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Opioid Pharmacotherapy for Chronic Noncancer Pain: The American Experience

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Chronic noncancer pain is a significant and growing public health challenge in the United States. Lacking effective alternative interventions for effective chronic noncancer pain management, many physicians have turned to opioid pharmacotherapy. Increased opioid prescribing brings not only gains in therapeutic benefit but also a higher incidence of adverse drug events including increased medication misuse and opioid related mortality. Currently the United States must confront the dual problems of widespread undertreated chronic noncancer pain and a prescription opioid abuse crisis. Withholding pain relieving drugs from patients in need is unjustifiable, yet drug diversion, abuse and adverse drug events have become major social as well as medical problems. At the heart of this crisis is the lack of definitive evidence about the risk to benefit ratio of opioid pharmacotherapy for chronic noncancer pain both on an individual case and on a population basis. This article describes the extent and severity of the American chronic noncancer pain problem and the history of opioid pharmacotherapy for chronic noncancer pain in the United States. It then discusses the concept of evidence based practice and reviews current evidence supporting opioid pharmacotherapy for chronic noncancer pain as well as adverse drug events related to opioid pharmacotherapy including misuse and abuse. Finally, it considers the conflict of providing pain relief versus protecting society and reviews steps that governmental agencies, industry and others are taking to contain and ultimately resolve the problems of excessive prescribing and conflicting priorities. (Korean J Pain 2013; 26: 3-13)

Key Words:
chronic pain, evidence-based practice, noncancer pain, opioid pharmacotherapy.

INTRODUCTION

Chronic noncancer pain is a significant and growing public health challenge in the United States. About one third of Americans suffer from chronic noncancer pain [1]. The pain is moderate to severe for about 25% of the population, and it is disabling for approximately 10% [2]. Society incurs substantial costs for chronic pain, not only in medical expenditures but also in disability compensation, lost work productivity, reduced family incomes and degraded quality of life. Lacking alternative interventions for effective chronic noncancer pain management, many physicians have turned to opioid pharmacotherapy, traditionally the mainstay of palliative care for patients with advanced

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cancer. The opioids prescribed in the United States, both immediate and extended release, are the μ agonists codeine, fentanyl, hydrocodone, hydromorphone, levorphalol, meperidine, methadone, morphine, oxycodone, and oxymorophone. Opioid prescription for acute pain, recurring pain and chronic pain has increased substantially over the last quarter century.

Opioids are among the most prescribed classes of medication in America. The United States, which has 5% of the world's population, now consumes 56% of the world's opioid medications, [3] while in many developing countries patients suffering with cancer related pain must do without them because of restrictive policies. Increased opioid prescribing brings not only gains in therapeutic benefit but also a higher incidence of adverse drug events including increased medication misuse and opioid related mortality. Moreover, unused prescribed opioids have become increasingly available in American homes and communities, providing unprecedented opportunity for diversion of prescription medications. Currently the United States must confront the dual problems of widespread undertreated chronic noncancer pain and the prescription opioid abuse crisis. Withholding pain relieving drugs from patients in need is unjustifiable, yet drug diversion, abuse and adverse drug events have become a major social as well as medical issues. At the heart of this crisis is the lack of definitive evidence about the risk to benefit ratio of opioid pharmacotherapy for chronic noncancer pain both on an individual case and on a population basis.

The purposes of this paper are to describe: 1) The extent and severity of the American chronic noncancer pain problem; 2) The history of opioid pharmacotherapy for chronic noncancer pain in the United States; 3) The concept of evidence based practice and current evidence supporting opioid pharmacotherapy for chronic noncancer pain; 4) Adverse drug events related to opioid pharmacotherapy including misuse and abuse; 5) The conflict of providing pain relief versus protecting society; and 6) Steps that governmental agencies, industry and others are taking to contain and ultimately resolve the problems of excessive prescribing and conflicting priorities.

CHRONIC PAIN IN THE UNITED STATES

Like other developed nations, the United States has a major problem with chronic pain. Despite major advances at the scientific level in defining the nature and mechanisms of pain and the development of interventions for relieving pain, the chronic pain problem continues to grow [1]. Several contributing factors exist. In developed nations, older populations increase because more people live longer. Longer lifespans mean that more people will develop diseases associated with chronic pain. In addition, more people survive catastrophic traumatic injuries that are likely to leave them with chronic pain. As the risk for chronic pain increases, the prevalence of chronic pain conditions continues to grow. Moreover, obesity is becoming a problem in developed countries and particularly in the United States. Obesity is a pro-inflammatory condition that increases the risk of chronic pain [4,5]. The estimated prevalence of obesity in Americans aged 60 years and older was 37% for 2010 [6]. Related to this is the lack of exercise and generally poor level of physical fitness in the United States, which are also associated with chronic pain.

The population of the United States is currently 313 million people. Of these, over 100 million suffer some form of chronic pain [1]. Examination of the nation's priority health conditions reveals that 25.8 million Americans have diabetes, 16.3 million have coronary heart disease and 11.9 million have cancer. Clearly, chronic pain represents an enormous problem that is more prevalent than diabetes, heart disease and cancer combined. Physicians in most specialties regularly encounter chronic pain problems.

The cost of chronic noncancer pain to American society is at least $560–$635 billion annually, and this includes the loss of work productivity [7]. This means that society loses about $2,000 per American citizen per year. In 2008 federal and state governments pain about $99 billion for pain related medical expenditures. The costs of chronic pain exceed those of diabetes, heart disease and cancer combined. Clearly, chronic pain is a major burden to American society.

The impact of undermanaged chronic noncancer pain on the patient is complex and serious [1]. It compromises the individual's normal activities of daily living, interferes with sleep, reduces the productivity of the patient in the workplace, and degrades quality of life. Studies show that the risk of suicide among patients with chronic pain is approximately twice that for control groups. Moreover, chronic pain affects the families, friends and coworkers of individual patients. Family roles changes when pain disables one of the family members, and loss of productivity

can impose a financial burden on the family.

The growing epidemic of chronic pain in America has set the stage for the opioid pharmacotherapy dilemma. Chronic pain, by definition, is neither self-limiting nor curable, and patients require skilled, effective pain management. By and large, chronic noncancer pain patients in the United States and elsewhere are under managed. The literature suggests that psychological interventions and physical therapies are effective, and interdisciplinary approaches appear to be the most cost-effective and definitive solutions to disabling chronic pain [8]. Nonetheless, in the United States providers and payers resist these approaches, forcing patients to undergo mono-disciplinary medical treatment in most cases. Apart from certified pain specialists, most American physicians are poorly prepared to diagnose, monitor and manage chronic pain conditions. Simple, straightforward, monotherapeutic pharmacological interventions, such as opioid pharmacotherapy, appeal in many settings.

THE EMERGENCE OF OPIOID PHARMACOTHERAPY FOR CHRONIC NONCANCER PAIN

Prior to about 1990, the use of opioid pharmacotherapy for chronic noncancer pain was rare, although it was the mainstay of palliative care for patients with advanced cancer. Portenoy and Foley [9] conducted a landmark study that ultimately shifted the indication for opioid pharmacotherapy beyond palliative care in the cancer setting to chronic noncancer pain. They studied 38 patients with chronic noncancer pain, and most received less than 20 mg/day (morphine equivalent). Of these, 19 had four years or more of treatment, and six had used opioids for more than seven years. Although 14 of these patients reported inadequate pain relief, 24 described partial but acceptable or fully adequate pain relief with opioid pharmacotherapy. Management problems occurred in only two cases, and these patients both had histories of prior drug abuse. The patients did not report improvement in employment or social function. A number of positive case studies subsequently appeared in the literature, and these showed that opioid medications can reduce disabling chronic pain to manageable levels for some patients.

The pharmaceutical industry quickly realized that opioid pharmacotherapy for chronic noncancer pain represented an enormous marketing opportunity. Multiple companies began to develop extended release opioid products and to market them aggressively. Industry claimed that such products could, in principle, produce more consistent pain relief, generate less euphoria with administration, reduce the rate of tolerance development and offer better side effect profiles. Industry marketing, supported by their development of patient advocacy programs and physician education efforts added substantially to the momentum of opioid prescribing for chronic noncancer pain.

In 1997, the American Pain Society and the American Academy of Pain Medicine published a joint consensus statement supporting opioid pharmacotherapy for chronic noncancer pain [10]. Shortly thereafter, the Federation of State Medical Boards of the United States liberalized the medical guidelines for opioid prescribing for chronic noncancer pain [11]. Advocates of opioid pharmacotherapy were able to ride on various campaigns to make pain control a priority in medicine, although most such efforts were independent of opioid advocacy. At that time, the short-term risks and long-term adverse drug events associated with opioid pharmacotherapy received little attention.

EVIDENCE BASED PRACTICE

American medicine aspires to evidence based practice. The definition of this, according to its chief pioneering advocate, Dr. David Sackett, is "… the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research" [12]. Best evidence comes from systematic review of published research that has sound methodology, as the Cochrane Collaboration advocates. The Cochrane Collaboration is an international network of more than 28,000 participants in more than 100 nations that prepares systematic literature reviews of published evidence. Cochrane standards are the highest for evidence based health care. Their meta-analytic reviews synthesize information from multiple primary randomized controlled trials, using rigorous methodologies and strategies that minimize bias and random error.

EFFICACY AND EFFECTIVENESS

Evidence based practice means that American physicians should link opioid prescribing for chronic noncancer pain patients to an extensive body of literature comprising multiple randomized controlled trials collectively analyzed, following Cochrane standards, with meta-analysis. Every product offered should have sound published evidence for both efficacy and effectiveness. Efficacy exists when an intervention proves successful when implemented properly under controlled conditions. Randomized controlled trials can demonstrate efficacy for various opioid products using well-defined protocols and highly selected patients recruited with stringent exclusion criteria. Efficacy is short term. It simply shows that an intervention can work for a given clinical condition. In contrast, effectiveness means that an intervention is successful in actual practice with typical patient populations. Trials demonstrating efficacy need mixed patient populations, take place under conditions of everyday practice, and are long term. The United States Food and Drug Administration requires evidence of efficacy to approve putting a new product on the market. Consequently, all existing opioid pharmacotherapy products have demonstrated efficacy, but there is no requirement for demonstrating effectiveness. Because opioid pharmacotherapy is a long-range intervention, typically prescribed for patients with multiple comorbidities, demonstrated effectiveness is crucial for a meaningful evidence base.

The literature should clearly define the nature and extend of therapeutic benefit, the adverse drug events and the risks associated with each of them, and the risk to benefit ratio. Ideally, the literature should guide the practicing physician in determining which patients are likely to benefit from opioid pharmacotherapy, which patients are likely to derive no benefit, which patients are at risk for harm, and which patients are at risk for misuse or diversion of opioid medication.

THE CLINICAL TRIALS EVIDENCE BASE FOR OPIOID PHARMACOTHERAPY

Portenoy et al. [13] undertook an open-label, multi-site, uncontrolled prospective longitudinal investigation of opioid pharmacotherapy for chronic noncancer pain. Patients used controlled-release oxycodone for up to 36 months to control chronic pain, returning at three-month intervals. They completed the Brief Pain Inventory at each return visit. Of the 233 patients enrolled, 39 completed the 36-month study. Of the 127 patients that discontinued therapy, 38 cited an adverse event, 17 reported ineffective pain relief, 24 were lost to follow up, and 48 left the study for other reasons. Of those who left the study, most did so during the first year. For those who remained, scores for worst pain decreased from 7.7 (± 1.6) at baseline to 5.4 (± 2.5) at the end of month three. The beneficial pain relieving effects of the drug proved largely stable over study duration. None of the patients met the DSM-IV criteria for drug dependence or abuse. This open-label, uncontrolled study lacks a comparison group and has other limitations, but it demonstrates that at least a subgroup of patients with chronic noncancer pain can sustain long-range benefits from opioid pharmacotherapy without complications.

To evaluate the state of knowledge about opioid pharmacotherapy for chronic noncancer pain up to 2008, the Evidence-Based Practice Center and Health Technologies Assessment Group (ECRI Institute) undertook a systematic review of all studies that looked at patients who used opioids for chronic noncancer pain for six or more months. This included transdermal and intrathecal in addition to oral routes of administration. Overall, patients reported a reduction in pain intensity of at least 30% on an 11-point numerical rating scale. It is not clear what this means, as no standards exist for a meaningful change in chronic pain [14]. Importantly, many patients ultimately discontinued opioid pharmacotherapy due to insufficient pain relief or adverse drug events. The panel noted the paucity of studies in the evidence base, the narrow outcome assessments, and the short-term nature of the studies that inform about efficacy but not effectiveness.

Papaleontiou et al. [15] published a systematic review of the evidence on the efficacy, safety and abuse/misuse potential of opioids for chronic noncancer pain in older adults. Forty-three randomized studies provided efficacy data. Eighteen of the studies compared opioid pharmacotherapy to placebo. Meta-analyses revealed significant pain intensity reduction and parallel reductions in physical disability. One patient in four discontinued opioid pharmacotherapy due to an adverse drug event, and 8% withdrew from the study due to insufficient drug efficacy. This report did not look at effectiveness. The authors concluded that

short-term opioid pharmacotherapy in patients aged 60-73 years who had no significant co-morbidities produced modest but favorable outcomes on both pain and physical functioning. Patients with neuropathic pain derived more benefit than patients with osteoarthritis-related pain. No significant improvements in sleep or quality of life occurred. Advancing age was associated with lower risk for abuse and misuse, but some of the studied excluded patients with substance abuse histories.

Carson et al., [16] at the Oregon Evidence-based Practice Center examined the comparative efficacy and harms of several long and short-acting opioids in adults with chronic noncancer pain. The main outcomes were pain intensity, pain relief and function. They identified 41 randomized trials that examined the effects of opioid pharmacotherapy on chronic noncancer pain. Nearly all of the trials proved to be of short duration, ranging from five days to 24 weeks, although one study had a 13 month duration. The heterogeneity in study populations constrained interpretation. It was not possible to demonstrate meaningful differences in outcomes across products or between long and short acting forms of particular drugs.

In summary, the evidence base for the effectiveness of opioid analgesic drugs for chronic noncancer pain is nearly nonexistent. Some evidence does exist for the efficacy of these medications. The literature is weak because the outcome measures are, with a few exceptions, limited mostly to pain rating scales. Restoring functional capability, improving quality of life, return to work, reduced health care utilization, improving sleep and several other outcomes are important therapeutic targets for opioid pharmacotherapy. The great deficiency in the evidence base is that only weak evidence exists to show that opioid pain medications are effective for chronic noncancer pain in some patients over months or years. Nonetheless, a large volume of anecdotal reports of successful long-term therapy from clinical practice cannot be easily dismissed. The major limiting issue is predicting who will benefit and who will be harmed by opioid pharmacotherapy over the long run.

ADVERSE DRUG EVENTS

1. Known and emerging adverse effects

Palliative care physicians have long known that opioid medications can produce opioid-induced bowel dysfunction, nausea, vomiting, dry mouth and sedation. The first of these is usually treatable and the others tend to resolve over time as tolerance develops. Most efficacy studies have assessed these adverse drug events, although some have looked at cognitive function and drug misuse. Moore and McQuay [17] examined the incidence of common adverse drug events in over 4,000 patients undergoing opioid pharmacotherapy for chronic noncancer pain. Dry mouth affected 25% of patients, nausea 21%, and constipation 15%. As noted above, patients in randomized trials of opioid pharmacotherapy often discontinue participation because of adverse drug events.

Several additional adverse drug events have emerged over the last two decades that were not evident in the acute pain and palliative care settings. They include opioid-induced endocrine deficiencies with increased risks for osteoporosis and bone fracture and diabetes [18,19], cardiac complications [20], hyperalgesia [21], and immunosuppression [22]. Misuse of medications including addiction, drug diversion and abuse of medications are also adverse drug events, and they have become the fastest growing drug problem in the United States. The most alarming adverse drug event is fatal prescription drug overdose [23]. Although the literature identifies these adverse drug events, large scale, randomized controlled studies of opioid pharmacotherapy have yet to include and quantify these events comprehensively. Comprehensive systematic reviews of the emerging opioid adverse events are not currently possible. Until more definitive information emerges about who is at how much risk for which adverse drug events, the risk benefit ratio for opioid pharmacotherapy in chronic noncancer pain patients must remain undefined.

2. The prescription opioid abuse crisis

From 1997 to 2010 in the United States, sales of opioid analgesic drugs quadrupled.

Physicians prescribed 96 mg morphine equivalent per person in 1997 but 710 mg morphine equivalent in 2010 [24]. With this increased prescribing rate, the societal costs of prescription opioid abuse and misuse also grew. Birnbaum et al. [25] estimated the societal costs of prescription opioid abuse in the United States to be $55.7 billion in 2007. Workplace costs were $25.6 billion, health care expenditures accounted for $25.0 billion, and criminal justice expenses totaled $5.1 billion. Clearly, prescription

opioid misuse and abuse has imposed a significant burden on American society. Yet, the total of these expenditures is only 5–10% of the total costs associated with chronic pain in the United States.

3. Aberrant drug behaviors

Patients who have a prescribed opioid can engage in abuse in multiple ways, collectively termed aberrant drug behaviors [26]. Instead of following instructions, they can take the drug at more or less than prescribed doses, take it more or less often than instructed, take the medication for purposes other than pain relief such as sedation or to cope with interpersonal stress, chew, crush or snort medications, hoard medication, or seek prescriptions from multiple prescribers (doctor shopping). Several community practice surveys estimate the overall rates of opioid misuse and abuse in a range from 4–26% [27]. In an 18-month study of more than 25 million patients, Cepeda et al., [28,29] estimated that three of 1,000 patients exposed to opioids exhibit doctor shopping behavior, typically eight months after first exposure.

4. Addiction and opioid use disorder

Virtually all patients taking extended release opioid medications over long periods of time will develop drug dependence. This decreases volitional control over drug use because cessation of drug intake will cause withdrawal symptoms. This dependence is not drug addiction, but it can compel patients to seek urgent prescription refills if they have consumed their medication ahead of the scheduled refill.

Patients qualify as addicted to prescribed medication when they engage in compulsive use of a substance despite obvious harm. Addicts typically deny that a drug use problem exists, become obsessed with obtaining the medication, neglect vocational and family responsibilities, and they often use more of the medication than planned. Opioid addicts may exaggerate or lie about an acute or chronic pain condition in order to obtain a prescription. The identification of true addiction in the chronic noncancer pain population is complex and challenging.

Fishbain et al. [30] conducted an evidence based structured review of 67 studies to determine the percentage of patients using chronic opioid pharmacotherapy that developed abuse/addiction or aberrant drug related behaviors. They estimated an abuse/addiction rate of 3.27%. If patients had no previous or current history of abuse or addiction, the rate was 0.19%. The aberrant drug related behavior rate was 11.5%, but those with no previous abuse/addiction history had a rate of only 0.59%. They concluded that long-term exposure to chronic opioid pharmacotherapy would lead to abuse or addiction in a low percentage of patients, particularly if this treatment were confined to those with no history of substance abuse or addiction.

Subsequently, Boscarino et al. [31] classified a sample of 705 chronic noncancer pain patients using opioid pharmacotherapy according the proposed Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) criteria for Opioid Use Disorder. Opioid use disorder is a maladaptive pattern of opioid use leading to clinically significant impairment of distress. They reported that 21.7% qualified as moderate and 13.2% as severe on Opioid Use Disorder. Although not synonymous with classical concepts of addiction and abuse, Opioid Use Disorder gauges patients on dependence and nontherapeutic compulsive use.

5. Diversion

Increased opioid prescribing rates have also led to increased diversion of opioid medications. Prescription drug diversion is the unlawful channeling of regulated pharmaceutical drugs from legal sources to the community or an illegal market place. The 2010 National Survey on Drug Use and Health [24] estimated that 22.6 million or 8.9% of Americans older than 12 years were current illicit drug users. New nonmedical users of prescription pain relievers numbered 2.0 million, and 55.0% of these reported that they had received prescription pain killer for free from a friend or relative. Another 11.4% bought the drug from a friend or relative, while 4.8% took them from a friend or relative without permission. Other forms of drug diversion include strategic doctor shopping on the part of patients with subsequent selling or release of the drugs in the community, theft on the part of pharmacy employees, and the purchase of prescribed medications for indigent patients [32]. Financially impoverished patients may sell all or part of their opioid medications to meet the costs of basic needs such as food, housing or even other medications.

6. Accidental opioid related overdose deaths

The most salient prescribed opioid misuse problem in the United States is accidental drug poisoning death. Warner et al. [23] examined death rates in the United States

from 1980–2008. They reported that in 2008, the number of drug poisoning deaths exceeded for the first time the number of deaths by motor vehicle accident in the United States. Opioid analgesics were involved in more accidental poisoning deaths than other drugs, including cocaine. The accidental drug poisoning death rate has nearly tripled since 1980. In 2008, opioid medications were involved in nearly 15,000 deaths. This problem is apparently related to medication diversion. Hall et al. [33] studied 295 patients who had died from unintentional drug overdose. Of these decedents, 275 took opioids (93.2%) but only 122 (44.4%) had prescriptions for opioid medication. From 2004–2008, the rate of emergency medicine visits for the nonmedical use of opioid medications doubled from 49 per 100,000 to 101 per 100,000. Patients at risk for accidental opioid-related overdose death may be those using methadone, those who have co-morbid substance abuse disorders, those using sedatives, anti-depressants or alcohol, and those with sleep-disordered breathing [34,35].

CONTAINING AND RESOLVING THE PROBLEM

1. The problem

A significant ethical and legal conflict exists in the United States. Chronic noncancer pain disables people, degrades quality of life, increases risk of suicide, and imposes a large economic burden on society. Opioid medications offer a time- and cost-efficient way to manage many chronic noncancer pain patients who do not respond to non-opioid drugs (e.g., nonsteroidal anti-inflammatory medications, acetaminophen, and other adjuvant analgesics), who do not have access to comprehensive interdisciplinary pain care (involving medical, rehabilitative and behavioral interventions or who are otherwise undermanaged. Despite the lack of an adequate evidence base for opioid pharmacotherapy in chronic noncancer pain patients, opioid prescribing in the United States has steadily escalated over the last quarter century. With escalated opioid prescribing has come a set of problems related to partly unanticipated adverse drug events. These include widespread drug misuse by patients and others share these drugs, medication diversion, Opioid Use Disorder and alarming increases in the rate of opioid-related overdose deaths. Prescribed opioids are rapidly becoming the primary misused medications in the United States and the primary cause of accidental death. Protecting the public against illicit use of opioid medications has become a high priority. This area of clinical practice remains highly controversial, with patient advocates on both sides of the issue voicing strong opinions.

The root cause of the problem is that prescribing patterns have outpaced the availability of evidence to support such prescribing, and without such evidence adequate education of prescribers on proper assessment, patient selection and management practices is impossible [27,36]. Sound evidence-based practice requires that physicians administer interventions according to knowledge gleaned from synthesized information in the literature. This knowledge should characterize both the potential benefits of a treatment and the potential harms. Most importantly, this characterization should go beyond simple efficacy to include effectiveness. It is crucial to determine the potential long-range benefits of opioid pharmacotherapy for typical patients and also the potential long-range harms. This information is simply unavailable in the literature, and there are no comprehensive federal or other funding initiatives in place to strategically generate the needed knowledge base in the foreseeable future.

2. Regulatory laws and bodies

In the United States, federal and state laws and regulations govern both the distribution and prescription of opioid medications. State regulatory agencies enforce these regulations. The federal Controlled Substances Act of is a subset of the Comprehensive Drug Abuse Prevention and Control Act of 1970. It is the major federal law controlling the prescribing of opioid medications, which are controlled substances. Under this law licensed medical practitioners can prescribe controlled substances for legitimate medical purposes according to standard medical practice. There are five classifications for controlled substances. Schedule I substances have no medical benefit coupled with extreme potential for abuse, and physicians cannot prescribe them. Heroin falls under this classification. Schedule II drugs have medical benefit but also have high potential for abuse. Opioid medications for chronic noncancer pain such as morphine and oxycodone fall under this classification. Drugs scheduled as III, IV and V have medical benefit but incrementally lower potentials for abuse, although hydrocodone, the most abused opioid, is a schedule III drug currently under review for possible rescheduling to

Schedule II due to its demonstrated abuse liability.

The Drug Enforcement Agency (DEA) is a part of the United States Department of Justice. Its job is to assure an adequate supply of controlled substances for legitimate medical use and research while also assuring that the prescription, dispensing, and administration of controlled substances is solely for legitimate medical purposes. American physicians who prescribed opioid medications must obtain DEA registration. The DEA may investigate individual physicians to determine whether their prescribing patterns reflect legitimate medical practice. It can revoke a physician's controlled substances registration. This happens infrequently.

Individual states have licensing boards that license and oversee medical practitioners. In general, state medical boards regulate opioid prescribing through licensure screening and promulgating medical practice guidelines. Such boards keep abreast of emerging findings in the literature and the development of new interventions or drug formulations. The Federation of State Medical Boards helps assure continuity in policy across states. In the late 1990s it produced a policy template, "Use of Controlled Substances for the Treatment of Pain" and produced its "Model Policy for the Use of Controlled Substances" [11], and it has commissioned a guide for clinicians [37].

Currently 43 states have adopted prescription drug monitoring programs. Such programs maintain a statewide electronic database that collects specific information on drugs dispensed within a state. The program can provide feedback to authorized professionals. Some states require physicians to report every controlled substance prescription they write, while others require pharmacist reporting. A doctor shopping patient seeking to fill multiple prescriptions for opioid medication will find that the dispensing pharmacist knows from the database that the patient is doing this. The United States Department of Justice fosters these programs. State licensing boards are increasingly instructing clinicians in the use of prescription monitoring program databases and asking them to query these sites on a regular basis before prescribing. An ongoing challenge is to have these databases fully secure to protect patient privacy, yet readily accessible with current information for all practitioners in routine clinical settings.

3. Steps toward resolving the opioid prescribing dilemma

The United States Executive Branch of the federal government under President Obama has taken action on the opioid pharmacotherapy problem through the Office of National Drug Control Policy. In 2011, it announced the Prescription Drug Abuse Prevention Plan, a set of guidelines to address the misuse of prescription opioid medications [38]. This plan encourages stakeholders to take action in four domains: 1) Education; 2) Tracking and Monitoring; 3) Proper Medication Disposal; and 4) Enforcement. The education effort aims to increase awareness of the dangers of prescription drug abuse among patients, young people, parents and providers. The tracking and monitoring effort focuses on state prescription drug monitoring programs. It seeks to improve and empower such programs by giving clinicians greater access and increasing inter-state operability and communication. The effort directed at proper medication disposal is concerned with the home storage of unused opioid medication. Patients need convenient ways to dispose of opioid medications that they do not intend to use and secure ways to store medications they are using. This requires the development of environmentally save options for medication disposal. Finally, the enforcement effort recognizes that a small minority of opioid prescribing physicians act outside of standard medical practice and often enable doctor shopping. Their actions are a threat to the patients in their care and to the communities in which they practice. The guidelines put forward a plan for more aggressive pharmaceutical crime investigation and prosecution. The goals of this five year plan include reducing nonmedical use of opioids among young people, implementing a Risk Evaluation and Mitigation Strategy, implement regulations for medication disposal, enhance the registration of controlled substances information and achieve prescription drug monitoring programs in all 50 states, and decrease the number of unintentional overdose deaths.

The Food and Drug Administration (FDA), an agency within the Department of Health and Human Services, has introduced a risk evaluation and mitigation strategy for both extended release and long-acting opioid medications [39]. The 20 companies that produce opioid medications must contribute to provider and patient education by providing educational grants to continuing education trainers. This is part of the agency's efforts to address the epidemic of prescription drug abuse and accidental overdose. The goals of this strategy are to assure that prescribers know how to prescribe safely and that patients understand the

risks of opioid pharmacotherapy. There are three components: 1) Training for prescribers according to an FDA blueprint; 2) A consumer friendly updated medication guide and patient counseling document; and 3) Assessment and auditing of company compliance with training requirements.

The pharmaceutical industry is also making efforts to reduce the opioid abuse problem. Most opioid abusers chew, crush or snort the drugs to maximize psychological effects. Pharmaceutical manufacturers are developing and marketing products that are tamper resistant [40,41]. One approach offers extended release morphine with sequestered naltrexone. Chewing or crushing of the tablet will cause release of the opioid antagonist naltrexone. Another product offers controlled release oxycodone in a crush resistant formulation and another in a high viscosity hard gelatin capsule; it is impossible to extract its contents with a needle. The impact of this approach to deterring prescription opioid abuse is still unknown but there is evidence of reduced street value of and opioid poisonings from the reformulated crush resistant long-acting oxycodone that has replaced the older formulation.

CONCLUSIONS

The United States has let opioid prescribing for chronic noncancer pain outpace both the growth of evidence about the long-range benefits and harms of opioid pharmacotherapy for chronic noncancer pain and also necessary clinician education and systems strategies that can reduce opioid-related morbidity and mortality. To date, the long-range benefits of opioid pharmacotherapy, its effectiveness, remains poorly defined while evidence on the negative effects of opioid pharmacotherapy accumulates at a greater rate. A number of unanticipated adverse drug effects have emerged. The long-range incidences and harms of these are also unknown. Initial concerns about addiction have largely given way to concerns about drug diversion and misuse, and these concerns include fatal accidental drug overdose. Moreover, the presence of opioid medications in large supply in the community has led to significant social problems.

Although the White House, other federal agencies and state medical boards and others have developed well-reasoned strategies for coping with the immediate problems of medication misuse, diversion and accidental opioid-related poisoning deaths, there is no national strategic plan for accruing a knowledge base on the effectiveness of opioid pharmacotherapy for chronic noncancer pain patients. Unless and until an adequate body of evidence on medication effectiveness becomes available, and all prescribers are knowledgeable about safe practices, the steps taken by federal and state governments and by industry will at best contain the problem, but they will not resolve it. The solution lies in reconciling practice patterns with a meaningful best practice evidence base.

The American crisis of opioid pharmacotherapy for chronic pain was at least partly foreseeable and preventable. Evidence suggests that similar problems are emerging in parts of Europe and Australia. Developed countries are at the greatest risk for repeating the American experience. Knowledge of the processes that led to the present crisis in the United States may help other nations avoid similar problems as they seek to improve their management of chronic noncancer pain.

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REFERENCES

1. Committee on Advancing Pain Research, Care, and Education; Institute of Medicine. Relieving pain in America: a blueprint for transforming prevention, care, education, and research. Edited by Institute of Medicine. Washington, D.C., The National Academies Press. 2011.
2. Croft P, Blyth FM, Windt D. Chronic pain epidemiology from aetiology to public health. Oxford, Oxford University Press. 2010.
3. International Narcotics Control Board. The Report of the International Narcotics Control Board for 2010. Vienna, Austria, United Nations Press. 2011.
4. Lipton RB. Chronic migraine, classification, differential diagnosis, and epidemiology. Headache 2011; 51 Suppl 2: 77-83.
5. McCarthy LH, Bigal ME, Katz M, Derby C, Lipton RB. Chronic pain and obesity in elderly people: results from the Einstein aging study. J Am Geriatr Soc 2009; 57: 115-9.
6. Mathus-Vliegen EM. Obesity and the elderly. J Clin Gastroenterol 2012; 46: 533-44.
7. Gaskin DJ, Richard P. The economic costs of pain in the United States. J Pain 2012; 13: 715-24.
8. Jeffery MM, Butler M, Stark A, Kane RL. Multidisciplinary pain programs for chronic noncancer pain. Technical brief No. 8. Rockville, Agency for Healthcare Research and Quality.

2011.
9. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. Pain 1986; 25: 171-86.
10. The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. Clin J Pain 1997; 13: 6-8.
11. The Federation of State Medical Boards of The United States, Inc. Model guidelines for the use of controlled substances for the treatment of pain. S D J Med 1999; 52: 25-7.
12. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996; 312: 71-2.
13. Portenoy RK, Farrar JT, Backonja MM, Cleeland CS, Yang K, Friedman M, et al. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. Clin J Pain 2007; 23: 287-99.
14. Ballantyne JC, Mao J. Opioid therapy for chronic pain. N Engl J Med 2003; 349: 1943-53.
15. Papaleontiou M, Henderson CR Jr, Turner BJ, Moore AA, Olkhovskaya Y, Amanfo L, et al. Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: a systematic review and meta-analysis. J Am Geriatr Soc 2010; 58: 1353-69.
16. Carson S, Thakurta S, Low A, Smith B, Chou R. Drug class review: long-acting opioid analgesics. Portland, Oregon Evidence-based Practice Center, Oregon Health & Sciences University. 2011.
17. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. Arthritis Res Ther 2005; 7: R1046-51.
18. Elliott JA, Opper SE, Agarwal S, Fibuch EE. Non-Analgesic Effects of Opioids: Opioids and The Endocrine System. Curr Pharm Des 2012 [in press].
19. Merza Z. Chronic use of opioids and the endocrine system. Horm Metab Res 2010; 42: 621-6.
20. Andrews CM, Krantz MJ, Wedam EF, Marcuson MJ, Capacchione JF, Haigney MC. Methadone-induced mortality in the treatment of chronic pain: role of QT prolongation. Cardiol J 2009; 16: 210-7.
21. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician 2011; 14: 145-61.
22. Brack A, Rittner HL, Stein C. Immunosuppressive effects of opioids--clinical relevance. J Neuroimmune Pharmacol 2011; 6: 490-502.
23. Warner M, Chen LH, Makuc DM, Anderson RN, Miniño AM. Drug poisoning deaths in the United States, 1980-2008. NCHS Data Brief 2011: 1-8.
24. Manchikanti L, Helm S 2nd, Fellows B, Janata JW, Pampati V, Grider JS, et al. Opioid epidemic in the United States. Pain Physician 2012; 15: ES9-38.
25. Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. Pain Med 2011; 12: 657-67.
26. Colburn JL, Jasinski DR, Rastegar DA. Long-term opioid therapy, aberrant behaviors, and substance misuse: comparison of patients treated by resident and attending physicians in a general medical clinic. J Opioid Manag 2012; 8: 153-60.
27. Von Korff M, Kolodny A, Deyo RA, Chou R. Long-term opioid therapy reconsidered. Ann Intern Med 2011; 155: 325-8.
28. Cepeda MS, Fife D, Chow W, Mastrogiovanni G, Henderson SC. Assessing opioid shopping behaviour: a large cohort study from a medication dispensing database in the US. Drug Saf 2012; 35: 325-34.
29. Cepeda MS, Fife D, Chow W, Mastrogiovanni G, Henderson SC. Opioid shopping behavior: how often, how soon, which drugs, and what payment method. J Clin Pharmacol 2012 [in press].
30. Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. Pain Med 2008; 9: 444-59.
31. Boscarino JA, Rukstalis MR, Hoffman SN, Han JJ, Erlich PM, Ross S, et al. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. J Addict Dis 2011; 30: 185-94.
32. Rigg KK, Kurtz SP, Surratt HL. Patterns of prescription medication diversion among drug dealers. Drugs (Abingdon Engl) 2012; 19: 144-55.
33. Hall AJ, Logan JE, Toblin RL, Kaplan JA, Kraner JC, Bixler D, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. JAMA 2008; 300: 2613-20.
34. Webster L, St Marie B, McCarberg B, Passik SD, Panchal SJ, Voth E. Current status and evolving role of abuse-deterrent opioids in managing patients with chronic pain. J Opioid Manag 2011; 7: 235-45.
35. Webster LR, Cochella S, Dasgupta N, Fakata KL, Fine PG, Fishman SM, et al. An analysis of the root causes for opioid-related overdose deaths in the United States. Pain Med 2011; 12 Suppl 2: S26-35.
36. Chapman CR, Lipschitz DL, Angst MS, Chou R, Denisco RC, Donaldson GW, et al. Opioid pharmacotherapy for chronic non-cancer pain in the United States: a research guideline for developing an evidence-base. J Pain 2010; 11: 807-29.
37. Fishman SM. Responsible opioid prescribing: a clinician's guide. 2nd ed. Washington, D.C., Waterford Life Sciences.

2012.
38. Office of National Drug Control Policy. Epidemic: responding to America's prescription drug abuse crisis. Edited by Office of National Drug Control Policy. Washington, D.C., US Government. 2011, p 10.
39. Gudin J. Risk Evaluation and Mitigation Strategies (REMS) for extended-release and long-acting opioid analgesics: considerations for palliative care practice. J Pain Palliat Care Pharmacother 2012; 26: 136-43.
40. Schneider JP, Matthews M, Jamison RN. Abuse-deterrent and tamper-resistant opioid formulations: what is their role in addressing prescription opioid abuse? CNS Drugs 2010; 24: 805-10.
41. Raffa RB, Pergolizzi JV Jr. Opioid formulations designed to resist/deter abuse. Drugs 2010; 70: 1657-75.