New Practice Guidelines for Chronic Pain Management

Introduction
In April 2010, the American Society of Anesthesiologists (ASA) Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine (ASRA) published an update to the 1997 guidelines on the management of chronic pain in adults (Anesthesiology. 2010;112(4):810-833). The guidelines were developed by a Task Force of 12 members (primarily practicing anesthesiologists) who evaluated peer-reviewed journals looking for articles related to chronic pain, assessed opinion-based evidence from experts in the field, and reached a consensus on the criteria for evidence evaluation.

For the purpose of these guidelines, chronic pain was defined as pain associated with a chronic medical condition or pain with a duration that extends beyond tissue injury and normal healing. In addition, the pain adversely affects a patient’s quality of life. The recommendations do not apply to patients with acute pain as a result of injury or surgery or for patients with chronic pain associated with cancer, degenerative joint disease, or various headache syndromes. The guidelines were developed to be used by anesthesiologists and other pain specialists; however, ASA/ASRA noted that the guidelines also serve as a good resource for other healthcare providers caring for patients with chronic pain.

Patient evaluation
The guidelines recommend 4 major components of the patient evaluation: a thorough history, a physical examination, a psychosocial evaluation, and diagnostic procedures. The history should start with an assessment of the patient’s pain symptoms and the timeframe surrounding the pain. Specifically, patients should be asked about the onset, quality, intensity, distribution, duration, course, and sensory and affective components of the pain. In addition, providers should try to assess what makes the pain worse versus better. The history should also include a review of previous diagnostic tests; the patient’s medical, surgical, social, and family history; and an assessment of current and past therapies used to treat the pain and their associated effectiveness.

A directed neurological and musculoskeletal evaluation is recommended for the physical examination and an assessment of psychological symptoms, psychiatric disorders, personality traits, and coping strategies is recommended for the psychosocial evaluation. Providers need to determine how the patient’s pain impacts their quality of life and their ability to perform normal daily activities. The psychosocial evaluation should also assess if a patient has addictive or aberrant behaviors, as this may affect which treatments patients receive (e.g., non-narcotic analgesics vs. opioids).

There are numerous diagnostic procedures that are discussed in the guidelines such as selective nerve root blocks, medial branch blocks, joint injections, and provocative discography; the appropriate use of these procedures goes beyond the scope of this review.

Interventions: a focus on medications
The guidelines discuss 12 single modality interventions including: 1) ablative techniques (e.g., chemical denervation, cryoneurolysis, and thermal); 2) acupuncture; 3) blocks (e.g., joint blocks, nerve and nerve root blocks); 4) electrical nerve stimulation; 5) minimally invasive spinal procedures; 6) restorative therapy; 7) psychological treatment; 8) trigger point injections; 9) botulinum toxin; 10) epidural steroids with or without local anesthetics; 11) intrathecal drug therapies; and 12) other pharmacological therapies. This review will focus on interventions 9...
through 12 above, since these involve the use of various pharmacologic therapies.

**Botulinum toxin**
Based on a review of randomized controlled trials, the guidelines recommend the use of botulinum toxin as an adjunct treatment for piriformis syndrome. This recommendation is based on assessment periods of 8 to 12 weeks, which showed that botulinum toxin was more effective than saline placebo for piriformis syndrome. The guidelines also recommend against the routine use of botulinum toxin for patients with myofascial pain because some data show that use of botulinum toxin for this condition results in similar outcomes compared to a saline placebo.

**Epidural steroids**
The guidelines recommend the use of epidural steroids with or without local anesthetics as part of a multimodal treatment regimen (see next section) for select patients with radicular pain or radiculopathy. Radicular pain is often described as pain that radiates along the dermatome (sensory distribution) of a nerve because of inflammation or other irritation of the nerve root at its connection to the spinal column. The guidelines stress the importance of discussing potential complications with patients considering epidural injections such as dural puncture, insertion-site infections, and cauda equine syndrome. In addition, the guidelines recommend image guidance (e.g., fluoroscopy) for transforaminal epidural injections to confirm correct needle position before injecting a therapeutic substance; image guidance for interlaminar may be considered as well.

**Intrathecal drug therapies**
Intrathecal drug therapies include neurolytic blocks; nonopioid injections such as steroids, ziconotide, and local anesthetics; and intrathecal opioid injections. For neurolytic blocks, the guidelines state that the current literature is insufficient to evaluate the efficacy of these agents for pain relief in chronic non-cancer pain; therefore, the use of these agents is not recommended for the routine management of patients with non-cancer pain. For nonopioid injections, observational data show that intrathecal injections of preservative-free steroids with or without local anesthetics can provide effective pain relief for patients with intractable postherpetic neuralgia nonresponsive to previous therapies. The guidelines also recommend the use of ziconotide for the treatment of select patients with refractory chronic pain.

Intrathecal opioid injections are recommended for patients with neuropathic pain. A drug trial is recommended to ensure efficacy and safety before the implantation of an intrathecal drug delivery system.

**Other pharmacologic therapies**
A variety of oral and topical pharmacologic therapies are discussed in the guidelines. A summary of the recommendations is presented in the table below. The guidelines recommend that all patients taking these therapies for an extended period of time should be monitored closely for adverse events and adherence.

<table>
<thead>
<tr>
<th>Class of Drugs</th>
<th>Guideline Recommendations</th>
</tr>
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<tbody>
<tr>
<td>Anticonvulsants</td>
<td>▪ Anticonvulsants (e.g., gabapentin, pregabalin, sodium-channel antagonists, and membrane-stabilizing drugs) can be used as part of a multimodal treatment strategy for neuropathic pain</td>
</tr>
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</table>
| Antidepressants | ▪ Tricyclic antidepressants can be used as part of a multimodal treatment strategy for chronic pain  
▪ Serotonin-norepinephrine reuptake inhibitors can be used as part of a multimodal treatment strategy for a variety of chronic pain patients  
▪ Selective serotonin reuptake inhibitors may be used for patients with diabetic neuropathy |
| Opioids | ▪ Extended-release oral opioids can be used as part of a multimodal treatment for neuropathic or back pain  
▪ Transdermal, sublingual, and immediate-release oral opioids may also be used |
| NMDA receptor antagonists | ▪ NMDA receptor antagonists (e.g., memantine) can be used for neuropathic pain |
| NSAIDS | ▪ NSAIDs can be used for back pain |
| Topical agents | ▪ Topical agents (e.g., capsaicin, lidocaine, and ketamine) can be used for peripheral neuropathic pain |
| Benzodiazepines/skeletal muscle relaxants | ▪ May be considered for patients with chronic pain; however, evidence is weak to support their use |

*NMDA = N-methyl-D-aspartate, NSAIDs = non-steroidal anti-inflammatory drugs.*

**Multimodal intervention**
The guidelines recommend a multimodal treatment approach for patients with chronic pain. This approach may include various nonpharmacologic interventions such as psychological treatment and acupuncture coupled with some of the pharmacologic therapies discussed above. This multimodal treatment plan should include periodic evaluations to assess the efficacy and safety of prescribed regimens. The guidelines state that the goal of a multimodal treatment plan is to effectively reduce pain while improving...
function and reducing psychosocial suffering.

Summary
The 2010 update discusses a broad range of interventions for adults with chronic pain. Clinicians should be familiar with these recommendations to ensure that patients with chronic pain are receiving treatment regimens that are supported by the latest evidence-based medicine.

Safety Concerns with Propoxyphene

Propoxyphene safety concerns
Propoxyphene has been associated with serious adverse events and reports of fatal overdose since the mid 1970’s. In 1979, propoxyphene was classified as a Schedule IV agent and a boxed warning was added discussing the avoidance of using this agent in patients prone to suicide. In addition, the labeling was modified to include warnings emphasizing the need to use this agent cautiously in patients taking other medications that suppress the central nervous system (CNS) and the need to educate patients about not exceeding recommended dosing limits and to limit their use of alcohol. Although common adverse events that occur with propoxyphene are similar to other opioids such as somnolence, dizziness, and gastrointestinal disturbances, the drug has also been reported to cause serious cardiac events. Accumulation of the major renally-excreted metabolite, norpropoxyphene, has been associated with precipitating cardiac depression, in addition to CNS and respiratory depression. The boxed warning states that fatalities occurring within the first hour of overdose are not uncommon. Another concern with propoxyphene, is that when overdoses do occur, naloxone does not appear to be that effective in treating cardiac toxicity. Most clinicians have reported this narcotic antagonist to be ineffective and stress the importance of supportive care (e.g., mechanical ventilation, fluid replacement, and inotropic drugs) as the main treatment modality for propoxyphene overdoses.

The safety concerns with propoxyphene prompted the European Medicines Agency (EMEA) to recommend a gradual withdrawal of propoxyphene-containing products from their markets. Removal occurred as a result of EMEA’s concerns about suicides and accidental fatal overdoses with the drug and the fact that the analgesic efficacy of propoxyphene is not superior to other marketed painkillers. In the U.S., the public watchdog group, Public Citizen, submitted a petition to the Food and Drug Administration (FDA) in 2006 asking for removal of propoxyphene from the market. A portion of the petition focused on the risk of cardiotoxicity and overdoses. The petition also focused on how use of propoxyphene in the elderly population, increases the risk of toxicity because these patients may have an accumulation of the propoxyphene metabolite as a result of reduced renal or hepatic function. In addition to adverse effects related to cardiotoxicity, Public Citizen believes that continued use of propoxyphene could lead to an increased incidence of CNS-related adverse effects and an increase in falls and subsequent bone fractures in the elderly. This is compounded with the fact that the 2002 Beers criteria recommends against the use of propoxyphene in the elderly because of its safety profile. Additionally, the petition argued that numerous studies have shown that using propoxyphene is either ineffective or only equally as effective as acetaminophen, ibuprofen, and aspirin. The last argument Public Citizen made against propoxyphene is the potential for addiction and abuse. They cited surveys taken from the National Youth Polydrug Study that showed nearly 20% of teenagers in their sample had used propoxyphene, which was the most common opiate; however, this study was conducted prior to propoxyphene being scheduled under the Controlled Substances Act.

FDA responds, propoxyphene not removed
The FDA responded to Public Citizen’s petition by discussing issues related to propoxyphene with the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee in January 2009. Although the advisory Committee members voted 14-12 against continuing to market propoxyphene, FDA ruled propoxyphene may stay on the market with labeling changes and other safety elements. The rationale behind FDA’s decision is summarized below.

Cardiotoxicity
The most glaring argument against propoxyphene is the potential for cardiotoxic side effects within a recommended dosing regimen, and the potential for naloxone to not effectively reverse them. The Public Citizen’s petition highlighted literature showing that dangerously high levels of norpropoxyphene may occur in patients despite normal doses of propoxyphene. The FDA responded by stating that there was not enough evidence to warrant product removal based on this fact and they went on to state that, the Adverse Event Reporting System (AERS) showed the majority of cardiac events with propoxyphene occurred after ingestion of excessive doses. Additionally, despite these reports of cardiotoxicity in AERS, there were a number of potentially confounding variables, such as underlying cardiac issues and other medications that could have contributed to the increase in cardiotoxicity. Data were also provided that showed the rate of propoxyphene cardiac events to be similar or even less than that of other commonly used opiates such as codeine. Lastly, the data that were cited from AERS regarding cardiac events did not suggest that increased levels of norpropoxyphene results in cardiotoxicity at normal doses. Due to the differences in cardiotoxicity data, labeling changes and the use of clinical trials to examine the relationship was deemed appropriate by the FDA.

Risk of overdose
Public Citizen stated that from 1981 to 1999, over 2,000 deaths attributed to propoxyphene use were reported to the Drug Abuse Warning Network (DAWN).
The FDA presented the inaccuracies of DAWN data and the use of multi-drug combinations in suicide attempts to downplay the overdose risk of propoxyphene. The FDA argued that inaccuracies in reporting figures during that time period make it difficult to determine how deaths related to propoxyphene are actually trending over time. Moreover, when looking at the number of deaths in 2007 alone, there were fewer cases with propoxyphene compared with oxycodone, hydrocodone, or methadone. The common use of multiple drugs in suicide attempts has made FDA also question how much removing propoxyphene would actually help in reducing the suicide rate. In the 91 deaths that were reported to AERS from 1969 to 2005, 74 cases involved the ingestion of multiple drugs.

Use in the elderly

The potential risk of adverse effects, both cardiotoxic and CNS-related, in the elderly population is a growing concern, especially given its frequent use in this patient population. A point that Public Citizen brought up was that the Beers criteria had placed propoxyphene on its list of inappropriate medications in the elderly. The FDA responded by saying that despite the Beers criteria not recommending the use of propoxyphene in senior citizens, there are also risks with alternative therapies. Specifically, FDA stated that using propoxyphene in patients who cannot tolerate acetaminophen alone, is a useful alternative to non-steroidal anti-inflammatory drugs (NSAIDs) which carry the risk of serious adverse effects such as life-threatening gastrointestinal bleeding and renal toxicity. Likewise, other opiate alternatives to propoxyphene carry similar risks of adverse effects, such as respiratory depression. Despite this, FDA has accepted that there is a risk of adverse effects with propoxyphene in the elderly, and has ensured that the product labeling and required medication guide will address the longer half-lives of both norpropoxyphene and its parent drug, as well as the lack of clinical studies that offer dosing recommendations for the elderly.

Lack of efficacy

The FDA responded to the claims that propoxyphene is no more effective than common over-the-counter analgesics like acetaminophen, ibuprofen, or aspirin. The FDA cited numerous clinical trials that accompanied the New Drug Applications (NDA) for propoxyphene showing its efficacy. They admit even though the techniques used in these clinical trials may be outdated, they still show that propoxyphene and propoxyphene/acetaminophen are superior to placebo. Furthermore, there is not substantial evidence available stating that propoxyphene’s efficacy should be questioned for its labeled use, which would be needed for withdrawal from the market.

Risk of abuse

Lastly, FDA agreed with Public Citizen that propoxyphene does have potential for addiction and abuse. However, the data provided by Public Citizen were largely outdated, and the one new article only confirmed that there is the potential for physical dependence with propoxyphene, with no comparison to other similar agents. The FDA responded by stating that propoxyphene has been classified as a Schedule IV controlled substance since 1979 for just these reasons of addiction and abuse potential. However, these properties are not unique to propoxyphene but similar to other opiates. The FDA again relied on recent DAWN data that showed similar rates of emergency department visits between propoxyphene and codeine. Lastly, FDA addressed Public Citizen’s argument that the abuse potential by teenagers should hasten the drug’s removal from market. The FDA noted that individuals seeking to abuse medications will do so with or without propoxyphene on the market, and removing propoxyphene will likely not affect the incidence of substance abuse. Despite this, they have made it known that the risks of propoxyphene abuse or addiction is apparent within the current labeling, and the update will only strengthen these warnings.

Recent labeling changes, future steps

The FDA has taken several actions to ensure that patients and prescribers know the risks of overdose. In July 2009, FDA required revisions to boxed warnings and are requiring a medication guide, which is part of a Risk Evaluation and Minimization Strategy (REMS), be distributed with each prescription. These will focus on educating users on propoxyphene’s potential for overdose and the importance of using the drug as directed. The FDA also strengthened the warnings already present on propoxyphene labels, focusing on the increased risk of side effects in the elderly, and the potential for drug abuse and dependence. Additionally, FDA is requiring clinical trials examining the effects of propoxyphene on the heart. Additional data will be gathered with help from the Veteran’s Administration and Centers for Medicare & Medicaid Services on how often propoxyphene is prescribed to the elderly, and its safety compared to other drugs in the elderly. The results of these studies and other data will dictate whether any further action will be needed by FDA.

Summary

Although the clinical studies that are being conducted may change clinical practice, for now the FDA believes that propoxyphene remains an adequate agent for the treatment of mild-moderate pain. Additionally, there is risk associated with alternative options like long-term acetaminophen and NSAIDs, and the FDA worries the removal of propoxyphene could leave a number of patients without adequate pain management or requiring more potent opiates. Clinicians should be aware of the potential safety concerns, both for propoxyphene and its alternatives, for the treatment of mild-moderate pain. There are many options available for pain management, and with each option there are associated risks.
Opioid Risk Evaluation and Mitigation Strategy

RiskMAPs and REMS

The FDA is the government body responsible for ensuring the safety and efficacy of the nation’s medications. Not only does this agency determine whether or not a drug will be approved for market, it continues to review these drugs to ensure the benefits outweigh the risks. Drug products are approved based on their risk-benefit profiles but this does not mean they are without risk. For most marketed products FDA has deemed their standard procedures sufficient in minimizing risk; however, in 2005 FDA implemented Risk Minimization Action Programs (RiskMAPs) to further minimize risk of specific drug products. Tools to carry out risk minimization range from education of patients and prescribers to reminder prompts within computer systems or even restrictions on access or distribution. Restricted access and distribution programs carry the highest risk of interfering with patients’ therapies. The iPledge program, used to monitor and prevent pregnancy in patients taking isotretinoin, is an example of a RiskMAP. In order for patients to take isotretinoin, prescribers, pharmacists, and patients must register with the program, read educational materials, and patients must submit urine and blood test results with each prescription.

The role of FDA was expanded in 2007 by the Food and Drug Administration Amendments Act of 2007 (FDAAA). Under this act the FDA can enforce REMS to ensure that a product’s benefits outweigh its risks. REMS can range from mild requirements such as medication guides and educational programs to more stringent restriction, including special certifications and registries. There are 3 major differences between REMS and RiskMAPs. A RiskMAP is voluntary for the manufacturer whereas REMS are enforceable by FDA and punishable by fine. RiskMAPs protect from known risks whereas REMS are meant to protect from either known or potential risks. Lastly REMS must be carried out within 120 days; RiskMAPs have no time limit. Over 100 REMS have been implemented thus far, including those for Aranesp, Epogen, Humira, Tracleer, and Victoza. Recently, discussion of a REMS for opioid agents has sparked great debate.

Opioids

Opioid agents have been in use for years and are an essential class of pain relieving agents. Unfortunately, they are also one of the more abused and misused classes of drugs on the market. Though opioids have long been utilized for analgesia, their abuse has recently increased exponentially. Patients who are prescribed opioids generally use them as directed, but issues with proper storage and disposal lead to diversion of these drugs. Seventy-eight percent of people addicted to opioids have not been prescribed the drugs. As shown in Table 2, the majority of OxyContin users obtained the product from a source other than their physicians. Most commonly it was a gift from a friend or relative.

<table>
<thead>
<tr>
<th>Source</th>
<th>Percentage (%)</th>
</tr>
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<tbody>
<tr>
<td>Got from doctor(s)</td>
<td>7</td>
</tr>
<tr>
<td>Gift; friend/relative got from doctor(s)</td>
<td>34</td>
</tr>
<tr>
<td>Gift; friend/relative got it elsewhere</td>
<td>11</td>
</tr>
<tr>
<td>Bought/took from a friend/relative</td>
<td>31</td>
</tr>
<tr>
<td>Bought from drug dealer or other stranger</td>
<td>13</td>
</tr>
<tr>
<td>Stole from healthcare provider/wrote fake Rx/Internet</td>
<td>4</td>
</tr>
</tbody>
</table>

Initially it was proposed that an opioid REMS be applied to all opioid agents; however, restricting the use of all opioids could be seen as detrimental to patients in true need of pain control. The FDA is now working towards implementing REMS on all long-acting and extended-release opioids. The decision to enact the REMS on just long-acting and extended-release opioids comes from emergency room data that demonstrates most opioid-related hospitalizations come from long-acting and extended-release formulations. In 2006 there were about 4 times the numbers of emergency department visits from abuse or misuse of extended-release versus immediate-release oxycodone.

In July 2010, a proposal for long-acting and extended-release opioid REMS was presented to a joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee. No time frame for implementation of REMS to all long-acting or extended release products has been established, though most agree it will take a year.

A variety of opioid products have already implemented a REMS program. Onsolis (fentanyl buccal soluble film for opioid-tolerant patients) is only available through a restricted access program, the Full Ongoing Commitment to User Safety (FOCUS) Program. Every patient, prescriber, and pharmacist who chooses to use, prescribe, or dispense Onsolis must enroll in the program. Educational materials and a medication guide must be provided to all involved. The goal is to limit the use of Onsolis to patients with breakthrough cancer pain, its intended indication. Embeda (morphine plus naltrexone extended-release capsules), used for continuous long-term analgesia in the setting of moderate to severe pain, also has a REMS. Again, healthcare provider education and medication guides are required. In addition, 2 extended-release products that have been marketed for some time have also implemented REMS: oxycodone controlled-release (OxyContin) and extended-release hydromorphone (Exalgo). Finally, several other opioid products are now

Table 2. OxyContin Users’ Sources in the Past Year.
dispensed with medication guides as part of REMS including: morphine oral solution, propoxyphene, and tapentadol.

Summary
Many health care groups, particularly oncologists, are concerned about the impact an opioid REMS may have on their patients’ pain control. They fear pain medications will not reach their patients in a timely manner. Some worried prescribers may forfeit their opioid prescribing capabilities because it will be too time-consuming or bothersome. These clinicians hope there will be a pilot program or phase-in period for health care teams to become comfortable with REMS, or for FDA to recognize its shortcomings early. On the other hand, the REMS may enhance FDA’s Safe Use Initiative to gain control of abused and misused products and be sure the benefits continue to outweigh the risks.

Finally, full implementation of the opioid REMS for all long-acting and extended-release products has not yet been implemented; however, some action is expected within the next year. Healthcare providers should continue to follow FDA’s progress on this initiative.

UIMC Patient-Controlled Analgesia (PCA) Guidelines in Adults

UIMC PCA guidelines were released in August 2010. The objectives are listed here and a complete copy is available on the UIMC website under Clinical Care Guidelines.

Objectives:

To ensure optimal pain control for select adult patients through the use of Patient-Controlled Analgesia (PCA). This will be achieved by:

1. Assessing the appropriateness of PCA therapy in adult patients anticipated to have moderate to severe pain (pain score ≥ 4/10) requiring intravenous (IV) opioid medication who are able to understand and participate in pain management.
2. Monitoring for efficacy (pain score < 4/10) and adverse effects of the opioid.
3. Appropriate weaning from IV PCA therapy to oral analgesics in patients whose pain is anticipated to continue at a level requiring significant doses of opioid analgesics.

Safety Concerns with Propoxyphene UPDATE:

Near the publication of this RxPress, the FDA announced the removal of propoxyphene from the US Market. The decision was based on all available data and data from a new study. The new study showed that propoxyphene even at therapeutic doses significantly changed the electrical conductivity of the heart which can be seen on an electrocardiogram. The FDA concluded that the risks of propoxyphene use outweighed the benefits of its use for pain relief. Xanodyne the maker of propoxyphene containing products, Darvon and Darvocet, agreed to withdraw propoxyphene from the US market.

P&T Committee Formulary Action

Additions
- Budesonide/formeterol (Symbicort)

Deletions
- Diltiazem SR

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