Innovations in Pain Management: New Drug Developments, Targets, and Strategies for Safe and Effective Analgesia

By Michele Matthews, PharmD

Upon successful completion of this continuing education activity, the pharmacist should be able to:

1. Describe the socioeconomic burden of pain and identify issues with current analgesic therapies.
2. Discuss new drug developments for pain management and provide education to patients who are prescribed these therapies.
3. Describe the abuse-deterrent and tamper-resistant strategies for the new formulations of opioid analgesics.
4. Identify novel drug targets for pain management, including the role of the endocannabinoid system.
5. Discuss the role of pharmacogenomics that may assist with choosing personalized medicine for patients with pain.

INTRODUCTION

According to the International Association for the Study of Pain, pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. However, any standardized definition does not fully appreciate the subjective nature of pain and its associated physical, emotional, and behavioral elements. The impact of pain is far-reaching; pain affects more Americans than heart disease, diabetes, and cancer combined, with an estimated 80 million people suffering from pain in the United States each year. Approximately 68 million of these cases are classified as chronic pain secondary to low back pain, arthritis, or headache. The cost of chronic pain is staggering, resulting in more than $100 billion each year from the combination of work absenteeism along with direct medical costs. Therefore, proper pain assessment and management is becoming an important health issue with forthcoming changes in the health care system and realization of the actual risks to the patient associated with some analgesics.

Pain is categorized based on factors including severity, duration, and quality. Pain can be classified as acute (lasting less than one month) or chronic (lasting greater than six months) and can arise from nociceptive and/or neuropathic origins. Nociceptive pain is experienced in the presence of an injury or trauma and can be described using terms such as sharp, dull, or achy. This type of pain can be localized or diffuse; examples of nociceptive pain include osteoarthritis and pancreatitis. Neuropathic pain, defined as pain initiated or caused by a lesion or dysfunction within the nervous system, is commonly described as one or more of the following: burning, shooting, or electrical shock-like pain that may not be easily localizable to a single point. Diabetic peripheral neuropathy and postherpetic neuralgia are classic examples of neuropathic pain. A detailed patient history and pain assessment are the guiding factors in choosing appropriate analgesic therapies for both acute and chronic pain, regardless of severity.

Useful Websites

- www.aspi.wisc.edu/
  This is the website of the Alliance of State Pain Initiatives (ASPI). Formerly known as the American Alliance of Cancer Pain Initiatives (AACPI), this is a network of state-based organizations that work through education, advocacy, and institutional improvements to remove the barriers that impede pain relief.
- www.painfoundation.org
  This is the website of the American Pain Foundation (APF), an independent nonprofit organization serving people with pain through information, advocacy, and support.
The pharmacology of pain management involves the modulation of the ascending and descending pathways within the pain process along with inhibition of the release of excitatory neurotransmitters and/or other substances that sensitize the nervous system to noxious stimuli. When the body experiences an injury or trauma, action potentials are generated from the site of damage and are transmitted from the peripheral nervous system to the central nervous system (CNS) via the spinal cord. Simultaneously, chemical mediators and neurotransmitters that sensitize neurons and enhance the pain process are released. Once the pain impulses have reached the higher centers of the CNS, a modulatory response is initiated within the descending pathway to inhibit pain impulses from being processed and ultimately preventing pain perception. The receptors involved in pain modulation include opioid receptors, alpha-2 adrenergic receptors, voltage-gated calcium channels, and NMDA receptors. Chemical mediators that sensitize neurons to pain include substance P, prostaglandins, bradykinin, and glutamate. Neurotransmitters that facilitate pain modulation include norepinephrine, serotonin, and GABA.

The various processes involved in pain perception allows for the targeting of different areas within the pain pathway with the use of pharmacological agents. Drugs used to treat pain are categorized as nonopioid, opioid, and adjuvant analgesics. Nonopioid analgesics include acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) and are commonly prescribed as monotherapy for mild to moderate pain or in combination with opioids for moderate to severe pain. Opioids analgesics are the mainstay of therapy for moderately severe to severe pain and are used in combination with nonopioid and adjuvant analgesics in the setting of chronic pain. They are involved in CNS-mediated mechanism of analgesia through their interaction with opioid receptors in the brain and spinal cord. Adjuvant analgesics, including antidepressants and anticonvulsants, can be used for any severity of chronic pain in combination with nonopioid and/or opioid analgesics.

The current arsenal in the management of both acute and chronic pain is limited. Even with several therapeutically available, there remains a need for innovative therapies based on the individualistic response to analgesics and the ever-growing understanding of pain and its processing. Additionally, the pharmacogenomics of pain are becoming increasingly understood and may explain these differences in patient response to therapy. The risk for dependency or abuse associated with opioid analgesics have also lead to opioid product formulations that may deter abuse and resist tampering. In tandem, the Food and Drug Administration (FDA) has developed a long-acting and extended-release opioid class Risk Evaluation and Mitigation Strategies (REMS) to further address such risks. This article will review new drugs, formulations, and strategies to address the challenges in pain management and will highlight the evolving science behind achieving effective analgesia.

NEW DRUGS OR FORMULATIONS
Nonopioid and Adjuvant Analgesics

_Neurokinin 1 Blocker (Bimataprisin)_

A new neurokinin 1 blocker (Bimataprisin) has been developed for the management of acute and chronic pain. This agent works by blocking the release of substance P, a chemical mediator that sensitizes neurons to pain.

Intravenous Ibuprofen (Caldolor)

Nonsteroidal anti-inflammatory drugs have been utilized for acute pain management, fever, and inflammation since aspirin was discovered in the 1800s. The approval of coX-2 inhibitors for use in the U.S. market in 1999 with celecoxib provided optimism for retaining the analgesic efficacy associated with nonselective NSAIDs, while avoiding gastrointestinal and renal toxicity. The subsequent withdrawal of multiple COX-2 inhibitors from the market due to cardiovascular events led to widespread re-evaluation of the risks associated with both selective and nonselective NSAIDs. A scientific statement from the American Heart Association established criteria to delineate patients at risk for NSAID-induced cardiovascular events and highlighted the need for improved drug safety regulations. Even though these agents play a significant role in pain management, the development of new NSAIDs or formulations may be received with caution. Consequently, the approval of intravenous (IV) ibuprofen (Caldolor) revisits the role of parenteral NSAIDs after years of experience with ketorolac tromethamine.

Approved by the FDA in June 2009, IV ibuprofen is indicated for the management of mild to moderate acute pain, moderate to severe acute pain as an adjunct to opioid analgesics, and reduction of fever in adults. In a multicenter, randomized, double-blind, placebo-controlled trial, 406 patients who were undergoing elective...
orthopedic or abdominal surgeries were randomized to IV ibuprofen 400 mg, IV ibuprofen 800 mg, or placebo every six hours in combination with morphine via patient-controlled analgesia (PCA) pumps for the management of postoperative pain. Twenty-four hours after surgery, patients in the IV ibuprofen 800 mg required significantly less morphine compared to the placebo group (P=0.030). The most common treatment-emergent adverse effects were nausea, vomiting, and constipation, all of which occurred at a much lower rate compared to the placebo group. A multi-center, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of IV ibuprofen for the treatment of fever from any cause. One hundred twenty patients were randomized to IV ibuprofen 100 mg, 200 mg, 400 mg, or placebo administered every four hours for a total of six doses. After four hours of therapy, the proportion of patients achieving a temperature of 101°F or lower was 61 percent for IV ibuprofen 100 mg (P=0.0264), 70 percent for 200 mg (P=0.0043), and 77 percent for 400 mg (P=0.0005) compared to 32 percent in the placebo group. This study also evaluated the effects of IV ibuprofen in critically ill versus non-critically ill patients and found that non-critically ill patients experienced a slightly more rapid reduction in temperature after administration of a 400 mg dose. In addition, the 400 mg dose was effective in both lowering and maintaining temperatures to normothermic range over the 24-hour period. The incidence of adverse effects was similar between all groups, with the exception of bacteremia with IV ibuprofen 100 mg (13%; n=4) compared to 0 percent placebo (0%; P=0.045).

The evidence regarding the use of IV ibuprofen for acute pain suggests that it can be used as an alternative to other analgesics or adjunctively to reduce opioid requirements in the postoperative setting. To date, there are no studies comparing the efficacy and safety of IV ibuprofen to ketorolac. Additionally, the use of IV ibuprofen has been limited to five days in clinical trials and is the same duration of therapy restriction that applies to the use of ketorolac. Patients receiving IV ibuprofen should be well hydrated and have no history of hypersensitivity to ibuprofen, other NSAIDs or aspirin. IV Ibuprofen is contraindicated in the coronary-artery bypass graft (CABG) post-operative setting. The cost of IV ibuprofen will also likely play a significant role in formulary decision-making ($9.19 for 400 mg, $13.13 for 800 mg; per dose).

**Milnacipran (Savella)**

An improved understanding of pain processing has led to focusing on the modulation of neurotransmitters that assist with preventing pain perception. Norepinephrine (NE) reuptake inhibition within the descending pain pathway of the central nervous system (CNS) has been proposed to suppress pain impulse transmission that is likely to be dependent upon patient-specific plasticity. Serotonin and NE reuptake inhibitors (SNRIs) such as duloxetine are beneficial for the treatment of both pain and associated depression. However, serotonin (5-HT) has been proposed to increase inflammation and hyperalgesia (such as exaggerated pain response), particularly in the presence of nerve injury. Milnacipran (Savella) selectively inhibits NE and 5-HT reuptake in a 3:1 ratio and is approved for the management of fibromyalgia. It is theorized that this specificity for NE over 5-HT may provide enhanced analgesia while minimizing adverse effects including 5-HT syndrome and hyperalgesia. Milnacipran has been studied in more than 2,000 patients with fibromyalgia, and when compared to placebo for up to 27 weeks, its use was associated with greater improvements in a composite endpoint that included pain, physical function, and patient global assessment. Milnacipran requires titration throughout the first week of therapy to a final recommended dose of 50 mg by mouth twice daily. To facilitate titration, it is supplied as a blister-pack for the first four weeks of therapy. Milnacipran carries a black box warning for suicidal ideation, thinking and behavior in children, adolescents and young adults. The most common adverse effects associated with milnacipran include nausea, headache, palpitations, and dry mouth, and it should be used cautiously in patients on other serotonergic drugs or those with seizure disorders; concomitant use with a MAOI is contraindicated. Discontinuation of milnacipran should be done gradually when possible to avoid withdrawal symptoms. Comparative efficacy studies involving milnacipran and other drugs for the treatment of fibromyalgia (such as duloxetine, pregabalin) are unavailable.
Opioid Analgesics

Extended-release Hydromorphone (Exalgo)

Hydromorphone is a hydrogenated, semi-synthetic ketone of morphine that is used in the management of moderate to severe pain. As a derivative of morphine, it is expected that hydromorphone is an effective alternative to morphine. Hydromorphone is available as an oral formulation, but the short elimination half-life of this drug requires frequent repeated dosing (every four to six hours) to gain effective around-the-clock pain control. The need for frequent dosing may lead to issues with adherence and consequently may reduce treatment outcomes and may negatively impact quality of life. Studies have shown that long-acting opioids can improve pain management and reduce opioid-related side effects in comparison to immediate-release (IR) formulations.

Exalgo is indicated for once daily administration for the management of moderate to severe pain in opioid tolerant patients. This long-acting formulation provides lower and longer sustained peaks than IR hydromorphone, as well as higher trough concentrations. This pharmacokinetic profile provides an easier dosing schedule, shows potential to lower medication abuse, and can eliminate the wearing off effect caused by low trough drug levels that may exist in patients using IR hydromorphone. Extended-release hydromorphone provides another option for patients with chronic cancer or noncancer pain who require long-acting opioid formulations. By reducing the number of pills needed on a daily basis, health care providers can improve patient adherence, enhance pain management, and decrease the likelihood of medication errors. Extended-release hydromorphone should be used cautiously in patients with hepatic and renal impairment, two to four-fold increases in plasma levels have been observed in these populations; consider a product which permits greater dosing flexibility. The cost and prescription coverage for Exalgo remains unknown at this time. Therefore, Exalgo provides little advantage over other currently available long-acting opioid preparations, and its use should be reserved for patients who cannot tolerate or do not have adequate analgesia with other long-acting opioid preparations. Additional studies that address comparative efficacy to other long-acting opioids and pharmacoeconomic analyses are warranted. There is a black box warning on this product flagging its potential for abuse, misuse, addiction and criminal diversion and limits its use to opioid tolerant patients. The warning also calls attention to the extended-release delivery system which is defeated if the tablet is broken, chewed, crushed or dissolved and can lead to a potentially fatal dose of hydromorphone. Exalgo should not be used with or within 14 days of discontinuing MAOI therapy.

Fentanyl Buccal Film (Onsolis)

The lipophilic nature of fentanyl has allowed it to be developed into multiple formulations for administration through various routes. Fentanyl buccal soluble film (FBSF, Onsolis) is FDA-approved for the treatment of breakthrough pain in patients with cancer, age 18 and older, who are managed on long-acting opioid therapy. It utilizes BioErodible MucoAdhesive (BEMA) technology and dissolves within 15 to 30 minutes. In a randomized, double-blind, placebo-controlled trial, 80 opioid-tolerant patients with chronic cancer pain were randomized to FBSF or placebo. After 30 minutes, significantly more patients in the FBSF group reported greater reductions in pain compared to placebo; this improvement in pain was detectable within 15 minutes after administration and was sustained for up to one hour. The most common adverse effects associated with FBSF include nausea, vomiting, and constipation and carries the same risks for respiratory depression, hypotension, and addiction as with other opioid analgesics. The recommended starting dose for FBSF is 200 mcg, and the dose can be increased as needed by applying additional films, up to 800 mcg. The FDA-approved dosing is no more than one film be used per episode, separated by at least two hours, no more than four doses per day. Available dosages are 200 mcg, 400 mcg, 600 mcg, 800 mcg, and 1,200 mcg. Plasma concentrations of FBSF and other fentanyl products may be increased with the co-administration of cytochrome P 450 (CYP) 3A4 isoenzyme inhibitors, and concomitant use should be avoided due to the risk of increased drug plasma concentrations. The addition of FBSF provides another option for patients suffering from breakthrough pain. However, its efficacy in comparison to other transmucosal fentanyl preparations is unknown. Onsolis is contraindicated in opioid non-tolerant patients, patients with acute or post-operative
pain (includes migraine and other headache pain, emergency department use) and known hypersensitivity to fentanyl. ONSOLIS carries a black box warning for abuse potential, patient selection and calls out potential for respiratory depression when used with a CYP3A4 inhibitor. ONSOLIS is available only through a restricted distribution program, called FOCU5 that requires patient, prescriber and pharmacy enrollment.

**Topical Agents**

**Capsaicin 8 Percent Topical Patch (Qutenza)**

Postherpetic neuralgia (PHN) is a form of neuropathic pain that occurs after an outbreak of herpes zoster (shingles). Pain associated with PHN can last for months after the infection has cleared and can be associated with significant depression, anxiety, and disruption of sleep patterns. The incorporation of the herpes zoster (Zostavax) vaccine into the Center for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices (ACIP) adult immunization guidelines will likely decrease the incidence of shingles. However, in those patients who develop PHN, pain management can be difficult. A mainstay of PHN management is topical capsaicin but often, patients are not compliant with the frequent and persistent application required to achieve analgesia. A topical patch of 8 percent capsaicin (Qutenza) has been developed for the management of neuropathic pain associated with PHN. Qutenza produces its analgesic effects by interacting with transient receptor potential vanilloid 1 receptors (TRPV1). The initial activation of these receptors produces a burning sensation due to their pro-nociceptive effects; however, over time and after continuous activation, their activity decreases and results in desensitization or analgesia. Qutenza is applied to the affected area, pretreated with a local anesthetic, under physician supervision, or by health care professionals under close physician supervision, for 60 minutes and can be reapplied no more often than every three months. Evidence from an intention-to-treat analysis suggested that the analgesic effect of Qutenza can last for up to 12 weeks. Qutenza can be used as an adjunct to other analgesics commonly used for PHN (such as pregabalin). However, cost of therapy ($675 for one patch) and need for application by a trained provider may limit its use.

**Diclofenac**

The use of compounded topical NSAIDs has been common practice for many years for the treatment of localized pain. Several commercial preparations of topical NSAIDs have recently been approved, all of which contain diclofenac. The first preparation on the market was diclofenac epolamine 1.3 percent topical patch (Flector) which is approved for acute mild to moderate pain due to minor strains, sprains, or contusions. Each patch contains 180 mg of diclofenac epolamine and should be applied to the affected area twice a day. The patch should not be applied to irritated or broken skin. In October 2007, diclofenac sodium 1 percent gel (Voltaren Gel) was approved for the treatment of osteoarthritis of the upper and lower extremities. The recommended dosage is 2 grams for each elbow, hand, or wrist and 4 grams for each knee, ankle, or foot, applied four times daily. The gel is applied using the included dosing card and can be used for gel application. The maximum daily dose is 32 grams over all affected joints. An additional diclofenac preparation was approved in November 2009 which contains diclofenac sodium 1 percent as a topical solution (Pennsaid) for the treatment of the signs and symptoms of knee osteoarthritis. The recommended dose is 40 drops applied to each affected knee four times daily, and the patient should be educated on applying 10 drops at a time, either into the hand or directly onto the knee, and the dose should be spread around the knee before the next 10 drops are applied. Patients should also be instructed to wait at least 30 minutes after the application before bathing. Additionally, patients should be educated about systemic adverse effects associated with NSAIDs, particularly with long-term use. These include increased risk of serious cardiac thrombotic events, MI and stroke and serious gastrointestinal adverse events. In post-marketing reports, the FDA identified cases of diclofenac-induced hepatotoxicity with the use of Voltaren Gel; therefore, it is recommended that when using any topical diclofenac preparations, liver functions tests be assessed after four to eight weeks of therapy and periodically thereafter. No diclofenac preparation should be used in the peri-operative setting of coronary artery bypass graft (CABG) surgery.
Multimodal Analgesics

Tapentadol (Nucynta)

Approved in 2009, tapentadol is a centrally-acting analgesic that inhibits the reuptake of NE and acts as an agonist at the mu-opioid receptor. Tapentadol is FDA-approved for the relief of moderate to severe acute pain in patients age 18 and older and has been studied in postsurgical models of pain as well as in patients with end-stage osteoarthritis who experienced acute exacerbations of pain. In clinical trials, tapentadol was shown to be noninferior to oxycodone 10 mg when given at doses between 50–75 mg every four to six hours and had a lower incidence of gastrointestinal adverse effects (such as nausea and vomiting). The maximum recommended dose per day is 600 mg. However, on the first day of therapy, patients can take one additional dose one hour after the initial dose, for a total daily dose of 700 mg. It is proposed that tapentadol lacks 5-HT reuptake inhibition; patients who were on stable doses of selective serotonin reuptake inhibitors (SSRIs) for at least 28 days were included in clinical studies on tapentadol, and no occurrences of 5-HT syndrome were identified. Tapentadol has also been studied in combination with SNRIs in a 90-day tolerability trial, and incidences of 5-HT syndrome or noradrenergic hyperactivity were not reported. However, the manufacturer includes precautions specifically about the potential risk of 5-HT syndrome in its prescribing information based on preclinical studies, and use of MAOI within 14 days is contraindicated. Tapentadol is a scheduled II substance, and a detailed patient history should be conducted to assess the risk of misuse and abuse for this medication. An extended-release formulation of tapentadol is currently being studied, along with the use of this drug for chronic pain syndromes.

NEW STRATEGIES

New Uses for Old Drugs

Vitamin D

The role of vitamin D in pain management is unclear, and the evidence to support its use in chronic pain is poor. It is known that hypocalcemia due to vitamin D deficiency induces the secretion of parathyroid hormone, which stimulates the breakdown of bone to enhance the release of calcium. This breakdown of bony surfaces may lead to characteristic complaints of dull and persistent musculoskeletal aches and pains. Indications of defective bone mineralization may include muscle weakness, fatigue, poor appetite and paresthesias. While vitamin D is well-tolerated and inexpensive, dosing of this fat-soluble vitamin for pain is not clearly defined. Some of the most aggressive regimens of vitamin D range from 5,000 IU/day to 50,000 IU/day for limited periods of time.

Researchers have found that daily supplementation of less than 800 IU was no better than placebo in the evaluation of muscle strength. Based on available evidence, an appropriate initial vitamin D dose would be a compromise between a dose greater than 800 IU/day and the more aggressive dosing regimens entailing 5,000 IU/day. This dose should be titrated based on tolerability and response. Patients should be advised that individual responses to this vitamin may vary. Some patients may notice improvements in their pain symptoms within a few weeks, while others may not see results for nine months or longer. The long-term use of vitamin D, when used at doses higher than those recommended for deficiency, have not yet been fully investigated.

Opioid Antagonists

Opioid antagonists have been used to reverse the toxic effects of opioids by displacing them from their respective receptors. Animal studies have demonstrated that low doses of naltrexone may stimulate the up-regulation of mu-opioid receptors in areas of the brain that control nociceptive responses, and may “reset” existing receptors to minimize opioid tolerance. Naloxone was originally synthesized in 1960. Its short duration of action made it useful for the reversal of opioid toxicity. Naltrexone was developed soon after, offering the advantage of good oral bioavailability, a longer duration of action, and twice the potency of naloxone. The proposed dosing for pain management, in combination with opioid agonists, is at a much lower dose than what is recommended for addiction therapy and opioid overdose. Gan et al reported a study using two small doses of naloxone together with intravenous morphine in 60 patients in a post-anesthesia care unit. From this study, they concluded that naloxone significantly reduced opioid-related adverse effects and reduced post-operative opioid requirements for pain control. Other trials and case reports
support the safety and efficacy of low-dose or ultra-low-dose opioid antagonists for the management of pain in opioid-tolerant patients. In summary, opioid antagonists offer promising new indications that extend beyond their role in opioid reversal and addition.

NEW STRATEGIES
Abuse-Deterrent and Tamper-Resistant Opioid Formulations
The misuse, abuse, and diversion of opioids pose significant challenges for health care professionals who must evaluate the appropriate use of opioids and their potential abuse. The abuse of prescription drugs is a growing public health concern that has gained the attention of several pharmaceutical companies who have reformulated many commonly used opioids to prevent drug abuse. The ideal dosage form would resist tampering by any method while still offering therapeutic effectiveness.

Embeda
Embeda (King Pharmaceuticals) is extended-release morphine sulfate with sequestered naltrexone that was approved for marketing in 2009 and is formulated as pellets contained in a capsule. Each pellet contains a sequestered naltrexone core surrounded by morphine. When ingested orally, morphine is absorbed but the naltrexone core remains intact, and no or little naltrexone is released. However, when this formulation is crushed, the euphoric effects of morphine are blunted because naltrexone is released with morphine. In clinical trials, most patients who received Embeda had negligible levels of naltrexone and those who had detectable levels had no increase in pain. Under tampering conditions, this drug releases levels of naltrexone that are similar to those achieved with immediate-release naltrexone.

Remoxy
Remoxy is an extended-release formulation of oxycodone awaiting FDA Approval. The formulation contains oxycodone in a highly viscous liquid formulation matrix and is intended to resist abuse by crushing or by dissolution in common liquids. This formulation is proposed to prevent oxycodone “dumping” from the capsule when it is ingested with alcohol, common solvents, or aqueous buffers across a wide range of pH, rendering oxycodone extraction difficult. Remoxy has not been studied in head-to-head trials with other extended-release opioids; therefore, it is unknown if the formulation sustains or reduces the efficacy of oxycodone and if the tamper-resistant mechanism contributes to tolerability issues. The manufacturer is targeting to resubmit a new drug application (NDA) for Remoxy after gathering additional stability data.

OxyContin Reformulation
A reformulation of OxyContin was approved for marketing in April 2010 and will utilize a polymer that makes the tablets difficult to break or crush. When introduced to a liquid, the formulation transforms into a viscous gel that resists extraction of oxycodone for injection. The manufacturer will be required to conduct post-marketing studies on the extent of misuse and abuse of the new formulation and will have a REMS that requires a medication guide to be dispensed with the medication, along with required prescriber education on the use of opioids for pain.

Opioid REMS
Due to the risks associated with opioid analgesics, the FDA has requested the inclusion of long-acting and extended-release opioid class REMS proposals with the submission of any new drug application. This is to ensure that the benefits of any new opioid or formulation outweigh its risks, with the ultimate goal of reducing opioid abuse and diversion. Certain opioid analgesics will be required to have REMS. These include all long-acting formulations and methadone when used for pain. The REMS for these drugs will include the use of medication guides and implementation of elements to ensure the safe use of these drugs. Example elements include requiring prescriber training and certification on the proper use of opioids, and requiring pharmacies to become certified before the dispensing of opioids.

NOVEL DRUG TARGETS
Cannabinoid Receptors
The use of Cannabis for medical purposes has increased with the passing of legislature in 14 states that allows the legalized use of medical marijuana. Delta-9-tetrahydrocannabinol (THC), the primary component of marijuana, is
responsible for its therapeutic, psychoactive, and adverse effects. The concerns with the use of marijuana have surrounded finding an appropriate delivery form. Smoking is the most efficient route of administration, but comes with dangers. Growing research has focused on an improved understanding of the endocannabinoid system to identify cannabinoid receptors, leading to the development of synthetic compounds to interact with this system. The first cannabinoid receptor, CB1, was identified in the 1990s and involves the modulation of several neurotransmitters such as dopamine and 5-HT. The activation of the CB1 receptor may be responsible for some of the therapeutic effects of marijuana but is also associated with impaired cognition and altered motor function. The CB2 receptor was subsequently discovered and is not as well-distributed throughout the body like CB1. Commercially-available cannabinoids such as dronabinol have been studied as analgesics, but their use is limited by their adverse effects at therapeutic doses. Ongoing research on the endocannabinoid system shows promise for the development of drugs that can interact with this system while minimizing the unfavorable effects of cannabinoids.

PHARMACOGENOMICS OF PAIN
There are many factors that play a role in the undertreatment of pain. Among the more common reasons, adverse effects and fear of addiction remain significant concerns for both providers and patients. The subjective nature of pain complicates its treatment, and the use of therapeutic agents may be used ultra-cautiously, leading to inadequate pain management. The pharmacogenomics of pain may provide an improved understanding of a patient’s individual risks associated specifically with the use of opioids. Because the CYP 450 system plays a role in opioid metabolism, variants of enzymes involved in the degradation of opioids (CYP2D6 and CYP2C19) have been linked to their efficacy and toxicity. Additionally, the mu-opioid receptor and its subtypes also play a role in the therapeutic and adverse effects of these agents. Therefore, these biomarkers have been identified as having relevance in determining a patient’s risk of adverse effects or toxicity and the potential for opioids to produce effective analgesia.

With regard to the CYP2D6 isoenzyme, patients may be poor, intermediate, extensive, or ultra-rapid metabolizers. About 8 percent of Caucasians and 2 percent of African Americans are considered to be CYP2D6 poor metabolizers, which could correlate to supratherapeutic concentrations of opioids as well as an inability to convert drugs into their active metabolites (such as codeine into morphine). Identifying CYP2D6 metabolizer status may assist with therapeutic decision-making when considering opioid analgesics for pain. Using the mu1 opioid receptor (OPRM1) as a biomarker, variances in alleles may be identified to possibly assess opioid dose requirements. The cost and practicality of such tests remains unknown, but the idea of personalized medicine has the potential to improve the safe and effective use of opioids for pain.

SUMMARY
There are significant challenges associated with the management of both acute and chronic pain. The development of new drugs, targets, and strategies are the first steps towards the safe and effective use of analgesics. Several new medications have been introduced to the market within the past few years, and while promising, their role in pain management continues to be unknown. However, the individualistic nature of pain warrants the need for several therapeutic options to ensure an appropriate analgesic regimen for each patient. Emerging science behind new drug targets and the pharmacogenomics of pain will undoubtedly show promise in the future of pain management and the role of personalized medicine. As pharmacists, it is important to recognize the current challenges associated with pain management and to be a resource for other clinicians as analgesic options are considered. Finally, our accessibility as health care providers puts us in position to serve as patient advocates to address barriers associated with inappropriate treatment or undertreatment of pain.

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CONTINUING EDUCATION QUIZ
Select the correct answer.

1. What is the estimated yearly cost of chronic pain in the United States?
   a. $10 million
   b. $100 million
   c. $10 billion
   d. $100 billion

2. Which one of the following neurotransmitters may produce analgesia when its reuptake is inhibited?
   a. Serotonin
   b. Dopamine
   c. Epinephrine
   d. Norepinephrine

3. Which one of the following may be used as an adjuvant to opioid therapy to manage post-operative pain as an adjunct to opioid analgesics?
   a. Ibuprofen IV following renal transplant
   b. Ibuprofen IV following totally knee arthroplasty
   c. Ketoprofen IV for a patient with a history of GI bleed on oral NSAIDs
   d. Ketorolac IV following single coronary bypass

4. Which one of the following drugs was recently approved for the management of fibromyalgia?
   a. Savella
   b. Qutenza
   c. Caldolor
   d. Acurox

5. Which one of the following is TRUE of Exalgo?
   a. It is the first twice daily formulation of hydro-morphone.
   b. Ambulatory patients should be monitored for orthostatic hypotension.
   c. No dose is adjustment needed for patients with moderate hepatic impairment.
   d. No dose adjustment is needed for patients with moderate renal impairment

6. Which one of the following formulations utilizes BioErodible MucoAdhesive (BEMA) technology?
   a. Pennsaid
   b. Exalgo
   c. Onsolis
   d. Nucynta

7. J.T. is a 64-year-old oncology patient who is stable on fentanyl transdermal patches 50 mcg/hr. Which regimen would be advised to manage breakthrough pain?
   a. Onsolis 200 mcg PRN no more than QID
   b. Onsolis 200 mcg QID PRN, space doses by two hours
   c. Onsolis 200 mcg no more than four films QID PRN breakthrough pain
   d. Onsolis 200 mcg 1–2 films q1hour prn breakthrough pain

8. Which one of the following statements about Qutenza is FALSE?
   a. It is a high potency capsaicin formulation that needs to be applied under the supervision of a trained clinician.
   b. It can be reapplied every three months and used adjunctively with other analgesics.
   c. Its mechanism of action is related to its activity at TRPV1 receptors.
   d. It is indicated for the treatment of the signs and symptoms of osteoarthritis.

9. Which one of the following statements is true of Qutenza?
   a. The Qutenza patch is applied by a health care professional and removed by the patient.
   b. The Qutenza patch may be cut to fit the treatment area.
   c. Local anesthetic use is contraindicated in conjunction with Qutenza patch application.
   d. The Qutenza patch is applied by a health care professional once monthly for 60 minutes.

10. Which one of the following is TRUE of a topical formulation of diclofenac?
    a. Local application avoids GI adverse effects
    b. Formulations include patch, gel and ointment
    c. Liver function tests are recommended at four to eight weeks and periodically thereafter
    d. Pennsaid should be washed off after 30 minutes to avoid local irritation.
11. Which one of the following is a multimodal analgesic that inhibits the reuptake of norepinephrine and acts as an opioid agonist?
   a. Dronabinol
   b. Duloxetine
   c. Milnacipran
   d. Tapentadol

12. Which one of the following statements with regard to Nucynta is TRUE?
   a. It is an extended-release formulation approved for the treatment of postherpetic neuralgia.
   b. It was found to be noninferior to oxycodone 10 mg when given at dosages between 50 to 75 mg.
   c. It was not studied in combination with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).
   d. It is a scheduled III controlled substance.

13. Which one of the following statements with regard to the use of vitamin D for pain is FALSE?
   a. The recommended dose for the treatment of chronic pain is 400 IU/day.
   b. Response to therapy will vary between patients.
   c. Its long-term use for chronic pain has not been evaluated.
   d. It may be effective for the treatment of symptoms associated with impaired bone mineralization.

14. Which one of the following therapeutic classes is being considered for use in pain management as an adjunct to opioid analgesics to “reset” opioid receptors and minimize opioid tolerance?
   a. Anticonvulsants
   b. Beta-blockers
   c. NSAIDs
   d. Opioid antagonists

15. Which one of the following is an abuse-deterrent opioid preparation that is formulated as extended-release morphine with sequestered naltrexone?
   a. Embeda
   b. Exalgo
   c. Remoxy
   d. Onsolis

16. Which one of the following statements with regard to the investigational drug, Remoxy is TRUE?
   a. It is a tamper-resistant formulation of immediate-release hydromorphone.
   b. It is a tamper-resistant formulation of extended-release oxycodone.
   c. It is easily dissolvable in common solvents.
   d. It is co-formulated with disulfiram.

17. Which one of the following long-acting opioid analgesics is conducting post-marketing studies on its reformulation which attempts to curb abuse and diversion?
   a. Duragesic
   b. MS Contin
   c. Opana ER
   d. OxyContin

18. Which one of the following receptors may produce analgesia but also unfavorable adverse effects including impaired cognition and altered motor function?
   a. Alpha-2 adrenergic receptor
   b. Cannabinoid receptor
   c. TRPV1 receptor
   d. Vanilloid receptor

19. Which one of the following opioid receptors may contribute determining individual opioid dose requirements?
   a. Delta receptor
   b. Kappa receptor
   c. Mu receptor
   d. Sigma receptor

20. Which one of the following patient factors may explain supratherapeutic concentrations of opioid analgesics such as morphine?
   a. Being an CYP2D6 ultra-rapid metabolizer
   b. Being a CYP2D6 poor metabolizer
   c. Being of Asian decent
   d. Being of Hispanic decent
21. Which one of the following biomarkers may assist in choosing personalized opioid regimens in the future?
   a. CYP1A2
   b. TRPV1
   c. OPRM1
   d. CB1

22. Which is the correct drug-receptor pairing?
   a. Milnacipran/COX-2
   b. Diclofenac/Vanilloid receptor
   c. Tapentadol/TRPV1 receptor
   d. Naltrexone/Mu receptor

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Jan. 3, 2011 (expires Jan. 3, 2014) • Activity Type: Knowledge-based

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