

EDUCATIONAL OBJECTIVES

Goal: To assist pharmacists in recognizing common pain types, triaging acute and chronic pain, and identifying appropriate medication selection for various pain types.

After participating in this activity, pharmacists will be able to:

- Describe the prevalence, consequences and costs of pain
- Discuss the emerging role of the pharmacist as ambassadors for implementing appropriate pain therapeutics
- Define common terms in pain management
- Describe the common types of pain and their presentation/symptoms
- Recall the pathophysiology of pain and perception
- Define dysesthesia, parathesias, allodynia, hyperalgesia, and hyperpathia
- Discuss the ways pharmacists can assess and monitor painful conditions



The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists are eligible to participate in the knowledge-based activities, and will receive up to 0.2 CEUs (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the online system.

ACPE #0009-9999-13-006-H01-P

Grant Funding: As of March 11, 2013, funding for this activity is as follows:

Supported by an educational grant from Purdue Pharma, L.P.

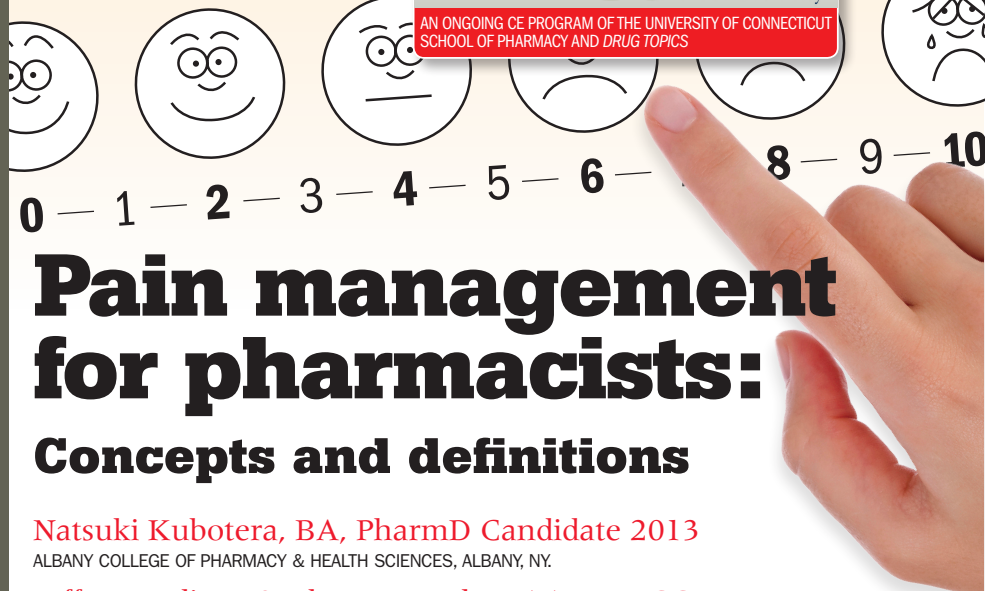
Activity Fee: There is no fee for this activity.

Initial release date: 4/10/2013

Expiration date: 4/10/2015

To obtain immediate CPE credit, take the test online at www.drugtopics.com/cpe. Just click on the link in the yellow box under **Free CPE Activities**, which will take you to the CPE site. For first-time users, please complete the registration page. For those already registered, log in, find, and click on this lesson. Test results will be displayed immediately. Complete the evaluation form and *Drug Topics* will be electronically uploading your CPE credit to CPE Monitor via your NABP e-profile ID. You should be able to view your credits earned within a two-week period of completing the evaluation.

For questions concerning the online CPE activities, e-mail: cpehelp@advanstar.com.



Pain management for pharmacists: Concepts and definitions

Natsuki Kubotera, BA, PharmD Candidate 2013

ALBANY COLLEGE OF PHARMACY & HEALTH SCIENCES, ALBANY, NY.

Jeffrey Fudin, BS, PharmD, RPh, DAAPM, FCCP

ADJUNCT ASSOCIATE PROFESSOR OF PHARMACY PRACTICE, ALBANY COLLEGE OF PHARMACY & HEALTH SCIENCES, ALBANY, NY.

Abstract

Pain and related symptom management involve complex polypharmacy, a keen understanding of pharmacotherapeutics, and interdisciplinary collaboration. This is the first in a series of pharmacist continuing education articles dedicated to pain management. Primary literature from pharmacy, medicine, and nursing recognize an inadequate time commitment to pain management and appropriate medication therapy. This, coupled with the necessary balance required for chronic opioid therapy, has become a therapeutic, political, and legal conundrum especially for prescribers and pharmacists. Epidemiologic and prevalence data for acute and chronic pain are reviewed along with recent FDA developments and associated regulatory debates. An overview of the pharmacist's role in pain and palliative care and the developing specialty practice in pain management are chronologically presented. Common medical terminology, pain pathophysiology, and descriptive pain types demarcated with respect to acute, chronic, nociceptive, visceral, somatic, and neuropathic pain are reviewed. Physical findings such as dysesthesia, parathesia, allodynia, hyperalgesia, and hyperpathia are differentiated, and appropriate medications by pharmacotherapeutic class are outlined. Opportunities for medication therapy management, responsibilities for the pharmacist provider, and the key role that pharmacists can provide for quality pain management outcomes are identified.

Faculty: Natsuki Kubotera, BA, PharmD Candidate and Jeffrey Fudin, BS, PharmD, RPh, DAAPM, FCCP

Ms. Kubotera is a 2013 PharmD candidate, Albany College of Pharmacy & Health Sciences, Albany, NY. She has accepted a PGY1 Residency position at Providence Health and Services, Providence Portland and St. Vincent Medical Centers in Portland, OR. Dr. Fudin is adjunct associate professor of pharmacy practice, Albany College of Pharmacy & Health Sciences, Albany, NY, and owner and managing editor of PainDr.com.

Faculty Disclosure: Ms. Kubotera has no actual or potential conflict of interest associated with this article. Dr. Fudin is on speakers' bureaus for Janssen Pharmaceuticals and Purdue Pharma. This commentary is the opinion of Dr. Fudin alone and does not reflect the opinions of his employers, employee affiliates, and/or pharmaceutical companies that he has consulted for currently or previously. He is a consultant to Practical Pain Management in the development of an online opioid analgesic calculator.

Disclosure of Discussions of Off-Label and Investigational Uses of Drugs: This activity may contain discussion of unlabeled/unapproved use of drugs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of *Drug Topics* or University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

Pain Management Considerations in Medication Therapy Management CPE Series

Welcome to a new CPE series, Pain Management Considerations in Medication Therapy Management, which has been designed for pharmacists in all areas of practice who need to further their clinical and MTM skills in the management of patients with pain. Beginning this month and continuing through August 2013, pharmacists can earn up to 10 hours of CPE credit with 5 monthly knowledge-based activities from the University of

Connecticut School of Pharmacy and *Drug Topics*.

This month, the professional development activity will cover concepts and definitions associated with pain management. In May and June, the CPE activities will include pharmacology and therapeutics of pain medications. In July, regulatory and ethical issues in pain management will be covered. The knowledge-based activities will conclude in August with man-

agement of common pain conditions by pharmacists, including osteoarthritis, low back pain, fibromyalgia, sprains, strains, contusions, and generalized headaches.

The Pain Management series will also be offering application-based activities for an additional 2 CPE credits. Online interactive case-based studies will be available with 1 hour of CPE credit, starting September and continuing in October 2013.

Pain and related symptom management often involves complex poly-pharmacy, a keen understanding of pharmacotherapeutics across several drug classes, and collaboration with other healthcare disciplines. Undoubtedly the time commitment to pain management education for entry-level graduates within schools of pharmacy, medicine, and nursing is lacking.¹ Given that most complex pain syndromes and palliative symptom management involve medications such as opioids, gastrointestinal (GI) agents, antidepressants, anticonvulsants, skeletal muscle relaxants, and other medication classes alone or combined for purposes of pain management and other comorbid conditions, it is incumbent on pharmacists to seek professional advancement in pain management and secure a comprehensive role as interdisciplinary healthcare team members in all practice settings. Perhaps most compelling is that even with numerous evidence-based pain practice guidelines in place, patients continue to suffer needlessly, outcomes overall are poor, and society pays a high price figuratively and practically through absenteeism, presenteeism (present at work under suboptimal health conditions), and costs of suboptimal treatment strategies, resultant clinic and emergency department (ED) visits, hospital admissions, and readmissions.¹⁻⁴

Chronic pain affects 100 million people in the U.S. and is the most common reason that patients visit healthcare practitioners, the leading cause of disability, and comes with a price tag of \$560 to

\$635 billion per year.⁵ An estimated 20% of adults (42 million) report that pain or physical discomfort disrupts their sleep several nights per week.⁵

Chronic pain affects 100 million people in the U.S. and is the most common reason that patients visit healthcare practitioners.

In 2006, 46 and 35 million inpatient and ambulatory surgeries, respectively, were performed in the U.S.^{6,7} In a national survey sampling 129 hospitalized surgical patients, 88% reported moderate, severe, or extreme pain on hospital discharge.⁸ In 2006, the Multum Lexicon database began collecting drug data for emergency rooms, and during that first year the most commonly prescribed drug classes for each visit included opioid analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) (collectively 36.8%).⁹ According to the National Hospital Ambulatory Medical Care 2009 Emergency Department Summary from the Centers for Disease Control and Prevention (CDC), 5 of the 10 leading principal reasons for ED visits included acute pain.¹⁰

Aside from the practical therapeutic reasons, federal and state governments have sought to more closely scrutinize and regulate opioids through prescription monitoring programs and nonvalidated opioid dose limitations to address increased deaths from opioid abuse.¹¹⁻¹³ This past January, an FDA hearing took place to discuss the rescheduling of hydrocodone combination products. On January 25, 2013, an FDA advisory panel voted 19 to 10 recommending to the FDA commissioner that rescheduling for hydrocodone combinations be changed to C-II status.¹⁴

On February 7-8, 2013, FDA held a public hearing on the "Impact of Approved Drug Labeling on Chronic Opioid Therapy."^{15,16} The purpose was to determine whether all or part of a recent citizen's petition that requested label changes to opioids should be adopted. The proposal included the following label changes:¹⁶

The petition requests 3 changes by the FDA to opioid-product labeling: (1) strike the term "moderate" from the indication of opioid analgesics for noncancer pain (leaving "severe pain" as the only indication); (2) add a maximum daily opioid dose, equivalent to 100 milligrams of morphine for noncancer pain; and (3) add a maximum duration of 90 days for continuous (daily) opioid use for noncancer pain.

These maneuvers require careful balance and must not project a negative impact on opioid availability to legitimate

TABLE 1

POTENTIAL PROBLEMS REGARDING PRACTICE ISSUES

Practice issue barriers	Potential problems
Failure to use multimodal approach	Miss the benefits of physical, behavioral, and psychological approaches to help retrain the central nervous system and maximize functional recovery.
Failure to target the mechanism of pain generation (somatic, inflammatory, neuropathic)	Suboptimal pain management. Avoidable costs when treatment ineffective.
Failure to treat neuropathic pain with adjuvant meds	Worsening nervous system hypersensitivity. Suboptimal pain management.
Heavy reliance on short-acting opioids instead of prescribing long-acting opioids	Increased breakthrough pain, disturbed sleep. Development of opioid tolerance. Acetaminophen toxicity (combination drugs). Increased risk of addiction in sub-population with potential for abuse.

Source: Ref 22 (reprinted with permission)

pain patients, honest prescribers, or pharmacists. Appropriate learning among pharmacists is therefore essential to ensure necessary monitoring of opioid therapy across diverse practice settings.

Recognizing that positive and negative barriers exist, that particular pharmacotherapy and pharmacokinetic expertise are essential, and that pain and symptom management outcomes are best served by an interdisciplinary group, the Strategic Planning Summit for Pain and Palliative Care Pharmacy Practice convened in 2009 to "identify strategies to improve the attitudes, knowledge, and skills of the profession as a whole..."¹ The summit included 79 participants and 5 professional stakeholder organizations represented by pharmacy, medicine, and nursing. Their summary statement said it well: "The opportunities available for pharmacist involvement in the care of these patients are plentiful, and the time is now for our profession to take the next steps in increasing pharmacy involvement in the interdisciplinary care of patients in pain and at the end of life."¹

At least in part at the behest of the summit, the Board of Pharmaceutical Specialties (BPS) issued a press release in June 2011 indicating that role delineation studies in pain and palliative care to establish a board certification for pain management pharmacists would move forward.¹⁷ A newly appointed Practice Analysis Task Force group had met in April 2011. In May 2012, however, BPS denied the petition to

move forward in establishing pain and palliative care as a specialty, although future BPS certification has not been ruled out.¹⁸ For now pharmacists can become credentialed through the American Academy of Pain Management or American Society of Pain Educators, although neither are recognized by the Joint Commission of Pharmacy Practice (JCPP) as a board certification. In the spirit of moving forward to encourage pain education and support the efforts of those continuing to pave the path, this is the first in a UCONN-initiated *Drug Topics* continuing education series to enhance pain education among pharmacists.

Epidemiology and costs

Pain is a primary health problem that can negatively impact outcomes of multiple disease states, significantly decrease the quality of life, delay hospital discharge, and increase healthcare costs overall.¹⁹ Additionally the majority of chronic pain patients suffer from anguish and mental health disorders because of pain; this frequently necessitates a complex codependent treatment.²⁰ The loss of productivity and concentration during work, lost work time, and increased number of hospital and physician visits for diagnosis and treatment all increase healthcare costs.² Presenteeism also contributes to cost and productivity. This occurs when an employee reports for work despite having an illness or medical condition that prevents the employee from functioning at full capa-

bility during work.² It leads to a significant decrease in productivity at work, incurring an economic estimate of \$150 billion per year in the U.S.²¹ Adequate treatment of chronic noncancer pain is necessary, but despite available guidelines, often such algorithms are not effectively implemented. **Table 1** illustrates the potential problems that may ensue if acceptable pain management needs are not adequately achieved.²²

Because the treatment of certain pain syndromes is complex, it is not uncommon to use rational medication combinations that include various pharmacologic mechanisms in an attempt to achieve synergistic or additive benefit while minimizing medication side effects.²³ Elevated doses of monotherapeutic analgesics are more likely to cause adverse effects than lower doses of analgesics in combination. For example, a higher dose of an antidepressant used as monotherapy may cause sedation; a NSAID may induce a gastrointestinal bleed; and an anticonvulsant may cause sedation and ataxia. Further, the use of opioids as monotherapy increase the risk of dependence and abuse liability.

Drug overdose deaths, the second leading cause of unintentional deaths due to injury, have been steadily increasing in the U.S. since 1970.

Drug overdose deaths, currently the second leading cause of unintentional deaths due to injury, have been steadily increasing in the U.S. since 1970.²⁴ According to CDC 2011 data, the most commonly reported source for nonprescribed opioids is from friends or relatives at 54.2%. Another 18.1% reported obtaining the medications from a prescriber, whereas only 3.9% bought their medications from a

drug dealer or stranger.²⁵ Among friends and family who supplied the medications, 81.6% reported getting the medication from a single prescriber.²⁵

Educating healthcare professionals on proper pain medication use and appropriate quantities for acute pain issues could aid in decreasing the number of legal prescriptions that end up in the wrong hands. Pharmacist involvement within community practice settings, as community educators, and on interdisciplinary healthcare teams caring for chronic pain patients can ease the pressure on prescribers and help communities and politicians better understand the societal impact of untreated pain, appropriate medication access, and mitigating opioid-associated risks.

Recently there has been an increase in marketing campaigns and headlines on the topic of opioid abuse and overdose deaths. This has increased the pressure on the pharmaceutical industry to provide more information and educational materials to their consumers. One pharmaceutical company has launched the “Turn to Help” campaign regarding opioid dependence and abuse.²⁶ Some urban healthcare facilities have seen new guidelines for opioid prescriptions. For example, New York City’s Mayor Bloomberg has proposed a restriction to the city’s public hospital EDs precluding a prescription for more than a 3-day supply of any opioid and without an option for extended-release dosage forms.²⁷ Certain states have

TABLE 2

INCIDENCE OF CHRONIC PAIN

Procedure	Estimated incidence of chronic pain	Estimated incidence of chronic severe (disabling) pain*	Number of surgeries in the United States
Amputation	10%		609,000
Coronary artery bypass surgery	30%-50%	5%-10%	598,000
Inguinal hernia repair	30%-40%	10%	Unknown
Breast surgery (lumpectomy or mastectomy)	20%-30%	5%-10%	479,000
Cesarean section	10%	4%	220,000

*More than 5 of 10 pain scores

Source: Ref 9,36,37

variously employed policy permutations of this, while others have created what some consider to be draconian strategies with potential adverse outcomes to legitimate patients.²⁸⁻³³ Such policy changes may give the wrong impression to prescribers and cause unnecessary suffering in those who have chronic pain.

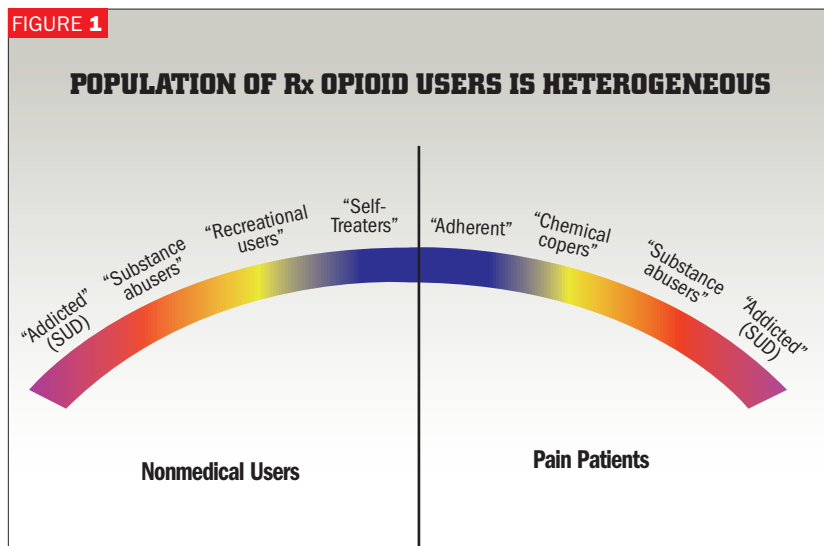
Definition

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” by the International Association for the Study of Pain (IASP).³⁴ Acute pain usually occurs as a “warning” of trauma to the affected tissue and has a sudden onset. It is usually temporary and is resolved when the cause is eliminated or healed, whether

that was an injury, surgery, or a disease. Chronic pain is pain that lasts longer than the expected healing time, is present for 3 months or longer, adversely affects sleep, and may not have an identifiable pathology.³⁴ The patient may have comorbidities associated with the pain, which may have a gradual or acute initial onset. Both cancer and chronic noncancer pain can be a combination of acute and chronic pain associated with different etiologies. For most chronic disorders the pain may be caused by the disease itself, associated diagnostic procedures, and/or the treatment.

During the process of treating acute pain, pharmacists play an important role to ensure medication compliance in terms of counseling on expected side effects (e.g., opioid-induced constipation, urinary retention, sedation, tolerance; NSAID-induced GI upset, bleed, fluid retention, elevated blood pressure) and avoiding or treating associated side effects effectively. It is also important to counsel on when to seek medical attention and when to intervene without a medical visit. The patient should understand the risks associated with pain management and the risk of not treating the acute pain. Chronic pain syndromes can develop from insufficient acute pain treatment from resultant neuroplasticity, including remodeling of nerves in the affected area.³⁵ This can occur after surgery and is most prevalent following amputation, breast surgery, Cesarean section, coronary artery bypass surgery, and hernia repair as listed in Table 2.^{9,36,37} The pain can persist long after the surgical wounds have healed.³⁸ Educating the patient on the importance of compliance is therefore

FIGURE 1



Abbreviation: SUD, substance use disorder

Source: Ref 42 (reprinted with permission)

TABLE 3

SPECTRUM OF ABERRANT DRUG-TAKING BEHAVIOR

More suggestive of addiction	Less suggestive of addiction
<ul style="list-style-type: none"> ■ Concurrent abuse of alcohol/illicit drugs ■ Evidence of deterioration in ability to function at work/in family/other social activity that appears related to drug use ■ Injecting oral formulations ■ Multiple dose escalations/nonadherence to therapy despite warnings ■ Obtaining prescription drugs from nonmedical sources ■ Prescription forgery ■ Repeated resistance to therapy changes despite clear physical/psychologic effects ■ Selling prescription drugs ■ Stealing/borrowing drugs from others 	<ul style="list-style-type: none"> ■ Aggressive complaining about need for medication ■ Drug hoarding during periods of reduced symptoms ■ Openly acquiring similar drugs from other medical sources ■ Repeating specific drugs ■ Reporting psychic effects not intended by physician ■ Resistance to change in therapy associated with tolerance to adverse effects accompanied by expressions of anxiety related to return of severe symptoms ■ Unapproved use of drugs to treat symptoms ■ Unsanctioned dose escalation or other nonadherence with therapy on 1 or 2 occasions

Source: Ref 42 (adapted with permission)

a critical role for the community pharmacist to incorporate into practice and is not easily achieved by other healthcare providers in any other practice setting.

Breakthrough pain has been defined as a “transient or episodic exacerbation of pain that occurs in patients with pain that is otherwise considered stable but persistent.”³⁹ The pain can occur with or without baseline pain and it can be a sudden onset or gradual increase.⁴⁰ There is no difference between the terms persistent pain and chronic pain; however, the former has become more acceptable among pain clinicians in an effort to lessen the negative perception often associated with difficult patients otherwise labeled with a diagnosis of “chronic pain”. Fibromyalgia seems particularly more prevalent among those who also have chronic fatigue syndrome.⁴¹

Addiction is defined as “a primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations.”³⁹ The characteristics associated with addiction are behaviors that include impaired control or compulsive drug use, cravings, and continued use despite harm to oneself.³⁹ There is no definitive technique to determine whether addiction will occur, although there are signs such as smoking, family history of substance abuse, and unsanctioned dose escalation, that clinicians can screen to stratify risk (See <https://painedu.org/tools.asp>). Intuitive signs of addiction are presented in Table 3, although these could also be indicative of drug misuse, abuse, or diversion.⁴² Dependence, however, is the adaptation associated with chronic use due to tolerance of the medica-

tion that can manifest itself physically or psychologically if the medication is discontinued abruptly. Pseudoaddiction is when the patient mimics behaviors associated with true addiction, but the behavior is fueled by inadequate pain management due to the distrust between the patient and the prescriber and can be better interpreted as “relief seeking” behavior.⁴³ The patient may self-medicate, which is the use of drugs without consulting a healthcare professional to alleviate the stressor or disease in an attempt to treat the undertreated.⁴² It is important for pharmacists to understand the differences between all of these terms to create a less-biased view on pain management. We owe it to patients who are newly placed on chronic opioid therapy to have these discussions. Figure 1 illustrates the broad spectrum of drug-seeking behavior that a healthcare professional may encounter.⁴²

Pain taxonomy and pathophysiology

Several types of pain need to be distinguished to understand the optimal medication treatment strategies. Nociceptive pain is typically classified as visceral or somatic. Visceral nociceptive pain arises from the internal organs, and somatic pain arises from the skin, bones, muscle, joint, or connective tissues. The characteristics associated with visceral nociceptive pain include deep, achy, poorly localized pain. Somatic pain is usually well localized, sharp, throbbing, and constant, and it may increase with movement.

There are 5 steps to nociception: transduction and inflammation, conduction, transmission, perception, and modulation.²² Transduction is the sensation from the pain receptors called the nociceptors. These distinguish between noxious and non-noxious stimuli that one feels every day and can be stimulated by chemical, mechanical, or thermal impulses. Inflammation occurs when there is trauma that causes damage to the cells, causing a release of inflammatory markers such as potassium ions, bradykinins, prostaglandins, histamines, leukotrienes, serotonin, and substance P. The activation of the nociceptors transmits the signal via action potential through the afferent nerve fibers toward the spinal cord; this is called

Pause&Ponder



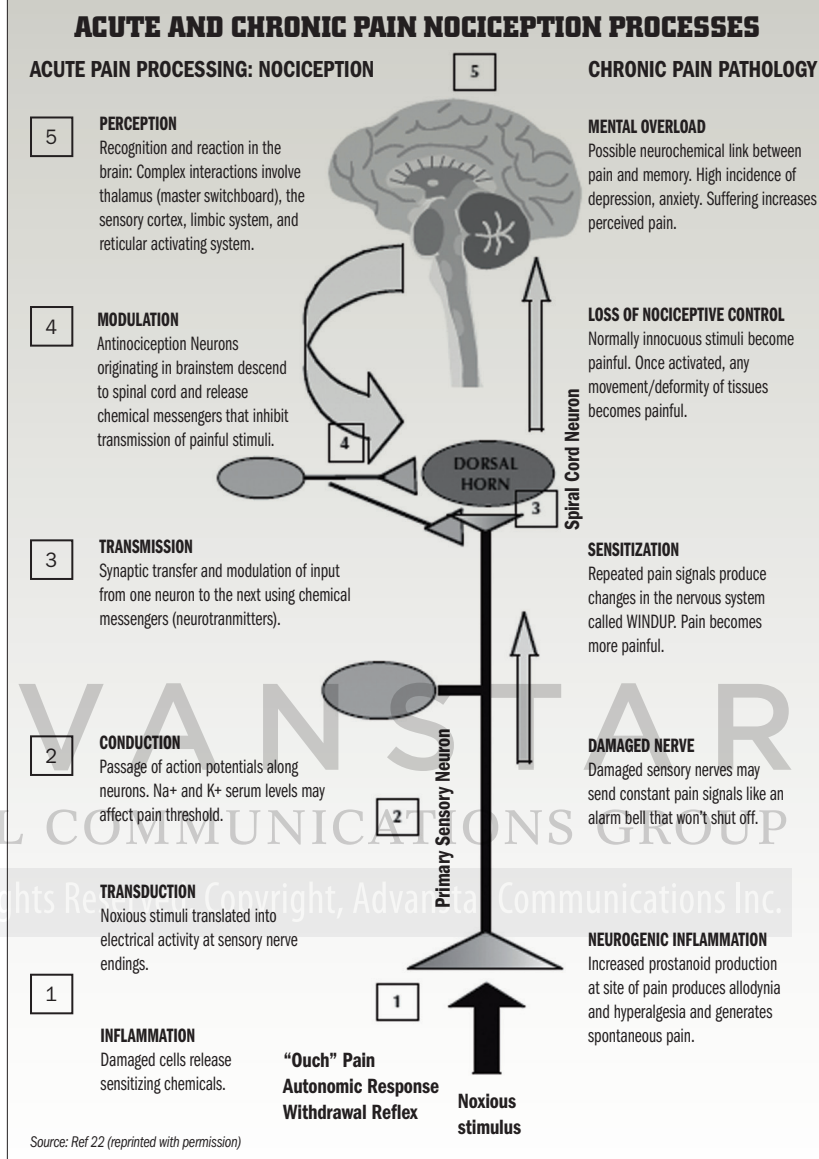
What can I do to inspire rational polypharmacy, avert drug interactions, mitigate medication misuse, and encourage best therapeutic outcomes for patients in need of pain management?

conduction. The large, myelinated A-delta nerve fibers transmit the signal for sharp, localized pain to the spinal cord, and the small, unmyelinated C fibers transmit signals for dull, achy, poorly localized pain that tends to linger on after the stimulus is no longer present. Transmission occurs where the nerve pathways end and the neurotransmitters travel across the synaptic cleft to continue the pathway. This occurs in 3 different locations: the spinal cord at the dorsal horn, between the spinal cord to the thalamus to the brain stem, and the thalamus to the cerebral cortex. In the dorsal horn, glutamate, substance P, and calcitonin are the neurotransmitters that are mainly involved in transmission.²² Norepinephrine and dopamine are involved with the signal transmission in the other 2 areas, hence the reason why certain antidepressants relieve pain more effectively than traditional pain medications.

In the synaptic cleft, glutamate released from the nociceptive neurons stimulates the AMPA receptors in the dorsal horn. In acute pain, the NMDA receptors do not respond to the glutamate released due to Mg⁺⁺ ions preventing the channels from opening. In chronic pain, the Mg⁺⁺ ions in the NMDA receptors are displaced due to repeated stimulation from the glutamate, opening the channels for activation. Ca⁺⁺ ions go through the NMDA receptor channels and activate the protein kinase C and nitric oxide activation and release. This causes substance-P release and increases c-fos expression, which may lead to neuroplasticity in the area. Unique NMDA receptor blockade activity by methadone and levophanol may therefore explain their notable efficacy compared to other opioids when treating chronic neuropathic pain.²²

The last 2 steps to nociception are perception and modulation. Perception occurs when the pain signal travels from the thalamus, the “switchboard” of the brain, to the cortex. In the cortex, the signal is routed to the regions involved in sensation, autonomic nervous system, motor responses, emotion, stress, and behaviors.²² This perception occurs in 3 main areas of the brain: the thalamus, limbic system, and the periaqueductal gray area. The interaction between these areas is the reason why anxiety and depression can worsen the pain sensation because

FIGURE 2



it causes changes in the neurochemical environment located in these areas, and may explain why distraction can cause the perception of pain to subside.²²

Modulation is the adjustment of the pain intensity we experience, which is performed by the antinoiceptive system. Endogenous opioids within this milieu involve a complex system that is heightened by opioid medications to decrease pain. Endogenous opioids include enkephalins and endorphins, and these are expressed in heightened quantities following injury to allow continued ambulation post injury with stress analgesia, when the limbic system temporarily inhibits

pain signals within the spinal cord.²² This inhibition, if prolonged, can actually produce hypersensitivity to pain stimuli called hyperalgesia.²² In chronic pain patients the prolonged stimulation increases their sensitivity to pain and increases pain intensity.²² Figure 2 explains the acute and chronic nociceptive pathways side by side.²²

Neuropathic pain

Neuropathic pain can be central or peripheral. Central neuropathy, also called autonomic neuropathy, is caused by damage to the central nervous system (CNS), such as the spinal cord and vital organs. This may

TABLE 4

TYPES OF DRUG-INDUCED NEUROPATHIES

Cause of neuropathy type	Type of damage	Drugs and drug types
Axonal degeneration	Most Common	Colchicine Dapsone Disulfiram Gangliosides Gold salts HMG-CoA reductase inhibitors Hydralazine Isoniazid Metronidazole Misonidazole Nitrofurantoin Nondepolarizing neuromuscular blocking drugs Nucleoside analogues Penicillamine Phenytoin Pyridoxine Sulfasalazine Suramin sodium Tacrolimus Thalidomide Paclitaxel Vidarabine Vincristine
	Occurs over weeks to months after initiation Damage only occurs at the axon Resolves after discontinuation of drug	
Cell death	Usually occurs at dorsal root ganglion	Cisplatin Carboplatin Oxaliplatin Suramin sodium Thalidomide
	Irreversible neuronal damage More physically debilitating	
Demyelinating	Less common	Amiodarone Interferon alpha Suramin sodium Perhexiline Chloroquine Tacrolimus
	Can mimic Guillain-Barré syndrome with acute onset	

Source: Ref 45

be caused by CNS disorders, trauma, brain injury, or stroke. Peripheral neuropathies are conditions in which the nerve damage is in the extremities, and roughly 30% of all peripheral neuropathies are secondary to diabetes.⁴⁴ Idiopathic pain is a type of pain with no etiology that usually manifests in the pelvic, head, and shoulders area. Many drugs may cause idiopathic neuropathies, which must always be ruled out prior to adding more drugs for neuropathies that incorrectly are labeled as “idiopathic” when a cause could be identified by current therapies. Common drugs that

cause idiosyncratic neuropathies include antiretroviral therapy, nitrofurantoin, thalidomide, sulfa products, statins, and chemotherapy drugs.^{45,46} Table 4 shows the types of drug-induced neuropathies and the drugs that are known to cause neuropathy.⁴⁵ Some drug-induced neuropathy is dose dependent and may be the reason for discontinuation of therapy, especially with antineoplastic chemotherapy medications.⁴⁶ It is incumbent on the pharmacist to identify the potential of such idiosyncratic causes and have an open line of communication with the prescribing prac-

itioner, because some of these medications can cause irreversible damage.

Drug-induced neuropathy has 3 different causes. The most common is axonal degeneration, which occurs after prolonged exposure to the medication, usually weeks to months after initiation, and the neuropathy will cease after discontinuing the medication.⁴⁵ The second is cell death, mostly in the dorsal root ganglion, because these cells are the most vulnerable due to the lack of blood-brain barrier. Thalidomide, carboplatin, and oxaliplatin all cause this type of neural damage, and because it is causing cell death, it is usually irreversible and most debilitating.⁴⁵ The third is demyelinating neuropathy, which is the least common and only occurs with specific agents: amiodarone, interferon alpha, chloroquine, tacrolimus, perhexiline, and suramin sodium.⁴⁵ This type of drug-induced neuropathy can mimic Guillain-Barré syndrome and may be misdiagnosed as such or overlooked as drug induced.⁴⁵

Neuropathic pain can manifest in various neuropathic disorders. Hyperpathia is a pain disorder that is characterized by experiencing increased pain from a stimulus, especially repetitive stimulus, that is often explosive and radiates, and the patient may not be able to identify the correct area from which the pain originates.³⁴ Hyperalgesia, as mentioned previously, is the increased sensitivity to pain stimulation and can be part of hyperpathia. When nonpainful stimuli transform to painful stimuli or painful stimuli escalate, which can be experienced with sunburn, it is called allodynia.^{22,34} Both of these can be classified under dysethesia, which is “an unpleasant abnormal sensation.”³⁴

Parathesia is an even broader term, referring to all abnormal sensations, whether it is intentional or not and incorporates dysethesia.³⁴ Hypoalgesia is decreased pain sensation with a painful stimulus. These terms are summarized in Table 5.³⁴

When selecting drugs to treat neuropathic pain, it is important to consider the upramping in both number and activity of the sodium channels. It is for this reason that we find usefulness from drugs affecting sodium channels. Examples include antidepressants that specifically block reuptake of norepinephrine such as tricyclic antidepressants,

TABLE 5

DEFINITIONS OF PAIN

The implications of some of the above definitions may be summarized for convenience as follows:		
Allodynia	lowered threshold	stimulus and response mode differ
Hyperalgesia	increased response	stimulus and response mode are the same
Hyperpathia	raised threshold: increased response	stimulus and response mode may be the same or different
Hypoalgesia	raised threshold: lowered response	stimulus and response mode are the same

Source: Ref 34

serotonin-norepinephrine reuptake inhibitors, and antiarrhythmics such as lidocaine and mexiletine. Although several anticonvulsants also have efficacy, the more contemporary gabapentinoids that affect voltage-gated calcium channels by combining with the alpha-2-delta subunit receptors, have gained favor due to their relative safety profile. These will be discussed in greater detail in a subsequent article in this series.

Pharmacist role in assessing/monitoring pain

Throughout this educational series, the importance of pharmacist involvement to positively impact patient care will be highlighted. Because the pharmacist is often the first healthcare professional sought by patients for minor-to-moderate pain and sees patients routinely subsequent to a provider who prescribes medication, it is essential that we provide adequate triage. This entails asking the right questions with regard to pain. On initial presentation, whether the patient is hospitalized or in an outpatient setting, there are basic important triage questions for appropriate pain evaluation. Patients will often present with unique descriptors such as: it feels like "there is a torch on my skin," "my head is in a vise," or "there's an ice pick in my back." These descriptors are helpful to determine if the pain is visceral, somatic, neuropathic, or a combination. Inquiries specific to pain should include time of onset, precipitating factors, location, activities that make it better or worse, quality (burning, shooting, radiating, dull, achy), quantity (visual analogue scale 0-10 or other suitable device), chronicity, and effect on sleep and mood. It is especially important to quantify the pain. The most common scale used is the visual analogue scale of 0 to 10, where "0" represents

no pain and "10" is the worst imaginable pain. The Wong-Baker Faces pain rating scale is often used for children or when there is a language barrier precluding accurate communication.⁴⁷ We must of course always keep in mind that pain is subjective and that one person's "5" may be another person's "8."

Pharmacists can monitor pain in both community and institutional settings, alleviating some of the responsibilities of other healthcare professionals.

With this information, the pharmacist can make recommendations for the next step in terms of visiting the appropriate healthcare provider (ED, primary care, or behavioral health). Especially for acute new-onset pain, the pharmacist needs to know what is treatable with over-the-counter medications and topical products versus what needs first aid and immediate medical attention. For example, headaches immediately following trauma require immediate attention, whereas intermittent chronic daily headaches or caffeine withdrawal headaches could be addressed by the pharmacist. A painful, recent laceration not requiring sutures might be well treated with an oral anti-inflammatory and triple an-

tibiotic cream containing lidocaine.

All of these assessment strategies and the information collected are important to effectively evaluate the pain and encourage accurate follow-up diagnostics to determine causation. Moreover this information is key for the pharmacist to make intelligent suggestions for medication selection.

Being a part of the healthcare team can elevate positive analgesic outcomes for patients with the appropriate training, didactic learning, and implementation of established protocols. Pharmacists can monitor pain in both community and institutional settings, alleviating some of the responsibilities of other healthcare professionals. Activities might include evaluating serum levels of pain medications, guiding clinicians when interpreting urine drug screens, evaluating for appropriateness of certain drug classes, recommending appropriate medication options, assessing the patient's current medication regimen, and monitoring the patient for any potential side effects associated with the medications.

Significant changes are on the horizon with regard to the pharmacist's role in medication therapy management. This has been driven by cost-efficiency, a clear therapeutics expertise involving all of the pharmaceutical sciences coupled with clinical training, expansion of complex rational polypharmacy associated with potential for important drug interactions, and best practices in terms of combining the knowledge and expertise of all healthcare providers to improve analgesic outcomes.

Given these exciting responsibilities and the recent recognition of pharmacists as providers, the opportunities for pharmacists in pain management are limitless. For all of these reasons, we encourage our readers to embrace the entire sequence of pain management continuing education in this and subsequent *Drug Topics* issues. •

For immediate CPE credit, take the test now online at



www.drugtopics.com/cpe
Once there, click on the link below
Free CPE Activities

TEST QUESTIONS

1. When considering medication therapy to treat chronic pain, which of the following is true?
 - a. Monotherapy is best to reduce medication exposure and potential toxicity.
 - b. Rational polypharmacy is often indicated to minimize side effects and maximize efficacy.
 - c. Opioids are never indicated chronically.
 - d. NSAID or acetaminophen is first-line therapy of any pain type.
2. Which of the following have potential usefulness in the treatment of pain?
 - a. Antidepressants
 - b. Anticonvulsants
 - c. Skeletal muscle relaxants
 - d. All of the above
3. Presenteeism means:
 - a. The pharmacist is present for a multidisciplinary pain intervention.
 - b. The pharmacist is NOT present for a multidisciplinary pain intervention.
 - c. Being present at work under suboptimal health conditions
 - d. Being present at work under optimal health conditions
4. Which of the following is/are true with regard to chronic pain?
 - a. It affects 100 million U.S. citizens.
 - b. It is the most common reason that patients visit healthcare practitioners.
 - c. It is the leading cause of disability and comes with a price tag of \$5 billion per year.
 - d. a and b
5. The 2009 Strategic Planning Summit for Pain and Palliative Care Pharmacy Practice had important recommendations for pharmacists. With regard to the summit, which of the following is/are true?
 - a. Educators need to identify strategies to improve the attitudes, knowledge, and skills of the profession as a whole.
 - b. The summit consisted of 79 participants and 5 professional stakeholder organizations represented by pharmacy, medicine, and nursing.
 - c. Pharmacists should be an integral part of the interdisciplinary care of patients in pain and at the end of life.
 - d. All of the above
6. Suboptimal pain management with medication is frequent because clinicians:
 - a. Fail to target the mechanism of pain generation (somatic, inflammatory, neuropathic)
 - b. Overprescribe opioids
 - c. Use anti-inflammatories to treat somatic pain
 - d. Use anticonvulsants to treat neuropathic pain
7. According to the International Association for the Study of Pain, which of the following definitions is/are true?
 - a. Acute pain usually occurs as a "warning" of trauma to the affected tissue and has a sudden onset, is usually temporary, and is resolvable.
 - b. Chronic pain lasts longer than the expected healing time, is present for 3 months or longer, adversely affects sleep, and may not have an identifiable pathology.
 - c. a and b
 - d. None of the above
8. It is especially important for pharmacists to counsel patients on the importance of keeping their pain levels manageable with prescribed medications and/or other means in an effort to avoid the conversion of acute pain to chronic pain as a result of:
 - a. Bad luck
 - b. Necrotitis
 - c. Neuroplasticity
 - d. Urosepsis
9. Which of the following best describes episodic pain?
 - a. Breakthrough pain that occurs occasionally on top of otherwise controlled chronic pain
 - b. Pain that occurs with certain scary television episodes
 - c. Continuous pain that subsides on rest
 - d. None of the above
10. Which of the following terms refers to a patient exhibiting drug-seeking behavior that is likely driven by inappropriately or undertreated pain?
 - a. Addiction
 - b. Dependence
 - c. Pseudoaddiction
 - d. Tolerance
11. Which of the following are proof-positive of an addiction disorder?
 - a. Aggressive complaining about the need for medication
 - b. Drug hoarding during periods of reduced symptoms
 - c. Openly acquiring similar drugs from other medical sources
 - d. None of the above
12. Transduction is the sensation from the pain receptors called:
 - a. Nociceptors
 - b. Bradykinins
 - c. Cytokines
 - d. Prostaglandins
13. Somatic pain arises from:
 - a. Skin, bones
 - b. Muscle, joint, connective tissues
 - c. a and b
 - d. Nerves and bones
14. Which of the following statements is/are true?
 - a. Inflammation occurs when there is trauma that causes damage to the cells, causing a release of inflammatory markers such as potassium ions, bradykinins, prostaglandins, histamines, leukotrienes, serotonin, and substance P.
 - b. Large, myelinated A-delta nerve fibers transmit signals for sharp, localized pain to the spinal cord.
 - c. Small, unmyelinated C fibers transmit signals for dull, achy, poorly localized pain that tends to linger on after the stimulus is no longer present.
 - d. All of the above
15. Certain medications that block NMDA receptors have a net effect to:
 - a. Increase pain and enhance neuroplasticity
 - b. Decrease pain and avoid neuroplasticity
 - c. Reduce inflammation
 - d. All of the above
16. The last 2 steps to nociception are:
 - a. Perception and modulation
 - b. Transmission and activation
 - c. Termination and deactivation
 - d. None of the above
17. When considering medication to treat neuropathic pain, an important first step for the pharmacist is to:
 - a. Try topical agents first
 - b. Review all medications for iatrogenic causes
 - c. Initiate an antidepressant or anticonvulsant
 - d. Initiate NSAIDs
18. Drug-induced neuropathy has 3 different causes, including:
 - a. Axonal degeneration, cell death, and demyelination
 - b. Sunburn, abrasions, and heat
 - c. Ice, frostbite, and chemical
 - d. All of the above
19. When evaluating a patient's pain, which of the following is/are key questions?
 - a. What is the level of your pain (scale of 0-10)?
 - b. Where is your pain located?
 - c. What does your pain sensation feel like (sharp, dull, achy, burning)?
 - d. All of the above
20. Since phantom limb pain is neuropathic, which of the following opioids could be most useful due to blockade activity at the NMDA receptor?
 - a. fentanyl
 - b. methadone
 - c. morphine
 - d. meperidine

References

- Herndon CM, Strassels SA, Strickland JM, et al. Consensus recommendations from the strategic planning summit for pain and palliative care pharmacy practice. *J Pain Symptom Manage*. 2012;43:925-944.
- Widera E, Chang A, Chen HL. Presenteeism: A public health hazard. *J Gen Intern Med*. 2010;25:1244-1247.
- Apolone G, Corli O, Caraceni A, et al; Cancer Pain Outcome Research Study Group (CPOR SG) Investigators. Pattern and quality of care of cancer pain management. Results from the Cancer Pain Outcome Research Study Group. *Br J Cancer*. 2009;100:1566-1574.
- Fairchild A. Under-treatment of cancer pain. *Curr Opin Support Palliat Care*. 2010;4:11-15.
- American Academy of Pain Medicine. AAPM Facts and Figures on Pain. <http://www.painmed.org/patient/facts.html#refer>. Accessed February 20, 2013.
- Cullen KA, Hall MJ, Golosinskyi A. Ambulatory surgery in the United States, 2006. *Natl Health Stat Report*. 2009 Jan 28;(11):1-25.
- DeFrances CJ, Lucas CA, Buie VC, Golosinskyi A. 2006 National Hospital Discharge Survey. *Natl Health Stat Report*. 2008 Jul 30;(5):1-20.
- Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be under-managed. *Anesth Analg*. 2003;97:534-540.
- Pitts SR, Niska RW, Xu J, Burt CW. National Hospital Ambulatory Medical Care Survey: 2006 emergency department summary. *Natl Health Stat Report*. 2008 Aug 6;(7):1-38. <http://www.cdc.gov/nchs/data/nhsr/nhsr007.pdf>. Accessed February 20, 2013.
- National Hospital Ambulatory Medical Care Survey: 2009 emergency department summary tables. http://www.cdc.gov/nchs/data/ahcd/nhamcs_emergency/2009_ed_web_tables.pdf. Accessed February 20, 2013.
- Rhodes C. Preventing injury and death from opioids: Are dosage ceilings the answer? *The Pain Practitioner*. 2012;22:27-30.
- Webster LR, Fine PG. Approaches to improve pain relief while minimizing opioid abuse liability. *J Pain*. 2010;11:602-611.
- Gudin JA. The changing landscape of opioid prescribing: Long-acting and extended-release opioid class-wide Risk Evaluation and Mitigation Strategy. *Ther Clin Risk Manag*. 2012;8:209-217.
- American Academy of Pain Medicine. FDA Panel Votes to Up-Schedule Vicodin: Tighter Controls. http://www.magnetmail.net/actions/email_web_version.cfm?recipient_id=579797123&message_id=2474456&user_id=AAPM&group_id=864439&jobid=12800979. Accessed February 21, 2013.
- FDA. U.S. Food and Drug Administration. FDA: Impact of Approved Drug Labeling on Chronic Opioid Therapy. Part 15 Public Hearing. February 7-February 8, 2013. <http://www.tworldwide.com/events/fda/130207/default.cfm>. Accessed February 21, 2013.
- Pain-Topics.org. News/Research Updates. Opioids on Trial - Part 2. <http://updates.pain-topics.org/2013/02/opioids-on-trial-part-2.html>. Accessed February 21, 2013.
- Board of Pharmacy Specialists. BPS Announces Practice Analysis Task Force for Pediatric Pharmacy; Critical Care Practice Analysis Taskforce to Follow. June 24, 2011. http://www.bpsweb.org/news/pr_062411.cfm. Accessed February 21, 2013.
- Pharmacy Pain Summit. BPS Omits Pain and Palliative Care in Call for Petitions. May 24, 2012. <http://www.pharmacypainsummit.com/2012/05/bps-omits-pain-and-palliative-care-in-call-for-petitions/>. Accessed February 21, 2013.
- Cleeland CS. Undertreatment of cancer pain in elderly patients. *JAMA*. 1998;279:1914-1915.
- Demyttenaere K, Bruffaerts R, Lee S, et al. Mental disorders among persons with chronic back or neck pain: Results from the World Mental Health Surveys. *Pain* 2007;129:332-342.
- Hemp P. Presenteeism: at work-but out of it. *Harv Bus Rev*. 2004;82:49-58, 155.
- Whitten CE, Donovan M, Cristobal K. Treating chronic pain: New knowledge, more choices. *Perm J*. 2005;9:9-18.
- Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: Evidence-based recommendations. *Pain*. 2007;132:237-251.
- Centers for Disease Control. Unintentional Drug Poisoning in the United States. July 2010. <http://www.cdc.gov/homeandrecreationalafety/pdf/poison-issue-brief.pdf>. Accessed February 21, 2013.
- U.S. Department of Health and Human Services. Substance Abuse and Mental Health Services Administration. Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings. NSDUH series H-44; 2012. <http://www.samhsa.gov/data/NSDUH/2k11Results/NSDUHresults2011.pdf>. Accessed February 21, 2013.
- Reckitt Benckiser Pharmaceuticals, Inc. Turn to Help. Could it be opioid dependence? <http://turntohelp.com>. Accessed February 21, 2013.
- New York City. Mayor's Task Force on Prescription Painkiller Abuse. Interim Report. January 2013. <http://www.nyc.gov/html/doh/downloads/pdf/basas/mayors-task-force.pdf>. Accessed February 21, 2013.
- The Florida Senate. CS/CS/HB 7095 - Prescription Drugs. <http://www.flsenate.gov/Committees/BillSummaries/2011/html/7095HR>. Accessed February 21, 2013.
- Guidelines for the Use of Controlled Substances in Pain Treatment. Modified September 18, 2003. http://media.kentucky.com/smedia/2008/08/01/19/UseofCSsinPainTreatment.source.prod_affiliate.79.pdf. Accessed February 21, 2013.
- Indiana Pain Society Legislative Report on Pain Clinics & Opioid Prescribing in Indiana 2012. Final July 11, 2012. http://www.naddi.org/aws/NADDI/asset_manager/get_file/50875/in-ips_final_legislative_report.pdf. Accessed February 21, 2013.
- Washington State Department of Health. Pain Management. 2010. <http://www.doh.wa.gov/PublicHealthandHealthcareProviders/HealthcareProfessionalsandFacilities/PainManagement.aspx>. Accessed February 21, 2013.
- Maine State Legislature. An Act to Reduce Opioid Overprescription, Overuse, and Abuse. 2011. http://www.mainelegislature.org/legis/bills/bills_125th/billpdfs/HP110201.pdf. Accessed February 21, 2013.
- West Virginia Legislature. Enrolled Version - Final Version: 2012. http://www.legis.state.wv.us/Bill_Status/bills_text.cfm?billdoc=sb437%20sub3%20enr.htm&yr=2012&sesstype=RS&billtype=B&houseorig=S&i=437. Accessed February 21, 2013.
- International Association for the Study of Pain. IASP Taxonomy. 2011. <http://www.iasp-pain.org/Content/NavigationMenu/GeneralResourceLinks/PainDefinitions/default.htm>. Accessed February 21, 2013.
- Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: Review of clinical and experimental evidence. *Pain*. 1993;52:259-285.
- Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. *Anesthesiology*. 2000;93:1123-1133.
- Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: Risk factors and prevention. *Lancet*. 2006;367:1618-1625.
- Fudin J. Opioid pain management: Balancing risks and benefits. *Drug Topics*. 2011;155:46-58.
- Chou R, Fanciullo GJ, Fine PG, et al; American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10:113-130.
- Manchikanti L, Singh V, Caraway DL, Benyamin RM. Breakthrough pain in chronic non-cancer pain: Fact, fiction, or abuse. *Pain Physician*. 2011;14:E103-E117.
- White KP, Speechley M, Harth M, Ostbye T. Co-existence of chronic fatigue syndrome with fibromyalgia syndrome in the general population. A controlled study. *Scand J Rheumatol*. 2000;29:44-51.
- Passik SD. Issues in long-term opioid therapy: Unmet needs, risks, and solutions. *Mayo Clin Proc*. 2009;84:593-601.
- Quinn TE. Pain Topics: What is pseudoaddiction? *Pain Relief Connection*. 2004;2:1.
- Neuropathy Association. About peripheral neuropathy: Facts. http://www.neuropathy.org/site/PageServer?pagename>About_Facts. Accessed February 21, 2013.
- Peltier AC, Russell JW. Advances in understanding drug-induced neuropathies. *Drug Saf*. 2006;29:23-30.
- Windebank AJ, Grisold W. Chemotherapy-induced neuropathy. *J Peripher Nerv Syst*. 2008;13:27-46.
- Hockenberry MJ, Wilson D. Wong-Baker FACES pain rating scale. *Wong's Essentials of Pediatric Nursing*, 8th ed. St. Louis, MO: Mosby;2009. <http://www.partnersagainstpain.com/printouts/AT012AS6.pdf>. Accessed February 21, 2013.