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Learning Objectives

After reading the three-part newsletter series for 2005, participants should be able to:

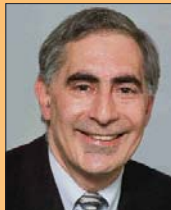
- Differentiate chronic pain from acute pain and describe the mechanisms of pain and sites of activation.
- Address common barriers that limit effective pain management for patients with chronic pain.
- Determine the recommended components for comprehensive assessment of pain and function in patients with chronic pain.
- Select more varied pharmacologic and nonpharmacologic strategies for initial and ongoing management of chronic pain.
- Describe therapeutic approaches to minimize potential adverse effects and drug interactions and identify safety issues and precautions.

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This is the **third issue of a three-issue CME newsletter series.**

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AN EXCLUSIVE INTERVIEW WITH DR BILL MCCARBERG

Risk Management in the Primary Care Setting

Nathaniel P. Katz, MD

Please describe your practice.

I have approximately 3,300 patients assigned to me: 20% are over the age of 75 and 40% over 60. I've garnered a huge chronic pain population, which is largely younger than the one I just described, who see me specifically because of chronic daily headache, myofascial pain, fibromyalgia, or back pain. I typically see 30 patients, get some 30 phone calls that require clinical decisions, and receive about 50 electronically generated prescription refill requests each day. Ideally, I would like to review the charts of all patients for refill requests, but, because of time constraints, usually only manage to screen the charts of those requesting opioid analgesics, specifically to determine if the timing for the refill is correct, among other concerns. The majority of my practice centers on pharmacotherapy and the issues involved in determining which medications and/or alternative therapies are appropriate in each situation. In the case of controlled substances, especially here in California, such safety factors as proper documentation, following state board requirements and guidelines, and submitting the proper forms, are major concerns for any primary care physician (PCP) treating pain patients.

How do you determine which medications are appropriate for your chronic pain patients?

It depends on the patient's diagnosis, pain level, history, and on my understanding of that patient's condition. It's all very personal and depends on my relationship with the patient

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Bill H. McCarberg, MD, founder of the Chronic Pain Management Program for Kaiser Permanente in San Diego, California, and its director until 2003, speaks with Nathaniel Katz, MD, past chair of the Advisory Committee to the FDA Division of Anesthetics, Critical Care, and Addiction Drug Products, on the safety concerns, risk management, and regulatory issues surrounding pain management from the primary care perspective. Dr McCarberg currently practices family medicine at Kaiser Permanente in San Diego and is an assistant clinical professor (voluntary) for the University of California, San Diego.

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Treating Pain: A Perfect Storm of Controversy and Confusion

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As we enter the second half of the Decade of Pain Control, we have seen tremendous gains in the awareness of pain and pain control, as well as some obstacles that few of us may have predicted. Recent unprecedented media coverage of issues related to pain management has emphasized not only the need for increased education on pain and its treatment, but also the staggering increase in prescription drug abuse and its collateral impact on pain care. These articles and programs have called attention to the fact that although medicine has succeeded at curing diseases and extending life, it has not done as well at improving quality of life. A recent ABC News/USA TODAY/Stanford University poll found that chronic pain affects one in five Americans with the majority being older people.¹ The results suggest that our "cure-focused" medical system is now at risk of creating victims of its own success.

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Drug Safety Update

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Drug safety is a concern of patients, clinicians, regulators, and the media. In perhaps the most widely publicized cases, rofecoxib (Vioxx) and valdecoxib (Bextra) were voluntarily withdrawn from the worldwide market due to emerging evidence of cardiovascular risks. This has recently led Pfizer Inc to fund a study involving 20,000 patients to determine the potential heart risk of its painkiller, celecoxib (Celebrex). Ironically, these events have decimated sales of the COX-2 inhibitors, a new class of analgesics that achieved blockbuster status based on evidence of improved gastrointestinal safety compared with traditional nonsteroidal inflammatory drugs (NSAIDs). Gabapentin (Neurontin) became the drug of choice based on the perception that it is safer for patients with neuropathic pain than the traditional alternative, tricyclic antidepressants. Tramadol (Ultram, Ultracet) is an opioid analgesic that has been successfully marketed based on the perception that it is safer from an abuse liability perspective than “strong opioids.” The success of these analgesics is clearly not based on efficacy, since evidence confirms that these products are, at best, equally efficacious compared with the alternatives. Safety sells, and for good reason. The maxim “First do no harm” is well-ingrained in the medical mindset. On the other hand, drugs with perceived safety risks quickly disappear from the market, and in doing so raise intense interest in the process by which the American public is protected from the harmful effects of pharmaceutical products.

In this issue, we present two interviews with individuals working in the forefront of safety and efficacy in Pain Medicine (see pages 1 and 3). Bill McCarberg, MD, is a family physician working in California and focusing primarily in pain management. He has long been an advocate for the role of the family physician in pain treatment, and will address the impact of drug safety concerns in primary care. Cynthia McCormick, MD, was the director of the Division of Anesthetic, Critical Care, and Addiction Drug Products of the FDA from 1997 to 2002, and is a leading expert on the regulatory aspects of analgesics. Their juxtaposed perspectives will provide the practicing clinician a much needed update on what is happening in drug safety. Of related interest is a timely article by Scott M. Fishman, MD, which discusses the recent issues and controversies related to pain management and their subsequent impact on physicians' practices (see page 1). Finally, to round out this special issue on drug safety and risk management, an article on the benefits and risks of chronic pain medications offers a concise review of pharmacologic options available to treat patients suffering from chronic pain (see page 4). *CS*

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This educational activity is a component of the NIPC[®] and is designed to heighten the knowledge of physicians and other healthcare providers about the serious impact of unresolved pain on patient care. Some of the agents included in this newsletter are discussed in the context of uses for which they have not been approved by the FDA.

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ABOUT THE NIPC

The National Initiative on Pain Control[®] (NIPC[®]) is an integrated CME education initiative that was established in 2001 to help physicians improve outcomes for their patients who have pain.

Living with pain has deleterious effects on many aspects of the patient's life, including deterioration of physical functioning, the development of psychological distress and psychiatric disorders, and impairment of interpersonal functioning. Of special concern, less-than-optimal training of physicians in pain disorders has led to the underassessment and undertreatment of patients who are living with pain. The program heightens physician awareness of the impact of pain on patient's daily living in terms of quality of life, lost workdays, and societal/familial consequences.

NIPC addresses the barriers to achieving pain control by providing potential pathways for action and expected amelioration of their patients' pain. By providing physicians with the latest advances and strategies in pain management, they will be better able to translate clinical data into clinical practice.

All NIPC programs are developed and continuously evaluated by the NIPC Education Council, an expert, multidisciplinary team of specialists, researchers, and practicing physicians in pain management. The NIPC Faculty includes nationally respected experts in the pain management field.

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AN EXCLUSIVE INTERVIEW WITH DR CYNTHIA McCORMICK



Insights into the FDA and Drug Safety

Nathaniel P. Katz, MD

Cynthia G. McCormick, MD, is a clinical and regulatory consultant in private practice in Bethesda, Maryland. Dr McCormick was Director of the Division of Anesthetic, Critical Care and Addiction Drug Products at the Food and Drug Administration (FDA) from 1997 to 2002.

During that time, she oversaw the review and approval of drugs for the treatment of pain and initiated strategies aimed at standardizing the development of drugs for pain. Dr McCormick previously worked at the National Institute of Neurological Disorders and Stroke at the National Institutes of Health (NIH). Dr McCormick discusses drug safety issues from the regulatory perspective with Dr. Nathaniel Katz, the past chair of the Advisory Committee to the FDA Division of Anesthetics, Critical Care, and Addiction Drug Products.

Dr McCormick has indicated that she is a consultant for Abbott, Acura, Alexza, Allergan, Alpharma, ARIUS, Avaniir, Avera, Cephalon, Dainippon, Depomed, DOV, Endo, EpiCept, GW Pharmaceutical, Johnson & Johnson, Kadmus, King, Labopharm, Medtronic, NeurogesX, Pain Therapeutics, Pozen, QRX, Ranbaxy, Schwartz, TheraQuest, Xenoport.

Dr Katz has indicated that he is a research consultant for Abbott, Adolor, Alpharma, Alza, Biovail, Cephalon, Dara, DOV, Endo, Forest, Grunenthal, GlaxoSmithKline, GW Pharmaceuticals, Janssen, Johnson & Johnson, NeurogesX, Neuromed, Pfizer, Purdue, QRX, Rinat, and Sontra.

Can you give a broad overview of how the FDA regulates drug safety?

The US Federal Food, Drug, and Cosmetic Act requires that drug approval is based on evidence of both safety and efficacy. Therefore, the FDA reviews both safety and efficacy data. Drug safety data are obtained first in animals and later in humans, in both healthy volunteers and patients with the disorder for which the treatment is developed. In clinical trials, safety data is accumulated after the drug is exposed generally to 1,500 patients or more and for up to a minimum of a year. Over time, this accumulated exposure creates a safety profile that can be evaluated against a comparator drug, placebo, or even a different dose of the investigated drug. In addition to administering the drug in the target population, the pharmaceutical company, known as the drug sponsor, will also evaluate the potential for interaction with other drugs and how the drug behaves in different groups of patients with regard to age, sex, and concomitant diseases. The FDA works with the sponsor in developing a package insert, or label, which describes that safety profile and cautions physicians to use the drug safely.

Could you also give us an introduction to the Office of Drug Safety, how it came about, and what will be different with it?

Drug surveillance of postmarketing adverse events has always been a responsibility shared by the FDA review divisions who approve the drugs and the postmarketing surveillance arm of the FDA who monitor the safety of the drug after approval. To avoid duplication of effort and to take maximum benefit from the skills of the postmarketing safety group, the responsibility for assessing reports of adverse events associated with approved drugs is focused primarily in the Office of Drug Safety. The Office of Drug Safety has been elevated to the same stature as the Office of New Drugs. Further-

more, in addition to the Medwatch program developed as a passive surveillance reporting system there are other programs that involve active surveillance and risk management evaluation, enabling the Office of Drug Safety to take a more proactive role in all aspects of postmarketing surveillance.

What do you think will be the consequence of the FDA's increased presence in all these decision-making areas?

We are going to see much more consistency across related products, a greater focus on risk communication, and a more collaborative interaction with pharmaceutical companies in developing risk management and postmarketing surveillance strategies. We are already beginning to see a greater interest in active surveillance in the area of pain therapeutics, particularly with the abuse potential of opioid analgesics.

How does the FDA react to a safety concern with a drug that is already on the market?

The FDA has many options for dealing with new safety concerns. Often the FDA meets with the sponsor to develop a plan for evaluating the safety concern. This plan may involve immediate or delayed action depending on the severity of the events and the likelihood that the drug is responsible. Sometimes a safety signal has been observed prior to approval but was of such small magnitude that it was not thought to be related to the drug. In such cases additional data may be required. Sometimes a signal might arise in a group of patients due to unapproved use, that is, one that was not evaluated prior to approval. Here the intervention may involve risk management strategies to reduce unapproved use. When the FDA detects a safety signal that it believes is drug related but whose seriousness has not yet been identified, the FDA may publish an advisory to alert both physicians and patients. In other

cases, an adverse event may be described in the precautions or warnings to the package insert or label. If the significance of the signal is not clear or not fully defined, large long-range Phase 4 trials may be required, as was the case with cyclooxygenase-2 (COX-2) inhibitors. Depending upon the population, risk thresholds vary. For instance, a very small and very ill population with few therapeutic alternatives might be able to accept a risk of a serious adverse event if given adequate warnings. On the other hand, a very large, potentially healthy population may not be willing to accept such a risk, and so the FDA's approach to these very different situations may be tailored to the clinical setting.

Does the FDA have sufficient authority to make pharmaceutical companies comply in a timely and expeditious manner with requests for additional safety studies?

The FDA has significant influence with pharmaceutical companies in requesting them to perform postmarketing studies. Sponsors will generally comply with such requests when there are important safety issues in question. The FDA does have the authority to withdraw a drug from the market if not appropriately labeled for a serious risk, but such actions are rare and generally occur by mutual agreement.

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Excerpts from a speech made before the American Pain Foundation on December 8, 2005, by Scott Gottlieb, MD, Deputy Commissioner for Medical and Scientific Affairs, Food and Drug Administration.

"The FDA views pain as a very important area of medicine and often undertreated and still not well understood and managed. The Agency is aware of the need for novel analgesic drug products and is supportive of all efforts to improve the analgesic armamentarium."

"Pain is something complex, often enigmatic and sometimes intangible that must be treated with full respect and compassion."

"The mission of medicine - and to all of us involved in the medical enterprise, especially the dedicated men and women of the FDA - is to promote healing where possible, to comfort always, and above all to avoid harm."

Chronic Pain Medications: Benefits vs Risks

Mark Palangio

Medical Writer, Thomson Professional Postgraduate Services[®]

Mr Palangio has indicated that he has no relevant financial relationships.

The goals of pain management are pain relief and improved function. To achieve these goals, an optimal treatment plan should encompass a biopsychosocial approach and address biological, psychological, and social aspects of the patient. This article, however, focuses only on pharmacotherapy, a major cornerstone of chronic pain management. Numerous pharmacologic agents, broadly classified as non-opioid, opioid, and adjuvant analgesics, have been developed, each with benefits and risks.^{1,2} A concise summary of these agent classes is presented below.

Non-opioid Analgesics

Non-opioid analgesics represent a pharmacologically heterogeneous group of agents that include nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen, and aspirin and other salicylates.^{1,2} Non-opioids are usually administered orally, although topical, parenteral, and rectal forms are available. Many formulations of NSAIDs, acetaminophen, and aspirin are available without a prescription. Used alone, non-opioid analgesics are effective for mild pain, and certain NSAIDs are even capable of relieving moderate pain. All non-opioids have a dosage ceiling (ie, a dose above which side effects worsen but no additional analgesia is achieved).

NSAIDs are commonly used to treat pain associated with rheumatoid arthritis, osteoarthritis, primary dysmenorrhea, and acute migraine headache. Benefits of NSAIDs include analgesic, antipyretic, and antiinflammatory effects. NSAIDs control pain primarily by inhibiting the synthesis of prostaglandins by cyclooxygenase (COX) in peripheral tissues.

Two forms of COX enzymes exist: COX-1 and COX-2. COX-1 is constitutively expressed in most tissues and produces prostaglandins that are beneficial to the gastrointestinal (GI) tract, kidneys, and platelets. In contrast, COX-2 is induced in response to inflammatory stimuli and produces prostaglandins that activate and sensitize nociceptors. Nonselective NSAIDs inhibit both COX-1 and COX-2 enzymes, whereas selective NSAIDs (“coxibs”) primarily inhibit the COX-2 enzyme. Examples of nonselective NSAIDs are ibuprofen (Advil,

Motrin), naproxen (Aleve, Naprosyn), naproxen sodium (Anaprox), diclofenac (Voltaren, Cataflam), and aspirin. Celecoxib (Celebrex) is the only selective COX-2 inhibitor currently on the market.

The most important side effect of nonselective NSAIDs is GI toxicity (eg, dyspepsia, ulceration, perforation, hemorrhage). Because the COX-1 enzyme produces prostaglandins that protect the lining of the GI tract, use of a selective COX-2 inhibitor might avoid GI problems, while providing comparable efficacy to a nonselective NSAID. It should be noted, however, that the selective COX-2 inhibitors rofecoxib (Vioxx) and valdecoxib (Bextra) were recently withdrawn from the market because of an increased risk for heart attack and stroke (see Table 1). It is speculated that rofecoxib and valdecoxib have prothrombotic effects that contribute to cardiovascular events. Additionally, the Food and Drug Administration (FDA) recently requested changes in the labeling of celecoxib and 18 nonselective NSAIDs to underscore the heightened risk of cardiovascular events.³ Strategies for the safe use of NSAIDs involve selecting patients at low risk of thrombotic events (eg, no history of ischemic heart disease or stroke, low risk-factor profile for vascular disease), initially prescribing agents with the lowest risk of thrombotic events, minimizing treatment duration, prescribing the lowest effective dose, and monitoring patients closely.⁴

Common side effects of NSAIDs as a class include headache, dizziness, drowsiness, and rash. Uncommon and rare side effects are hypersensitivity and bronchospasm in

patients with asthma or nasal polyps, elevated liver enzymes, nephrotoxicity, hypertension, and bleeding disorders. Because the COX-2 enzyme is vital to maintaining renal perfusion, both nonselective NSAIDs and selective COX-2 inhibitors can cause kidney damage and renal failure. Furthermore, NSAIDs can interact with warfarin, digoxin, beta-blockers, diuretics, and angiotensin-converting enzyme inhibitors. Celecoxib is contraindicated in patients who are allergic to sulfonamides.

Acetaminophen (Tylenol) is an alternative to NSAIDs for treating mild pain.¹ Although its mechanism of action is unclear, acetaminophen might inhibit prostaglandin synthesis in the central nervous system (CNS), in addition to blocking peripheral pain impulses. Unlike NSAIDs, acetaminophen has negligible antiinflammatory actions.

Acetaminophen has a low side-effect profile at therapeutic doses and does not damage the gastric mucosa or inhibit platelet function, as do NSAIDs and aspirin.^{1,2} Acute or chronic acetaminophen overdose may lead to liver or renal toxicity. Serious or fatal cases of liver toxicity have been reported with acetaminophen overdose and rarely with therapeutic doses among patients at increased risk for hepatic complications (eg, alcohol abusers and patients with hepatitis or cirrhosis). To avoid accidental overdose, patients taking prescription combination analgesics containing acetaminophen should be cautioned not to use nonprescription acetaminophen products. Additionally, acetaminophen may increase the anticoagulant effects of warfarin.

Aspirin, which also works by inhibiting prostaglandin synthesis, is equivalent in efficacy to other non-opioid analgesics and can precipitate upper GI disturbances and bleeding. Salicylate salts such as choline magnesium trisalicylate (Tricosal, Trilisate) are NSAID preparations with fewer GI side effects than aspirin and no effect on platelet aggregation or bleeding time.

Other non-opioids with mechanisms distinct from NSAIDs, acetaminophen, and aspirin are available for treating chronic pain. Tramadol (Ultram), a weak mu opioid agonist that also inhibits the reuptake of norepinephrine and serotonin, is approved for the management of moderate to moderately severe pain and is not scheduled by the Drug Enforcement Administration, as are opioids. Taken orally, the parent compound (tramadol) and a primary metabolite are both active and have a complementary 2-fold mechanism of action. Common side effects include dizziness, nausea, constipation, headache, and sedation. Corticosteroids may

Table 1. US Regulatory Status of Selective COX-2 Inhibitors

COX-2 Inhibitor	Status
Celecoxib	Approved December 1998
Rofecoxib	Approved May 1999 Withdrawn September 2004
Valdecoxib	Approved November 2001 Withdrawn April 2005

Risk Management

CONTINUED FROM COVER

that I've developed over a long period of time. Basically it depends on what I think is generating the pain, whether it's neuropathic or nociceptive pain. If I think it's neuropathic, and I think the patient can tolerate a drug, I have a list of drugs that I try. My organization requests that I first try a tricyclic antidepressant, such as amitriptyline or nortriptyline, and I do that if I think the patient can tolerate it. But if I don't think the patient can tolerate it, because of age, I will probably try an anticonvulsant next. If the pain level is high and it's neuropathic, I may try two drugs simultaneously, such as an anticonvulsant and an opioid, or an anticonvulsant and a topical analgesic, such as the lidocaine patch 5%.

How do you handle the safety factors for controlled substances that you mentioned above, such as proper documentation and state board requirements?

First of all, you have to consider your specific state law requirements regarding controlled substances. For me that is the Intractable Pain Act in California, which involves multiple factors. As to documentation, when I see a patient for the first time, I consider if there is a specific diagnosis based on appropriate history and physical examination. At follow-up visits, I routinely use the four As as guidelines to quickly monitor my patients for level of pain, functionality, side effects, and diversion. The As stand for analgesia, activities of daily living, adverse reactions, and aberrant behavior and provide a practical assessment tool for physicians. As to safety with controlled substances, I usually prescribe medication for only a month at a time; if there are additional risk factors, prescribe smaller amounts. I routinely use contracts or patient agreements, do urine drug screening when appropriate, and I see patients every 6 months because that's what the state law requires.

Have the recent safety issues related to NSAIDs and COX-2 inhibitors influenced the primary care management of pain?

Currently, most of my colleagues are not using COX-2s. Most were using them because they thought the COX-2s were intrinsically safer than other medications and guidelines recommended them. However, most stopped once all of the cardiovascular issues surfaced. The general feeling in the primary care environment is that COX-2 selective or the non-selective agents are not very dangerous, and most of what has been published about the COX-2 agents is overblown. Although these drugs are really not as dangerous as portrayed in the media, they, like any drug, can be potentially dangerous, depending on the relative risk for the particular patient. And the impact from the media coverage has been dramatic. I have elderly patients who were getting life-enhancing improvements from nonsteroidals, yet they have stopped taking them. I can't even discuss the risks and bene-

fits with these patients because they've already made up their minds. Many of these patients used these drugs intermittently, taking them only when their back hurt or their arthritis flared up, but not on a daily basis. So, considering these drugs from that perspective they probably aren't as dangerous as the long-term studies show.

How do you handle such situations in your practice? How much do you allow your patients to impact on your therapeutic decisions?

My first premise is that the patient is right. If a patient doesn't want to take a drug because he or she feels it is too risky, then that patient is right. Even if their perception of the risk is wrong—they have overblown the risk based on what they have heard or read—I will try to discuss that fact with them, but in reality I don't think we should try to persuade patients to take drugs that they consider to be too risky. There's a variety of reasons for that. For example, if a patient does have a side effect, you are at high liability. I try to find out why patients think a drug is so risky, where they got their information, and if they had been taking a drug and stopped, if the medication had helped and in what way. This usually leads to a discussion of how pain is affecting their functionality and ultimately which is greater, the risk or their suffering.

Let me use an example. When the Women's Health Initiative study on hormone replacement therapy (HRT) was published a couple of years ago and showed that the risks of HRT were greater than the benefits, most women in my practice stopped the therapy. Many, however, discovered that the side effects and lack of quality of life were worse than the risks of the therapy and elected to continue HRT. It boils down to deciding if the quality is worth the risk, and exactly how much risk there is. These are the kinds of discussions we as PCPs should be having with our patients about pain management, whether considering treatment with opioid analgesics, COX-2 selective agents, or any of the nonsteroidals. Is the quality worth the risk, and exactly how much risk is there?

What role should the media play in covering drug safety issues?

Most importantly, I think the coverage should be more balanced. With all drugs there is a risk-benefit ratio. The media should not minimize the fact that there are risks in taking COX-2 selective agents, because the fact is that deaths have occurred. However, it also needs to be emphasized that the risks seem to be equal throughout the entire class of nonsteroidals. While there are some increased risks with the COX-2s, this fact was overblown, while the fact that not treating pain causes great disability was totally underplayed. You need to know the risks and you need to know the benefits. The media has lost sight of this benefit side of the risk-benefit ratio. It's all about risk and placing blame.

What would be most beneficial in helping you in your day-to-day practice achieve this balance of the risk vs benefit ratio with all the different pharmacotherapeutics for pain treatment?

There is a certain large segment of the primary care population that would just like to refer pain patients to a specialist. Because that is not possible, what would be most helpful would be a definitive consensus on how to treat a patient for pain given various parameters. There are so many different algorithms and guidelines that it is totally daunting for the PCP. For instance, managed care tells us we have to start with a tricyclic antidepressant, but the pain experts say that's dangerous. What can we do? It's said that doctors do not want to be using clinical cookbooks, but when you've got 7 minutes with a patient, you'd love to have a cookbook. We don't have that for pain. Even when we send the patient to a specialist, there are often very mixed messages, which tends to produce even more confusion for PCPs. Pain specialists need to get together as a group and decide the best treatment approaches and develop a more definitive algorithm than is currently available. Finally, we need guidelines with recommendations that are agreeable as well with industry and insurance regulations.

Considering that approximately half the US population suffers from chronic pain, why isn't this being done?

There is just not enough clinical evidence based on long-term trials for chronic pain conditions, and guidelines are not going to be published without evidence. What do PCPs do in the absence of guidelines? We use the best information we have, largely based on experience and what we've read. I think that one of the problems is simply lack of knowledge. By this I mean lack of knowledge first of all in correctly diagnosing neuropathic pain and lack of knowledge of what specific drugs and general classes of drugs have been shown to be helpful in managing neuropathic pain and the parameters for choosing one agent over another. [For more information on chronic pain medications see article on page 4.] For example, if a patient is frail and elderly, and has localized pain, and side effects, especially systemic side effects, are a concern, the topical agents are the best option. For patients with other clinical profiles, an anticonvulsant, antidepressant, or opioid analgesic may be a better choice. Actually there is some progress being made regarding chronic pain guidelines. The American Pain Society has just published evidence-based guidelines for treating fibromyalgia and is in the process of producing them for chronic low back pain, which are due out probably in 2 or 3 years.

What about the role of the FDA in helping PCPs deal with drug safety issues?

In the primary care setting I hear both sides—it takes too long for drugs to get to the market, because the FDA is too restrictive. But I also hear the opposite, that certain

drugs get on the market too soon, without adequate trials, and later are found to be unsafe. There's all this rumbling about industry pressures and that the FDA buckles to industry because of the money. Everyone seems to have an opinion, but in general my colleagues think that the FDA is just trying to do a job.

Is that job adequate to meet the needs of the primary care physician?

Yes, I think so. It's a big government agency, and even though it is criticized, I think it is trying to present good quality evidence for physicians to use as a basis for prescribing. My perception is the FDA is probably doing as good a job as it can, given the surrounding political environment and the logistical difficulties in getting adequate clinical studies designed and completed.

What's your view on the role of the DEA and the use of opioid therapy in the primary care setting? Has the agency's approach changed over the years?

I think that the DEA should be more worried about the street use of drugs than about a physician's legitimate use of prescription drugs. I personally feel more fear from the DEA as opposed to feeling protected as a member of society. I don't know if the DEA's approach has changed, but my perception of the approach has changed. I think it would be very helpful if the agency acted as more of a liaison with the doctors who are actually prescribing opioid analgesics. Right now the medical board laws make many PCPs feel that the number of steps required in order to comply are onerous, and if any steps are missed then they will be found not to be compliant. For me, instead of the DEA being helpful, it is the opposite.

Specifically, how can the DEA be more helpful instead of instilling fear?

I think the DEA would be much more helpful if it took a strong, positive stance with physicians about treating pain, acknowledging that yes there is diversion with drugs, and we have to be careful about that, but treating pain is as important as protecting society. What has happened is that doctors are so worried about that enforcement aspect that they don't use drugs for appropriate situations. It's really about perception, and right now that perception is totally negative and needs to be reversed. The typical PCP perception of the DEA is that any involvement with the agency will be negative. It's unfortunate because we're working toward the same goal. Most doctors do not want any of their drugs to be diverted. They want to treat pain adequately and most doctors would treat pain more aggressively and liberally if they thought that there would not be somebody looking over their shoulder all the time. For example, the Intractable Pain Act in California was set up to stimulate primary care doctors to prescribe more opioids. But because of the requirements and steps that need to be followed in order not to get prosecuted, the act has had the opposite effect.


Given the recent changes in FDA policies, scrutiny from the DEA, and the influence of the media, what are your recommendations to other PCPs for protecting themselves and their practices while providing their patients with adequate analgesia?

There are many ways to provide analgesia besides opioids. Other medications do not have the same risks as opioids, although opioids are still the best option for some patients. PCPs should become familiar with all the options, and despite what the experts write, the decision is still clinical and dependent on what happens with each physician-patient encounter. The decision to use or not use opioids will always be made without enough information. PCPs are constantly making decisions without knowing a precise diagnosis or certainty of a treatment approach. Perceptions of risk are not reality but drive PCP behavior.

Do you have any other comments regarding any of the issues we have discussed?

Analgesic management for most patients is very complex, requiring skills perhaps not familiar to many PCPs. Given an option, many, perhaps most PCPs, would prefer to opt out of pain treatment. This must not be an option, nor should the barriers (real or perceived) be so great that PCPs begrudgingly treat patients with pain. Physicians should not feel that it is so risky to treat pain. Such notions that you will make your patients addicts or that the DEA will review your practice if you use a certain amount of drugs, and so on, are just myths and misconceptions. There are many PCPs who are comfortable prescribing opioid analgesics. However, I think that the average doctor is really very fearful, which need not be since there are many steps that the PCP can take to feel more comfortable prescribing analgesics and to protect his or her clinical practice.

In conclusion, could you summarize these basic steps.

Essentially, I think there are two basic steps that should be followed. First are the four A's that I previously mentioned. Except for the initial office visit, this useful mnemonic device prompts doctors to adequately cover most items at follow-up sessions. Secondly, I think doctors should have concise printed forms or checklists to indicate that they have covered all items required by state board regulations, something that would be quick and easy to do by either writing a simple sentence or a couple of words or just checking boxes to indicate that all subjects were addressed with the patient. These are simple things that can be done that would be protective for the doctor. Treating chronic pain conditions requires expertise and often more time than other chronic diseases, such as hypertension or diabetes. But we, as a profession and as caring individuals with compassion, cannot back away from patients' suffering. And if we do that, the amount of suffering is just going to multiply in the United States. So we, as PCPs, have to develop skills and become more educated about pain management, and I emphasize the fact that we are uniquely suited to do this because of our associations with our patients. 

Treating Pain

CONTINUED FROM COVER

In the first half of 2005, Pain Medicine was featured in numerous national print venues including *The New York Times*, *The Wall Street Journal*, and the covers of *TIME* and *USA TODAY*. In March 2005, the Today Show aired a 5-part series focused on pain² and *ABC News* and *USA TODAY* followed in May with a week-long series of multiple network programs that examined pain and pain management from medical and social perspectives.³ While much of this focus was on pain and its many new advances, *ABC News'* Nightline program included an investigative report that explored the legal and political issues surrounding pain care and the obstacles facing physicians who aggressively treat pain.

Media attention on pain recently has been shifting toward social and legal concerns. Much of this is a result of current governmental and other legal events such as the activities of the Food and Drug Administration (FDA), the Drug Enforcement Administration (DEA), and high profile court cases involving physicians. In recent months, medical practice related to pain care has become more regulated than ever, not by health agencies, but by law enforcement. In the past year, Congress passed legislation for a national prescription monitoring program (NASPER) that targets opioid prescribing. Such prescription monitoring programs can offer useful physician tools to enhance safe care, but when administered with the appearance of law enforcement may also be perceived as a physician mouse-trap that impedes effective prescribing to those in need.⁴

The DEA also has been increasingly in the news regarding its messy public relations debacle over the handling of a frequently asked question (FAQ) document that the organization and a group of pain experts created to clarify the confusion over the use and abuse of prescription pain medication.⁵ The DEA abruptly pulled the FAQ from its website and rescinded its support. It later announced an interim policy statement that was even more frightening to physicians. Regardless of the real motives, such government tactics catch fire with the media and have the unintended effects of intimidating doctors who are then unwilling to take aggressive action against pain. Surveys show that physicians fear legal, regulatory, or administrative sanctions and will often prescribe other less scrutinized medications even if they are less effective and/or potentially harmful.

A particularly disturbing trend has been the rare but highly publicized cases of physicians

CONTINUED ON PAGE 11

Chronic Pain Medications

CONTINUED FROM PAGE 5

Kadian, Avinza) have been developed to lengthen the drug's effect to 12 to 24 hours. Also available is a controlled-release oral formulation for oxycodone (OxyContin) and a controlled-release transdermal formulation for fentanyl (Duragesic). An extended-release formulation of hydromorphone (Palladone), FDA approved in 2004 for treating persistent moderate to severe pain, was withdrawn from the market in July 2005 because of potential alcohol interaction. Methadone, which has a long and variable half-life, with drug accumulation over several days, needs to be administered with caution and requires close monitoring for a prolonged period to avoid delayed toxicity.⁵

Opioids are often combined with non-opioids to increase efficacy and allow for lower doses (an opioid-sparing effect). Commercially available, fixed-dose, analgesic combinations contain a weak opioid and a non-opioid analgesic. The use of these combinations in chronic pain, however, is limited by the short duration of action of the opioid component and dosage limitations of the non-opioid analgesic component.

The binding of opioids to mu receptors in different anatomic sites (eg, CNS, GI tract) is responsible for a wide array of side effects in addition to therapeutic effects. As a class, opioids can cause sedation, mental clouding or

Opioids are becoming more accepted as treatments for chronic pain, even in the elderly

confusion, nausea and vomiting, constipation, pruritus, urinary retention, bradycardia, and, rarely, respiratory depression. Except for constipation, most side effects tend to abate with time. Opioids should be used with caution in patients with impaired ventilation, bronchial asthma, liver failure, or increased intracranial pressure. Opioid-induced respiratory depression is typically transitory, provoked by pain, and largely occurs in opioid-naïve patients. Naloxone, a mu opioid receptor antagonist, can be administered intravenously to reverse respiratory depression.

Other concerns with opioid use are psychological dependence (addiction), physical dependence, and tolerance. Addiction is an overwhelming drug-seeking behavior and compulsive use that can occur with opioid administration, although it is rarely encountered in acute medical situations. Physical dependence, which commonly occurs in the clinical setting, is an altered physiological state necessitating repeated opioid adminis-

Table 2. World Health Organization 3-Step Analgesic Ladder

Step	Pain Level	Analgesic
1	Mild	Non-opioid ± Adjuvant
2	Mild to moderate	Opioid for mild to moderate pain ± Non-opioid ± Adjuvant
3	Moderate to severe	Opioid for moderate to severe pain ± Non-opioid ± Adjuvant

Adapted from: World Health Organization's Pain Relief Ladder. Available at: <http://www.who.int/cancer/palliative/painladder/en/>. Accessed November 10, 2005.

tration to prevent a withdrawal syndrome. Tolerance is a lack of efficacy that develops with continuous opioid administration that requires dose escalation. Despite apprehensions related to psychological and physical dependence, a number of expert organizations support the judicious use of opioids for chronic pain.¹

The World Health Organization (WHO) Ladder

Physicians are often uncertain as to how or when to use multiple classes of pharmacologic agents for pain. The World Health Organization (WHO) has developed a 3-step conceptual model ("analgesic ladder") for the rational selection of pain medications according to these classes (see Table 2).⁶ Originally developed as a guide for cancer pain management, the WHO analgesic ladder may now be considered appropriate for all types of pain.

Of note, the use of opioid agents as first-line for "Step 2," mild-to-moderate pain will require evaluation of each patient's individual level of pain, clinical circumstances, and risk-to-benefit ratio. Importantly, however, the WHO ladder emphasizes the point that sufficient pain control is needed for physical relief, productive function, and emotional well-being, and if pain is not controlled with non-opioid agents, providing such control with opioid agents may be indicated. In addition, providing appropriate documentation and monitoring of the reasons for using opioid agents at this level should be helpful to the physician who is apprehensive about their use.


Conclusions

When selecting pharmacotherapy for chronic pain, it is important to be aware of the benefits and risks of each agent. Newly discovered safety issues with selective COX-2 inhibitors and nonselective NSAIDs have focused attention on other analgesics, such as opioids and adjuvant analgesics. Opioids are becoming more accepted as treatments for chronic pain, even in the eld-

erly.⁷ Adjuvant analgesics, especially anticonvulsant agents, TCAs, and topical local anesthetics, are considered mainstay treatments for chronic neuropathic pain.¹ No matter which agent is chosen, chronic pain treatment should be initiated with the medication capable of alleviating pain and with the least potential side effects.

Refractory cases may require combination therapy. "Multimodal analgesia" or "rational polypharmacy" is a strategy using agents with different mechanisms of action in combined therapeutic doses to maximize efficacy and minimize potential side effects.⁸ Although chronic pain is a formidable clinical challenge, the broad range of therapeutic options offers great hope to patients suffering from continuous pain states.

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POSTTEST

MULTIPLE CHOICE

Rapoport article - Arthritis and the COX-2 Conundrum: A Case Study (Vol 5, No 1)

- An alternative to COX-2 inhibitors for the treatment of osteoarthritis is:
 - Intra-articular injection
 - Cognitive-behavioral strategies
 - Topical therapy with capsaicin or the lidocaine patch 5%
 - Massage
 - Assistive devices
 - All of the above

Passik/Kirsh article - Treating Chronic Pain: Biopsychosocial Approach in Primary Care Practice (Vol 5, No 1)

- Which of the following is NOT one of the "4 A's" related to monitoring pain management outcomes?
 - Analgesia
 - Adjuvant medications
 - Activities of daily living
 - Adverse events
 - Aberrant drug-taking behaviors

King article - Managing Diabetic Peripheral Neuropathic Pain: Case-Based Treatment Options (Vol 5, No 1)

- _____ provide(s) analgesia through both peripheral and central actions.
 - Antidepressants
 - Anticonvulsants
 - Duloxetine
 - A and B
 - All of the above

Chevlen article - Unraveling the Mechanisms of Neuropathic Pain (Vol 5, No 2)

- _____ are of two varieties: small molecules that immediately affect a neuron's ability to generate an action potential, and peptides that affect the activity of target neurons over a longer time frame.
 - Synapses
 - Sodium channels
 - Neurotransmitters
 - None of the above

Passador article - Physical Pain Aggravates Majority of Americans (Vol 5, No 2)

- Which of the following can hinder the reporting and necessary treatment of pain?
 - Ethnic/cultural practices
 - Language barriers
 - Mistrust of physicians
 - Religious beliefs
 - All of the above

Nicholson article - Ask the Expert (Vol 5, No 2)

- The American Geriatric Society does not recommend the use of which tricyclic antidepressant (TCA) in patients aged 65 or older?
 - Nortriptyline
 - Desipramine
 - Amitriptyline
 - Imipramine
 - Doxepin

McCarberg interview - Risk Management in the Primary Care Setting (Vol 5, No 3)

- Which of the following is NOT listed by Dr Bill McCarberg as a concern for any primary care physician (PCP) treating patients with pain using controlled substances?
 - Use of an appropriate pain scale
 - Appropriate documentation
 - State medical board requirements and guidelines
 - Submission of proper forms
 - None of the above

TRUE OR FALSE

What's Hot in Pain Control (Vol 5, No 1)

- In a recent study published in the *New England Journal of Medicine*, combination therapy of gabapentin and morphine was shown to be more effective than monotherapy in treating painful diabetic neuropathy and postherpetic neuralgia.
 - True
 - False

McCormick interview - Insights into the FDA and Drug Safety (Vol 5, No 3)

- In the drug approval process, the FDA requires comparative studies against existing approved drugs for the disease condition.
 - True
 - False

Palangio article - Chronic Pain Medications: Benefits vs Risks (Vol 5, No 3)

- Local anesthetics work by inhibiting impulses in pathologic neurons by reversibly blocking sodium channels and stabilizing neuronal membranes.
 - True
 - False

ANSWERS

- f. Several treatments are available as alternatives to COX-2 therapy for the treatment of osteoarthritis: intra-articular injection; cognitive-behavioral strategies; exercise; attaining/maintaining ideal weight; physical/occupational therapy; assistive devices; massage; glucosamine; a nonselective NSAID with misoprostol or a proton-pump inhibitor; topical therapy with capsaicin or the lidocaine patch 5%; surgical intervention. (Volume 5, Number 1, page 3)
- b. The so-called 4-A's - analgesia, activities of daily living, adverse events, and aberrant drug-taking behaviors - are the clinical domains that reflect progress toward the larger goal of a full and rewarding life. A successful outcome in pain therapy must provide meaningful relief but does not end solely with the provision of pain control. (Volume 5, Number 1, page 4)
- d. Antidepressants and anticonvulsants appear to provide analgesia both peripherally and centrally. (Volume 5, Number 1, page 8)
- c. Broadly speaking, neurotransmitters are of two varieties: small molecules that have an immediate effect on a neuron's ability to generate an action potential, and peptides that affect the activity of target neurons over a longer time frame. (Volume 5, Number 2, page 8)
- e. Ethnic and cultural practices, stoicism, language barriers, mistrust of physicians, religious beliefs, or fear that the pain might indicate a serious medical problem can all hinder the reporting and necessary treatment of pain. (Volume 5, Number 2, page 4)
- c. Because intolerable side effects are more frequent with amitriptyline, the American Geriatrics Society does not recommend its use in elderly patients. (Volume 5, Number 2, page 4)
- a. According to Dr McCarberg, "In the case of controlled substances, especially here in California, such safety factors as proper documentation, following state board requirements and guidelines, and submitting the proper forms, are all major concerns for any primary care physician (PCP) treating pain patients." (Volume 5, Number 3, page 1)
- a. According to a recent study by Gilron, et al, gabapentin and morphine combined achieved better analgesia at lower doses of each drug than either as a single agent for treatment of painful diabetic neuropathy and postherpetic neuralgia. (Volume 5, Number 1, page 11)
- b. Dr McCormick states that "The European regulatory requirement for efficacy studies to incorporate a comparison against existing drugs has not been the rule in the US." (Volume 5, Number 3, page 12)
- a. Local anesthetics are used to treat various pain syndromes, and work by inhibiting impulses in pathologic neurons by reversibly blocking sodium channels and stabilizing neuronal membranes. (Volume 5, Number 3, page 5)

EDUCATIONAL ACTIVITY EVALUATION FORM

National Initiative on Pain Control[®](NIPC[®]) CME Newsletter Series Pain Management Today[®]

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EDUCATIONAL OBJECTIVES (Please indicate the extent to which each of the following objectives was met.)

By reading the three issues of *Pain Management Today*[®], this activity met the stated objectives in such a way that I am better able to:

	Not Met		Completely Met			
	1	2	3	4	5	6
1. Differentiate chronic pain from acute pain and describe the mechanisms of pain and sites of activation.	1	2	3	4	5	6
2. Address common barriers that limit effective pain management for patients with chronic pain.	1	2	3	4	5	6
3. Determine the recommended components for comprehensive assessment of pain and function in patients with chronic pain.	1	2	3	4	5	6
4. Select more varied pharmacologic and nonpharmacologic strategies for initial and ongoing management of chronic pain.	1	2	3	4	5	6
5. Describe therapeutic approaches to minimize potential adverse effects and drug interactions and identify safety issues and precautions.	1	2	3	4	5	6

EDUCATIONAL ACTIVITY CONTENT/FORMAT (Please rate the following statements.)

	Strongly Disagree			Strongly Agree		
	1	2	3	4	5	6
1. The format/teaching methods were appropriate to meet the activity objectives.	1	2	3	4	5	6
2. Overall, the activity was presented in a fair-balanced manner.	1	2	3	4	5	6
3. I am better prepared to treat patients who are experiencing pain.	1	2	3	4	5	6

What additional information/topics do you feel should be included in future issues of *Pain Management Today*[®]?

Treating Pain

CONTINUED FROM PAGE 7

who are charged with criminal offenses that occurred within their practice of medicine. The concern here is not to protect physicians who cross the line into criminal activities but rather to enforce the necessary separation of standard medical practice from criminal activities. This separation is articulated in the Controlled Substances Act and is necessary for ensuring that as long as physicians try to help their patients within the bounds of medicine they will not be negatively impacted by the threat of criminal charges. A recent case provides an example of the problem.

William E. Hurwitz, MD, a Virginia physician, was found guilty in a federal court of 50 counts including racketeering and drug trafficking and sentenced to 25 years in federal prison. Controversy heightened when a letter sent to the court from six past presidents of the American Pain Society (APS) repudiated the testimony of the prosecution's expert witness, a former APS president and assistant to Senator Orin Hatch.⁶⁻⁷ Another intriguing aspect of the case involved the DEA, which abruptly withdrew the FAQ described above shortly after it was admitted as evidence in the trial. Although the DEA stated that it was withdrawn because of inaccuracies and had never been officially sanctioned, the temporal connection to the Hurwitz case made many suspect otherwise.

Some believe that Dr Hurwitz received a just outcome from the legal system while others insist he was a well-intended clinician who

How physicians and the public interpret the recent clash of pain control and the law will almost certainly influence the climate of pain management in America.

served his patients with dedication and compassion. Irrespective of the standard of his care, the case raised serious questions about whether Dr Hurwitz was inappropriately prosecuted in the criminal justice system instead of through civil and administrative processes since his offenses were within the scope of professional medical practice. The case is currently under appeal in the 4th District Federal Court of Appeals and several groups have filed amicus briefs to help the court understand the flaws in how the case was tried. In particular, the American Academy of Pain Medicine (AAPM) filed a brief specifically focused on how the court handled the precedent-setting jury instructions that did not distinguish the extreme or substandard practice of medicine from drug dealing. The appeal is still being considered at the time of this writing.

How did physicians get caught in the crossfire?

Several medical, social, and political trends have converged to create a perfect storm of controversy and confusion.⁸ In recent years, new pain medications have offered more effective pain relief; simultaneously, some of these potent new drugs have been diverted to a changing black market. The backdrop of this new crisis in pain treatment is the well-documented escalation of prescription drug abuse in the United States. In response, law enforcement has worked to limit these medications to reduce their diversion. Unfortunately, targeting prescribers, with the hope that they will prescribe less abusable drugs, as was suggested in the recent President's National Drug Control Strategy, is unlikely to curb drug abuse in America. Such programs merely shift street abuse back to illicit drugs while limiting those who have legitimate need from access to effective medications. The real answers to these problems need not come at the expense of patients in pain. Nonetheless, how physicians and the public interpret the recent clash of pain control and the law will almost certainly influence the climate of pain management in America. Societies need to simultaneously eliminate prescription drug abuse as well as the undertreatment of pain, as these may cause further intersection of both public health crises in the future.

If pain control is to be available to patients when it is needed most, we must avoid putting physicians in the middle of two heated health-care crises. All clinicians should be aware of recent governmental admonishments to increase their vigilance in prescribing abusable drugs for patients who have suspected risk of abuse. However, instructions by the DEA and the Drug Czar to improve screening of patients who abuse drugs suggest that there are validated tools for such screening. While screens are currently available (ie, the Screener and Opioid Assessment for Patients with Pain™ [SOAPP™]), the clinical utility of these instruments has not been clearly demonstrated. Hopefully, we will have screening tools that accurately identify abuse risk, but until then, the average clinician is left appropriately confused by these most recent government directives.

Neither the serious epidemics of drug abuse nor undertreated pain are served by attempting to fix one problem at the expense of the other.⁹ The troubling shift of governmental roles in pain care from health agencies to law enforcement—focusing on preventing drug abuse rather than easing suffering—is also unlikely to help either of these problems. Moreover, criminalizing physicians has an unfortunate chilling effect on the average clinician's willingness to treat pain. Appropriate medical decisions should not be dictated by the actions of the DEA or other branches of law enforcement, but must remain in the hands of medical professionals.

As awareness of the public health crisis of undertreated pain has grown, the need for pain care has expanded. As the specialty of Pain Medicine has also grown and matured, it has become clear that the solution to the problem of undertreated pain will not be solved by a single specialty. Pain care is the responsibility of every treating physician, and the front line of pain care will have to rest with the primary care clinicians who are the main caregivers for most of the patients in pain. However, the average primary care physician may feel damned if he does and damned if he doesn't in light of the onslaught of negative press ranging from the risks of using certain NSAIDs to being accused of elder abuse for undertreating or drug dealing for overtreating pain.

In addition, most physicians are not well trained in pain management and there are just too few Pain Medicine specialists. Helping our primary care colleagues to shoulder this responsibility has become a primary challenge for our field, and furthering safe and effective treatments in Pain Medicine will require major advancements in appropriate education for all levels of medical training. This education will have to be broad-based and multidisciplinary, as well as address the prevalent fear and resistance to treating pain with substantial reassurance that treating pain is safe for everyone involved.

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Insights into the FDA

CONTINUED FROM PAGE 3

Besides safety issues with the drug in question, what other considerations must the FDA take into account before withdrawing a drug from the market?

Before withdrawing a drug from the market or asking a sponsor for a voluntary withdrawal, the FDA carefully considers the alternative medications that are available to the population and the risks of those alternatives.

When reviewing a drug, does the FDA consider that there might be another drug already on the market with a more favorable benefit-to-risk ratio, even though the drug under review might be approvable on its own merits?

The FDA errs on the side of approving drugs regardless of what else is on the market because it is mindful that patients need alternatives and that not everyone responds to a given drug. The European regulatory requirement for efficacy studies to incorporate a comparison against existing drugs has not been the rule in the US. Therefore direct comparisons of safety and effectiveness are rarely available for most drugs in a class, and drugs are generally approved based on their own merits.

In the last few years, there has been a particular upsurge of criticism of the FDA vis-a-vis their role in regulating drug safety. What, if any, are the substantive criticisms?


Some patient interest groups have voiced the opinion that the FDA is collaborating too closely with industry based on the knowledge that some of the financing for drug review comes from a fee paid by sponsors to the FDA under the Prescription Drug User Fee Act (PDUFA). A related concern is that the time frames for approval under PDUFA are too short to allow the FDA to do an adequate job reviewing a drug. Regarding the first issue, there is absolutely no basis for the belief that the pharmaceutical industry has any direct or indirect influence on the FDA in the drug approval process. There are laws governing the FDA's ethics and behavior toward regulated industry. The FDA is conscious of its role in regulating the pharmaceutical industry and is required to consider each product on its own merit.

Regarding the second issue, while the time frames are much shorter now than 15 years ago, all relevant reviewers are focused during the finite period of review (6 to 10 months), which in most cases is sufficient for a careful review. The added benefit has been greater real-time collaboration across various specialties during the review cycle. There is less backlog of old applications and therefore much more

time to focus on the immediate pending applications. Perhaps one change that has occurred is that development times for drugs are becoming shorter. As a result, in some cases the safety exposures by the time of approval are not as long today for chronically administered drugs as they were in the past, giving the FDA less data from which to detect safety signals that occur over prolonged exposure.

What drug safety issues should the practicing primary care physician be most aware of?

Unapproved use of drugs may elicit unforeseen risks in the population without the benefit of adequate safety evaluation of such usage. Therefore, increased caution should be exercised by practitioners who choose to prescribe drugs that have not been fully evaluated by the FDA.

Finally, clinicians should help their patients realize that all drugs carry risks, even though the drug-approval process and postmarketing surveillance system strives to reduce those risks. Practicing primary care physicians should be aware of their responsibility to appropriately communicate the risks of therapies to their patients in addition to explaining their benefits. Such important risk communication strategies are a part of the responsibility shared with the FDA for the safe use of approved drug products. 

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B357-002	Wed, March 15, 2006	5:00 PM	6:00 PM	7:00 PM	8:00 PM	Eric M. Chevlen, MD
B357-003	Thu, March 16, 2006	4:00 PM	5:00 PM	6:00 PM	7:00 PM	David A. Fishbain, MD
B357-004	Mon, March 20, 2006	9:00 AM	10:00 AM	11:00 AM	12:00 PM	Eric M. Chevlen, MD
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