodone	2D6		
Tramadol	2D6		

CYP, cytochrome P-450.

NSAIDs

NSAIDs are considered alternatives for patients whose pain is not relieved by acetaminophen. Their mechanism of action is involved with blocking prostaglandin formation, both centrally and peripherally, via the inhibition of cyclooxygenase (COX). Nonselective NSAIDs, such as ibuprofen, aspirin, and naproxen, inhibit both COX-1 and COX-2. By so doing, they inhibit the formation not only of prostaglandins involved in pain but also of those involved in gastroprotection. COX-2–selective inhibitors, on the other hand, inhibit formation of only the prostaglandins involved in pain and

inflammation.[24,35,37] Patients taking nonselective NSAIDs, including aspirin, should be advised to report symptoms such as blood in their stool, nausea, stomach pain, or vomited blood, all of which might indicate NSAID-related bleeding.[38]

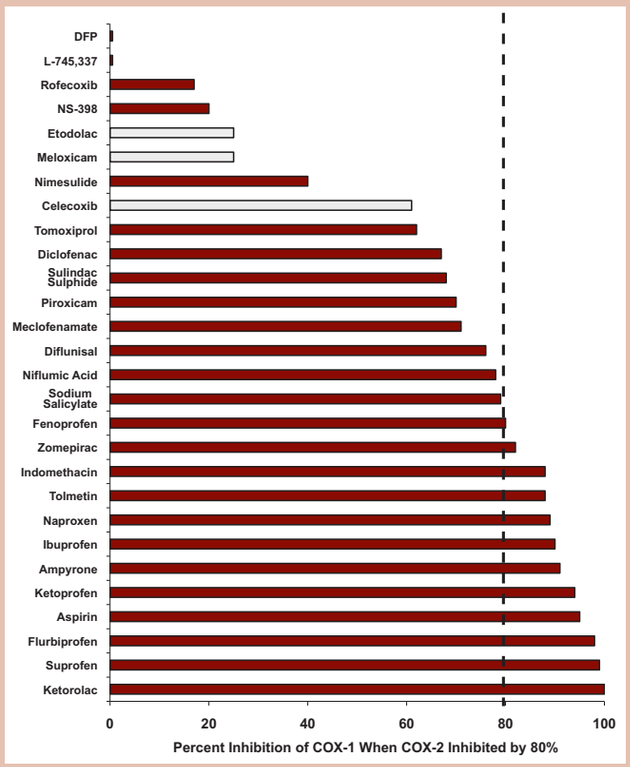
The primary safety concern with COX-2–specific inhibitors centers around the elevated risk of cardiovascular events seen in several clinical trials. Because of this risk, the US Food and Drug Administration (FDA) has requested that manufacturers withdraw such agents from the market. Currently, celecoxib is the only COX-2–specific inhibitor marketed as such within the United States. The label for celecoxib has been revised to include a boxed warning that celecoxib should be used at the lowest possible dosage for the shortest possible time and only for patients whose pain is not controlled by nonselective NSAIDs. Etodolac and meloxicam have been shown in vitro to have very high COX-2 selectivity similar to or more pronounced than that of celecoxib **(Figure 5)**.[39] The addition to the label includes a caution that patients with or at risk for cardiovascular disease may be at greater risk with the use of COX-2 inhibitors or any other NSAID as well. That said, the American Heart Association noted that the FDA advisory panel advised against adding warnings to the labels of OTC products so as not to cause undue concern by the lay public. The American Heart Association went on to state that the risks and benefits of treatment with any of these agents must be weighed and individual decisions made for each patient.[37]

Topical Analgesia

The term "topical analgesia" is used often to represent both topical agents (which target the site of application) and transdermal products (which are intended to reach systemic drug levels).[40] Topical analgesia may be appropriate for some types of mild to moderate pain, especially for patients for whom NSAIDs cause severe gastrointestinal adverse effects.[35]

Topical therapy includes counterirritants such as capsaicin cream, which is intended to desensitize nociceptors, as well as camphor and menthol. The anesthetic lidocaine is available in a patch and a gel, and in a cream in which it is combined with prilocaine. Creams containing salicylic acid are available OTC.[40] Topical NSAID formulations have been used in Europe for some time. Two topical formulations of diclofenac, a gel and a patch, were approved recently in the United States.[41]

Figure 5. Relationship Between 80% ("Therapeutic") Inhibition of COX-2 and Inhibition of COX-1 in an In Vitro Human Whole Blood Assay[39]



COX, cyclooxygenase; DFP, diisopropyl fluorophosphate.

Analysis of the percent inhibition of COX-1 seen when COX-2 is inhibited by 80% in the William Harvey Human Modified Whole Blood Assay. The dotted line indicates equiactivity (ie, an 80% inhibition of COX-1).

Adapted with permission from Warner TD et al. *Proc Natl Acad Sci U S A.* 1999;96(13):7563-7568.

Adjuvant Analgesia

Adjuvant analgesia has been shown to be effective primarily in neuropathic pain. This group of agents, comprising antidepressants and anticonvulsants, interact with neurotransmitters involved in the central processing of pain in the brain.[42]

Anticonvulsants

The anticonvulsants act at several sites to limit neuronal excitation and enhance inhibition. Their actions include blockade of sodium (carbamazepine, gabapentin, lamotrigine) and calcium (gabapentin, pregabalin) channels. Carbamazepine is indicated for treating trigeminal neuralgia and has shown some efficacy in other types of neuropathic pain.[42] Unfortunately, carbamazepine also has a number of potentially limiting interactions with other drugs, including benzodiazepines, antihistamines, antibiotics, β-blockers, and other anticonvulsants.[30] The newer anticonvulsants, such as gabapentin and pregabalin, which are both effective in treating neuropathic pain, have no clinically significant CYP-450 interactions with other drugs.[43]

Antidepressants

Tricyclic antidepressants are considered first-line treatment for neuropathic pain. They are believed to affect spinal cord pain transmission via their inhibition of norepinephrine and serotonin reuptake, their affinity for the histamine H_1 receptor, and their effects on sodium channels. They achieve analgesia at lower concentrations than are necessary for an antidepressive effect. Tricyclic antidepressants are classified as either secondary amines (nortriptyline, desipramine), which are relatively selective inhibitors of norepinephrine reuptake, or tertiary amines (amitriptyline, imipramine), which are more balanced inhibitors of norepinephrine and serotonin but also have more anticholinergic side effects than do the secondary amines.[24,42]

Fluoxetine and paroxetine are selective inhibitors of serotonin reuptake that do not affect norepinephrine. Venlafaxine and duloxetine, both shown to be effective in treating diabetic neuropathy, have balanced reuptake inhibition of both serotonin and norepinephrine, but they do not block other neuroreceptors, as do the tricyclics. Venlafaxine exhibits serotoninergic properties at dosages lower than 150 mg/day and mixed serotoninergic and noradrenergic properties at dosages higher than 150 mg/day. Dosages for patients whose venlafaxine treatment is being stopped should be tapered gradually, as there is a risk of discontinuation syndrome with abrupt cessation of therapy. The mechanism of action of bupropion is thought to involve mostly blockade of dopamine uptake with minor effects on norepinephrine as well.[24,42,43]

The most common adverse effects of agents used in adjuvant analgesia are shown in **Table 5, page 6**.[42,43] As described above, antidepressants may interact with other medications depending on how each drug is metabolized and which is an inhibitor or inducer of specific CYP isoforms. Of particular concern with the antidepressants is the cumulative effect of serotonin reuptake inhibition by several drugs, which can be similar to the cumulative gastrointestinal effects of OTC and prescription NSAIDs. Thus, caution should be used when patients are prescribed multiple drugs that effect serotonin uptake.[44] Additionally, tricyclics may interact with epinephrine-containing local anesthetics, opioids, tryptans, and antihistamines.[30]

Opioid Analgesia

The opioids, a class of diverse but related drugs, are used to treat moderate to severe pain that has not responded to nonopioids. Their general mechanism of action involves binding to opioid receptors in the central nervous system.[24]

Tramadol

Classification of tramadol, a relatively new synthetic opioid, is difficult. Although it is a weak μ-opioid agonist, tramadol also inhibits norepinephrine and serotonin reuptake, as do most antidepressants. Tramadol has demonstrated abuse liability only slightly higher than that of NSAIDs and much lower than that of traditional opioids.[45] Tramadol has a low potential for the development of tolerance because of its low opioid receptor affinity.[46] As a result, it is not a scheduled opioid; in fact, tramadol's low abuse liability and dual mechanism of action have led some people to believe that it should be classified in a category of its own.

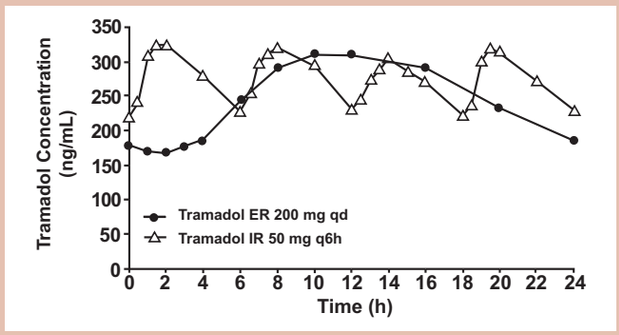
The efficacy of tramadol has been demonstrated in several clinical trials in neuropathic and musculoskeletal pain. Tramadol is approved for relief of moderate to moderately severe pain in adults.[47] It can be used in combination with NSAIDs to lower NSAID doses and potentially reduce their gastrointestinal risk.[46] The extended-release

Table 5. Common Adverse Effects of Adjuvant Analgesia[42,43]

Class/Agents	Adverse Effects
Anticonvulsants: first generation	
Carbamazepine	Dizziness, nausea, diplopia
Phenytoin	Dizziness, ataxia, slurred speech, confusion, nausea, rash
Anticonvulsants: second generation	
Gabapentin	Drowsiness, dizziness, fatigue, nausea, sedation, weight gain, peripheral edema
Anticonvulsants: newer	
Lamotrigine	Dizziness, constipation, nausea
Pregabalin	Drowsiness, dizziness, fatigue, nausea, sedation, weight gain, peripheral edema
Antidepressant: SNRIs	
Atypical (bupropion)	Anxiety, insomnia or sedation, weight loss, seizures (at >450 mg/d)
Duloxetine	Nausea, dry mouth, constipation, dizziness, insomnia
Venlafaxine	Headache, nausea, sweating, sedation, hypertension, seizures
Antidepressant: SSRIs	
Fluoxetine, paroxetine	Nausea, sedation, sexual dysfunction, decreased libido, headache, weight gain
Antidepressant: TCAs	
Amitriptyline, desipramine, imipramine, nortriptyline	Dry mouth, constipation, weight gain, urinary retention, sedation

SNRI, serotonin/norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Figure 6. Pharmacokinetics of Extended-Release vs Immediate-Release Tramadol[15]



Reprinted with permission from McCarberg B. *Ther Clin Risk Manag.* 2007;3(3):401-410.

(ER) formulation of tramadol has been compared with the immediate-release (IR) formulation and has shown a steadier rise in plasma concentration (**Figure 6**) as well as superior control of chronic noncancer pain.[15,19]

The incidence of adverse events in tramadol clinical trials has been low. The most frequent adverse events among more than 21,000 patients studied were nausea (6.1%), dizziness (4.6%), drowsiness (2.4%), fatigue (2.3%), and sweating, vomiting, dry mouth, and constipation (<2.0% each).[46] The 2 potential adverse effects of tramadol that are of concern to most people are seizure risk and the potential for serotonin syndrome.

Serotonin syndrome results from excessive serotoninergic activity. It can develop whenever multiple drugs with the same mechanism of serotonin reuptake inhibition are layered, including triptans, antidepressants, antipsychotics, anticonvulsants, antibiotics, some OTC products (eg, those containing dextromethorphan), and some herbal supplements (eg, Saint-John's-wort). The capacity to metabolize certain drugs and other patient factors also influence susceptibility to serotonin syndrome.[44] Most medical professionals are aware of this risk when 2 antidepressants are layered. The risk with tramadol, however, has been less publicized,[48] and there may, thus, be less clarity about the context and extent of the risk with tramadol. Ultimately, however, the risk for development of serotonin syndrome is the same when tramadol is one of the layered drugs as it would be with 2 antidepressants. Therefore, although community pharmacists should be aware of this risk and explain it to patients, it simply indicates, once again, that polypharmacy with tramadol should be as rational as should all polypharmacy with other medications sharing similar pharmacology. As with all potential interactions, the community pharmacist needs to consider all contributing factors and weigh the benefits and risks of all available recommendations.[44]

The risk of seizure with tramadol use was noticed shortly after the drug's approval. A subsequent retrospective cohort study indicated that less than 1% of almost 10,000 patients taking tramadol experienced seizures.[49] Studies also have demonstrated that the majority of patients taking tramadol who do experience seizures either are taking concomitant medications (such as drugs that interact with the CYP2D6 isoform or any drug that reduces the seizure threshold) or have conditions (such as diagnosed epilepsy, head trauma, alcoholism, or stroke) that predispose them to seizure activity.[49] Therefore, caution should be used when patients with these predisposing factors have been prescribed tramadol.[43]

Traditional Opioids

The traditional opioids have been scheduled by the Drug Enforcement Administration based on abuse potential, as shown in **Table 6**.[19]

The opioids are classified chemically into 4 classes.[50] They are also classified by their mechanisms of action. They can have affinity, which describes the strength of a drug's interaction with its receptor, and efficacy, which describes the strength of effect of the binding. Most are opioid receptor agonists that stimulate the μ-opioid receptors in pain pathways. Some are partial agonists, with high affinity but low efficacy at the μ-opioid receptor, which is thought to mediate analgesia; δ-opioid receptors elicit spinal analgesia; κ-opioid receptors are associated with dysphoria and sedation. Opioid classifications and sites of activity are shown in **Table 7**.[19,27,50-52]

Table 6. Schedules of Controlled Drugs[19]

Schedule	Criteria	Examples
I	No medical use; high addiction potential	Heroin, marijuana
II	Medical use; high addiction potential	Fentanyl, methadone, morphine, oxycodone
III	Medical use; moderate addiction potential	Codeine, hydrocodone
IV	Medical use; low abuse potential	Benzodiazepines, butorphanol, propoxyphene
V	Medical use; low abuse potential	Buprenorphine

Adapted with permission from Trescot AM et al. *Pain Physician.* 2008;11 (2 suppl):S5-S62.

Although there is controversy regarding the long-term use of traditional opioids in noncancer pain, they have shown efficacy in reducing chronic noncancer pain in clinical studies, particularly neuropathy and musculoskeletal pain.[19,43] A review of several opioid clinical trials, with information from more than 4000 patients, found that dry mouth (25%), nausea (21%), constipation (15%), dizziness (14%), drowsiness (14%), and pruritus (13%) were the most common adverse effects reported.[53] Several of these potential adverse effects can be prevented, as discussed earlier. Community pharmacists should counsel patients regarding sedation, both in terms of driving and in the context of concomitant use of other possibly sedating substances.[54] More serious adverse effects include respiratory depression.[19]

The topics of opioid analgesic misuse and addiction are discussed frequently and can be deterrents to effective control of chronic pain. In one survey, 57% of physicians reported reluctance to prescribe opioids because of the potential for addiction.[7] Estimates from studies of the frequency of misuse or addiction range from 5% to 50%, although it is not clear what the frequency would be in a population comprising only patients with chronic noncancer pain.[43] It is important that community pharmacists, in addition to prescribers, be familiar with the differences between addiction, physical dependence, tolerance, pseudoaddiction, and abuse, as outlined in **Table 8, page 8**.[34] Pseudoaddiction typically results from undertreatment of pain. The behaviors associated with pseudoaddiction, shown in **Table 9, page 8**, are, unfortunately, frequently misidentified as drug-seeking behavior, whereas undertreated pain should be the top-of-mind cause.[55,56] Community pharmacists need to help patients put this issue into perspective, perhaps by using an analogy with other medications the patients are taking, to help patients overcome their fear of appropriate treatment for their pain.

"I like to use the analogy of something my patients are already taking. For example, I tell them that if they stopped taking their β-blocker abruptly, they risk experiencing a hypertensive crisis; similarly, if they stopped their antidepressant, they might experience serotonin withdrawal, yet they don't consider themselves addicted to these medications, nor do they refuse to take them."
– Jeffrey Fudin, PharmD

ISSUES SURROUNDING MANAGEMENT OF CHRONIC PAIN

In addition to the properties of different pain medications and the attitudes of health care practitioners and patients, certain other factors can influence the optimal management of chronic noncancer pain.

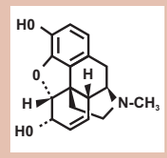
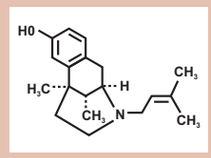
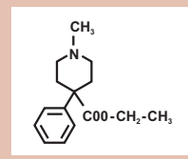
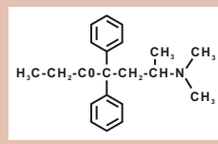
Substitution

As is true with antiepileptic drugs and in contrast to other types of medications such as statins, the differences between various analgesics are not negligible. Rather than switching, for example, from a Fuji to a Macintosh apple, substituting one analgesic (or one opioid) for another is likely to be more like switching from apples to bananas, even if they are all fruits and all come from trees, or even if the drugs' general descriptions sound similar or identical. This caveat applies not only between classes and drugs within classes but also to formulations of a single drug.

"Bioequivalence does not necessarily translate into therapeutic equivalence."
– Jacquelyn Bainbridge, PharmD

The topic of generic substitution is one of ongoing debate. Generic versions of brand-name analgesics may cost the patient less up front if the branded version is not in a high tier of the patient's formulary or if an insurance company charges lower copays for generics.[57] This can be a strong motivator for community pharmacists to substitute generic formulations. In the long run, however, this might not be beneficial to the patient. Bioequivalence implies equivalent release of the same drug substance from 2 formulations, leading to an equivalent rate and extent of absorption from the 2 formulations.[58] The FDA permits a generic drug to release 80% to 125% of active ingredient into the bloodstream compared to the amount released from a dose of the original formulation. Some experts, however, believe that this range is too broad, especially in the context of a drug with a narrow therapeutic index—one that is not effective below a certain dosage and becomes toxic at a dosage only slightly higher than that. The rate at which the active ingredient is released, as well as the amount released, can vary and may not always be predictable. Thus, the 80% bioequivalence seen in the required studies (which are not always conducted with subjects who match the typical patient population) may not predict real-world variations that could lead

Table 7. Chemical Classification and Receptor Effects of Opioid Analgesics[27,50,52]

Class	Examples	Receptor μ[a]	Receptor δ[b]	Receptor κ[c]
PHENANTHRENES				
 (Morphine)	Buprenorphine	Partial agonist		Antagonist
	Butorphanol	Agonist/antagonist		
	Codeine	Weak agonist	Weak agonist	
	Hydrocodone	Weak agonist		
	Hydromorphone	Agonist		
	Levorphanol	Agonist	Agonist	Agonist
	Morphine	Agonist		Weak agonist
	Nalbuphine	Agonist/antagonist		
	Oxycodone	Weak agonist		
	Oxymorphone	Agonist		
BENZOMORPHANS				
 (Pentazocine)	Pentazocine	Antagonist		Agonist
PHENYLPIPERIDINES				
 (Meperidine)	Fentanyl	Agonist (highest affinity)		
	Meperidine	Agonist	Agonist	
DIPHENYLHEPTANES				
 (Methadone)	Methadone	Agonist		
	Propoxyphene	Agonist		

[a]μ-1: analgesia; μ-2: sedation, vomiting, respiratory depression, pruritus, euphoria, anorexia, urinary retention, physical dependence.

[b]Analgesia, spinal analgesia.

[c]Analgesia, sedation, dyspnea, psychomimetic effects, miosis, respiratory depression, euphoria, dysphoria, dyspnea.

Table 8. Dependence Terminology[34]

Term	Definition
Addiction	Neurobiologic, multifactorial disease characterized by impaired control, compulsive drug use, continued use despite harm
Physical dependence	Normal adaptive state that results in withdrawal symptoms if drug is stopped or decreased abruptly
Pseudoaddiction	Relief-seeking behaviors misinterpreted as drug-seeking behaviors; resolve with effective analgesia
Substance abuse	Use of any substance for nontherapeutic purposes or purposes other than those for which it is prescribed
Tolerance	Physiologic state from regular drug use in which increased dosage is needed to sustain effect

Table 9. Signs of Pseudoaddiction[55,56]

- Borrowing drugs from others
- Obtaining prescription drugs from nonmedical sources
- Unsanctioned dosage increases
- Running out of medications prematurely
- Requesting higher dosages
- Requesting specific drugs
- Hoarding drugs when symptoms are not severe
- Prescription forgery (may indicate other problems)
- Recurrent prescription loss (may indicate other problems)
- Obtaining drugs from multiple medical sources (may indicate other problems)
- Stealing drugs (may indicate other problems)

to toxicity and/or insufficient pain control. These differences should be considered carefully in the decision to substitute generics for branded pain medications, and their possible implications should be discussed with patients.[57,59]

Another area of substitution that may prove troublesome is that of an IR formulation of a drug for its ER formulation. The community pharmacist again might believe that he or she is saving a patient some money by requesting permission from the prescriber to make this switch. In the context of controlling chronic pain, however, as in other areas, this may be more of a disservice than a help. Two issues of great concern to patients with chronic pain are inadequate pain control and the impact of their pain on their ability to sleep. In a large survey by McCarberg and colleagues, 81% of patients taking short-acting pain medications reported inadequate pain control.[2] Whereas IR opioids cause rapid increases and decreases in serum opioid levels, ER formulations tend to cause gradual increases to therapeutic levels, extended maintenance at those levels, and gradual declines. Thus, ER formulations are more likely to provide patients with consistent pain relief and the likelihood of uninterrupted sleep.[2,51] Before requesting permission to substitute an IR formulation for an ER formulation, therefore, community pharmacists should talk with patients about the possible ramifications of such a switch.

Patient Variations

Variations both between and within patients can cause differences in their responses to specific analgesic drugs.

As patients age, their renal and hepatic function may deteriorate, which could result in drug accumulation.[9,11] Multiple comorbid medical conditions are also common, particularly among older patients. In the large survey mentioned above, 42% of patients with chronic pain also had high blood pressure, 21% had diabetes, and 14% had congestive heart failure or angina, for which most were being treated.[7] This strongly suggests that patients will likely be taking other prescribed medications, OTC drugs, and CAM, all of which have the potential for drug-drug interactions. It can also result in drug-disease interactions, such as those discussed previously.[9]

Patients' responses to various drugs, including opioids, can also be influenced by genetic variations, as well as by the nature, source, and degree of each patient's pain.[43,51] Finally, there are variations between and within patients' responses to medications that simply have no apparent explanation.

CONCLUSION

Community pharmacists play an integral and very important role in helping patients manage their chronic noncancer pain, and everyone, including prescribers and patients, benefits when they proactively adopt and fulfill this role. Community pharmacists need to counsel patients to help them understand how important it is to treat their pain, both to avoid the evolution of acute to chronic pain and to prevent the potentially devastating and debilitating effects of uncontrolled chronic pain. They also need to communicate assertively with both prescribers and patients to ensure that patients are reaping maximal benefit from their pain treatment.

To accomplish these tasks, community pharmacists require a command of information regarding commonly prescribed pain treatments, including the principles behind treatment selection and the criteria for changes in treatment. They also need to be alert to possible barriers to successful treatment, such as patients' concurrent use of other medications and comorbidities. The more community pharmacists understand pain management, the more they can help their patients. The Sidebar below provides some information resources regarding chronic pain.

Resources: Information on Chronic Pain

- American Chronic Pain Association: www.theacpa.org
- American Pain Foundation: www.painfoundation.org
- American Pain Society: www.ampainsoc.org
- NovaPain.net: www.paindr.com
- Pain Treatment Topics: www.pain-topics.org
- Pain.com: www.pain.com
- PainEDU.org: www.painedu.org

Community pharmacists are in an ideal position to ensure that patient safety is protected and to promote the optimal use of rational polypharmacy for patients with chronic pain via:

- Investigation: asking patients about other medications, other conditions, and any concerns they may have; asking patients if their pain is sufficiently controlled by whatever medication they are using
- Notation: updating patients' medication profiles, including OTC and CAM
- Education: allaying patients' fears regarding certain medications; reminding them about safe use and storage; advising them about the possible pitfalls of substitution
- Communication: advising patients to stay with one pharmacy; relaying concerns about treatment to prescribers

With the use of up-front counseling, rational polypharmacy, appropriate formulations, and reassurance, community pharmacists can help their patients use analgesic medications to reduce their chronic pain and increase their productivity and quality of life.

Scion Educational Resources
Department OP466a
PO Box 373
Long Valley, NJ 07853

CME MATERIALS ENCLOSED

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OPTIMIZING CHRONIC PAIN MANAGEMENT: INTEGRATING PHARMACOKINETICS AND PHARMACODYNAMICS

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