American Pain Society

RESEARCH
EDUCATION
TREATMENT
ADVOCACY

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To Whom It May Concern:

Thank you for your important work on the Opioids REMS educational blueprint. We believe that the draft does a good job of assembling key elements that should be included in Opioid REMS education. We understand that you were tasked with integrating diverse input from many stakeholders.

We have two substantive comments, however, for which we would appreciate your consideration: we believe that the document must consistently remind the reader that even the appropriate use of ER/LA medications are only one element in any pain treatment plan and, further, we believe it is important to aim not only for the dissemination of educational content, but also for the development of competence in prescribing.

The current iteration of the blueprint focuses primarily on educating prescribers in preventing misuse and abuse of ER/LA opioids, and does not identify and require education regarding the safe and appropriate prescribing of these drugs for their essential purpose - the treatment of pain. The recently released consensus report from the Institute of Medicine, *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*, provides evidence of the inadequate prescriber training in pain management and the consequential inadequate treatment of pain. We assert that improving prescribers' knowledge of pain management in general, in addition to the appropriate use of ER/LA in the treatment of pain is essential for any effort to address opioid misuse and abuse. Treatment with ER/LA opioids (or other opioids) is often an important option but is rarely a complete treatment strategy for patients in pain.

The current blueprint provides "a basic outline and the core message the FDA believes should be conveyed to prescribers," but does not define essential competencies for ER/LA prescribers as measureable or observable knowledge, skills, abilities and behaviors critical to safe and effective treatment of patients with this class of opioid analgesics. Again we can reference the recently released consensus report from the Institute of Medicine, *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*, which identifies the lack of proven relationship between CME and actual changes in clinical practice. To address the knowledge to practice translation gap, the IOM recommends competency-based education in pain management. If the purpose of the ER/LA opioid class-wide REMS is to improve practice, then it is imperative that the FDA blueprint provide more than a passive educational outline and instead use competency-based objectives.

Please find below some specific suggestions aimed at addressing our first concern regarding education. During implementation we would encourage the FDA to determine for each educational element how best to evaluate competency improvements as a result of this education. Thank you for consideration of our comments.

Blueprint for Prescriber Continuing Education Program

I. Introduction: Why Prescriber Education is Important

It is estimated that chronic pain affects 116 million Americans and costs the nation up to $635 billion each year in medical treatment and lost productivity (IOM report). Pain is a major driver for visits to physicians, a major reason for taking medications, a major cause of disability, and a key factor in quality of life and productivity. Therefore, prescriber knowledge of pain management is an essential clinical practice competency.

Extended-release and long-acting opioids are indicated for moderate to severe pain in patients who require around the clock opioids for an extended period of time. Most patients with chronic pain do not require around the clock opioids. Opioids are only one potential component of an interdisciplinary approach to the treatment of patients with chronic debilitating pain.

Health care professionals who prescribe extended-release (ER) and long-acting (LA) opioids are in a key position to balance the benefits of prescribing ER/LA opioids to treat pain against the risks of serious adverse outcomes including addiction, unintentional overdose, and death. Opioid misuse and abuse, resulting in injury and death, has emerged as a major public health problem.

Public health experts estimate that more than 35 million Americans age 12 and older have reported non-medical use of opioid analgesics during 2010 – up from 29 million in 2002[1]. In 2009, nearly 342,000 emergency department visits were associated with nonmedical use of opioid analgesics[2]. In 2007, nearly 28,000 Americans died from unintended consequences of drug use, and of these, nearly 12,000 involved prescription drug pain relievers.[3]

[2] http://oas.samhsa.gov/NSDUH/2k10NSDUH/tabs/Sect7peTabs1to21.pdf Detailed Tables: National Estimates, Drug-Related Emergency Department Visits for 2004 - 2009. http:://dawninfo.samhsa.gov/data/ http://dawninfo.samhsa.gov/data/ accessed October 19, 2011

[3] http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm252649.htm; accessed September 8, 2011.

Although many of these deaths stem from opiate diversion, appropriate prescribing practices and patient education are important steps to help address this public health problem. Health care professionals who prescribe ER/LA opioids have a responsibility to help ensure the safe and effective use of these drugs. Prescribers should:

- understand how to assess patients for treatment with ER/LA opioids.
- be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioids.
- be knowledgeable about how to manage ongoing therapy with ER/LA opioids.

- know how to counsel patients and caregivers about the safe use of ER/LA opioids, including proper storage and disposal.
- be familiar with general and product specific drug information concerning ER/LA opioids.

II. Assessing Patients for Treatment with ER/LA Opioid Therapy

a. Prescribers should have an awareness of the diverse methods available for pain treatment and thoughtfully consider the relative role, risks and benefits of opioids for individual patients in the context of their overall health and treatment needs. Pain assessment should include:

- Comprehensive pain assessment
- Pain treatment history and responses
- General medical and psychiatric histories

b. Prescribers should consider risks involved with ER/LA opioids and balance these against potential benefits.

1. Common targeted benefits may include:
   - Pain reduction
   - Improved level of function
   - Enhanced quality of life
2. Risks include:
   - Risk of overdose due to the high dosage of opioid available in an ER/LA formulation
   - Intentional abuse by patient or household contacts
   - Addiction
   - Interactions with other medications and substances (see table below for specifics)
   - Inadvertent exposure to household contacts, especially children

c. In considering ER/LA opioid prescribers should assess each patient's risk of opioid misuse, including history of substance abuse and serious mental illness. Prescribers should:

- Be knowledgeable about risk factors for opioid abuse and risk-assessment methods.
- Complete a comprehensive history and physical examination, including assessment of psychosocial factors and family history of substance abuse, as well as special considerations for the elderly, women, children, and cultural/ethnic groups. Identify appropriate referrals when the condition warrants.
- Understand and appropriately utilize screening tools for addiction or abuse, such as Prescription Drug Monitoring Programs (PDMPs), to help manage patients using opioids products and minimize risks associated with chronic opioid therapy
- Understand and appropriately utilize laboratory assessment tools including urine drug screens
- Adequately document all evaluations and treatment plans.

d. Prescribers should be able to determine if a patient is opioid-tolerant and should know which products are safe for use only in opioid-tolerant patients.

III. Initiating Therapy, Modifying Dosing, and Discontinuing Use of ER/LA Opioids

a. Prescribers should have awareness of federal and state regulations on opioid prescribing.

b. Prescribers should create a mutually agreed upon, individualized treatment plan with the patient, based on comprehensive assessment that balances benefits and risks for the patient and accounts for the patient's goals, preferences, and risks. **If ER/LA opioids** are considered appropriate for the patients treatment plan they should implement strategies to address risks involved with ER/LA opioids

c. Prescribers should engage in a meaningful informed consent process that educates the patient, family, and caregivers about the benefits and risks of chronic opioid therapy, including evidence for long-term efficacy, side effects, opioid precautions, and potential medication interactions.

d. When initiating therapy with an ER/LA opioid, prescribers should be aware that:

- Dose selection is critical, particularly when initiating therapy with an ER/LA opioid as the first opioid.
- Titration should be based on efficacy and tolerability.

e. Prescribers should be knowledgeable about converting patients from immediate-release to ER/LA products and from one ER/LA opioid product to another.

f. Prescribers should be aware of the concept of incomplete cross-tolerance in order to safely convert patients from one opioid to another.

g. When modifying the dose of an ER/LA opioid, prescribers should understand equianalgesic dosing concepts and follow patients closely during all periods of dose adjustments.

h. Prescribers should understand that tapering the opioid dose is necessary to safely discontinue treatment with ER/LA opioids when therapy is no longer needed.

IV. Managing Therapy with ER/LA Opioids

a. Prescribers should establish goals for therapy and continuously evaluate pain as well as level of function and quality of life (including mood).

b. Prescribers should be aware of the existence of Patient Provider Agreements (PPAs even though FDA is not requiring their use.

- PPAs are documents signed by both prescriber and patient at the time an opioid is prescribed.
- PPAs can help ensure patients understand the goals of treatment, the risks, and how to use the medications safely.

- PPAs can include commitments to return for follow-up visits, to comply with appropriate monitoring (such as random drug screens) and to safeguard the medication.

c. Prescribers should monitor patients' adherence to the treatment plan and monitor patients for misuse and abuse by

- Recognizing aberrant behavior
- Utilizing PDMPs where available to identify potential abuse
- Understanding the role of drug testing, performing drug screens as indicated and understanding how to interpret common findings and/or how to access assistance to interpret findings
- Screening and referring for substance abuse treatment when indicated
- Performing medication reconciliation at each visit

d. Prescribers should understand how to manage adverse events associated with ER/LA opioid products.

e. Prescribers maintaining patients on ER/LA opioids should over time reassess the efficacy of opioid therapy and monitor patients for tolerance and hyperalgesia and understand strategies for managing these effects when they occur.

f. Prescribers maintaining patients on ER/LA opioids should over time reassess whether opioids continue to be necessary for management of the patient's pain.

g. Prescribers should understand the need for reevaluation of patients' underlying medical condition if symptoms change over time.

V. Counseling Patients and Caregivers About the Safe Use of ER/LA Opioids

a. Prescribers should give patients and caregivers product-specific information about the prescribed opioid.

b. Prescribers should explain how to take the opioid as prescribed.

c. Prescribers should explain adherence to dosing regimen and how to handle missed doses.

d. Prescribers should warn that under no circumstances should an oral ER/LA opioid be broken, chewed or crushed, and patches should not be cut or torn prior to use, as this may lead to rapid release of the ER/LA opioid causing overdose and death.

e. Prescribers should caution patients that the use of other CNS depressants, alcohol, or illegal drugs with ER/LA opioids can cause overdose and death. Patients should only use other CNS depressants under the instruction of their prescriber.

f. Prescribers should discuss that withdrawal symptoms can occur if an ER/LA opioid is discontinued suddenly. Patients should discuss plans to stop the ER/LA opioid with their prescriber. Patients should discuss a tapering regimen with their prescriber.

g. Prescribers should explain that sharing ER/LA opioids with others may cause serious side effects including death, and that selling or giving away ER/LA opioids is against the law.

h. Prescribers should counsel patients to store their ER/LA opioid in a safe and secure place away from children and pets and to read the product-specific disposal information included with the ER/LA opioid product.

i. Prescribers should caution patients that ER/LA opioids can cause serious side effects that can lead to death. Patients should call their prescriber or get emergency medical help if they have symptoms of overdose or respiratory depression; symptoms of stomach or intestinal blockage; or allergic reactions. Patients should also be counseled on the most common side effects of ER/LA opioids and be cautioned about the risk of falls, working with heavy machinery, and driving.

j. Prescribers should encourage patients to call their prescriber for advice about side effects.

k. Prescribers or patients are encouraged to report side effects to the FDA at 1-800-FDA-1088.

VI. General Drug Information for ER/LA Opioid Products

a. Prescribers should be knowledgeable about general characteristics, toxicities, and drug
    - Respiratory depression is the most serious adverse effect of opioids as it can be immediately life-threatening.
    - Constipation is the most common long-term side-effect but can often be managed.
    - Drug-drug interaction profiles vary among the products. Knowledge of particular opioid-drug interactions, and the underlying pharmacokinetic and pharmacodynamic mechanisms, allows for the safer administration of opioid analgesics.
    - Central nervous system depressants (sedatives, hypnotics, tranquilizers, tricyclic antidepressants) and alcohol can have a potentiating effect on the sedation and respiratory depression due to opioids. Alcohol consumption should be avoided entirely with some oral products (e.g. morphine, hydromorphone, oxymorphone) because ethanol increases the plasma concentration of the drug substance.
    - Opioids may enhance the neuromuscular blocking action of certain muscle relaxants (e.g. pancuronium) and produce an increased degree of respiratory depression.
    - Using opioids with monoamine oxidase inhibitors (MAOIs) may result in possible increase.
    - Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic Hormone (ADH).
    - Some opioids (methadone, buprenorphine) can prolong the QTc interval.

- Some opioids interact with various cytochrome P450 enzyme inhibitors and inducers and thus may result in higher or lower than expected blood levels of the drug. See detailed drug information table.

b. Tolerance to sedating and respiratory-depressant effects is critical to safe use of certain products, certain dosage unit strengths, or certain doses of some products. Opioid tolerance must be demonstrated before using any strength of ER/LA fentanyl and ER/LA hydromorphone. For other ER/LA opioids the use of certain doses of the drug requires that the patient be opioid tolerant. See detailed drug information table.

c. Tablet and capsule dosage forms must be swallowed whole. The pellets from capsule dosage forms can be sprinkled on applesauce and swallowed without chewing.

d. For transdermal products, external heat, fever, and exertion can increase absorption, leading to fatal overdose. Transdermal products with metal foil backings are not safe for use in MRIs.

VII. Specific Drug Information for ER/LA Opioid Products

Prescribers should be knowledgeable about specific characteristics of the ER/LA opioid products they prescribe, including the drug substance, dosage form/strength, dosing interval, key instructions, major drug interactions, and use in opioid-tolerant patients, drug-specific adverse events, and relative potency to oral morphine. The attached table is a reference. For detailed information, prescribers can refer to prescribing information available online via DailyMed at dailymed.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda

(NOTE: Industry to provide specific information in table below for FDA review).

Drug	Drug Substance	Dosage Form/ Strengths	Dosing Interval	Key instructions	Major Drug Interactions	For opioid-tolerant patients only?	Drug Specific AEs	Relative Potency to oral morphine
Butrans	Buprenorphine							
Duragesic	Fentanyl							
Exalgo	Hydromophone ER							
Dolphine	Methadone							
Embeda	Morphine ER/naltrexone							
Kadian	Morphine ER							
Avinza	Morphine ER							
MS Contin	Morphine ER							
Oramorph	Morphine ER							
OxyContin	Oxycodone							
Opana ER	Oxymorphone ER							
Nucynta ER	Tapentadol HCl							