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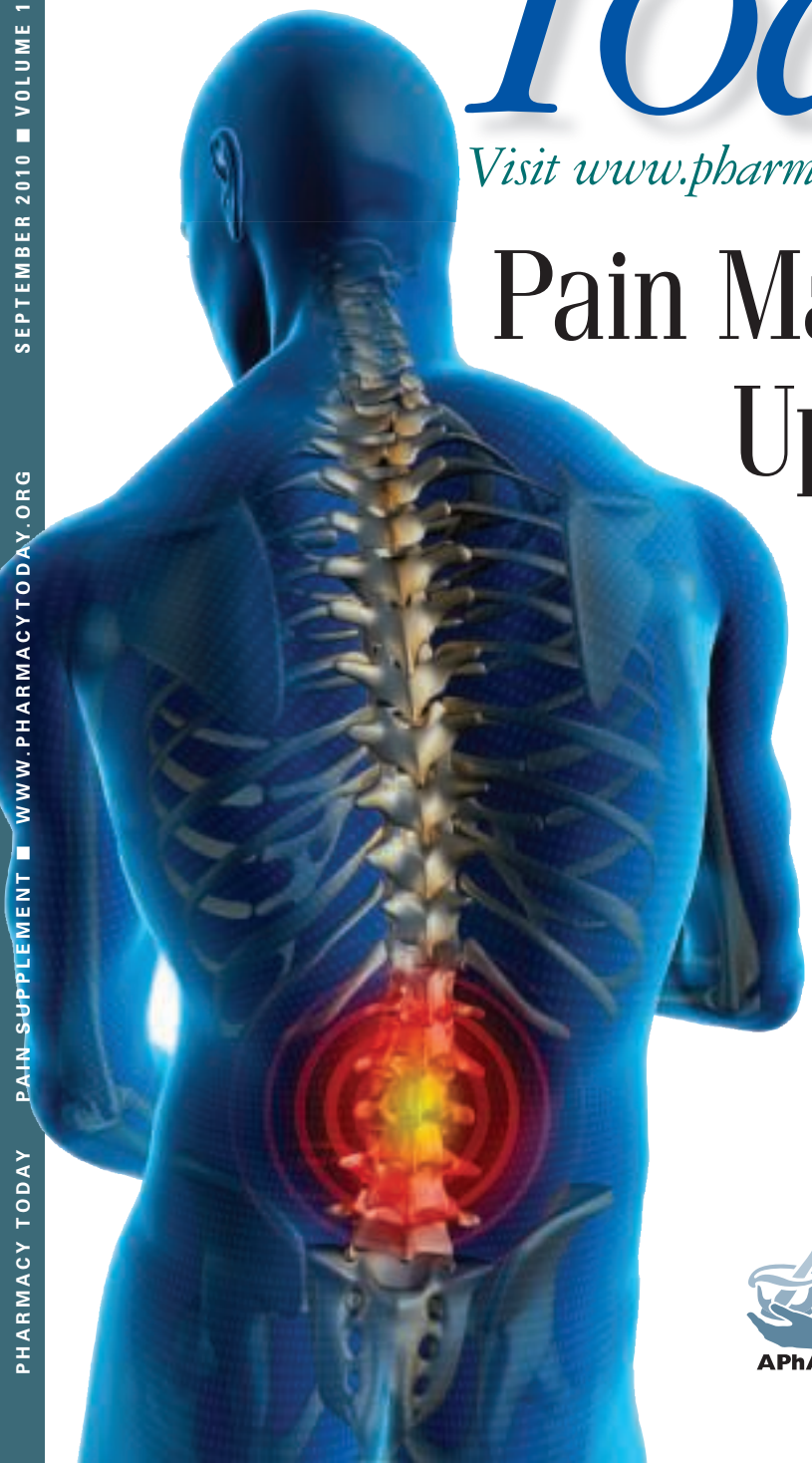
Pain Management Update



Inside:

- Update on REMS
- Opioid guidelines being developed in Washington State
- Managing pain with PCA

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PHARMACY TODAY ■ PAIN SUPPLEMENT ■ WWW.PHARMACYTODAY.ORG ■ SEPTEMBER 2010 ■ VOLUME 16, NUMBER 9 (SUPPL 1)

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Pain management: Time for pharmacists to take action

Several months ago, we had a patient (I'll call her Stephanie) who was caught in the middle of a growing tug-of-war between successful pain management and the problem of opioid misuse and diversion.

Stephanie has severe chronic low back pain and knee osteoarthritis. She requires rather high doses of potent opioids to maintain normal functioning throughout the day. Stephanie is a model pain patient. She abides by her treatment agreement, always keeps her appointments, and even provides her pain clinic with a daily journal of her symptoms. Unfortunately, Stephanie's son is, or was, anything but a model—he stole all her medications, sold half of them, and kept the rest for himself. The son, as well as one of his friends, died tragically from an opioid-related overdose.

Chris Herndon, PharmD, BCPS, CPE, Assistant Professor
Southern Illinois University Edwardsville

Unfortunately, this is not a unique story.

The prevalence of pain and the problems associated with our most common remedies for this symptom have become syndemic, interacting synergistically in ways that make matters worse. CDC estimates that approximately one-third of the U.S. population suffers from low back pain, and an additional 10% to 15% experiences either head pain or various types of arthritis. These numbers are only expected to rise.

The problem of prescription opioid abuse, addiction, and diversion is also increasing alarmingly, as discussed in this supplement. This "perfect storm" of increasing pain, as well as increasing misuse and diversion, has left the health care community in a conundrum of how to successfully balance access to care and the necessary medications to treat pain, while addressing the growing public health concern of substance abuse. Consensus among regulatory, law enforcement, and patient advocacy groups has been almost nonexistent. Mandatory provider and pharmacist education, patient registries, controlled-access programs, and now, as discussed in this supplement, state-mandated ceiling doses of opioid analgesics (see page 13), create an undue burden on those providing patient care throughout all facets of the continuum.

Pharmacists are well-positioned to be active and accountable participants in the care of these patients. Recently, the concept of practicing "Universal Precautions" in pain management has become more frequent within hospitals and outpatient clinics. Adopting these precautions and screening methods, discussed on page 16, has implications for our profession as well. Who better to ensure the safe and effective use of these medications? Community pharmacists are especially equipped to identify and differentiate between safe medication use and potentially dangerous practices. Each of us can make a difference in our patients' lives by incorporating at least two of the following pharmacist-specific universal precautions:

1. Communicate questionable behavior to prescribers, including early refills, unfamiliar persons picking up or dropping off prescriptions, and aggressive or hostile behavior.
2. Request identification when patients drop off or pick up opioids and other controlled substances.
3. Personally check, or delegate, review of the prescription monitoring program if available.
4. Consider the patient's previous opioids when dispensing new prescriptions. Does the new medication or dose make sense as a safe titration or wean?
5. Encourage all persons with prescriptions for opioids or other controlled substances to store these medications under lock and key.
6. Counsel patients to quickly destroy unused or discontinued opioids using currently recommended medication disposal procedures.

Would the story of Stephanie and her son be different had she been urged to obtain a lockbox? It could well have been. The time is now for pharmacists, even in the busiest of settings, to become more proactive in learning about pain control and taking accountability for the outcomes (either positive or negative) related to pain medications.

—Chris Herndon, PharmD, BCPS, CPE
Guest Editor

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Pharmacy Today

Features

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Enhancing pain management training for pharmacists

Summit recommendations released

Proper pain management requires balancing of positive and negative aspects of medication use, as in so many aspects of health care. For patients in pain, opioids and other analgesics make all the difference in quality of life. When abused, however, these agents can wreck lives, as is apparent when one looks at the human toll of the nation's epidemic of abuse of prescription painkillers.

For pharmacists looking to shift this equation to the positive side, enhanced training and skills development are key, according to a 40-page list of recommendations from the Pharmacy Pain and Palliative Care Summit, held in October 2009. The list of recommendations was released at the 29th Annual Scientific Meeting of the American Pain Society in Baltimore in May 2010. Chris Herndon, PharmD, BCPS, CPE, Assistant Professor at Southern Illinois University Edwardsville (SIUE) and Editor of ***Pharmacy Today***'s Pain Supplement, coordinated the multidisciplinary summit.

The summit was unique for the pharmacy profession, as far as Herndon knows. "These recommendations are geared toward how we prepare pharmacists, as well as those already practicing, to deal with pain and symptom management, a course of training rarely offered at pharmacy schools," he told ***Today.***

Herndon said that SIUE is one of the few schools that offer specialized training for pharmacists in pain management. "The adoption of these recommendations by schools of pharmacy, state boards, and accrediting bodies would result in pharmacists becoming better educated and more active in managing patients with pain and related symptoms," he stated. He plans to take these recommendations to state boards and schools of pharmacy across the country with the hope of increasing pain management education for all pharmacists.

Identifying educational goals

The agenda for the summit was based on information presented at the National Pain and Palliative Care Summit held in 2003 at Ohio State University. There, a group of pharmacists recognized the need for a profession-specific summit that addressed the shortcomings in pain and palliative care training and assessment among pharmacists.

Based on those discussions in 2003, summit planners outlined a variety of topics for workgroups to address, including care standards and assessment, curriculum enhancement, residency and fellowship training, certificate program content development, and credentialing.

The objectives of the summit were to:

- Develop curricular recommendations for schools of pharmacy on the delivery of pain and palliative care education
- Identify collaborative opportunities with accrediting bodies and licensing boards to ensure assessment of pain and palliative care knowledge
- Recommend general competencies for pharmacists pursuing postgraduate training in this area
- Develop a model certificate program for provision of continuing education that will be applicable to pharmacists across practice settings
- Reach a consensus on the best methods for demonstrating expertise in this area by pharmacists

Enhancing curricula

The Curricular Workgroup was asked to provide recommended outlines, competencies, and learning experiences on pain and palliative care that can be applied throughout pharmacy's professional degree program. The group's primary goals were to develop recommendations on increasing and standardizing exposure to pain and palliative care during the didactic curriculum, introductory and advanced patient care experiential rotations, and clerkships.

The workgroup acknowledged that existing curricula of most schools of pharmacy barely fit into the available time slots of doctor of pharmacy programs, and members were doubtful that a dedicated, required course could be devoted to this topic. Therefore, the workgroup recommended that a total of six 50-minute lectures be incorporated within a course already offered in the curriculum.

The workgroup developed specific recommendations for content and time commitment for pain and palliative care instruction for this required coursework (Table 1). The group dedicated a bulk of the coursework time to the treatment of common pain etiologies such as management of acute pain, musculoskeletal

Table 1. Content and time commitment for required coursework

Content (time commitment)
Introduction and overview (10 minutes)
Definition of pain and palliative care (10 minutes)
Physiologic issues (0 minutes, previously covered in earlier coursework)
Pain and symptom assessment and management (15 minutes)
Pharmacologic issues (0 minutes, previously covered in earlier coursework)
Nonpharmacologic approaches to pain (5 minutes)
Management of common pain etiologies (180 minutes)
Management of common nonpain symptoms (20 minutes)
Analgesic dosing strategies (30 minutes)
Pharmaceutical concerns (10 minutes)
Ethical/legal issues (20 minutes)

pain, headache pain, neuropathic pain, and pain associated with advanced illness (e.g., cancer or HIV/AIDS). In addition, 30 minutes of coursework were dedicated to analgesic dosing strategies, including dosing in opioid-naive patients, dosage escalation and de-escalation, impact of genetic variability on analgesic metabolism, opioid conversion calculations, and dose-stacking strategies.

Table 2. Required competencies to be integrated into experiential experiences

- Interview a patient about a pain report or symptom.
- Participate in a family meeting or discussion with a patient about goal-setting regarding pain and/or symptom management.
- Program a patient-controlled analgesia pump.
- Counsel a patient on use of a nonprescription analgesic.
- Counsel a patient on use of long-acting opioid and rescue opioid therapy.
- Perform opioid conversion calculations, including converting from one route of administration to another route (same opioid) or from one opioid to another; convert a patient to both a different route of administration and different drug.
- Counsel a patient on how to manage adverse events associated with opioid therapy.

The workgroup developed a model syllabus for elective didactic coursework in the area of pain and palliative care and acknowledged that because elective courses are generally more flexible in terms of time, topics can be covered in greater detail and depth. The group also developed recommendations on competencies for pain and palliative care that should be integrated into required experiential rotations (Table 2).

Proposed activities were drafted for elective rotations in this area as well. Some of the recommended teaching activities for elective rotations included writing a condolence letter, completing a journal, visiting a funeral home, and attending morbidity and mortality rounds. The workgroup acknowledged that experiences and opportunities in individual rotations would vary greatly.

Training after college

Learning doesn't stop at the edge of campus, and members of the Postgraduate Training Workgroup sought to discuss ways to increase exposure to pain and palliative care during the first postgraduate year (PGY1), review accreditation standards for the second postgraduate year (PGY2) specialty residencies in pain and palliative care, and improve consistency among PGY2 specialty residencies in areas of practice outside of pain. The workgroup acknowledged that formal postgraduate training in this area is lacking and that increased institutional commitment to expanding opportunities in pain and palliative care is needed.

The group developed a list of 21 competencies for consideration by PGY1 and PGY2 residency program directors that would ensure adequate training in pain and palliative care. Three of these competencies were understanding the unique aspects of providing evidence-based, patient-centered medication therapy management (MTM) within multidisciplinary teams for patients with pain and those requiring palliative care; differentiating among behaviors associated with physiological dependence, tolerance, pseudoaddiction, and substance dependence; and educating patients, caregivers, and/or health care providers on appropriate MTM for patients with pain or needing palliative care.

The workgroup also reviewed the current American Society of Health-System Pharmacists accreditation standards for the PGY2 residency in pain and palliative care and agreed that the current outcomes, goals, and objectives of these programs are sound.

Certificate programs

The Core Certification and Site Dependent Workgroups developed criteria for certificate programs. Members sought to determine the best way to improve the skills, attitudes, and knowledge base of practicing pharmacists in the area of pain and palliative care that could be applied across different practice settings.

Three levels of educational programming were proposed for pharmacists. These included basic competencies that should be achieved by all pharmacists (core certificate program), more advanced practice-specific training modules, and a train-the-trainer program given by pharmacists who have completed all the modules.

The core certification program would cover areas such as the epidemiology of pain, pain taxonomy, pathophysiology of pain, pain and symptom assessment, palliative care, and end-of-life care. The practice-specific modules would be more focused on areas such as inpatient care, community practice, ambulatory care, and managed care.

Both workgroups developed a long list of competencies for these certification modules.

Credentialing pharmacists

Two credentialing examinations are available to pharmacists to demonstrate their expertise in this area: Diplomate of the American Academy of Pain Management and Certified Pain Educator, a designation given by the American Society of Pain Educators.

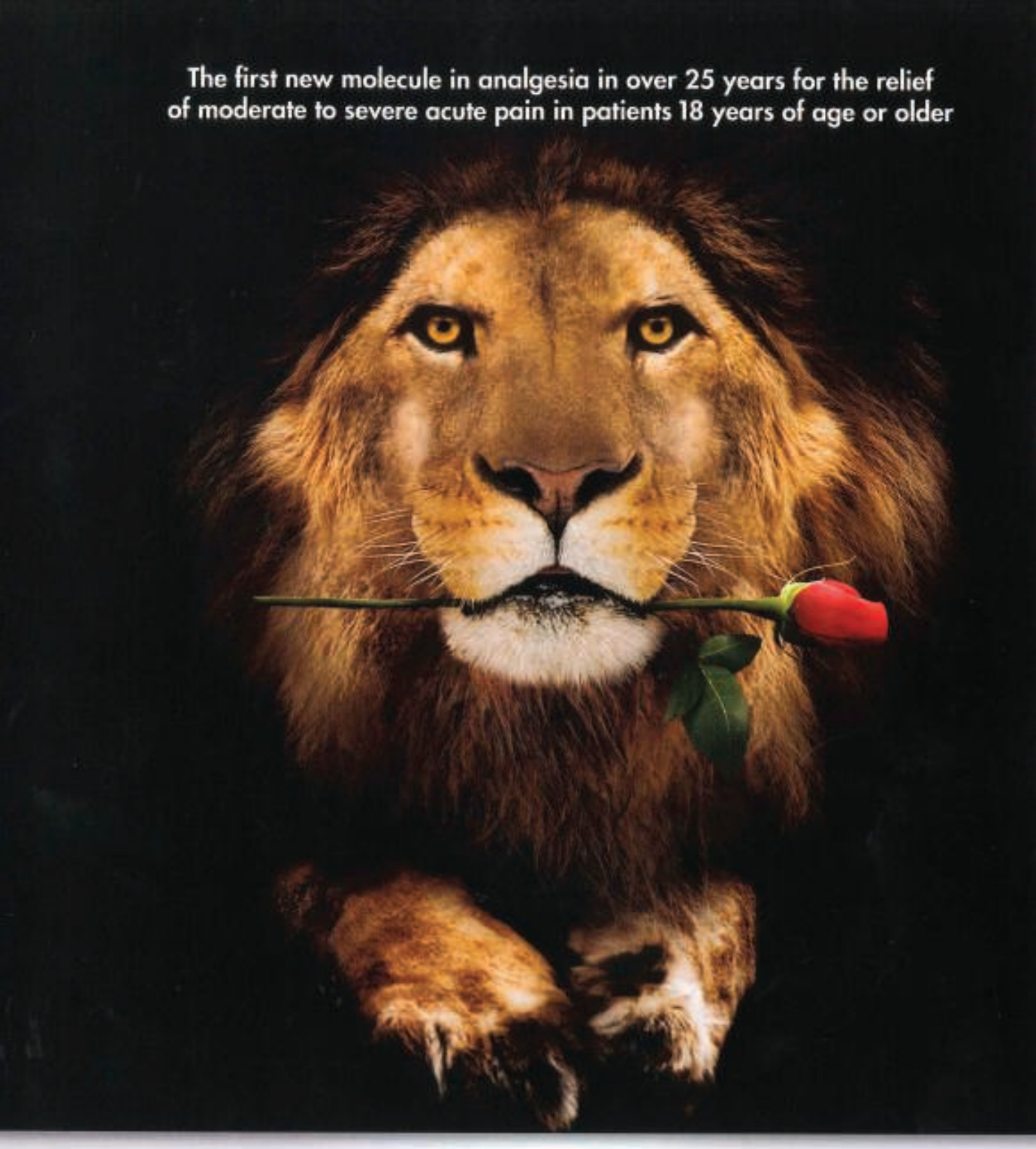
The Credentialing Workgroup determined that a petition for specialty recognition through the Board of Pharmacy Specialties for Pain and Palliative Care is needed. Members recommended that one or more organizations be identified to collaborate on the development of a board examination for pharmacists in this area. If no sponsoring organization can be found, members recommended that a pharmacist-specific organization should be developed for pharmacists interested in pain and palliative care.

Planning for the future

The recommendations put forth by the summit help address educational barriers and opportunities for pharmacists in pain and palliative care at every step of their professional career. With more education and enhanced counseling and clinical skills, pharmacists will be ready to help improve the use of analgesic medications and thereby advance patient care. A copy of the recommendations is at www.pharmacypainsummit.com.

—Maria G. Tanzi, PharmD

The first new molecule in analgesia in over 25 years for the relief of moderate to severe acute pain in patients 18 years of age or older



NUCYNTA® CII

tapentadol

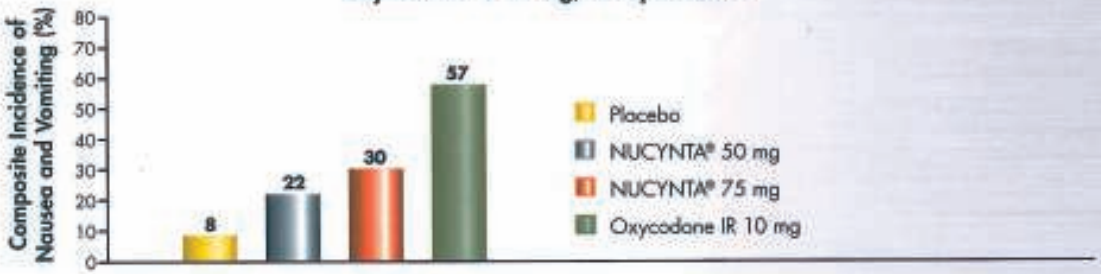
OPIOID EFFICACY MEETS UNEXPECTED TOLERABILITY

Proven opioid efficacy

- NUCYNTA® 50 mg and 75 mg demonstrated analgesic efficacy in a 10-day trial supporting the acute pain indication[1]

GI tolerability profile demonstrated in a clinical trial

Composite incidence of nausea and/or vomiting with NUCYNTA® 50 mg and 75 mg, oxycodone IR 10 mg, and placebo[1,2]



Safety population (N=666) with a mean baseline pain intensity score of 6.7 was randomized to 50 mg or 75 mg of NUCYNTA®, 10 mg oxycodone IR, or placebo dosed every 4 to 6 hours while patients were awake. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

NUCYNTA® CII
tapentadol

Visit www.NUCYNTA.com for more information.

Please see Important Safety Information on the following page.

References: 1. Harrick C, Van Hove I, Stegmann J-U, Oh C, Upmalis D. Efficacy and tolerability of tapentadol immediate release and oxycodone HCl immediate release in patients awaiting primary joint replacement surgery for end-stage joint disease: a 10-day, phase III, randomized, double-blind, active- and placebo-controlled study. Clin Ther. 2009;31(2):1-12. **2.** Data on file. Ortho-McNeil-Janssen Pharmaceuticals, Inc.

PriCara

August 2010 02TL10093R2

For the relief of moderate to severe acute pain in patients 18 years of age or older

IMPORTANT SAFETY INFORMATION

- Like other drugs with mu-opioid agonist activity, NUCYNTA® (tapentadol) is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma or hypercapnia in unmonitored settings or in the absence of resuscitative equipment. NUCYNTA® is contraindicated in patients who have or are suspected to have paralytic ileus. NUCYNTA® is also contraindicated in patients currently using or within 14 days of using monoamine oxidase inhibitors (MAOIs) due to potential additive effects on norepinephrine levels, which may result in adverse cardiovascular events.
- Respiratory depression is the primary risk of mu-opioid agonists. Respiratory depression occurs more frequently in elderly or debilitated patients and in those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction, in whom even moderate therapeutic doses may significantly decrease pulmonary ventilation. NUCYNTA® should be administered with caution to the elderly, debilitated patients, and patients with conditions accompanied by hypoxia, hypercapnia or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression, or coma. In such patients, even usual therapeutic doses of NUCYNTA® may increase airway resistance and decrease respiratory drive to the point of apnea. Alternative non-mu-opioid agonist analgesics should be considered and NUCYNTA® should be employed only under careful medical supervision at the lowest effective dose in such patients. If respiratory depression occurs, it should be treated as any mu-opioid agonist-induced respiratory depression.
- Patients receiving other mu-opioid agonist analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUCYNTA® may exhibit additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, coma or death may result if these drugs are taken in combination with NUCYNTA®. When such combined therapy is contemplated, a dose reduction of one or both agents should be considered.
- Opioid analgesics can raise cerebrospinal fluid pressure as a result of respiratory depression with carbon dioxide retention. Therefore, NUCYNTA® should not be used in patients susceptible to the effects of raised cerebrospinal fluid pressure such as those with head injury and increased intracranial pressure. Opioid analgesics may obscure the clinical course of patients with head injury due to effects on pupillary response and consciousness. NUCYNTA® should be used with caution in patients with head injury, intracranial lesions, or other sources of preexisting increased intracranial pressure.
- NUCYNTA® is a mu-opioid agonist and is a Schedule II controlled substance. Such drugs are sought by drug abusers and people with addiction disorders. Diversion of Schedule II products is an act subject to criminal penalty. NUCYNTA® can be abused in a manner similar to other mu-opioid agonists, legal or illicit. This should be considered when prescribing or dispensing NUCYNTA® in situations where the physician or pharmacist is concerned about an increased risk of misuse and abuse. All patients treated with mu-opioid agonists require careful monitoring for signs of abuse and addiction. NUCYNTA® may be abused by crushing, chewing, snorting or injecting the product. These practices pose a significant risk to the abuser that could result in overdose and death.
- Experience with NUCYNTA® overdose is very limited. Management of overdose should be focused on treating symptoms of mu-opioid agonism. Primary attention should be given to reestablishment of a patent airway and institution of assisted or controlled ventilation when overdose of NUCYNTA® is suspected. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.
- Patients should be cautioned that NUCYNTA® may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. This is to be expected especially at the beginning of treatment, at any change of dosage as well as in combination with alcohol or tranquilizers.
- NUCYNTA® has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. NUCYNTA® should be prescribed with care in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures.
- The development of a potentially life-threatening serotonin syndrome may occur with use of SNRI products, including NUCYNTA®, particularly with concomitant use of serotonergic drugs such as SSRIs, SNRIs, TCAs, MAOIs and triptans, and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome may include mental-status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea).
- Withdrawal symptoms may occur if NUCYNTA® is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely, hallucinations. Withdrawal symptoms may be reduced by tapering NUCYNTA®.
- Pregnancy Category C. There are no adequate and well-controlled studies of NUCYNTA® in pregnant women. NUCYNTA® should be used during pregnancy ONLY if the potential benefit justifies the potential risk to the fetus. NUCYNTA® is not recommended for use in women during and immediately prior to labor and delivery. Neonates whose mothers have been taking NUCYNTA® should be monitored for respiratory depression. NUCYNTA® should not be used during breastfeeding.
- NUCYNTA® is not recommended in patients with severe renal or hepatic impairment. NUCYNTA® should be used with caution in patients with moderate hepatic impairment. Like other drugs with mu-opioid agonist activity, NUCYNTA® may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.
- The most common adverse events are nausea, dizziness, vomiting, somnolence and headache.

Please see Brief Summary of Prescribing Information on adjacent page.

NUCYNTA® (tapentadol)
immediate-release oral tablets C-II

Brief Summary: The following is a brief summary only. Before prescribing, see complete Prescribing Information in NUCYNTA® (tapentadol) Tablets labeling.

INDICATIONS AND USAGE

NUCYNTA® (tapentadol) is indicated for the relief of moderate to severe acute pain in patients 18 years of age or older.

CONTRAINDICATIONS

Impaired Pulmonary Function

Like other drugs with mu-opioid agonist activity, NUCYNTA® is contraindicated in patients with significant respiratory depression in unmonitored settings or the absence of resuscitative equipment. NUCYNTA® is also contraindicated in patients with acute or severe bronchial asthma or hypercapnia in unmonitored settings or the absence of resuscitative equipment *[see Warnings and Precautions]*.

Paralytic Ileus

Like drugs with mu-opioid agonist activity, NUCYNTA® is contraindicated in any patient who has or is suspected of having paralytic ileus.

Monoamine Oxidase Inhibitors

NUCYNTA® is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days due to potential additive effects on norepinephrine levels which may result in adverse cardiovascular events *[see Drug Interactions]*.

WARNINGS AND PRECAUTIONS

Respiratory Depression

Respiratory depression is the primary risk of mu-opioid agonists. Respiratory depression occurs more frequently in elderly or debilitated patients and in those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction, in whom even moderate therapeutic doses may significantly decrease pulmonary ventilation.

NUCYNTA® should be administered with caution to patients with conditions accompanied by hypoxia, hypercapnia or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, central nervous system (CNS) depression, or coma. In such patients, even usual therapeutic doses of NUCYNTA® may increase airway resistance and decrease respiratory drive to the point of apnea. Alternative non-mu-opioid agonist analgesics should be considered and NUCYNTA® should be employed only under careful medical supervision at the lowest effective dose in such patients. If respiratory depression occurs, it should be treated as any mu-opioid agonist-induced respiratory depression *[see Overdosage]*.

CNS Depression

Patients receiving other mu-opioid agonist analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUCYNTA® may exhibit additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, coma or death may result if these drugs are taken in combination with NUCYNTA®. When such combined therapy is contemplated, a dose reduction of one or both agents should be considered.

Head Injury and Increased Intracranial Pressure

Opioid analgesics can raise cerebrospinal fluid pressure as a result of respiratory depression with carbon dioxide retention. Therefore, NUCYNTA® should not be used in patients who may be susceptible to the effects of raised cerebrospinal fluid pressure such as those with evidence of head injury and increased intracranial pressure. Opioid analgesics may obscure the clinical course of patients with head injury due to effects on pupillary response and consciousness. NUCYNTA® should be used with caution in patients with head injury, intracranial lesions, or other sources of preexisting increased intracranial pressure.

Misuse and Abuse

Tapentadol is a mu-opioid agonist and is a Schedule II controlled substance. Such drugs are sought by drug abusers and people with addiction disorders. Diversion of Schedule II products is an act subject to criminal penalty.

NUCYNTA® can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing NUCYNTA® in situations where the physician or pharmacist is concerned about an increased risk of misuse and abuse. Concerns about abuse and addiction should not prevent the proper management of pain. However, all patients treated with mu-opioid agonists require careful monitoring for signs of abuse and addiction, since use of mu-opioid agonist analgesic products carry the risk of addiction even under appropriate medical use *[see Drug Abuse and Dependence]*.

NUCYNTA® may be abused by crushing, chewing, snorting or injecting the product. These practices pose a significant risk to the abuser that could result in overdose and death *[see Drug Abuse and Dependence]*.

Driving and Operating Machinery

Patients should be cautioned that NUCYNTA® may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. This is to be expected especially at the beginning of treatment, at any change of dosage as well as in combination with alcohol or tranquilizers *[see Drug Interactions]*.

Interactions with Alcohol and Drugs of Abuse

Due to its mu-opioid agonist activity, NUCYNTA® may be expected to have additive effects when used in conjunction with alcohol, opioids, or illicit drugs that cause central nervous system depression, respiratory depression, hypotension, and profound sedation, coma or death *[see Drug Interactions]*.

Seizures

NUCYNTA® has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. NUCYNTA® should be prescribed with care in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures.

Serotonin Syndrome Risk

The development of a potentially life-threatening serotonin syndrome may occur with use of Serotonin and Norepinephrine Reuptake Inhibitor (SNRI) products, including NUCYNTA®, particularly with concomitant use of serotonergic drugs such as Selective Serotonin Reuptake Inhibitors (SSRIs), SNRIs, tricyclic antidepressants (TCAs), MAOIs and triptans, and with drugs that impair metabolism of serotonin (including MAOIs). This may occur within the recommended dose. Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

Withdrawal

Withdrawal symptoms may occur if NUCYNTA® is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely, hallucinations. Withdrawal symptoms may be reduced by tapering NUCYNTA® *[see Drug Abuse and Dependence]*.

Hepatic Impairment

A study of NUCYNTA® in subjects with hepatic impairment showed higher serum concentrations than in those with normal hepatic function. NUCYNTA® should be used with caution in patients with moderate hepatic impairment *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3) in full PI]*.

NUCYNTA® has not been studied in patients with severe hepatic impairment and, therefore, use in this population is not recommended.

Use in Pancreatic/Biliary Tract Disease

Like other drugs with mu-opioid agonist activity, NUCYNTA® may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.

ADVERSE REACTIONS

The following treatment-emergent adverse events are discussed in more detail in other sections of the labeling:

- Respiratory Depression *[see Contraindications and Warnings and Precautions]*
- CNS Depression *[see Warnings and Precautions]*

Because clinical studies are conducted under widely varying conditions, adverse event rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice. A treatment-emergent adverse event refers to any untoward medical event associated with the use of the drug in humans, whether or not considered drug-related.

Based on data from nine Phase 2/3 studies that administered multiple doses (seven placebo- and/or active-controlled, one noncontrolled and one Phase 3 active-controlled safety study) the most common adverse events (reported by ≥ 10% in any NUCYNTA® dose group) were: nausea, dizziness, vomiting and somnolence.

The most common reasons for discontinuation due to adverse events in the studies described above (reported by ≥ 1% in any NUCYNTA® dose group) were dizziness (2.6% vs. 0.5%), nausea (2.3% vs. 0.6%), vomiting (1.4% vs. 0.2%), somnolence (1.3% vs. 0.2%) and headache (0.9% vs. 0.2%) for NUCYNTA®- and placebo-treated patients, respectively.

Seventy-six percent of NUCYNTA®-treated patients from the nine studies experienced adverse events.

NUCYNTA® was studied in multiple-dose, active- or placebo-controlled studies, or noncontrolled studies (n = 2178), in single-dose studies (n = 870), in open-label study extension (n = 483) and in Phase 1 studies (n = 597). Of these, 2034 patients were treated with doses of 50 mg to 100 mg of NUCYNTA® dosed every 4 to 6 hours.

The data described below reflect exposure to NUCYNTA® in 3161 patients, including 449 exposed for 45 days. NUCYNTA® was studied primarily in placebo- and active-controlled studies (n = 2288, and n = 2944, respectively). The population was 18 to 85 years old (mean age 46 years), 68% were female, 75% white and 67% were postoperative. Most patients received NUCYNTA® doses of 50 mg, 75 mg, or 100 mg every 4 to 6 hours.

Commonly-Observed Treatment-Emergent Adverse Events in Double-Blind Controlled Clinical Trials

Table 1 lists the adverse events reported in ≥ 1% or more of NUCYNTA®-treated patients with acute moderate to severe pain in the pooled safety data from nine Phase 2/3 studies that administered multiple doses (seven placebo- and/or active-controlled, one noncontrolled, and one Phase 3 active-controlled safety study).

Table 1: Treatment-Emergent Adverse Events* Reported by ≥ 1% of NUCYNTA®-Treated Patients in Seven Phase 2/3 Placebo- and/or Oxycodone-Controlled, One Noncontrolled, and One Phase 3 Oxycodone-Controlled Safety, Multiple-Dose Clinical Studies: System/Organ Class MedDRA Preferred Term first, followed by NUCYNTA® 21 mg – 120 mg (n=2178) % second, and Placebo (n=619) % third: Gastrointestinal disorders: Nausea 30, 13; Vomiting 18, 4; Constipation 8, 3; Dry mouth 4, <1; Dyspepsia 2, <1; General disorders and administration site conditions: Fatigue 3, <1; Feeling hot 1, <1; Infections and infestations: Nasopharyngitis 1, <1; Upper respiratory tract infection 1, <1; Urinary tract infection 1, <1; Metabolism and nutrition disorders: Decreased appetite 2, 0; Musculoskeletal and connective tissue disorders: Arthralgia 1, <1; Nervous system disorders: Dizziness 24, 8; Somnolence 15, 3; Tremor 1, <1; Lethargy 1, <1; Psychiatric disorders: Insomnia 2, <1; Confusional state 1, 0; Abnormal dreams 1, <1; Anxiety 1, <1; Skin and subcutaneous tissue disorders: Pruritus 5, 1; Hyperhidrosis 3, <1; Pruritus generalized 3, <1; Rash 1, <1; Vascular disorders: Hot flush 1, <1. * A treatment-emergent adverse event refers to any untoward medical event associated with the use of the drug in humans, whether or not considered drug-related.

Other Adverse Reactions Observed During the Premarketing Evaluation of NUCYNTA®

The following adverse drug reactions occurred in <1% of NUCYNTA®-treated patients in the pooled safety data from nine Phase 2/3 studies that administered multiple doses (seven were placebo- and/or active-controlled, one noncontrolled, and one Phase 3 active-controlled safety study):

Cardiac disorders: heart rate increased, heart rate decreased

Eye disorders: visual disturbance

Gastrointestinal disorders: abdominal discomfort, impaired gastric emptying

General disorders and administration site conditions: irritability, edema, drug withdrawal syndrome, feeling drunk

Immune system disorders: hypersensitivity

Investigations: gamma-glutamyltransferase increased, alanine aminotransferase increased, aspartate aminotransferase increased

Musculoskeletal and connective tissue disorders: involuntary muscle contractions, sensation of heaviness

Nervous system disorders: hypoesthesia, paresthesia, disturbance in attention, sedation, dysarthria, depressed level of consciousness, memory impairment, ataxia, presyncope, syncope, coordination abnormal, seizure

Psychiatric disorders: euphoric mood, disorientation, restlessness, agitation, nervousness, thinking abnormal

Renal and urinary disorders: urinary hesitation, pollakiuria

Respiratory, thoracic and mediastinal disorders: oxygen saturation decreased, cough, dyspnea, respiratory depression

Skin and subcutaneous tissue disorders: urticaria

Vascular disorders: blood pressure decreased

In the pooled safety data, the overall incidence of adverse reactions increased with increased dose of NUCYNTA®, as did the percentage of patients with adverse reactions of nausea, dizziness, vomiting, somnolence, and pruritus.

Post-marketing Experience

The following additional adverse reactions have been identified during post-approval use of NUCYNTA®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably. **Nervous system disorders:** headache
Psychiatric disorders: hallucination

DRUG INTERACTIONS

NUCYNTA® is mainly metabolized by glucuronidation. The following substances have been included in a set of interaction studies without any clinically significant finding: acetaminophen, acetylsalicylic acid, naproxen and probenecid *[see Clinical Pharmacology (12.3) in full PI]*.

The pharmacokinetics of tapentadol were not affected when gastric pH or gastrointestinal motility were increased by omeprazole and metoclopramide, respectively *[see Clinical Pharmacology (12.3) in full PI]*.

Drugs Metabolized by Cytochrome P450 Enzymes

In vitro investigations indicate that NUCYNTA® does not inhibit or induce P450 enzymes. Thus, clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur *[see Clinical Pharmacology (12.3) in full PI]*.

Drugs That Inhibit or Induce Cytochrome P450 Enzymes

The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. To a lesser extent, tapentadol is additionally metabolized to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19 to hydroxy tapentadol (2%) by CYP2D6, which are further metabolized by conjugation. Since only a minor amount of NUCYNTA® is metabolized via the oxidative pathway clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur *[see Clinical Pharmacology (12.3) in full PI]*.

Centrally-Acting Drugs and Alcohol

Patients receiving other opioid agonist analgesics, general anesthetics, phenothiazines, antiemetics, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUCYNTA® may exhibit an additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with NUCYNTA®. When such combined therapy is contemplated, a dose reduction of one or both agents should be considered *[see Warnings and Precautions]*.

Monoamine Oxidase Inhibitors

NUCYNTA® is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days due to potential additive effects on norepinephrine levels which may result in adverse cardiovascular events *[see Contraindications]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C.

Tapentadol HCl was evaluated for teratogenic effects in pregnant rats and rabbits following intravenous and subcutaneous exposure during the period of embryofetal organogenesis. When tapentadol was administered twice daily by the subcutaneous route in rats at dose levels of 10, 20, or 40 mg/kg/day [producing up to 1 times the plasma exposure at the maximum recommended human dose (MRHD) of 700 mg/day based on an area under the time-curve (AUC) comparison], no teratogenic effects were observed. Evidence of embryofetal toxicity included transient delays in skeletal maturation (i.e. reduced ossification) at the 40 mg/kg/day dose which was associated with significant maternal toxicity. Administration of tapentadol HCl in rabbits at doses of 4, 10, or 24 mg/kg/day by subcutaneous injection [producing 0.2, 0.6, and 1.85 times the plasma exposure at the MRHD based on an AUC comparison] revealed embryofetal toxicity at doses ≥ 10 mg/kg/day. Findings included reduced fetal viability, skeletal delays and other variations. In addition, there were multiple malformations including gastroschisis/thoracogastroschisis, amelia/phocomelia, and cleft palate at doses ≥ 10 mg/kg/day and above, and ablepharia, encephalopathy, and spina bifida at the high dose of 24 mg/kg/day. Embryofetal toxicity, including malformations, may be secondary to the significant maternal toxicity observed in the study.

In a study of pre- and postnatal development in rats, oral administration of tapentadol at doses of 20, 50, 150, or 300 mg/kg/day to pregnant and lactating rats during the late gestation and early postnatal period [resulting in up to 1.7 times the plasma exposure at the MRHD on an AUC basis] did not influence physical or reflex development, the outcome of neurobehavioral tests or reproductive parameters. Treatment-related developmental delay was observed, including incomplete ossification, and significant reductions in pup body weights and body weight gains at doses associated with maternal toxicity (150 mg/kg/day and above). At maternal tapentadol doses ≥ 150 mg/kg/day, a dose-related increase in pup mortality was observed through postnatal Day 4.

There are no adequate and well controlled studies of NUCYNTA® in pregnant women. NUCYNTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of tapentadol on labor and delivery in humans is unknown. NUCYNTA® is not recommended for use in women during and immediately prior to labor and delivery. Due to the mu-opioid receptor agonist activity of NUCYNTA®, neonates whose mothers have been taking NUCYNTA® should be monitored for respiratory depression. A specific opioid antagonist, such as naloxone, should be available for reversal of opioid induced respiratory depression in the neonate.

Nursing Mothers

There is insufficient/limited information on the excretion of tapentadol in human or animal breast milk. Physicochemical and available pharmacodynamic/toxicological data on tapentadol point to excretion in breast milk and risk to the suckling child cannot be excluded. NUCYNTA® should not be used during breast-feeding.

Pediatric Use

The safety and effectiveness of NUCYNTA® in pediatric patients less than 18 years of age have not been established. NUCYNTA® is not recommended in this population.

Geriatric Use

Of the total number of patients in Phase 2/3 double-blind, multiple-dose clinical studies of NUCYNTA®, 19% were 65 and over, while 5% were 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. The rate of constipation was higher in subjects greater than or equal to 65 years than those less than 65 years (12% vs. 7%).

In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, consideration should be given to starting elderly patients with the lower range of recommended doses *[see Clinical Pharmacology (12.3) in full PI]*.

Renal Impairment

In patients with severe renal impairment, the safety and effectiveness of NUCYNTA® has not been established. NUCYNTA® is not recommended in this population *[see Dosage and Administration (2.1) in full PI]*.

Hepatic Impairment

Administration of NUCYNTA® resulted in higher exposures and serum levels to tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function *[see Clinical Pharmacology (12.3) in full PI]*. NUCYNTA® should be used with caution in patients with moderate hepatic impairment *[see Dosage and Administration (2.2) in full PI]*.

NUCYNTA® has not been studied in patients with severe hepatic impairment, therefore, use of NUCYNTA® is not recommended in this population *[see Warnings and Precautions]*.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

NUCYNTA® contains tapentadol, a mu-opioid agonist and is a Schedule II controlled substance. NUCYNTA® has an abuse potential similar to hydromorphone, can be abused and is subject to criminal diversion.

Abuse

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

Concerns about abuse and addiction should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

"Drug seeking" behavior is very common in addicts, and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of mu-opioid agonists can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Careful recordkeeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Abuse of NUCYNTA® poses a risk of overdose and death. This risk is increased with concurrent abuse of NUCYNTA® with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of drugs with mu-opioid agonist properties.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Warnings and Precautions]*. Use of NUCYNTA® in this population has not been characterized. As NUCYNTA® has mu-opioid agonist activity, infants whose mothers have taken NUCYNTA®, should be carefully monitored.

Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, increased blood pressure, respiratory rate, or heart rate.

Generally, tolerance and/or withdrawal are more likely to occur the longer a patient is on continuous opioid therapy. In a safety study where drug was administered up to 90 days, 82.7% of patients taking NUCYNTA® who stopped abruptly without initiating alternative therapy and were assessed 2 to 4 days after discontinuation, did not have objective signs of opioid withdrawal using the Clinical Opiate Withdrawal Scale. Moderate withdrawal symptoms were seen in 0.3% of patients with the rest (17%) experiencing mild symptoms. Withdrawal symptoms may be reduced by tapering NUCYNTA®.

OVERDOSAGE

Human Experience

Experience with NUCYNTA® overdose is very limited. Preclinical data suggest that symptoms similar to those of other centrally acting analgesics with mu-opioid agonist activity are to be expected upon intoxication with tapentadol. In principle, these symptoms may particularly appear in the clinical setting: miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Management of Overdose

Management of overdose should be focused on treating symptoms of mu-opioid agonism. Primary attention should be given to re-establishment of a patent airway and institution of assisted or controlled ventilation when overdose of NUCYNTA® is suspected. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

Pure opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. Administration of an opioid antagonist is not a substitute for continuous monitoring of airway, breathing, and circulation following an opioid overdose. If the response to opioid antagonists is suboptimal or only brief in nature, an additional antagonist should be administered as directed by the manufacturer of the product.

Gastrointestinal decontamination may be considered in order to eliminate unabsorbed drug. Gastrointestinal decontamination with activated charcoal or by gastric lavage is only recommended within 2 hours after intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities. Before attempting gastrointestinal decontamination, care should be taken to secure the airway.

PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the following issues with patients for whom they prescribe NUCYNTA®:

Instructions for Use

Patients should be advised NUCYNTA® should be taken only as directed and to report episodes of breakthrough pain and adverse experiences occurring during therapy to their physician. Individualization of dosage is essential to make optimal use of this medication. Patients should be advised not to adjust the dose of NUCYNTA® without consulting their physician *[see Dosage and Administration (2) in full PI]*. Patients should be advised that it may be appropriate to taper dosing when discontinuing treatment with NUCYNTA® as withdrawal symptoms may occur *[see Drug Abuse and Dependence]*. The physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.

Misuse and Abuse

Patients should be advised that NUCYNTA® is a potential drug of abuse. Patients should protect NUCYNTA® from theft, and NUCYNTA® should never be given to anyone other than the individual for whom NUCYNTA® was prescribed *[see Warnings and Precautions]*.

Interference with Cognitive and Motor Performance

As NUCYNTA® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles *[see Warnings and Precautions]*.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with NUCYNTA® *[see Use in Specific Populations]*.

Nursing

Patients should be advised not to breast-feed an infant during treatment with NUCYNTA® *[see Use in Specific Populations]*.

Monoamine Oxidase Inhibitors

Patients should be informed not to take NUCYNTA® while using any drugs that inhibit monoamine oxidase. Patients should not start any new medications while taking NUCYNTA® until they are assured by their healthcare provider that the new medication is not a monoamine oxidase inhibitor.

Seizures

Patients should be informed that NUCYNTA® could cause seizures if they are at risk for seizures or have epilepsy. Such patients should be advised to use NUCYNTA® with care *[see Warnings and Precautions]*. Patients should be advised to stop taking NUCYNTA® if they have a seizure while taking NUCYNTA® and call their healthcare provider right away.

Serotonin Syndrome

Patients should be informed that NUCYNTA® could cause rare but potentially life-threatening conditions resulting from concomitant administration of serotonergic drugs (including Serotonin Reuptake Inhibitors, Serotonin and Norepinephrine Reuptake Inhibitors and tricyclic antidepressants) *[see Warnings and Precautions]*.

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs as there is a potential for interactions *[see Drug Interactions]*.

Alcohol

Patients should be advised to avoid alcohol while taking NUCYNTA® *[see Drug Interactions]*.

Medication Guide

See Medication Guide (17.10) in full PI.

Revised: June 2010

Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
PriCara®, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Raritan, NJ 08869

PriCara®

Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

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FDA proposes REMS for certain opioids

APhA: Pharmacists key ingredient in successful programs

Two FDA Advisory Committees told the agency that its proposed Risk Evaluation and Mitigation Strategies (REMS) for long-acting and extended-release opioid analgesics did not go far enough. During the public comment part of the July 22–23 meeting, held in the suburbs of Washington, DC, APhA recommended that pharmacists receive outreach and educational materials about the REMS program and that FDA recognize the role pharmacists play as the medication experts on the health care team.

Pharmacists won't see changes until there's an FDA-approved REMS for this drug class. What may happen from here is unclear. At the meeting, APhA, the Accreditation Council for Pharmacy Education (ACPE), and the American Academy of Pain Medicine (AAPM) were among those recommending that REMS education be linked to continuing education for pharmacists and physicians.

Abuse, misuse

In announcing the meeting, FDA had provided this background: "The need for adequate pain control is an element of good medical practice. In this context, some persons suffering from pain need access to potent opioid drug products; however, inappropriate prescribing, addiction, and death due to prescription opioid abuse and misuse have been increasing over the last decade."

The medical use of opioid painkillers has increased at least 10-fold in the past 20 years because of a movement toward more aggressive management of pain, according to "Unintentional Drug Poisoning in the United States," a CDC document released in July. Drug overdose rates have risen steadily in this country since 1970; in 2007, the number of deaths involving opioid analgesics was 1.93 times the number for cocaine and 5.38 times the number for heroin. In 2008, more emergency department visits resulted from use of legal drugs than illegal ones.

Voting no

Members of FDA's Anesthetic & Life Support Drugs Advisory Committee and Drug Safety & Risk Management Advisory Committee "agreed that a REMS was needed, but they voted no because they didn't think the proposal from FDA was all that they thought was needed," John Jenkins, MD, Director, Office of New Drugs, Center for Drug Evaluation and Research, FDA, said at a news conference after the meeting. Specifically, the committee wanted training for prescribers to be mandatory, rather than voluntary, as FDA had proposed. Many also recommended expanding the REMS program to include short-acting opioids.The panelists voted 25–10 against FDA's proposed REMS.

While FDA will consider the advisory committees' recommendations, it doesn't have to follow them exactly. "I don't think I can give you a specific timeline, but we do want to move on this as rapidly as possible," Jenkins told reporters. "We have to go back inside internally and discuss it—decide whether we want to make significant modifications to what we had proposed based on the committees' feedback, or whether we want to go forward with what we had proposed."

FDA told ***Pharmacy Today*** in an e-mail that the agency convened its advisory committees to provide advice on this "very complex" class-wide proposed REMS, which would affect multiple sponsors, several million patients, almost a million prescribers, and almost all pharmacies in the United States.

History, goal

The proposed REMS under discussion has a recent history. In February 2009, FDA notified manufacturers of long-acting and extended-release opioids that their products would require a REMS "to ensure that the benefits of those products continued to outweigh their risks," according to FDA briefing information for the meeting. The list of targeted opioids includes long-acting and extended-release products formulated with any of several medications: fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone.

A series of FDA meetings in 2009 to gather public input on REMS for this class of drugs led to the formation of an internal FDA steering committee that, in turn, formed seven work groups, according to the briefing information. Two of the work groups focused on pharmacist education and on pharmacy systems. The work group for pharmacist education recommended no additional training or regulatory oversight for pharmacists. The work group for pharmacy systems recommended that FDA ask drug manufacturers "to develop a system that works within the existing retail pharmacy system to verify prescriber" education and certification before the drug can be dispensed. FDA's proposed REMS did not include specific requirements for pharmacists beyond dispensing of a medication guide.

The goal of the proposed REMS would be to reduce addiction, unintentional overdose, and death resulting from inappropriate prescribing, misuse, and abuse of long-acting and extended-release opioids, while maintaining patient access to these medications, according to the briefing information. The proposed REMS would comprise medication guides, voluntary education for prescribers and for patients (see sidebar), a timetable for assessment, and metrics. In addition to the proposed REMS, FDA intends to partner with other federal agencies and stakeholders "to more broadly address the problem of misuse and abuse of prescription opioids, including appropriate storage and disposal, and avoidance of improper sharing." FDA also intends to use its own Safe Use Initiative as a nonregulatory pathway to address the issue.

APhA speaks

While the proposed REMS did not include ispecific requirements for pharmacists,

APhA advocated for the important role played by pharmacists, as the medication experts on the health care team, in safe medication use and patient care. "With appropriate time and resources, pharmacists can further improve public health and education for those medications requiring a REMS," Marcie Bough, PharmD, APhA Director of Federal Regulatory Affairs, said in the APhA comments. "We challenge FDA and sponsors to continue to evaluate the potential impact, need for, and ability to compensate for counseling services at the point of dispensing as part of a REMS program."

Bough also expressed appreciation for FDA's dedication of time and resources toward evaluating and proposing a REMS program and support for several elements of the proposed program.

Other voices

APhA's was not the only voice calling for more education. ACPE representatives spoke during the meeting, recommending that REMS education be linked to accredited continuing pharmacy education (CPE) programs as a means of providing an incentive to pharmacists. "CPE providers should be encouraged to develop independent activities that support the proper use of medications under REMS, and ACPE will be working with other key stakeholders to track, evaluate, and measure the effectiveness of those activities," Peter H. Vlasses, PharmD, DSc (Hon), Executive Director of ACPE, said in a news release issued after the meeting.

During the meeting, AAPM offered several recommendations. "They all really fit under the umbrella of balancing efforts to curb abuse and misuse with efforts to maintain appropriate access for legitimate patients," Executive Director Philip Saigh told ***Today***.

—Diana Yap

APhA to FDA at meeting: REMS programs need structure, standardization

Finding better, more consistent, more organized methods for ensuring drug safety is needed as FDA's Risk Evaluation and Mitigation Strategies (REMS) effort goes forward. That was a central message delivered by APhA and other stakeholders to agency officials in some 70 presentations made during a public meeting at FDA headquarters on July 27–28 in suburban Washington, DC. While hearings held the previous week on REMS for opioid drugs revolved around how much more FDA needed to do, those speaking on the REMS process in general focused on the multiplicity of approaches FDA has mandated for the more than 100 products that now have such requirements. "Everybody understood that FDA has this authority to help manage the risks of some of these medications," Marcie Bough, PharmD, APhA's Director of Federal Regulatory Affairs, told ***Pharmacy Today***. "But we need a better process to get there. A standardized approach really resonated with people." Bough's comments reflected APhA's previous statements and APhA's 2009 REMS White Paper (available at www.japha.org/REMS).

In presentations at the meeting, Bough explained that APhA would like to see a more standardized, system-based approach to the REMS process and more involvement of pharmacists and prescribers in program development up front. In addition, to better manage the growing number of REMS, "FDA should consider organizing REMS programs based on tiers or levels—similar to Schedules of controlled substances," she said. "The structure of each level could consist of a standard set of components to choose from based on the level or risk." Similar to messaging at the previous week's FDA opioid REMS meeting, Bough recommended that FDA and manufacturers recognize the potential impact of pharmacist-provided medication therapy management services as a potential Element to Assure Safe Use (ETASU) of a REMS program, when such an intervention is warranted, and the need for a viable compensation model for implementing such a REMS requirement. In Bough's presentations, APhA also recommended integrating REMS with existing electronic technologies and infrastructures in pharmacy and medical practice systems, recognizing the role pharmacists can play in safe medication use through REMS programs, pilot testing any program before a nationwide launch, ensuring that REMS do not prevent or delay patient access, ensuring that programs are flexible to adjust to data showing successes or failures of certain components, and using accredited continuing education materials from accredited providers that include specific information on safety, risks the REMS is designed to mitigate, and outcomes measures that capture practice changes.

The meeting was organized around six topics and featured a variety of presenters who provided input to FDA. These included pharmacy, medical, nursing, and industry associations; managed care groups and associations; health care providers; consumer groups; and companies marketing relevant products and services.

A citizen petition by Kaiser Permanente (KP) in December 2009 led to this FDA meeting. "Some REMS requirements, in particular ETASU, are unduly burdensome on health care systems and could adversely impact appropriate patient access to drugs," the petition said. (Disclosure: KP provides health benefits to APhA employees.)

In an interview, KP Director of Drug Use Management Richard Wagner, PharmD, said, "Our focus in the citizen petition was really that FDA is required by statute to consult with providers and health care organizations like Kaiser Permanente. And that's in contrast to the agency's preferred route historically with drug manufacturers. We believe that when REMS with ETASUs are considered, Kaiser physicians or pharmacists need to be at the table." The "more elaborate" REMS programs that involve ETASUs "are the minority" of REMS programs, but have the most impact on health care providers and "are of concern regarding the burden on providers and health systems," Wagner said.

FDA told ***Today*** in an e-mail, "We will be examining our program to see whether some of the suggestions we've heard can be incorporated into REMS that are under development. We will be looking at the risk management programs that are already in place with an eye toward increased standardization of REMS. And we will be reaching out to stakeholders about the design of REMS to further discuss how to better integrate REMS into the health care system."

— L. Michael Posey, BPharm, and Diana Yap

Washington State health care groups to develop opioid guidelines

Initiative aims to improve care, safety for patients with pain

The legislature of Washington State recently passed a bill aimed at reducing the risk of fatalities caused by prescription pain medication overdose. HB 2876 directs a panel of physicians, nurses, regulators, and others to adopt new rules and objective standards for prescribing opioids for patients with chronic noncancer pain.

The panel will work collaboratively to ensure that the new rules are as uniform as possible for prescribers, including physicians, dentists, and osteopaths. The guidelines must be adopted by June 30, 2011.

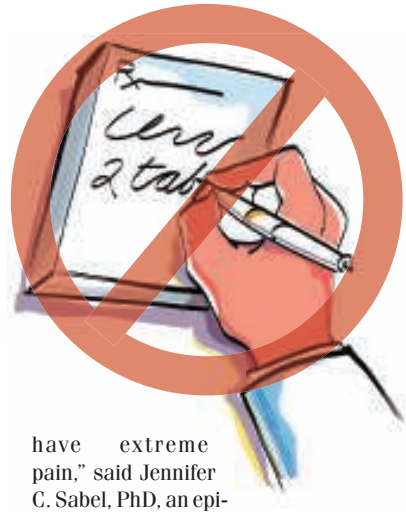
While a collaborative effort to develop pain guidelines isn't new territory, the fact that the initiative is directed by the legislature is a departure from the norm. "Usually this kind of thing is handled at the level of the licensing boards—the medical board, the nursing board, the pharmacy board," said Joseph L. Fink III, BPharm, JD, FAPhA, Professor of Pharmacy at the University of Kentucky College of Pharmacy. "It has never before been escalated to the level of having a state legislature involved."

For an update on FDA actions regarding long-acting opioids, see page 11 of this supplement.

Startling statistics

Death caused by prescription opioid overdose is on the rise across America, but the problem in Washington State is nearly double the national average. According to a report published last year by CDC, in 2006, Washington's opioid overdose death rate was 8.2 per 100,000 population, compared with the national rate of 4.6 per 100,000.

"Prescription opioid narcotics used to be almost exclusively prescribed for end-of-life care or cancer patients who



have extreme pain," said Jennifer C. Sabel, PhD, an epidemiologist with the Washington State Department of Health in an interview with ***Pharmacy Today***. "That changed nationally in the late 1990s … when there was a shift toward an increase in opioid prescriptions for more chronic pain conditions, such as back pain, neck pain, or any kind of pain where a physician felt it was warranted."

According to Washington's HB 2876, the new rules must contain the following elements: dosing criteria, including a dosing threshold of 120 morphine equivalents in 24 hours and consultation with a pain specialist should that daily dose be exceeded; guidance on when to seek specialty consultation and ways in which electronic specialty consultations may be sought; guidance on tracking clinical progress by using assessment tools; and guidance on tracking the use of opioids. The guidelines would not affect how pain medications are used to treat patients with cancer or those at the end of life.

The rules will be designed to help "properly manage and monitor a patient once they get to a higher dosage of pain medication," said William E. Fassett, PhD, BPharm, Professor and Vice-Chair of the Department of Pharmacotherapy at the Washington State University College of Pharmacy. In addition, the rules are aimed at "patients who have been allowed to get out of control and may eventually end up dying of an overdose."

Although many agree that guidelines should be in place to increase patient safety, the rules do raise some concerns. Washington is a "relatively rural state," said Fink. "In some areas, pain consultations may not be available or there may not be enough pain specialists, resulting in long delays." Additionally, pain consultations can be expensive. The bill also presents liability concerns for prescribers, and this may discourage them from treating patients with pain.

Pharmacist's role?

While the bill focuses on prescribers, the rules could also present an opportunity for pharmacists to expand their counseling role and become more involved in patient care. "Just like the management of lipids or anticoagulation, managing patients with chronic pain is something that pharmacists could really do very well," Fassett told ***Today***. "If there is a set of desired goals, then a pharmacist can monitor patients and identify when goals are being met. Because pharmacists are at the point of distribution, they are in a good position to monitor medications."

Fink believes that the focus should always be on the patient. "When you have a patient in pain, their pain needs to be resolved in a fashion that does not result in habituation to the medication, so it's a balancing act where the prescriber, the patient, and the pharmacist need to be involved," he said.

Until the final guidelines are hammered out and approved, speculation remains. "There is a lot of uncertainty about what the outcome will be," said June Dahl, PhD, Professor of Pharmacology at the University of Wisconsin School of Medicine and Public Health. "Until the new rules on pain management are written and implemented, there is no way to know what their impact will be."

—Amy K. Erickson
Contributing writer

New opioid formulations: Reducing abuse

Researchers tinker with long-acting formulations

In recent years, many manufacturers have focused their efforts on bringing abuse-deterrent or abuse-resistant opioids to market. Their efforts have reached fruition—and not a moment too soon.

Opioid abuse has been on the rise, with extended-release (ER) products among those most commonly identified as problematic. According to results from the U.S. Department of Health and Human Services 2008 National Survey on Drug Use and Health, 6.2 million people aged 12 years and older have misused prescription psychotropic drugs; pain relievers were one of the main medication types abused.

Opioid abuse generally begins with oral use. Persons at risk for addiction may begin consuming large quantities of these agents. This can gradually escalate over time to manipulation, or milling, of formulations, or altering the route of delivery (e.g., nasal, injection) so that a more rapid euphoria can be obtained.

New formulations of opioids are being designed so that they are more tamper resistant, unable to be taken via alternative routes, or combined with low doses of naltrexone (Table 1) to prevent untoward effects from illicit use. Many clinicians are left wondering whether these formulations are truly less likely to be abused.

Single-agent formulations

FDA has approved a new formulation of OxyContin (oxycodone—Purdue) with extraction-resistant physical properties. Purdue has reported that this new formulation appears to be resistant to crushing, milling, injecting, and extraction, and is more difficult to manipulate than the original formulation. Unfortunately, whether the formulation will be the answer remains to be seen. Purdue noted in a news release, "There is no evidence that the reformulation of OxyContin is less subject to misuse, abuse, diversion, overdose, or addiction."

Exalgo, an ER formulation of hydromorphone by Covidien, is thought to have reduced abuse potential compared with immediate-release (IR) hydromorphone because of delayed absorption properties.

A crossover study in 38 patients with a history of opioid abuse showed that overall drug liking scores were lower for an intact 16-mg ER tablet compared with an intact 8-mg IR tablet, a milled 8-mg ER tablet, or an intact 32-mg ER tablet. In addition, the subjective drug values at 10 hours postdose were lower for intact 16- and 32-mg ER tablets compared with an intact 8-mg IR tablet or milled 8-mg ER tablet. Therefore, intact ER tablets of lower doses of hydromorphone appear to be "less liked" compared with the IR tablets. Once the ER tablets are milled, however, the abuse potential appears to be similar.

Other manufacturers are in the process of developing tamper-resistant

Table 1. New extended-duration opioid formulations

Drug name—Manufacturer	Formulation characteristics	FDA status
Single agents		
New Oxycontin—Purdue (ER oxycodone)	Hard plastic polymer rendering the tablet difficult to crush or dissolve	Approved
Exalgo—Covidien (ER hydromorphone)	Osmotic-release oral system that alters the pharmacokinetics resulting in potentially lower abuse potential	Approved
COL-003—Collegium (ER oxycodone)	Uses DETERx, a multiparticulate matrix formulation shown to be resistant to chewing and crushing	Investigational New Drug Application accepted
Remoxy—King, Pain Therapeutics (CR oxycodone)	Highly viscous, liquid formulation in a hard gelatin capsule; cannot be drawn into or expressed from needles	New Drug Application submitted in 2008; resubmission required
ReXista—Intellipharmaceutics (CR oxycodone)	A paste in a capsule which is difficult to abuse if crushed	Pilot clinical study completed
Combination agents		
Embeda—King (ER morphine with sequestered naltrexone)	Naltrexone is released when the product is crushed, blunting the effects of morphine	Approved
ELI-216—Elite (CR oxycodone with sequestered naltrexone)	Naltrexone is released when the product is crushed, blunting the effects of oxycodone	Phase III trials

Sources: Pain Med. 2009;10(Suppl 2):S124–33; J Pain. 2010;11(7):602–11.

Note: ER = extended-release; CR = controlled-release

formulations of oxycodone (COL-003—Collegium; Remoxy—King, Pain Therapeutics; ReXista—Intellipharmaceutics). These products have been shown to be more resistant to tampering and dose dumping, and some are even alcohol resistant. Again, evidence is needed to demonstrate that these products will be abused less than others.

Monitor patients closely for signs of opioid abuse.

Combination agents

Both Embeda by King and ELI-216 by Elite are combination opioid agonist and antagonist products that contain naltrexone. In Embeda, naltrexone is sequestered in the core of each bead of morphine and remains latent if the drug is taken intact. If the beads are crushed, the naltrexone is released, thereby blunting the euphoric effects of morphine.

ELI-216 is similarly designed, with capsules composed of beads of oxycodone and beads of naltrexone. In a drug-liking study with Embeda, IR morphine was preferred over both crushed and whole capsules of Embeda. No data are available to confirm that these products are actually abused less than others.

Place in therapy

The introduction of new opioid formulations is a step forward in trying to curb opioid abuse. It is hoped that the incorporation of physical barriers and opioid antagonists will deter some patients from abusing these products.

As these agents reach the marketplace, clinicians should continue to monitor patients closely for signs of opioid abuse, and researchers should be prepared to generate data showing whether these formulations reduce emergency department visits and deaths associated with opioid abuse.

—Maria G. Tanzi, PharmD

Universal precautions for pain medicine: A guide for pharmacists

Analgesics needed, but risks are real

The fear of opioid abuse, addiction, and diversion may cause some practitioners to avoid using these medications in patients who truly need them. Physicians and pharmacists fear scrutiny from DEA or state licensing boards if large amounts of opioids are prescribed or dispensed. Unfortunately, such fears may leave millions of pain sufferers without needed therapy.

Some of these concerns may be alleviated with the implementation of universal precautions for pain medicine (Table 1). These guidelines, as described by Douglas L. Gourlay, MD, MSc, FRCPC, FASAM, and colleagues in a 2005 *Pain Medicine* article, provide recommendations aimed at improving patient care, reducing stigma, and containing overall risk when prescribing and/or dispensing pain medications.

Pharmacists can apply these precautions and thereby get more involved in identifying patients who may be at risk for misusing opioids, minimizing the occurrence of these events, and ultimately improving outcomes.

Screening patients

Substance abuse is a real problem, with approximately 20.1 million Americans reporting illicit drug use in 2008; 6.2 million of these patients reported using prescription-type psychotherapies, including pain relievers. All patients should be screened for risk of abuse or addiction before initiating opioid treatment. Some patient characteristics—such as prescription forgery, recurrent prescription losses, and cutaneous signs of drug abuse—are predictive of opioid misuse, but other characteristics may not be so obvious (Table 2). Pharmacists need to be aware of these signs.

Patients can also be triaged into different risk categories (e.g., low, medium, or high) for opioid misuse based on a number of validated screening tools that are easy to administer in a primary care setting.

Two of these tools are SOAPP-R (Screener and Opioid Assessment for Patients with Pain-Revised Version) and the Opioid Risk Tool. SOAPP-R is a self-administered questionnaire that helps determine how much monitoring a patient on long-term opioid therapy may require before the prescription is written. Patients are asked to answer 24 questions using a scale of 0 (never) to 4 (very often). Cumulative scores of 18 or higher indicate a high risk for opioid misuse.

With the Opioid Risk Tool, patients mark each box that applies with respect to risk factors such as personal or family history of substance abuse, age (16–45 years), history of preadolescent abuse, and presence of various psychological diseases. The items marked are then scored and patients with a total score from 0 to 3 are classified as low risk, those with a score between 4 and 7 are at moderate risk, and those with a score of 8 or higher are considered to be at high risk for misuse.

Obtaining a urine screen before initiating opioid treatment is also a beneficial tool for identifying patients with aberrant behaviors. Urine testing can help identify patients who use alcohol or illicit substances or do not use reported medications (i.e., diversion or unauthorized dose escalation).

In addition, some states maintain prescription monitoring programs that track all controlled substance prescriptions received by patients. These searchable databases should be checked before prescribing or dispensing opioids to identify patients who obtain opioids from multiple providers or pharmacies.

Obtaining informed consent, treatment agreement

Once patients are deemed appropriate for opioid therapy, they need to have a

Table 1. Universal precautions for pain medicine

Make a diagnosis with appropriate differential
Psychological assessment, including risk of substance abuse
Informed consent
Treatment agreement
Pre- or postintervention assessment of pain level and function
Appropriate trial of opioid therapy with or without adjunctive medication
Reassessment of pain score and level of function
Regularly assess the four As of pain medicine (analgesia, activity, adverse effects, and aberrant behaviors)
Periodically review pain diagnosis and comorbid conditions, including addictive disorders
Documentation

Source: Gourlay et al. Universal precautions in pain medicine: A rational approach to the treatment of chronic pain. Pain Med. 2005;6:107–12.

Table 2. Signs of potential for drug-seeking behavior

Exhibits unusual behavior in the waiting room
Exhibits unusual appearance such as extremes of either slovenliness or being overdressed
Calls or comes in after regular hours, such as on the weekends or when the physician's office is closed
Must be taken care of right away
May show unusual knowledge of controlled substances
Is reluctant or unwilling to provide reference information; usually has no regular physician and often no health insurance
States he or she is traveling through town, is visiting friends or relatives, and does not have a permanent address
Pressures the practitioner by eliciting sympathy or guilt or by direct threats
Uses a child or elderly person when seeking pain medication

Source: DEA, Office of Diversion Control. Available at: www.deadiversion.usdoj.gov/pubs/brochures/drugabuser.htm.

Table 3. Example of opioid pain medication agreement

If my activity level or general function gets worse, the medication will be changed or discontinued by my clinician.
I will participate in other treatments that my clinician recommends and will be ready to taper or discontinue opioid medications.
I will take my medications exactly as prescribed and will not change the medication dosage or schedule without my clinician's approval.
I will keep my regular appointments and will call at least 24 hours in advance if I have to reschedule.
I will not obtain medications from other clinicians or pharmacies unless I am hospitalized.
I understand lost or stolen prescriptions will not be replaced, and I will not request early refills.
I agree to abstain from excessive alcohol use and all illegal and recreational drug use and will provide urine or blood specimens at the clinician's request.
If I am unable to follow these conditions, I understand it may not be safe for me to continue the medication.

Source: Adapted from the opioid pain medication agreement developed by the University of Wisconsin Pain Treatment and Research Center, Madison, WI. Available at: www.ampainsoc.org/societies/mps/downloads/opioid_medication_agreement.pdf

clear understanding of the risks and benefits of treatment—this is known as informed consent. Patients should be educated on measurable goals for pain reduction and improvement of function, as well as any foreseeable risks associated with prescribed therapies.

Patients, prescribers, and pharmacists should collaboratively draft and sign a treatment agreement. A written treatment agreement will clearly spell out the expectations and obligations of both the patient and the practitioners. An agreement should be designed to set boundary limits for patients with regard to properly obtaining, filling, and using opioids (Table 3). By signing the agreement, patients are acknowledging that they are aware of these limits and that they agree to abide by them.

Monitoring patients

The frequency of monitoring depends on the patient's risk for opioid misuse, as described in the screening section above. High-risk patients need more frequent follow-up visits (e.g., weekly) compared with moderate- (e.g., every 2 weeks initially) or low-risk patients (e.g., monthly at first).

For patients at greater risk for opioid misuse, medications should be prescribed and dispensed in limited quantities, with patients given just enough medication to last until their next appointment.

In addition, these patients should be given random urine drug screens throughout the course of treatment and regular checks of the state's prescription monitoring database should be performed. Pill or patch counts can also be useful in determining how much medication patients are consuming.

> Complete recording of all patient encounters is essential to the safe use of opioids.

COMM (Current Opioid Misuse Measure) is another validated tool that can be used to help identify whether a patient on long-term opioid therapy may be exhibiting aberrant behaviors associated with opioid misuse. This tool is different from SOAPP-R in that it monitors behaviors while patients are receiving therapy. This 17-item patient self-assessment is also easy to administer in a primary care setting and can be completed by patients in less than 10 minutes.

Documenting interventions

Complete recording of all patient encounters is essential to the safe use of opioids. Key elements that should be documented in patient charts include medical and medication history, results of screening tool assessments, treatment goals and agreements, medication use, and any aberrant drug-taking behaviors. Lack of documentation can result in adverse clinical and regulatory outcomes.

—Maria G. Tanzi, PharmD

Pain relief at the patient's fingertips

When used properly, PCA pumps offer fast, convenient treatment

For patients undergoing the nearly 50 million inpatient surgical procedures performed annually in the United States, patient-controlled analgesia (PCA) can be a godsend. The simple push-of-a-button relief provided with PCA can also cause problems, but these can be avoided with proper controls and procedures.

"PCA has been used for a long time, and I think it is now more or less the standard of care in postop patients," Scott Strassels, PharmD, PhD, BCPS, Assistant Professor of Pharmacy Practice and Adjunct Assistant Professor of Public Health at the University of Texas in Austin, told ***Pharmacy Today***.

One of the primary advantages of PCA is that it "gives control back to the patient," said Strassels. Patients don't have to wait for the nursing staff to order and administer the drug.

"If a patient has PCA, they can hit the button, get the dose, and it's a very straightforward process," said Strassels. In addition to offering around-the-clock pain relief, the pump is programmable, which means that the dosage is controlled, ensuring that the patient receives the correct dose and the correct medication. Dosing at regular intervals also reduces the overall amount of medication needed to control pain.

Common PCA errors

Strassels noted that one of the biggest risks of using a medication pump is PCA by proxy, where "it is not the patient who is pushing the button," he said. "It could be a spouse, an aunt, a brother, or a friend who is pushing the button for the patient. This is a real problem because it could turn into an overdose situation."

Conversely, the dosing regimen may be set so that the patient does not receive enough analgesia, where the bolus doses are set too low or lockout is too long. When the patient sleeps, the analgesic wears off so they awake in pain.

The Institute for Safe Medication Practices has guidelines for safe PCA use (see "PCA safety" sidebar). Clinicians must carefully review candidates for PCA. Patients should have the mental alertness and the cognitive, physical, and psychological ability to manage their own pain.

Programming the pump may lead to errors such as confusing milliliters and milligrams, confusing PCA bolus doses with a basal rate dose, or programming a loading dose where a basal rate should have been entered. Programming of pumps should be double checked and decimal points should be avoided in orders and programming. Use of standard order sets (see "Medications and doses" sidebar) can help avoid such errors.

As medication experts, pharmacists are key in optimizing PCA outcomes.

—Amy K. Erickson
Contributing writer

Medications and doses

According to the American Pain Society (APS), standard order sets with the following medications and doses should be considered:

- Morphine: 1 mg bolus every 5 to 10 minutes
- Hydromorphone: 0.2 mg every 5 to 10 minutes
- Fentanyl: 10 µg every 5 to 8 minutes

In addition, standard drug concentrations should be established to avoid confusion. APS discusses these issues further in its 2003 book, *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain*, 5th edition. A news story on PCA is available on MedScape at www.medscape.com/viewarticle/557394_4.

PCA safety

The Institute for Safe Medication Practices recommends the following guidelines for the proper use of PCA pumps:

- Establish selection criteria for PCA and nurse-controlled analgesia. While PCA can be used for a wide range of patients to safely manage pain, some patients are unsuitable candidates because of level of consciousness, psychological reasons, or limited intellectual capacity. Periodically reassess the appropriateness of therapy.
- Develop protocols and standardized order sets to guide the selection of drugs, dosing, lockout periods, and infusion devices.
- Monitor patients carefully. Opiates, even at therapeutic doses, can suppress respiration, heart rate, and blood pressure, so the need for monitoring and observation cannot be overemphasized.
- Require two clinicians to independently double check patient identification and PCA device dose settings before use and before each pump refill to detect possible errors.
- Educate patients and families about the proper use of PCA (this process should begin during the preoperative testing visit). Warn family members and staff about the danger of pressing the button for the patient, except when the patient requires physical assistance and has clearly expressed the need and desire for a bolus of medication.
- Educate staff about proper use of PCA. Encourage clinicians to think about the cumulative dose the patient could receive if the maximum dose limits were given. Ensure that they understand the hazards of using analgesics.

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Rise and fall of glucosamine, chondroitin sulfate

Are herbals appropriate for pain management?

Despite some $31 billion a year Americans are pumping into the dietary supplements industry, evidence that many of these products actually work continues to lag. Consider the case of glucosamine/chondroitin, popular herbals that were once poster children for dietary supplements. Several studies reported that these natural remedies showed promise in their ability to relieve osteoarthritis (OA) pain or possibly even reverse the narrowing of affected joints. But now come more studies with equivocal or negative results.

What's the answer for patients with OA and the clinicians caring for them?

Mixed results

The Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) was a major hurdle for dietary supplements. The study was funded by the National Institutes of Health, with part of the money coming through the National Center for Complementary and Alternative Medicine, which had been established in 1998, perhaps the high-water mark for dietary supplements.

When GAIT results appeared in the *New England Journal of Medicine*, in February 2006, everyone was disappointed. Glucosamine plus chondroitin sulfate did not provide significant relief from OA pain among all participants. Only in a subgroup with moderate to severe pain did the combination provide significant relief.

Focusing on those patients with moderate to severe OA pain, a paper published this summer in the *Annals of the Rheumatic Diseases* compared the safety and effectiveness of glucosamine and/or chondroitin with placebo or celecoxib.

The study enrolled 662 GAIT participants with moderate to severe knee OA. For 2 years they received glucosamine 500 mg three times daily, chondroitin sulfate 400 mg three times daily, glucosamine plus chondroitin sulfate at the above doses, celecoxib 200 mg once daily, or placebo. The primary outcome measure was a 20% reduction in pain scores using the Western Ontario and McMaster Universities (WOMAC) pain scale. No treatment was better than placebo.

Study design

"This is not the first study to show no benefit from glucosamine and chondroitin. The majority of well-designed studies fail to show benefit," said Arthur Schuna, MS, FASHP, Clinical Professor of Pharmacy at the William S. Middleton Memorial Veterans Hospital in Madison, WI, and Section Advisor for rheumatology in the *APhA DrugInfoLine*. "Part of the problem may be the lack of a dependable and reliable tool of measuring response. There are no objective measures."

A study published in 2007 in *Arthritis & Rheumatism* randomly assigned patients to oral glucosamine sulfate, acetaminophen, or placebo. The primary efficacy outcome measure was change in the Lequesne index. On this instrument, glucosamine sulfate was more effective than placebo for treating knee OA symptoms.

Perhaps the glucosamine source makes a difference. That conclusion was reached by Towheed in a 2005 *Cochrane Review* article. Trials using glucosamine produced the European manufacturer, Rottapharm, showed benefit, but glucosamine from other sources did not produce significant benefits in other trials.

What to tell patients

Evidence on both sides of the glucosamine equation has left pharmacists puzzled when it comes to counseling OA patients. Other herbals for pain also have mixed patterns of supportive evidence (Table 1).

"Some well-designed studies fail to show benefit for these supplements," said Schuna. "However, others do suggest glucosamine with or without chondroitin may be beneficial. On the other hand, toxicity from these supplements is minimal and I see no harm in a trial if the patient is interested. A 3-month trial should be adequate to determine if it does anything. If it does not help at that point, discontinue. Whether those who respond would also respond equally well to placebo is an unanswered question."

—Amy K. Erickson
Contributing writer

Table 1. Herbal supplements used frequently for pain management

Herbal	Type of pain	Supporting controlled data in humans
Aconite	Joint; inflammation	Not enough data
Bromelain	Anti-inflammatory properties for osteoarthritis in the knee	Yes
Capsaicin	Postherpetic neuralgia; muscle	Yes
Cat's claw	Osteoarthritis	Yes
Comfrey	Back	Yes
Curcumin	Anti-inflammatory	Often used, but no data
Devil's claw	Degenerative rheumatic disorders	Yes
Feverfew	Migraine prevention	Yes
Ginger extract	Osteoarthritis; dysmenorrhea	Yes
Glucosamine	Osteoarthiritis	Conflicting efficacy data
St. John's wort	Migraine prevention	Yes, but drug interactions limit use
Willow bark	Musculoskeletal	Conflicting efficacy data

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