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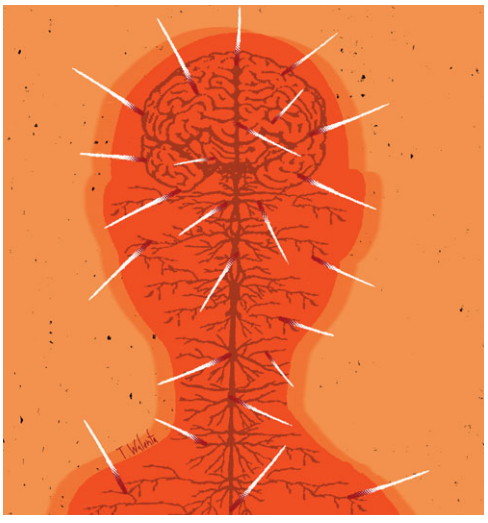

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—john dewey
philosopher and educator

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Central pain states: a shift in thinking about chronic pain

Emerging data show that for some patients with chronic pain, the problem is not in the periphery.

RICHARD E. HARRIS, PhD
Assistant Professor, Department of Anesthesiology
University of Michigan, Ann Arbor

What do we mean when we talk about pain? Traditionally pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[1] Pain can result when intense or noxious stimuli activate peripheral nociceptors. It serves as a warning against impending tissue damage and acts reflectively to protect against or minimize that damage.

We have known since the time of Descartes about the existence of an ascending sensory pain pathway that sends "distress" signals from the source of tissue damage to the brain. We also know of the Gate Control theory described by Melzack and Wall in 1965, in which stimulation of the skin evokes responses that transmit signal injury to transmission cells (the "gate") in the dorsal horn of the spinal cord that continues to the brain, triggering response signals that modulate the activity of inhibitory cells (which close the "gate"), thereby decreasing the intensity of pain.[2] But how do we explain pain in the absence of tissue damage, pain that is not

Disclosure
Dr. Harris reports no financial relationship with any company whose products are mentioned in this article, or with manufacturers of competing products.

triggered in the periphery, that often appears long after the noxious stimulus has stopped exerting its unpleasant effect?

Types of chronic pain

An estimated 116 million American adults suffer from chronic pain, defined as pain that lasts more than 3 months after onset and well into the phase of healing.[1,3] According to a 2006 report from the Centers for Disease Control and Prevention with a special focus on pain, almost 57% of adults age 65 or older and 37% of younger adults ages 20–44 reported pain that lasted one year or more [Figure 1].[4] Chronic pain exacts a cost of between $560 billion and $635 billion annually in medical treatment and lost productivity.[5] There is a tremendous need to understand the molecular and cellular mechanisms of chronic pain in an effort to develop new, more effective treatments for these patients. This understanding may come as a result of our recent advances in visualizing the peripheral and central processes involved in pain. The emerging data suggest that for some individuals central factors play a key role in the maintenance and establishment of certain chronic pain conditions. That is, for some, the problem is really not in the periphery.

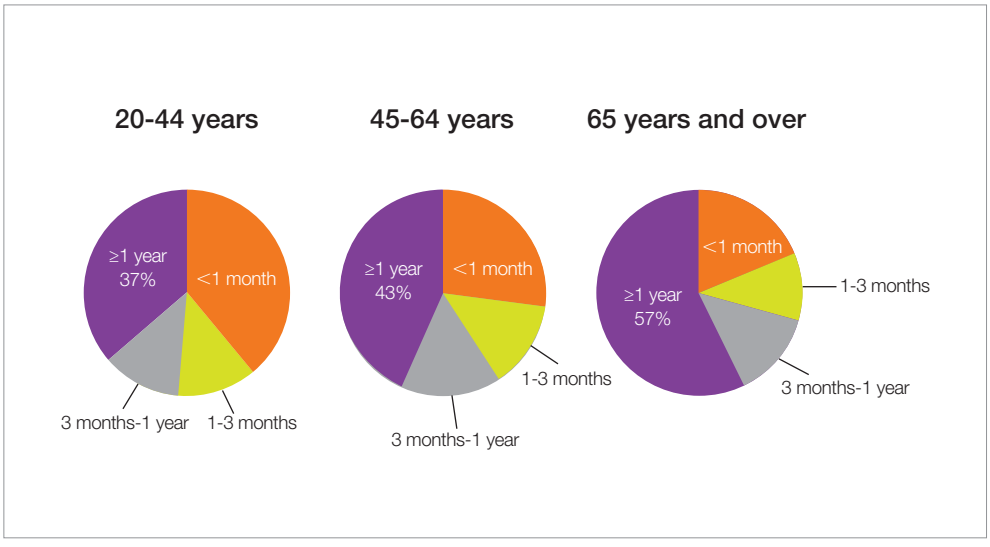
Knee and hip pain. When peripheral tissue damage is unavoidable, the inflamed tissues and those nearby become hypersensitive, a protective response to guard the area during the period of healing. Conditions like chronic low-back pain and knee or hip osteoarthritis classically have been thought to be due to inflammation or damage to tissues in the back, knee, or hip. However, recent studies show that these conditions may have complex factors entailing both the peripheral and central nervous systems.

Analysis of data from the National Health and Nutrition Examination Survey (NHANES I) of patients with radiographic evidence of structural damage to the knee due to osteoarthritis found discordance between the amount of damage visible on x-ray and patients' self-report of the degree of pain. In 319 patients with radiographic stage 2–4 knee osteoarthritis, only 47% reported knee pain, suggesting that something more than the degree of tissue injury was involved in the perception of pain.[6,7] One explanation of these findings is that pain is a complex system incorporating structural changes, peripheral and central pain mechanisms, and subjective factors, including the patient's history, psychological experience, genetics, and culture.

Diabetic neuropathy and postherpetic neuralgia. Chronic neuropathic pain results when there is actual damage to the nervous system—the peripheral nerve, dorsal root, or central nervous system. Peripheral neuropathic

An estimated 116 million American adults suffer from chronic pain.

FIGURE 1: Pain duration by age group, 1999-2002



Respondents in the CDC National Health and Nutrition Examination Survey who reported pain lasting more than 24 hours in duration in the month prior to interview were asked a follow-up question about the duration of that pain.
Source: Centers for Disease Control and Prevention, National Center for Health Statistics, Health, United States, 2006. Data from the National Health and Nutrition Examination Survey.

pain occurs after damage or alterations to sensory neurons. Some neuropathic pain disorders, such as diabetic neuropathy and postherpetic neuralgia, are well-defined disorders in which symptoms are unrelated to a stimulus and pain is related to peripheral as well as central processing.[8]

Stroke. Central poststroke pain, in which pain and hypersensitivity occurs in a body part due to injury to the corresponding part of the brain affected by the cerebrovascular lesion, is also considered a neuropathic pain syndrome. The onset of central poststroke pain typically occurs more than one month after the stroke, and exists with somatosensory abnormalities.[9-11] For these types of neuropathies, altered function due to loss or damage of neuronal tissue is likely the cause of the pain condition.

Many of the people suffering from these central chronic pain conditions find it difficult to obtain relief, and probably will not benefit from surgeries or manipulations in the periphery. Instead, they may benefit from a targeted approach that addresses the central nervous system.

Recent studies on fibromyalgia and pain

Fibromyalgia (FM) may be considered the prototypical central pain disorder, in which the pain originates or is maintained in part in the central nervous system. Although new diagnostic criteria are being validated for this disorder, FM classically has been diagnosed by the detection of 11 of 18 tender points and the presence of chronic widespread pain for 3 months or longer.[12]

FM is a common disorder found to affect between 2% and 4% of the US population.[13] It was one of the first disorders shown to have central factors predominant in the pathology, and as a result it has been the focus of numerous studies. Irritable bowel syndrome and chronic fatigue syndrome, often comorbid with FM, are also commonly studied. Until recently, these disorders have largely been considered "wastebasket" terms to categorize the complaints of patients with unexplained symptoms, because there were no objective signs to support their complaints. However with the advent of new imaging techniques to look into the brain and the central nervous system, researchers are finding very real physiological differences. For example, one study using sensory testing with thermal, mechanical, and electrical stimuli showed a correlation between FM patients' subjective reports of pain and significantly altered cold and heat thresholds when compared with controls.[14] Based on such studies it appears that patients with FM perceive stimuli as noxious at lower levels than healthy, pain-free controls.

Recent studies of FM have incorporated the use of functional magnetic resonance imaging (fMRI) to look at brain activations in response to painful stimuli. A study that included patients with FM and others with chronic low-back pain used fMRI to visualize the participants' response to equal amounts of thumbnail pressure. In the FM and groups, 5 areas of neuronal activation within the cortex related to pain were detected, compared with only one activation in controls.[15] Another study to evaluate the pattern of cerebral activation in FM patients found that in response to similar thumbnail pressures there were 13 regions of greater activation in the FM group compared with one region in the healthy control group.[16] Additionally, mild pressure resulted in subjective pain reports and cerebral responses in the FM group that were similar to responses produced by twice the pressure applied in controls.

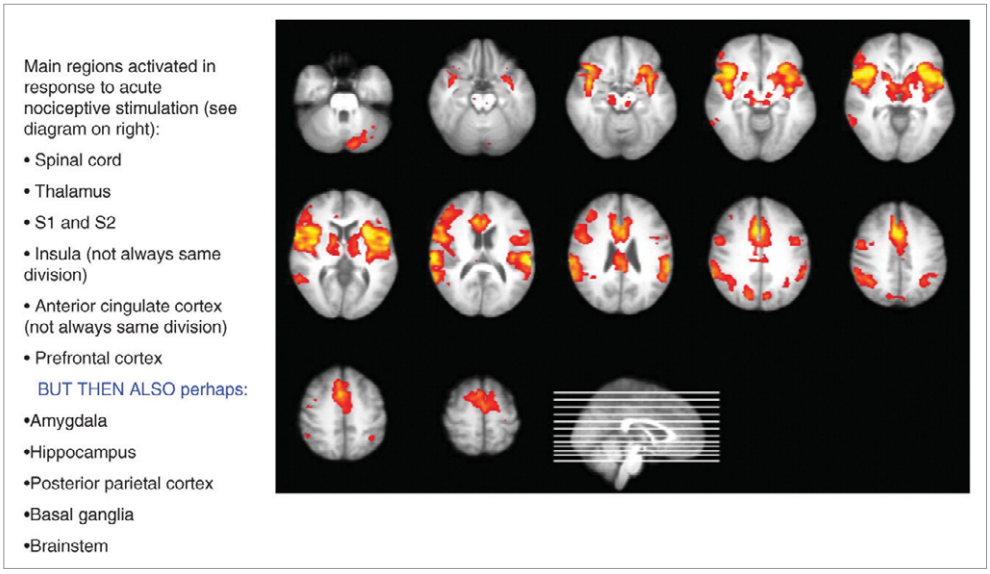
Another important area of research in pain processing looks at gray matter in the brain using voxel-based morphometry. A study of patients with FM found significantly less volume of gray matter and an age-associated decrease in gray matter that was 3.3 times greater than healthy controls.[17]

Using MRI to look at gray matter volume in patients with chronic musculoskeletal pain, significant differences in gray matter volume were found in osteoarthritis patients prior to hip arthroplasty compared with healthy controls. Specifically, areas of the thalamus, understood to play a role in central pain processing, showed decreased gray matter volume in the osteoarthritis group. Significantly, a comparison of gray matter volume 9 months after surgery showed that the levels of reduced thalamic gray matter volume in osteoarthritis patients "reversed" to levels similar to the those of the healthy control group.[18]

Although the mechanism that drives the loss or degradation of brain tissue in patients with chronic pain remains to be determined, one theory is that pain is associated with certain areas of the brain becoming hyperactive. Imaging studies using fMRI show that a constellation of regions typically are activated in pain processing, including the insula,

Many people suffering from central chronic pain probably will not benefit from surgeries or manipulations in the periphery.

FIGURE 2: Neuroanatomy of pain processing. Main brain regions that activate during a painful experience are highlighted as bilaterally active but with more dominant activation on the contralateral hemisphere (red)



Source: Tracey I. Imaging pain. *Br J Anaesthes.* 2008;101:32-39, by permission of Oxford University Press.

cingulate, primary somatosensory and secondary somatosensory cortices, amygdala, and thalamus [Figure 2].[19] These regions have been shown to be more active in chronic pain states when patients respond to stimuli such as painful pressure or heat. Indeed, these regions have shown overamplification or augmentation of neural activity.

Since overstimulation of nerve cells can trigger a toxic release of glutamate into surrounding tissues of the brain, this may cause nerve cells to die, ultimately reducing the amount of gray matter visualized in the brains of patients with chronic pain. In addition, some studies of FM have shown elevated levels of glutamate, an excitatory neurotransmitter that is known to cause excitotoxicity.[20]

Fibromyalgia may be considered the prototypical central pain disorder.

Another significant consequence of long-term pain appears to be alterations in the normal connectivity of the brain, including the "default mode network" (DMN) which is noted to be important during the resting state. Recent studies of chronic pain suggest alterations in key DMN regions that may be related to the chronic pain state and existing comorbidities.[21]

The role of stress and depression in pain

The association among physical and psychosocial stressors, depression, and chronic pain syndromes has been the subject of numerous studies.

Posttraumatic stress disorder (PTSD) has been closely correlated with chronic pain. An example of one such stressor may be deployment to a military conflict. Soldiers and military personnel throughout history have reported a cluster of symptoms such as pain, fatigue, and cognitive impairment that are very similar to FM. From US military conflicts, these syndromes include Gulf War illness, the condition known as "shell shock" in World War I, and "soldier's heart" during the Civil War.

A review of the literature addressing the association between chronic pain and PTSD by the Department of Veterans Affairs found such a high degree of correlation that the authors suggested clinicians who conduct diagnostic assessments for one disorder should also assess for the other.[22] In a study that evaluated patients for FM, chronic fatigue, and psychiatric symptoms, patients with FM who had both tender points and diffuse pain were significantly more likely to have an increased prevalence of lifetime PTSD.[23]

The relationship between depression and chronic pain has been well documented. Kaiser Permanente surveyed patients seen in primary care and found that a significantly higher proportion of patients with major depressive disorder (MDD) reported chronic pain than did patients without MDD (66% vs

43%, respectively).[24] These conditions share common physiologic features and a high degree of comorbidity.

A study of patients with FM and depressive symptoms or MDD looked at neural responses to painful pressure and found no association between the extent of depressive symptoms or MDD and neural activation in the primary and secondary cortices, areas associated with the sensation of pain. However, activation was seen in the amygdala and contralateral anterior insula, areas associated with affective pain processing.[25]

These findings were supported in a more recent study in which patients who met the criteria for FM were given a series of questionnaires to assess depressive symptoms, anxiety, and catastrophizing, and were tested for painful pressure responses using fMRI. The results established a correlation between this cluster of affective symptoms, but there was no correlation with clinical pain symptoms or responses to painful pressure.[26] Rather than suggesting that there is no alignment between the mental and physical aspects of pain, results from both of these studies suggest that 2 independent pain networks exist to process the sensory and affective dimensions of pain, and that these pathways may operate simultaneously.

Pain in the clinical setting

The evidence is strong that many patients experience chronic pain that is not site-specific and arises not merely from the periphery but from intricate neural systems. With a new appreciation for the complexity of pain processing, the clinician is compelled to probe beyond, "Where does it hurt?" [Table].

When patients complain of widespread or chronic pain, the clinician is well advised to take the time to examine further by inquiring about depression, anxiety, fatigue, sleep disturbances, and cognitive difficulties in order to understand what is driving the patient's symptoms.[13] The results may be revealing. In a study of primary care patients, participants who complained of muscle pain, headache, and stomach pain were found to be 2.5 to 10 times more likely to screen positively for panic disorder, generalized anxiety, or MDD.[27]

An article in a following issue will discuss practical tools that can be used to assess comorbidities such as anxiety and depression, and interventions that might be helpful for central pain and neurorehabilitation. An approach that acknowledges the patient's account of pain, recognizes the cluster of symptoms and conditions that can accompany pain, and utilizes a multidisciplinary approach for diagnosis and treatment will have the best chance of yielding positive outcomes.

Acknowledgement—The author wishes to thank Kristen Georgi for her assistance in the research and writing of this article.

TABLE
Clinical diagnosis of central pain

In a 1990 letter to the *British Journal of Medicine*, researcher David Bowsher, MD, stated that the clinical diagnosis of central pain is relatively simple:

- Patients often describe pain as burning or scalding, less often as shooting or stabbing, and sometimes both
- Burning pain is felt even in response to cold stimuli
- A painful sensation is felt in response to light pressure, but not deep pressure.

Source: Bowsher D. *BMJ.* 1990;300:1652.

When patients complain of chronic widespread pain, take the time to inquire about depression, anxiety, fatigue, sleep disturbances, and cognitive difficulties.

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Use of complementary therapies to treat the pain of osteoarthritis

Evidence shows that an integrative approach to therapy with complementary treatments improves patient outcomes.

JAMES N. DILLARD, MD, DC, LAc
Private practice, Manhattan and East Hampton, NY
Former Medical Director, Rosenthal Center for Complementary & Alternative Medicine, Columbia University Medical Center

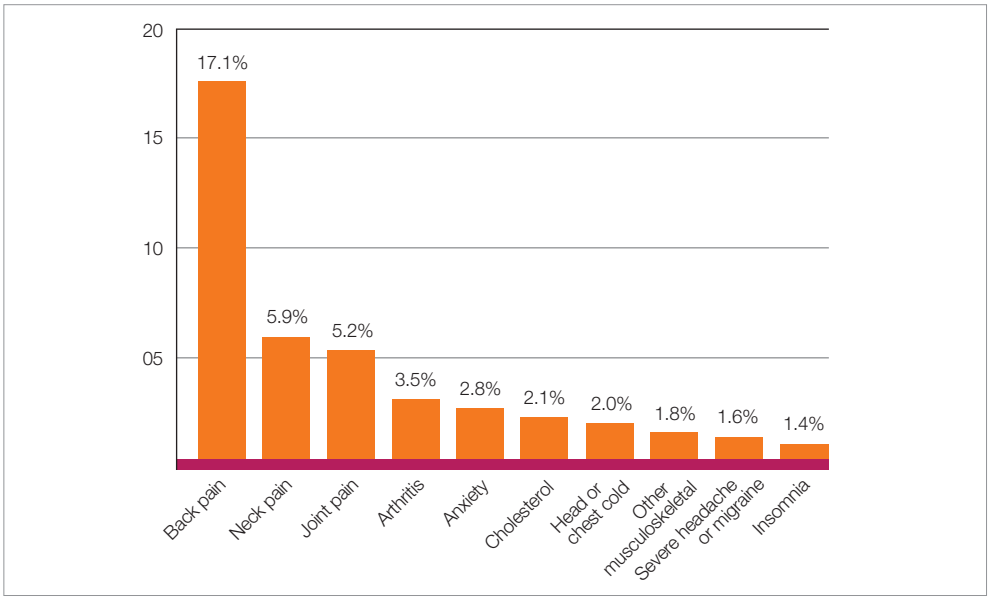
At last count in 2008, 27 million Americans were suffering with osteoarthritis (OA), by far the most common form of arthritis.[1] That number has undoubtedly risen and will continue to do so as Baby Boomers age. Despite the benefits of conventional nonpharmacologic measures and available pharmacologic agents, many patients with OA achieve less than satisfactory pain relief and have impaired joint mobility, which can significantly limit their daily activities.[2] Numerous studies have found that a host of complementary and alternative (CAM) therapies can provide safe and effective pain relief and enhanced joint mobility. The National Center for Complementary and Alternative Therapies found that musculoskeletal problems such as back pain, neck pain, joint pain, and arthritis were the top conditions for which adults used CAM therapies in 2007 [Figure 1].[3]

A survey to gather detailed information about CAM use by patients with arthritis

Many patients with OA achieve less than satisfactory pain relief and have impaired joint mobility.

Disclosure
Dr. Dillard reports no financial relationship with any company whose products are mentioned in this article, or with manufacturers of competing products.

FIGURE 1: Diseases/conditions for which CAM is most frequently used among US adults – 2007



Source: Barnes PM, Bloom B, Nahin R. CDC National Health Statistics Report #12. Complementary and alternative medicine use among adults and children. United States, 2007. December 2008.

Most patients followed by specialists and primary care physicians tried at least one CAM therapy for relief of OA symptoms.

(n = 2140) found that most patients followed by specialists (90.5%) and a slightly smaller percentage followed by primary care physicians (82.8%) had tried at least one CAM therapy for relief of OA symptoms. The authors suggested that the higher percentage for specialist care may be because these patients have more severe disease and therefore experience more pain.[4] An understanding of these therapies will allow primary care and specialist physicians to better communicate with and advise patients who seek options outside the usual spectrum of care.

Definition and therapeutic goals

OA is a progressive deterioration of joint tissues.[5] A decrease in protective proteoglycans and collagen compromises joint cartilage.[5-8] Deterioration of cartilage in turn leads to bone erosions, osteophyte formation, and bone restructuring. Inflammation, too, may result in reaction to cartilage degradation byproducts entering synovial spaces.[6,7]

Joint pain aggravated by physical activity and alleviated by rest is typical of OA. Also common are joint instability and stiffness upon rising in the morning or after extended inactivity.[9] A patient's history may additionally reveal that the level of pain experienced with activity has steadily increased with time. Physical examination may reveal bony enlargement or deformity of involved joints, crepitus, and restricted range of motion.[9] The value of laboratory and radiology studies lies mainly in ruling out alternative diagnoses.

The goals of OA treatment are pain relief and preservation of joint function. Because the experience of pain is influenced by physical, psychological, and emotional factors, individuals vary in how they respond to specific therapies and in how they *wish* to achieve pain relief. Some patients may experience side effects from anti-inflammatory pain medications.[10] Others may be hesitant to resort to surgery.[9] All major guidelines agree that, for most patients, therapy combining nonpharmacologic measures and pharmacologic agents is required to achieve optimal relief of pain and preservation of joint mobility.[11-14]

Conventional treatment options for OA

Selecting appropriate treatment begins with consideration of the patient's report of chronic pain and limitations in ambulation or other activities. Also important is assessment of the patient's level of pain on manipulation, as well as muscle strength and ligament stability.[7,8] Depending on physical examination results, a reasonable approach may be to start with nonpharmacologic measures and add pharmacologic agents in a stepwise manner to control

pain.[8] Self-management programs have been shown to improve symptoms as well as quality of life, and should be incorporated into the treatment plan.[15]

Nonpharmacologic measures, prescribed as needed for each individual, include weight loss for those who are overweight or obese.[11-14] Weight loss has been shown to improve mobility and reduce pain. For every one pound of weight lost, there is a 4-pound reduction in the load exerted on the knee for each step taken during daily activities.[16] A weight loss of only 15 pounds can cut knee pain in half for overweight individuals with arthritis.[17] A low-carbohydrate diet has been shown to reduce weight in obese patients by ≥10% and lead to improvements in self-reported scores for overall progress and functional ability.[18] A diet of fruits and vegetables (including alliums and cruciferous vegetables) that is high in phytonutrients has been shown to have a protective effect in patients with hip OA.[19]

Other measures are physical and occupational therapies, assistive devices for walking or accomplishing other daily tasks, and joint taping.[11-14] Patient (and family) education regarding the progressive nature of OA is crucial to bolstering patient resolve in following through with self-management activities.[15] Healthcare professionals can provide factual, disease-specific information on some effective self-management strategies for use between office visits that yield short- and long-term benefits. Self-management strategies can incorporate pain management education; joint-sparing exercise advice including daily walking, balance tips, and falls prevention; and emotional and cognitive skills to improve quality of life.

Pharmacologic intervention is best begun with the least risky agent, at the lowest effective dose, for the shortest possible duration.[12] For mild-to-moderate pain, the Osteoarthritis Research Society International recommends acetaminophen as initial therapy, given up to 4 g/d. If pain relief is insufficient, consider adding or switching to an oral or topical nonsteroidal anti-inflammatory drug (NSAID), keeping in mind the possibility for gastrointestinal (GI) adverse effects with oral agents. When using an oral NSAID in patients at risk for GI effects, give a proton-pump inhibitor (PPI) as well. A topical NSAID or capsaicin may provide additional local pain relief.[20]

If pain remains inadequately controlled, or if a patient is intolerant to NSAIDs, a selective COX-2 inhibitor given alone or in combination with acetaminophen may be an appropriate choice—provided the patient undergoes thorough evaluation for cardiovascular (CV) and GI risks.[12,21] For those with GI risks taking a COX-2 inhibitor, give either misoprostol or a PPI concomitantly. Monitor those with CV risks closely.

When OA pain is severe or unresponsive to the previous medications, alternative agents include tramadol with or without acetaminophen, or opioid analgesics. In either instance, start at the lowest possible dosage (adjusted, as needed, for renal or hepatic impairment) and then titrate upward slowly to minimize adverse effects.[9,12]

Evidence-based complementary treatment options for OA

In its executive guidelines for US hospitals, the Joint Commission clearly states that institutions seeking accreditation, or wishing to maintain it, must include in its options for treating chronic pain such complementary measures as massage, acupuncture, and mind-body therapy. The Joint Commission's basis for mandating an integrative approach to pain control is the growing body of clinical evidence supporting the efficacy of complementary treatments. In addition, many patients prefer nonpharmacologic options for personal reasons.

Hyaluronic acid. In a recently published meta-analysis of studies looking at intra-articular hyaluronic acid (IAHA) for knee OA pain, the authors reported therapeutic effectiveness beginning at 4 weeks, reaching a peak effect at 8 weeks, and exerting a residual effect still detectable at 24 weeks.[22] Moreover, the peak effect of IAHA is greater than published effects for acetaminophen, NSAIDs, and COX-2 inhibitors.[22] IAHA could be useful in combination with other therapies, and in certain clinical situations such as when patients are undecided about surgery. Other studies and meta-analyses of IAHA have yielded different results regarding length of efficacy.[23,24]

Acupuncture. While studies of acupuncture for OA have varied in quality and duration of effect, many show benefits. One meta-analysis found that patients who received acupuncture reported clinically relevant short- and long-term pain reduction and improved function compared with control patients who received usual care.[25] In a study of 294 patients with OA of the knee, patients received 8 weeksof acupuncture, minimal

The Joint Commission's basis for mandating an integrative approach to pain control is the growing body of clinical evidence supporting the efficacy of complementary treatments.

acupuncture (superficial needling at nonacupuncture points), or no treatment. Based on the Western Ontario and McMasters Universities Osteoarthritis (WOMAC) questionnaire assessing pain, function, and stiffness due to OA, those who received acupuncture had significantly better scores than the other 2 groups. However, after 26 and 52 weeks, the differences between acupuncture and minimal acupuncture were no longer significant.[26]

In the largest study ever conducted on acupuncture for OA of the knee, 570 patients were randomly assigned to receive acupuncture, sham acupuncture, or education.[27] At 26 weeks postintervention, based on the WOMAC function score those who underwent true acupuncture experienced significantly greater pain relief and functional improvement than those who received sham acupuncture or education only.

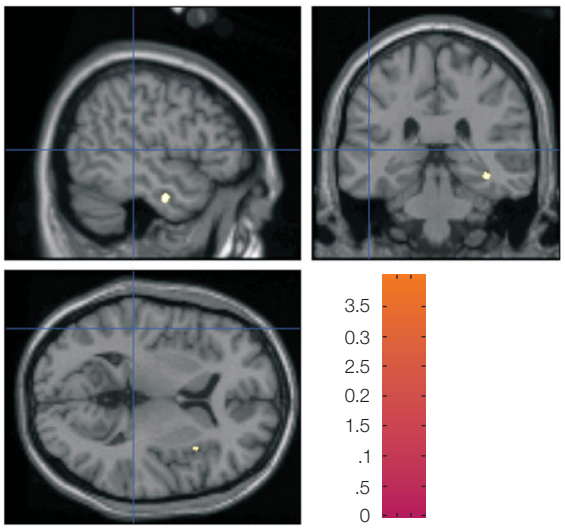
Mindfulness-Based Stress Reduction (MBSR), pioneered by Jon Kabat-Zinn, PhD, uses mindfulness meditation to alleviate chronic pain. First reported in a 1982 study, 88% of enrolled patients with chronic pain of 6 months to 48 years' duration who were trained in stress reduction using mindfulness meditation perceived a decrease in pain of at least 50%.[28] This method of focusing on the mind and body does not simply "distract" patients from their pain but achieves measurable changes in how pain is perceived. With MBSR, pain reduction reported by patients was significantly greater than that achieved with morphine and other drugs.[29] Brain scans show that, after MBSR, regions normally associated with processing painful stimuli become quiescent.[29] MBSR has also been shown in imaging studies to increase gray matter concentrations in regions of the brain associated with learning and memory, regulation of emotion, and self-referential processing [Figure 2].[30]

The MBSR method of focusing on the mind and body does not simply "distract" patients from their pain but achieves measurable changes in how pain is perceived.

A 2004 meta-analysis of 20 reports on mindfulness meditation that met study criteria included patients with anxiety, cancer diagnoses, chronic pain, coronary artery disease, depression, fibromyalgia, obesity and binge eating disorders, and psychiatric disorders. The analysis found a relatively consistent and strong effect, suggesting that mindfulness training may enhance the ability to cope with distress and disability and the sense of physical well-being.[31]

Chiropractic. One small randomized controlled trial (RCT) matched participants with knee OA pain measured by visual analog scale (VAS) and assigned them to receive either treatment according to the Macquarie Injury Management Group Knee Protocol or nonforceful contact.[32] The treatment

FIGURE 2: Gray matter is more concentrated for persons who meditate compared with nonmeditators



Greater gray matter concentration for meditators compared to non-meditators ($P < .001$; uncorrected; > 20 voxels) in the left inferior temporal gyrus (upper left panel; cluster size: 157 voxels), right anterior insula (lower left panel; cluster size: 22 voxels) and right hippocampus (upper right panel; cluster size: 106 voxels). MNI coordinates of shown slices: x, y, z: −49, −32, 6; color bar indicates t-values.

Source: Holzel BK, et al. Investigation of mindfulness meditation practitioners with voxel-based morphometry. *Soc Cogn Affect Neurosci*. 2008;3:55-61, by permission of Oxford University Press.

group reported significantly decreased knee symptoms such as crepitus and improvement in mobility and ability to perform general activities. A systematic review found fair evidence for efficacy of manipulative therapy of the knee combined with multimodal or exercise therapy for knee OA.[33]

Transcutaneous electrical nerve stimulation (TENS). Evidence for the effectiveness of TENS for OA is mixed. A 2009 Cochrane systematic review of TENS for knee OA concluded that available studies were too small and poorly designed to judge its effectiveness.[34] However, its use in tibiofemoral OA has yielded good results.[35]

Tai Chi. This ancient form of meditative exercise has long been acknowledged as a means for enhancing balance and dexterity, but studies of chronic pain reduction and improved mobility with Tai Chi have been few and usually underpowered to yield reliable results. One systematic review of 9 RCTs, 23 non-RCTs, and 15 observational studies included studies that showed benefits for osteoarthritic symptoms with improved functional mobility and quality of life.[36] Another systematic review of 5 RCTs and 7 nonrandomized clinical trials found that Tai Chi was effective for pain control of OA of the knee, but that evidence was inconclusive for pain reduction or mobility improvement.[37] In a long-term study comparing Tai Chi with regular exercise in patients with symptomatic OA of the knee, researchers found that those in the Tai Chi group showed greater improvement in pain, physical function, self-efficacy, depression, and health-related quality of life, with some improvements lasting as long as 48 weeks.[38]

Massage. A longitudinal analysis of the use of a variety of alternative therapy offerings by older adults with OA found that the most commonly utilized treatment during a 20-week intervention period was massage (57%) followed by chiropractic (20.7%).[39] In the first prospective randomized trial to evaluate the efficacy of massage for adults with OA of the knee, participants who received 8 weeks of Swedish massage therapy showed significant improvements in pain, stiffness, and physical function. These improvements persisted at the 16-week evaluation.[40]

Dietary supplements. Omega-3 fatty acids have shown promise in reducing chronic neuropathic pain when taken at levels that exceed 2 g/d of eicosapetaenoic acid and docosahexaenoic acid.[41] This effect is probably enhanced when combined with a dietary reduction of omega-6 fatty acids and saturated fats. This dietary measure may also have some effect on joint pain.[42]

Glucosamine/chondroitin has been shown in a meta-analysis to reduce OA pain,[43] although another meta-analysis showed no effect on either joint pain or narrowing of joint space.[44] More recently, data from the long-term Glucosamine/Chondroitin Arthritis Intervention (GAIT) trial found that patients who took glucosamine or glucosamine/chondroitin in combination had similar results to those who took celecoxib or placebo. Over the 2-year study period, all groups showed improvement in pain and function.[45]

It is worth noting that not all supplements are made the same, and there may be varying potencies. For example, some glucosamine products work better than others.[46] When discussing supplements, to get the most potential benefit it is advisable to suggest those with a strong body of evidence or refer patients to providers who are familiar with CAM therapies.

Other promising dietary aids for reducing OA pain include soy protein,[47] avocado-soybean unsaponifiables,[48] Cat's claw,[49] white willow,[49] green tea,[49,50] turmeric,[51] ginger,[52] and propolis.[53]

Widening your integrative approach to OA treatment

There is emerging evidence that integrating multiple conventional and CAM therapies such as glucosamine and walking may provide the best results for OA patients.[54] The realization that many patients with pain and diminished mobility are already exploring CAM therapies presents an opportunity for you to discuss their decisions and direct their attention to options that are supported by strong evidence. By evaluating the increasing body of evidence in support of specific CAM therapies, you can feel confident in offering your patients a wider range of choices than standard pharmacologic and nonpharmacologic OA options, and integrate these options to improve care.

The realization that many patients are already exploring CAM therapies presents an opportunity to direct their attention to options that are supported by strong evidence.

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The promise of telemedicine: providing curbside consults for chronic care, urgent care, and pain

Videoconferencing can help improve outcomes in underserved areas. Project ECHO™ paves the way.

KEN TERRY
Freelance medical writer and editor of FierceHealthIT

With the increased availability of high-speed Internet connections in rural areas, the use of telemedicine to improve access to specialty care is growing. In rural areas, where a shortage of specialty care exists, telemedicine programs enable primary care providers to reach out to urban academic specialists hundreds of miles away to obtain advice about challenging cases. Other programs allow urban specialists to virtually "examine" patients in remote settings and consult with the patients' local providers to

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establish a diagnosis and develop a plan of care. One award wining example of this collaborative model is the University of New Mexico Hospital's (UNMH) Project ECHO™ (Extension for Community Healthcare Outcomes), discussed below, where a multispecialty team hosts telemedicine clinics to treat complex medical problems, including chronic pain [Figure 1].

Many studies show the benefits of telemedicine

Over the past several decades, telemedicine has been demonstrated to:

- Improve access to healthcare for a wide range of conditions, including heart and cerebrovascular disease, diabetes, cancer, psychiatric disorders, and trauma
- Improve access to services such as radiology, pathology, and rehabilitation
- Promote patient-centered care at lower cost and in local environments
- Enhance efficiency in clinical decision-making, prescription ordering, and mentoring
- Increase effectiveness of chronic disease management in both long-term care facilities and in the home
- Promote individual adoption of healthy lifestyles and self-care.[1]

Telemedicine has been particularly effective in providing care for rural patients who might find it difficult to travel farther than their local hospital. In Louisiana, for example, 28 rural hospitals are using video teleconferencing to bring patients together with specialists at the Louisiana State University Health Sciences Center (LSUHSC) in Shreveport. Without this option, some patients would face a 5-hour drive to see an LSUHSC specialist in person.

The ability to send large volumes of data such as high-definition video over the Internet enables specialists to "examine" patients and view diagnostic images remotely. In some programs, the patient's electronic health records are transmitted over the Web to aid in diagnosis and treatment.[2]

Military and prison telemedicine programs

The Department of Defense and the Veterans Health Administration (VHA) have used telemedicine extensively in caring for combat veterans with traumatic brain injuries.[3] Telemedicine is employed for neurological assessment, acute medical and neurosurgical treatment, psychiatric intervention, behavioral therapies, and occupational and physical rehabilitation.

The ability to send large volumes of data over the Internet allows physicians to "examine" patients remotely.

FIGURE 1: The multidisciplinary team working with primary care physicians in the Project ECHO™ pain clinic

Reprinted with permission from Project ECHO™.

According to one description of the VHA program:

"Veterans once at risk of being left untreated can now be monitored and cared for in their homes and communities. VHA home telehealth programs are reducing hospitalizations, emergency room visits, and length of hospital stays, while improving the quality of life for veterans."[3]

Some state prisons rely on telemedicine to reduce the travel and security expenses associated with inmate care. New Jersey, Georgia, and Texas have incorporated university-based care into their telemedicine programs for prisoners, and California will soon be adding similar telemedicine programs.[4] Texas has saved $215 million by using this approach, and telemedicine has been linked to improvements in inmates' blood glucose levels, cholesterol levels, and hypertension.[4]

A neurological exam conducted via videoconferencing can be as effective as a bedside exam for nonacute stroke patients.

Studies of telemedicine use in acute and chronic care

Telemedicine can play a role in acute care situations. A 2009 scientific statement from the American Heart Association/American Stroke Association recommends the use of telemedicine for stroke in the absence of specialist care. The consensus statement found that a neurological exam conducted via videoconferencing can be as effective as a bedside exam for nonacute stroke patients. Also recommended are specialist use of teleradiology for computed tomography brain scans in suspected stroke patients, and in thrombolysis and IV tissue plasminogen activator decision-making for stroke patients in collaboration with on-site medical care.[5]

In an prospective evaluation of pediatric patients in emergency departments in Vermont and upstate New York, telemedicine was used to provide specialist consultations and to support transport teams. Providers found it to be superior to telephone consultations and to improve patient care.[6]

A 2009 randomized study compared telemedicine case management with usual care in older, ethnically diverse, medically underserved patients who had diabetes mellitus. Over a 5-year follow-up period, the study group achieved net overall reductions in hemoglobin A1c, systolic and diastolic blood pressure, and low-density lipoprotein cholesterol. Despite these improvements, however, mortality rates were about the same in the interventional and usual-care groups.[7]

In the area of pain management, a 2010 randomized trial involving cancer patients with pain and depression saw positive results from the use of case management by telephone and automated symptom monitoring. Of the 274 patients with pain, those in the intervention group had greater improvements in pain severity over the 12 months of the trial than did those in the usual-care group.[8]

An 18-month cost analysis study comparing the use of telemedicine versus in-person consultation for patients with chronic pain found that direct costs were lower in the telemedicine group than the in-person group (median cost $133 vs $433, respectively). In addition, more chronic pain patients reported they were highly satisfied with telemedicine consultations (56%) compared with those who were highly satisfied with in-person consultations (24%).[9]

A rural telemedicine success

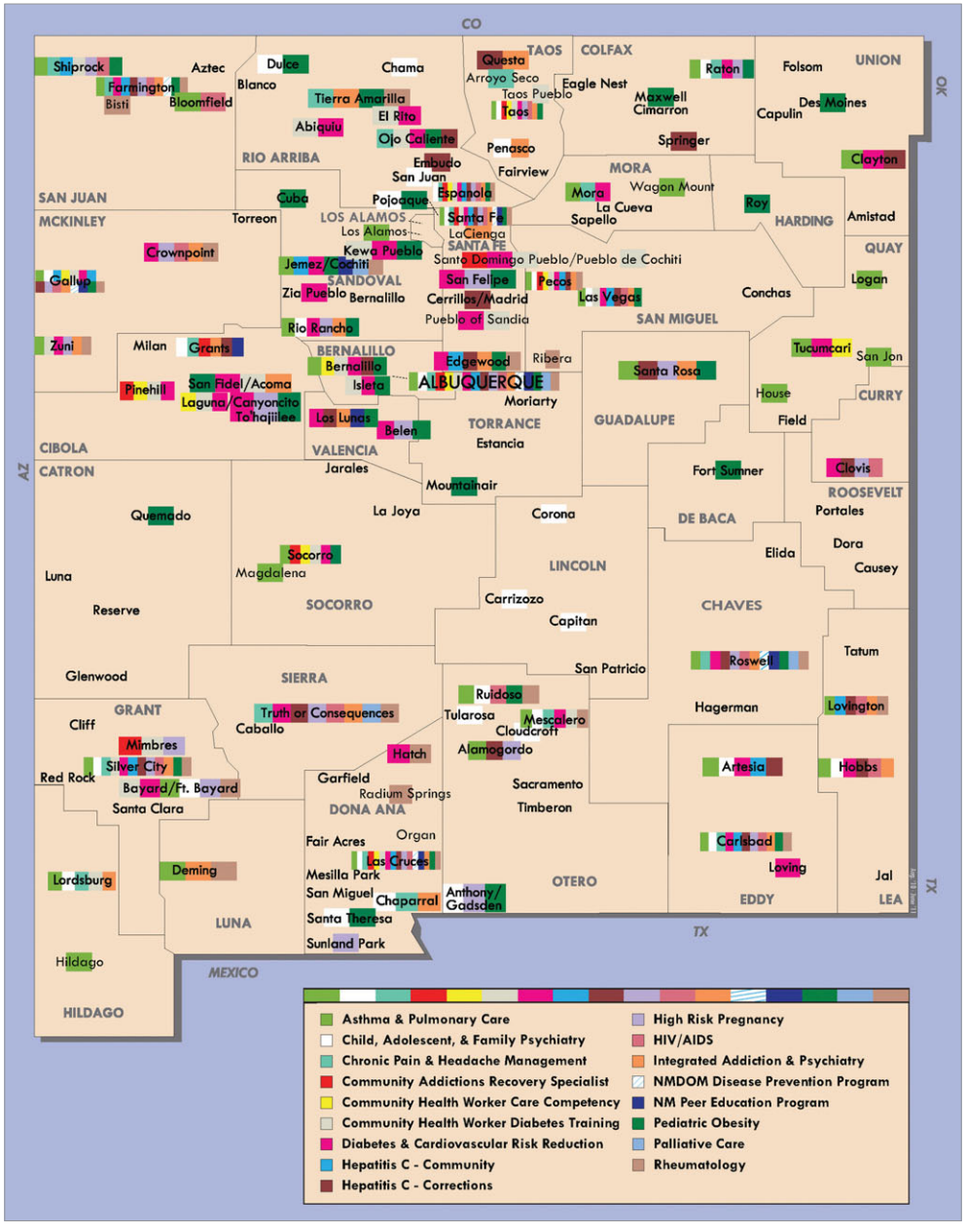
A recent study shows the significant impact a rural telemedicine program can have on clinical outcomes. Researchers looked at outcomes of patients with hepatitis C whose providers participated in the UNMH's Project ECHO™. In ECHO, academic specialists offer long-distance training and support for rural primary care providers. Among hepatitis C patients of these providers, 58% had a sustained viral response as a result of treatment. That was nearly identical to the percentage of sustained viral response in patients seen in person at the academic medical center in Albuquerque.[10] The ECHO study involved 16 community sites and 5 prisons.

Today, the ECHO program encompasses 255 sites, the majority of them in New Mexico [Figure 2]. The Universities of Washington and Nevada have adopted the ECHO strategy in rural areas of their states, and the University of Chicago is using it to help underserved urban patients.

Since its beginning in 2002, Project ECHO™ has grown to include separate hepatitis C virtual "clinics" for communities and prisons, as well as clinics for a range of conditions from addiction to asthma, dementia, diabetes, high-risk pregnancy, and palliative care. Because Project ECHO™ also includes a pain management clinic, this program holds some valuable lessons for pain specialists.

ECHO's chronic pain and headache management clinic includes a neurologist, a psychiatrist and addiction specialist, an internist, a

FIGURE 2: This map illustrates the 255 partner teams in rural areas and prisons in New Mexico that work with ECHO clinics



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family physician, a physiatrist, an interventional pain specialist, and a clinical psychologist. All members of the team attend most of the video teleconferences.

Weekly pain clinics attract an average of 35 primary care providers, including physicians, nurse practitioners, and physician assistants. While some are located in the Albuquerque area, the majority come from rural parts of New Mexico and Oklahoma, with some coming from army hospitals and locations overseas.

Many providers use videoconferencing equipment, including TV sets, speakers, and a high-speed Internet connection to participate in the clinics from their own offices. Some join the clinics via webcam or telephone. If a practice or community health center wants to use videoconferencing and doesn't have the equipment, UNMH technicians will travel to their offices and install it.

Videoconferencing gear for a clinic such as Project ECHO™ is expensive, costing $20,000

Weekly ECHO pain clinics attract an average of 35 primary care providers.

to $30,000 to set up. Project ECHO™ is able to cover the costs of its services through grants from the state of New Mexico and the Robert Wood Johnson Foundation.

Case-based weekly presentations on pain

Project ECHO™ offers one 2-hour pain clinic per week that provides a mix of didactic and hands-on instruction using case-based learning. In addition, providers can present their own challenging cases and receive guidance from the multidisciplinary specialty team. Providers who plan to participate in a pain clinic fill out questionnaires about their patients beforehand, and everyone who wants to present is given an opportunity to do so. Providers are also encouraged to contact ECHO's academic specialists between clinics if they have specific questions about a case.

The main goal of ECHO's pain clinic is to educate rural providers about how to provide comprehensive pain management.

The purpose behind Project ECHO™ is to meet the needs of patients who have difficulty obtaining appointments at the medical center or who may have to travel a long distance to get there. However, the main goal of ECHO's pain clinic is to educate rural providers about how to provide comprehensive pain management themselves, to enable a greater degree of confidence and comfort in prescribing pain medications, and to support providers in striking a balance between offering prescription analgesics and other pain therapies.

Marlene Baska, a PA in Lordsburg, NM, agrees that her participation in ECHO has been very beneficial in treating patients with chronic pain. "The multidisciplinary panel has given me education, suggestions, and guidance on specific cases. It has helped me develop some effective plans of care for my patients. When I see patients with chronic pain, I make them aware of my participation in Project ECHO™ and they're very appreciative."

Baska, who works for Hidalgo Medical Services, a multisite community health center that covers 2 counties, says she has learned to use an integrative approach that combines the appropriate use of opiates with adjunctive medications and referrals to professionals who offer behavioral therapy, massage therapy, acupuncture, physical therapy, occupational therapy, and dietetics.

Measuring outcomes

Measuring outcomes is an important component of the Project ECHO™ design. Providers participating in the pain clinic are trained to use functional status assessments, including the Brief Pain Inventory and the Pain Outcomes Profile of the American Academy of Pain Management. The provider outcomes data show that as a result of training self-efficacy has grown among participants.

The program itself has been assessed and honored. In 2010, Project ECHO™ was a recipient of the American Pain Society's Clinical Centers of Excellence in Pain Management Award.

Only 12 states require insurers to cover telemedicine: California, Colorado, Georgia, Hawaii, Kentucky, Louisiana, Maine, New Hampshire, Oklahoma, Oregon, Texas, and Virginia. To date only one insurance company—Molina, a Medicaid plan—has agreed to pay providers who participate in Project ECHO's™ pain clinics.

What providers who work with Project Echo™ do receive is CME credit, a newfound collegial relationship that reduces professional isolation, and greater confidence in their ability to manage even complex cases thanks to the use of remote technology.

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REMS: red tape, or a remedy for opioid abuse?

A new FDA program will affect how you prescribe opioid analgesics for your chronic pain patients. Here's what you need to know about it.

STEPHEN PORADA
VP REMS Communications and Project Development
Aventine Co.*
Montclair, NJ
*Aventine is a medical communications agency focused on pain and neuroscience and host of the PAINWeek® national conference.

Are you aware that a significant change is coming to the way you prescribe opioid pain relievers for your patients? After 3 years of debate among the Food and Drug Administration (FDA), drug industry stakeholders, members of the pain and addiction communities, patient advocacy groups, and the public, the first large-scale, class-wide REMS is here. REMS is the acronym for Risk Evaluation and Mitigation Strategies. There is a good chance you are prescribing one or more of the affected medications, and adherence to the REMS requirements will be essential if you wish to continue prescribing them.

Before getting into the fine points of the opioid REMS, a little background about how it came into being is in order. On March 25, 2008, the Food and Drug Administration Amendments Act went into effect, granting the FDA authority to require a REMS for any product or product class it deemed to be a public health, safety, or welfare threat. Basically, REMS is an FDA-imposed "safety" program. The first medication to now have a single or class REMS is the class of extended-release (ER) and long-acting (LA) opioid analgesics.

Why opioid analgesics? In 2007, attempts to mitigate targeted risks associated with

After 3 years of debate, the first large-scale, class-wide REMS is here.

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30 drugs using RISKMaps were cited as inadequate by the FDA. RISKMaps are safety programs designed to minimize significant risks of certain medicines through FDA-approved labeling, reporting of adverse events, prescriber and patient education about risks, reminders, and performance-linked access systems that tie access to medications with documentation and laboratory testing.[1] Passage of the FDA Amendments Act allowed the FDA to use its REMS authority to "improve" existing risk plans.

In 2009, primary care physicians were the top prescribers of ER/LA and IR opioid analgesics.

Forces for change

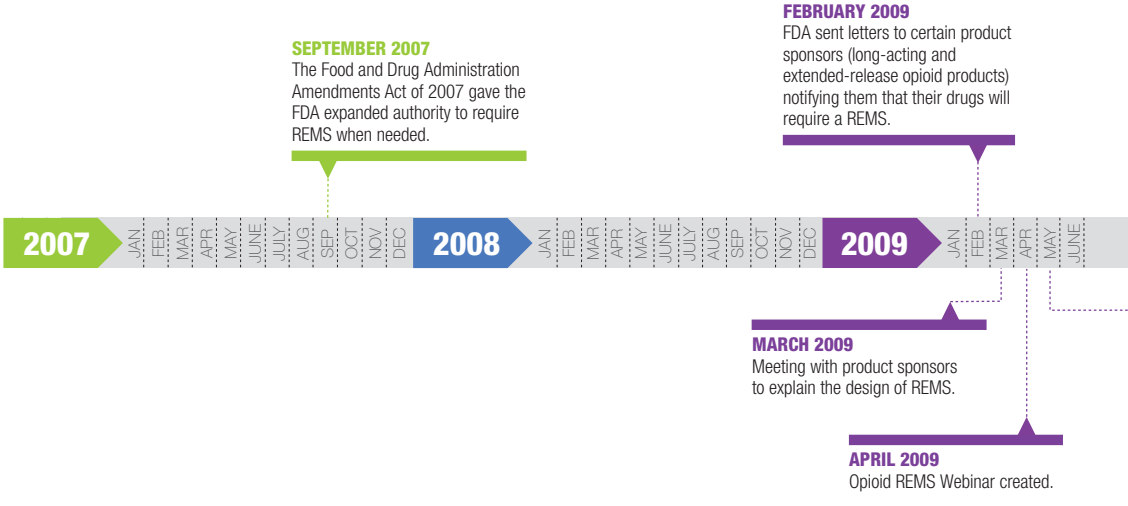
The FDA cites many good reasons for this change, primarily to ensure that the benefits of prescribing opioid analgesics outweigh the risks, and that patients in pain who need these drugs have access to them. Driving factors behind this move centered on the highly visible consequences associated with what FDA experts describe as misuse, abuse, and improper prescribing of 12 ER/LA opioid analgesics. According to FDA estimates, in 2007 more than 33 million Americans age 12 and older misused ER/LA opioids. Of the almost 28,000 Americans who died from unintended consequences of drug use, nearly 12,000 were associated with prescription analgesics.[2]

In my opinion, voluntary continuing medical education (CME) and professional organization guidelines added to the problem by failing to decrease overdoses and unintended deaths. This may come as no surprise, as such deaths often stem from diversion, and diverters typically are not subject to a CME requirement.

The ER/LA segment of the class was targeted for a variety of reasons. First, higher doses of ER/LA opiates packed into single units are believed to pose a greater threat than the millions of short-acting, immediate-release (IR) opioid analgesics units abused annually.[3] Another reason for the move focused on the burden to the health system caused by more than 24 similar individual REMS existing in this class. That alone created a virtual paper, regulatory, and health system encumbrance that is expected to be alleviated by a class-wide REMS.

Increasing numbers of prescriptions were an additional consideration. The number of outpatient retail prescriptions dispensed for ER/LA and IR opiates rose dramatically between 2000 and 2009, from 9.3 million to 22.9 million ER/LA opioids and from 164.8 million to 234 million IR opioids [Figure 1].[3] Who is prescribing them? You are. In 2009, primary care physicians were the top prescribers of ER/LA (43.8%) and IR (42.1%) opioid analgesics [Figure 2].[3] Who are you prescribing them for?

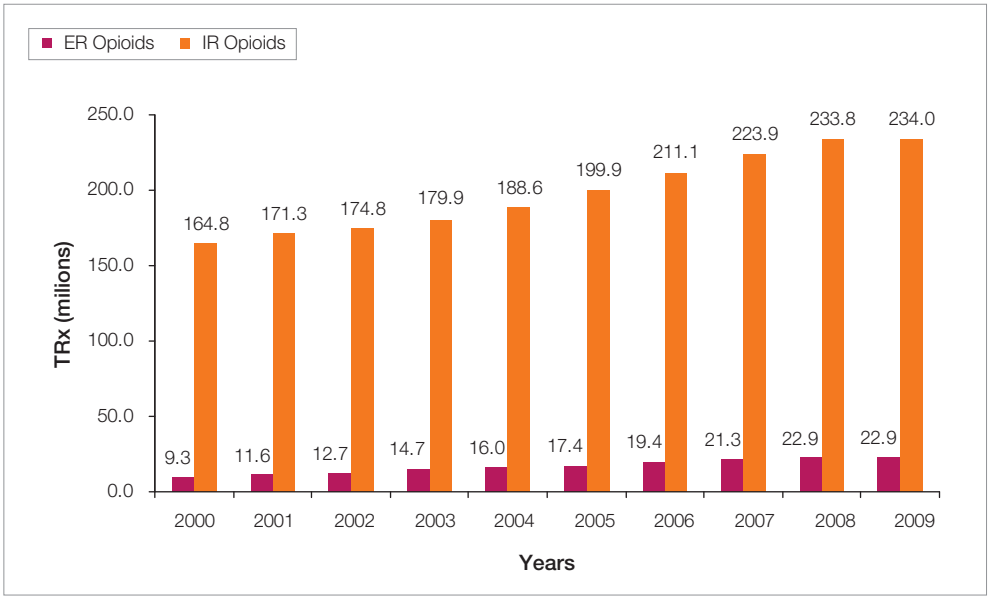
A history of opioid REMS



Not the elderly age group you might expect. The largest number of prescriptions were written for men and women between ages 50 and 59 [Figure 3].[3]

And what are you prescribing them for? Data from a 2009 survey of the prescribing habits of 3200 office-based physicians in 30 specialties showed that most prescriptions

FIGURE 1: Total number of prescriptions dispensed for ER/LA and IR opioids from US outpatient retail pharmacies, 2000-2009



ER, extended release; IR, immediate release; LA, long acting; TRx, total prescriptions.
Source: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM220950.pdf.

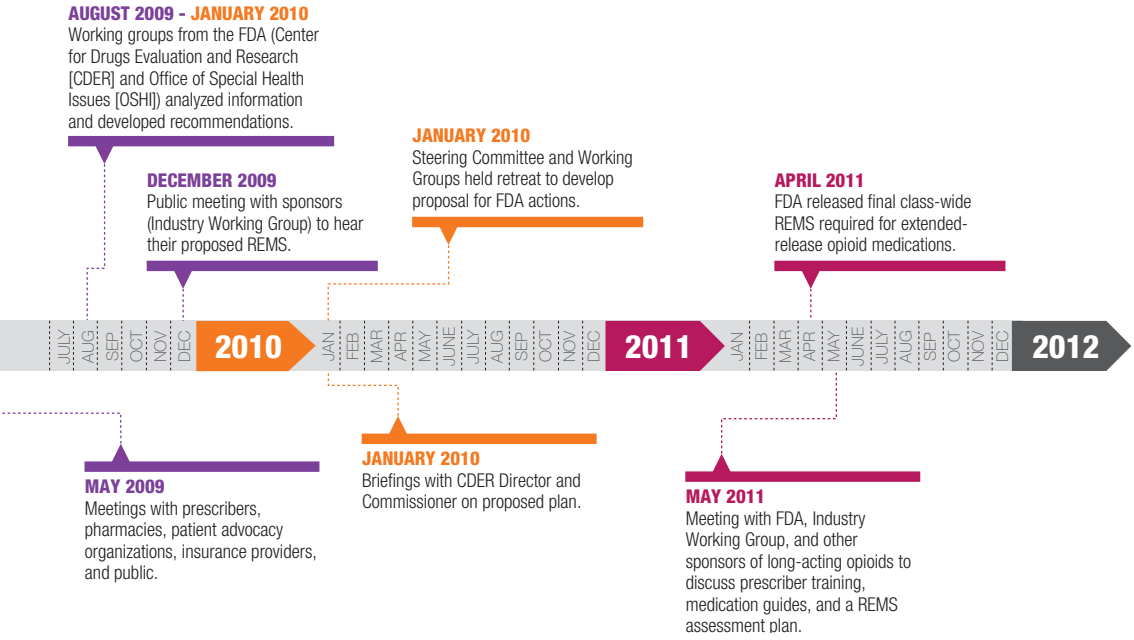
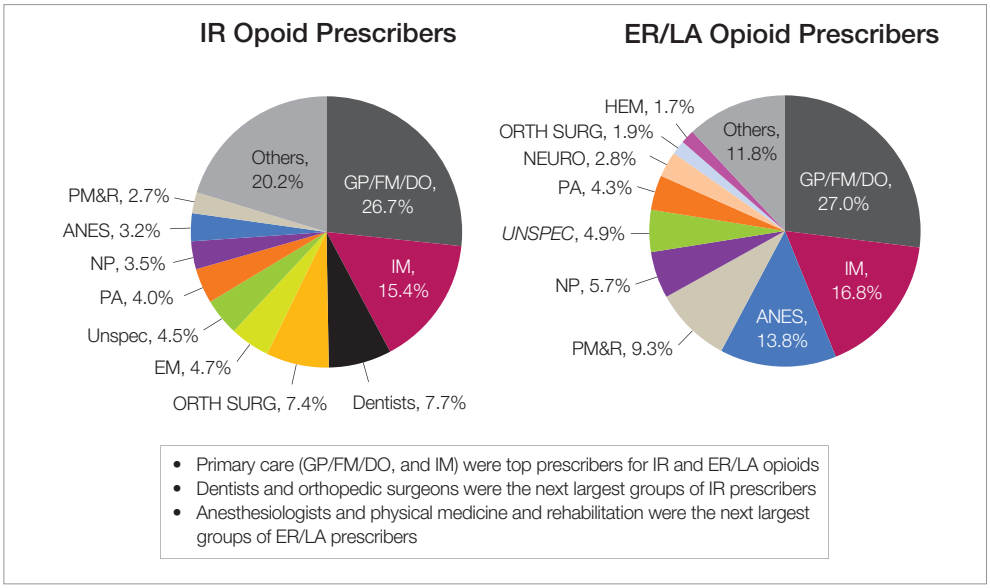


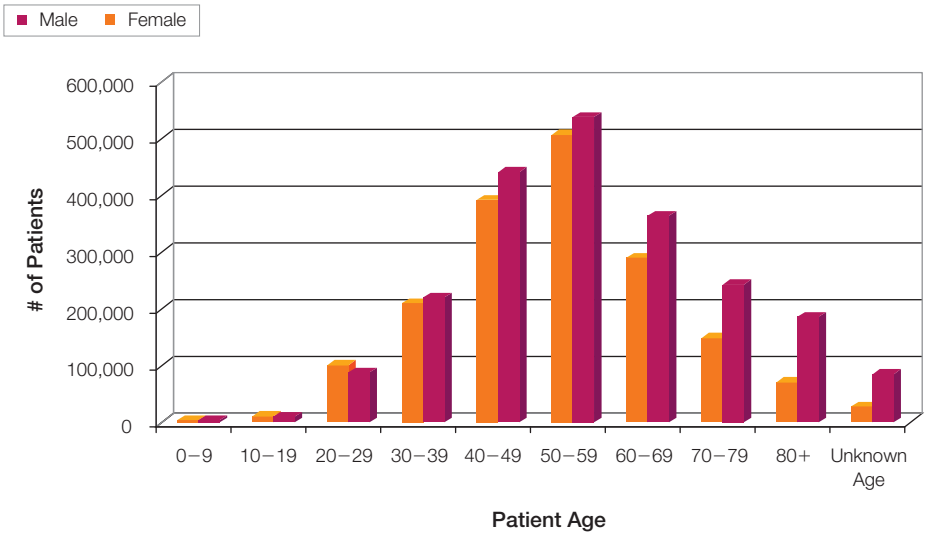
FIGURE 2: Total number of prescriptions dispensed in the United States by top 10 prescribing specialties for IR and ER/LA opioids, 2009



ANES, anesthesiologist; DO, doctor of osteopathy; EM, emergency medicine; ER, extended release; FM, family medicine; GP, general practitioner; HEM, hematologist; IM, internal medicine; IR, immediate release; LA, long acting; NP, nurse practitioner; ORTH SURG, orthopedic surgeon; NEURO, neurologist; PA, physician assistant; PM&R, physical medicine and rehabilitation; TRx, total prescriptions.

Source: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM220950.pdf.

FIGURE 3: Total number of unique patients, stratified by age and sex, receiving a dispensed prescription for an ER/LA opioid product from US outpatient retail pharmacies, 2009

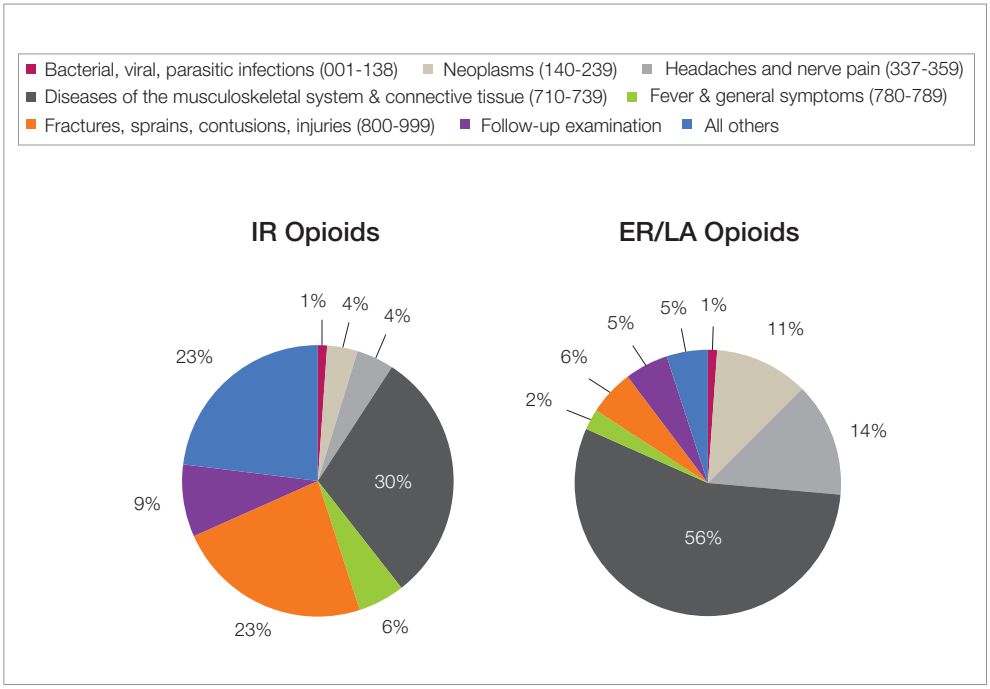


ER, extended release; LA, long acting.

Source: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM220950.pdf.

written for ER/LA and IR opioids are associated with diagnoses related to pain in the musculoskeletal system and connective tissue (56% [ER/LA] and 30% [IR]). For ER/LA prescriptions the second most common diagnoses were headaches and nerve pain (14%), while for IR prescriptions they were fractures, sprains, and contusions (23%) [Figure 4].[3]

FIGURE 4: Diagnoses associated with use (by grouped ICD-9 codes) for IR and ER/LA opioids as reported by office-based physicians in the United States, 2009



ER, extended release; IR, immediate release; LA, long acting.
Source: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM220950.pdf.

According to Janet Woodcock, MD, Director of the FDA's Center for Drug Evaluation and Research, some physicians may not be clear about who should receive these drugs or how to manage patients in pain. As a result, some physicians may be reluctant to prescribe opioid analgesics, leaving patients without adequate pain relief. At the same time, other physicians overprescribe them, putting patients—and anyone with access to the family medicine cabinet—at risk.[4]

A REMS by any other name

And so REMS was conceived. On February 6, 2009, manufacturers of certain opioid drug products received a letter from the FDA informing them that their drugs would be required to have a risk management program, and inviting them to meet to discuss the design and development of such a REMS.[5]

Two years later, on April 19, 2011, an alarm in the form of an action plan was released by the Obama administration through the Office of National Drug Control Policy. The plan, *Epidemic: Responding to America's Prescription Drug Abuse Crisis*, outlined a set of measures to remedy the problem through education, monitoring, proper disposal of prescription drugs, and enforcement.[6]

REMS for opioids was the FDA's response in support of the President's plan. On the same day in April, 32 manufacturers of ER/LA opioids received a letter from the FDA informing them that they must meet new safety requirements concerning these medications under a single shared, standardized system [Table].

As outlined in this REMS, manufacturers must provide for the training of prescribers of opioid medications—training that covers proper patient selection, patient counseling in specific product use and risk, and assessment for addiction and tolerance. Manufacturers must also develop factual, nonpromotional patient information and medication guides that will be FDA regulated and approved. Finally, they will be asked to adhere to a timetable to assess whether REMS is meetings its goals.[4,5]

In May 2011, the FDA met with manufacturers to expand on how to coordinate and implement the REMS requirements.

Your decision to participate in REMS will need to be made soon.

TABLE
Long-acting and extended-release opioids requiring an opioid REMS*

Brand Name Products

	Trade Name	Generic Name	Sponsor
1	Duragesic	Fentanyl transdermal system	Ortho-McNeil-Janssen
2	Dolophine	Methadone HCl tablets	Roxanne Laboratories
3	Avinza	Morphine sulfate extended-release capsules	King Pharmaceuticals/Pfizer
4	Kadian capsules	Morphine sulfate extended-release capsules	Actavis
5	MS Contin	Morphine sulfate controlled-release tablets	Purdue Pharma
6	Oramorph	Morphine sulfate sustained-release tablets	Xanodyne Pharmaceuticals
7	OxyContin	Oxycodone HCl controlled-release tablets	Purdue Pharma
8	Opana ER	Oxymorphone HCl extended-release tablets	Endo Pharmaceuticals
9	Exalgo	Hydromorphone HCl extended-release tablets	Mallinckrodt Inc/Covidien
10	Butrans	Buprenorphine transdermal system	Purdue Pharma

Generic Products

	Drug Name	Generic Name	Sponsor
1	Fentanyl	Fentanyl extended-release transdermal system	Actavis
2	Fentanyl	Fentanyl extended-release transdermal system	Lavipharm Labs
3	Fentanyl	Fentanyl extended-release transdermal system	Mallinckrodt Inc/Covidien
4	Fentanyl	Fentanyl extended-release transdermal system	Mylan Technologies
5	Fentanyl	Fentanyl extended-release transdermal system	Noven Pharmaceuticals
6	Fentanyl	Fentanyl extended-release transdermal system	Teva Pharmaceutical Industries
7	Fentanyl	Fentanyl extended-release transdermal system	Watson Pharmaceuticals
8	Methadone hydrochloride	Methadone HCl tablets	The Pharmanetwork
9	Methadone hydrochloride	Methadone HCl tablets	Mallinckrodt Inc/Covidien
10	Methadone hydrochloride	Methadone HCl tablets	Sandoz

TABLE (continued)
Long-acting and extended-release opioids requiring an opioid REMS*

Generic Products

	Drug Name	Generic Name	Sponsor
11	Methadone hydrochloride	Methadone HCl oral solution	Roxane Laboratories
12	Methadone hydrochloride	Methadone HCl oral solution	VistaPharm
13	Morphine sulfate	Morphine sulfate extended-release tablets	Endo Pharmaceuticals
14	Morphine sulfate	Morphine sulfate extended-release tablets	KV Pharmaceuticals
15	Morphine sulfate	Morphine sulfate extended-release tablets	Mallinckrodt Inc/Covidien
16	Morphine sulfate	Morphine sulfate extended-release tablets	Watson Pharmaceuticals
17	Morphine sulfate	Morphine sulfate extended-release tablets	Rhodes Pharmaceuticals
18	Oxycodone hydrochloride	*Oxycodone HCl extended-release tablets	Mallinckrodt Inc/Covidien
19	Oxycodone hydrochloride	*Oxycodone HCl extended-release tablets	Impax Laboratories
20	Oxycodone hydrochloride	*Oxycodone HCl extended-release tablets	Teva Pharmaceutical Industries
21	Oxycodone hydrochloride	*Oxycodone HCl extended-release tablets	Endo Pharmaceuticals
22	Oxymorphone hydrochloride	Oxymorphone HCl extended-release tablets	Impax Laboratories
23	Oxymorphone hydrochloride	Oxymorphone HCl extended-release tablets	Actavis

*Tentatively approved products.
Source: U.S. Food & Drug Administration Web site. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm251735.htm.

Hope for a "new normal"

Will REMS for other large medication classes eventually reach beyond opioid analgesics, perhaps warranting practitioners to view REMS as being a good thing as opposed to a nuisance? Your decision to participate in REMS or pass and alter your care approach will need to be made soon. What will you do?

For you as an opioid prescriber, education is the focus, and you will soon be presented with voluntary prescriber education programs. The "hope" is that you will volunteer to take the opioid education program, fill out an electronic or fax form, and send it in to an administrator who will track all those who participate. Since "hope" will unlikely drive large-scale participation, when hope finally runs out the education will become mandatory. This will occur in a year or 2, and will likely become a Drug Enforcement Administration requirement for you to procure CII scheduling.

Unfortunately, there is no guarantee that deaths and overdoses will stop with the opioid REMS. The only guarantee is you will not be able to prescribe these medications at some point if you do not participate in the REMS.

So act now. To be notified when the opioid REMS training becomes available go to www.opioidREMS.com and register. It's vital that you do ... and relatively painless.

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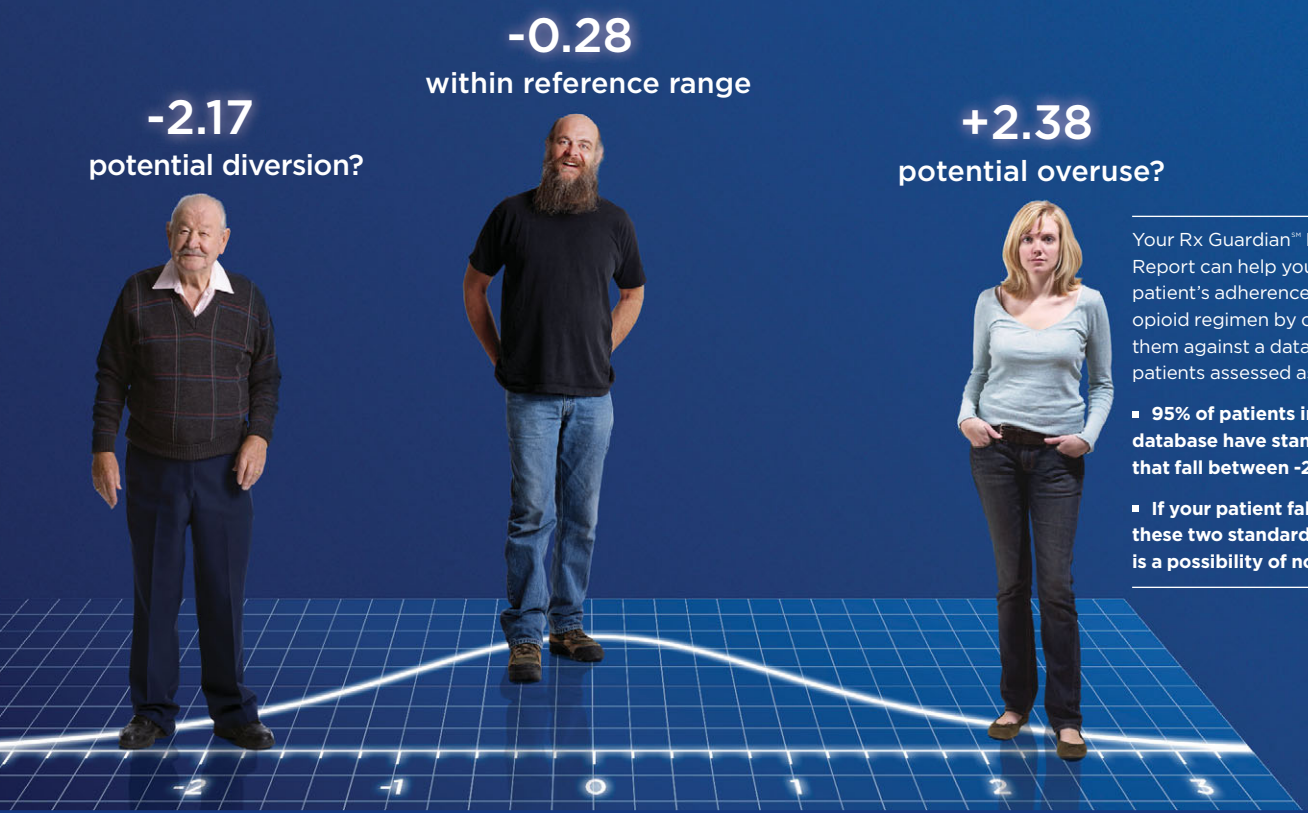
PRESCRIBING OPIOIDS?
KNOW WHERE THEY STAND



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1. Bronstein K, Passik S, Munitz L, Leider H. Can clinicians accurately predict which patients are misusing their medications? Poster presented at: American Pain Society 30th Annual Scientific Meeting; May 18–21, 2011; Austin, TX.

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