

Building a Science of Patient Safety for Pain Management:
Striking the Balance between Safety, Access and Choice.

September 2010



Executive Summary:

Pain is an untold epidemic in America. More than 76 million Americans are currently living in pain, according to the National Centers for Health Statistics and American Pain Foundation.¹ Since the early 1980's, opioids that previously were primarily used to treat cancer pain have been used to treat nonmalignant chronic pain as well. Today, many patients have come to rely on these powerful medications to manage their chronic pain, as a means to once again engage in the activities of normal living.

But while the need for pain medication has grown fast, so has the abuse of pain medication: just over the last decade, the number of Americans seeking treatment for addiction to prescription pain medications increased 400 percent, according to a recent U.S. federal government study.²

Unfortunately, the drastic increase in prescription volume – and subsequent availability of opioids to patients and their families – has increased far more rapidly than awareness about how best to use these drugs while preventing their misuse and abuse. All too often, these pills are unintentionally misused by patients. For instance, a common practice to save money in prescription medications is to split a pill in two – a dangerous practice when applied to many drugs, including extended release (ER) opioids. An equally dangerous practice is for patients to share their drugs with other family members who may not be able to tolerate them – or to leave the drugs in an unsecure place where they can be taken by a visitor, a friend or another family member. More than 70 percent of opioid medication used outside the supervision of a healthcare professional was obtained from a friend or family member.³

Today, prescription drugs are one of the most commonly abused types of drugs, second only to marijuana, according to the U.S. Department of Health and Human Services. Specifically, the number of individuals who recreationally use opioid analge-

sics has increased⁴ and the relatively serious risks related to opioid analgesics make this trend particularly troubling.⁵ In turn, prescription opioid analgesics have become the most commonly abused prescription drug in the United States, with the highest rate of abuse occurring among those ages 18 to 25. Factors contributing to the prolonged and alarming rise in prescription opioid drug abuse – particularly opioid analgesics – include the perception of relative safety when compared to illicit drugs, as well as the ease of access to opioids by recreational users due to the high volume of prescriptions and the often unprotected storage of this medication in bathroom medicine cabinets.⁶

All opioids can be addictive and often carry a stigma. As a result, patients who ask for more drugs to relieve their pain are increasingly eyed as potential addicts, and doctors who prescribe pain medications too frequently fear being arrested for it.

Prolonged and serious misuse, abuse, and related overdose have resulted in a backlash against use of prescription pain medication, and have adversely affected treatment for legitimate pain patients. Studies show that up to half of doctors cited fear of investigation affects how they treated chronic pain, and some doctors have been frightened out of pain management altogether, according to a 2005 report by The Cato Institute.

The problems of abuse and, too often, overdose are driven primarily by diversion, or the movement of a legitimate medication outside of legitimate channels. For example, genuine pain patients may share or fail to safeguard their medication, which is in turn diverted – for example, stolen by or given to a friend or family member. A lack of understanding of the seriousness of the medication fuels diversion, which ensures a steady supply of potentially lethal drugs in the hands of those least equipped to deal with the risks.

So far, efforts to balance the rising need to treat chronic pain sufferers while stemming the rising tide of prescription pain medication misuse and abuse have not succeeded. Now, the latest effort underway to achieve this balance is a Congressionally-mandated effort by the U.S. Food and Drug Administration (FDA) to establish a class-wide Risk Evaluation and Mitigation Strategy (REMS) for long acting (LA) and ER opioids – a strategy proposed to manage known or potential risks of a drug and make sure the benefits outweigh those risks.⁷ While many patient groups and physicians fear this effort will go too far in restricting the ability of patients who genuinely need this class of drugs to treat their pain and lead to the prescribing of a less restricted, yet still dangerous, class of drug, such as Immediate release (IR) opioids, others fear these efforts will be too ineffectual to make a dent in the continuing trend toward abusing these drugs

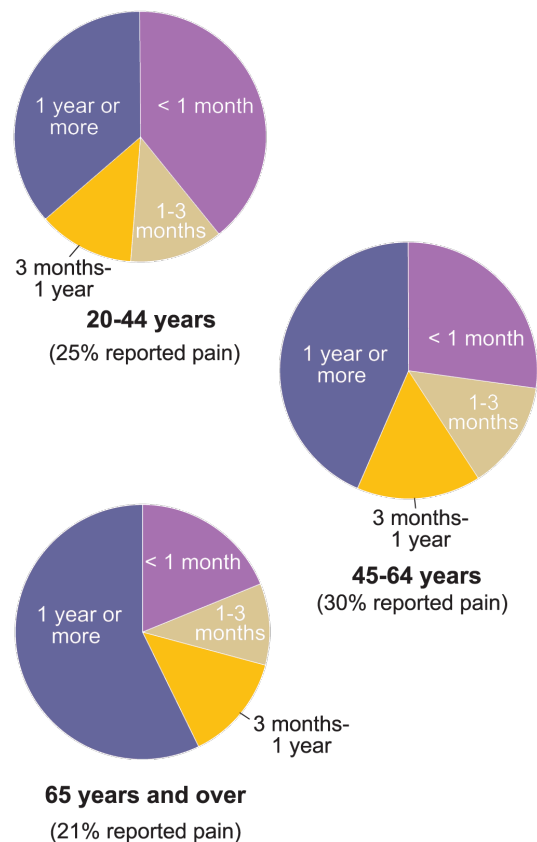
The C.A.R.E.S. (Collaborating & Acting Responsibly to Ensure Safety) Alliance, created and sponsored by Covidien, the largest U.S. manufacturer of opioid pain medicine, was established to allow leading patient advocacy organizations, healthcare professional associations, health professionals, policymakers, industry organizations and others to collaboratively address these growing issues. The C.A.R.E.S. Alliance exists to improve the outcomes of patients and their loved ones by filling the void in needed research, education and awareness, and by providing resources for patients and healthcare professionals to support safe and responsible prescribing, dispensing and use of pain medications.

Educating healthcare professionals on safe and appropriate opioid prescribing and helping patients understand how to minimize the various risks associated with their pain medications can decrease the diversion of opioids. The abuse, misuse, addiction and overdose of opioids among legitimate patients can be reduced, without restricting appropriate access to these needed drugs

As Pain Medication Prescriptions Rise, So Does Concern Over Their Abuse and Misuse

Chronic pain constitutes a major public health problem in the United States. From a quarter to a third of all Americans are estimated to suffer from chronic, non-cancer pain from such maladies as arthritis, low back pain and fibromyalgia.⁸ Just over one-quarter of American adults – an estimated 76.5 million Americans —report that they have had a problem with pain that persisted for more than 24 hours in the past month. Notably, 57 percent of older adults who reported pain indicated that the pain lasted for more than one year.⁹ As the population ages and the incidence of cancer increases, the pain problem is expected to grow.

Duration of pain among adults reporting pain by age: United States, 1999-2002



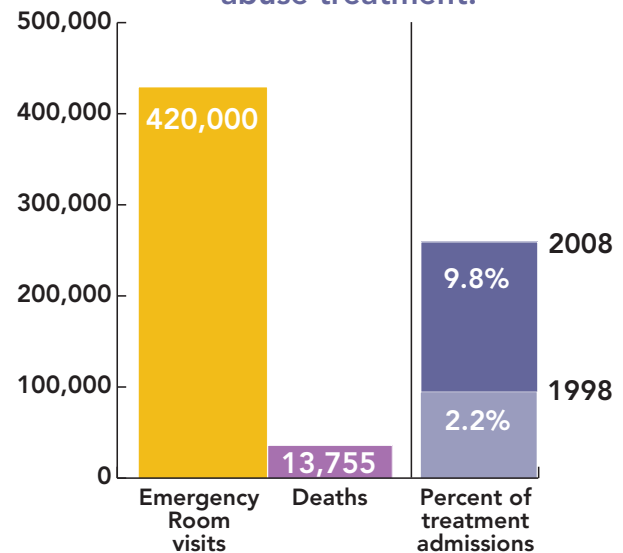
Source: Centers for Disease Control and Prevention, National Center for Health Statistics, National Health and Nutrition Examination Survey.

Treating pain has resulted in a rapid increase in the use of prescription pain medications such as opioids. In 2009, 257 million prescriptions for opioids were dispensed, a 48 percent increase from 2000. About 23 million of those prescriptions were for ER opioids – analgesics specifically formulated to enter the bloodstream over an extended period of time to prolong the effect of the medication – a 146 percent prescribing increase since 2000.¹⁰ The number of unique patients receiving a dispensed prescription for an ER or LA opioid reached 3.9 million in 2008, an increase of approximately 46 percent from 2002.

Unfortunately, many of these opioids, including ER opioids, are being misused and abused both by patients and non-patients. In 2007, 5.2 million Americans 12 years old or older reported using a prescription pain reliever for a non-medical use in the last month¹¹ – resulting in more than 165,000 emergency department visits related to non-medical use of hydrocodone, oxycodone and methadone-containing products alone.¹² Overall, there were 13,755 deaths from opioids in 2006¹³ and 420,000 emergency room visits for misuse and abuse.¹⁴ Another study found that more than 9,000 children were accidentally exposed to prescription opioid drugs between 2003 and 2006.¹⁵ The number of patients seeking substance abuse treatment for the use of prescription pain medications also is increasing rapidly. In 1998, 2.2 percent of substance abuse treatment admissions among those 12 years old or older were for abuse of prescription pain relievers. By 2008 that number had reached 9.8 percent, according to a recent study by the Substance Abuse and Mental Health Services Administration (SAMHSA).¹⁶

What's contributing to this dramatic increase? A variety of behaviors among both prescribers of the drugs and legitimate pain patients who receive opioid prescriptions are likely behind the increase in the misuse and abuse of opioids.

Number of ER visits and deaths, and the increase in substance abuse treatment.



Warner M, Chen LH, Makuc DM. Increase in fatal poisonings involving opioid analgesics in the US, 1999-2006. NCHS Data Brief, 2009; no 22.

Substance Abuse and Mental Health Services Administration. Office of Applied Studies, Drug Abuse Warning Network. Detailed tables: national estimates of drug-related emergency department visits 2004-2008.

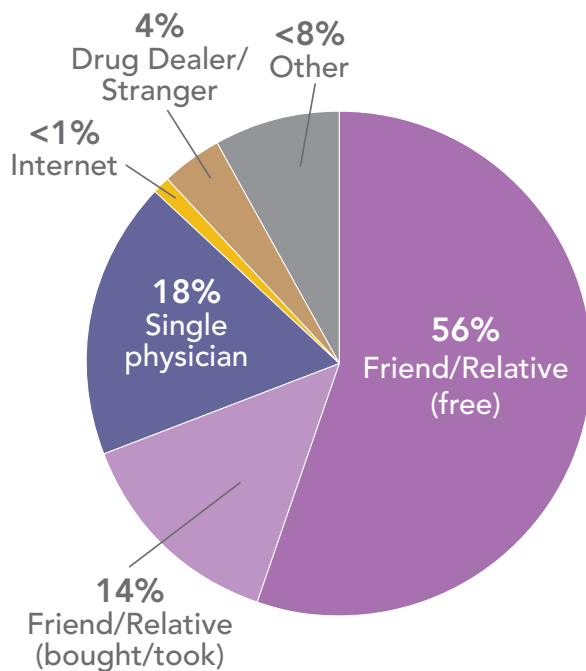
Results from the 2008 National Survey on Drug Use and Health: National Findings. U.S. Department of Health and Human Services. Substance Abuse and Mental Health Services Administration. <http://www.oas.samhsa.gov/nsduh/2k8nsduh/2k8results.cfm>. Accessed Aug. 18, 2010.

As the demands on a prescriber's time increase, the prescriber may feel pressured to offer a solution for their patient's immediate pain, all without adequate time to counsel and monitor the patient or provide specialized education on opioids. Meanwhile, once patients receive their medications, they do not always use them appropriately. Reasons for misuse may include ignorance of the risks and seriousness of the drug, patient error, escalation of pain or undiagnosed addiction. In addition, patients may not be storing and disposing of their medication properly to prevent house guests, friends, and family members from using them. An inability or unwillingness by patients to recognize signs of recreational use, abuse, and/or addiction in others also plays a major role in the lack of proper storage of their medication(s).

Addiction also plays a role in the non-medical use of opioids, which is why detecting signs of addiction among patients and potential patients is so important. Addiction is a primary chronic neurobiological disease influenced by genetic, psychosocial and environmental factors that requires a predetermined genetic framework with repeated exposures. An estimated 10 percent to 15 percent of the population appears to have been born with a genetic predisposition to substance abuse, which “means exposure to opioids may lead to the misuse of controlled substances when prescribed for pain,” says Jeffrey Gudin, MD, pain management and addiction specialist at the Englewood Hospital and Medical Center in Englewood, N.J., one of the Mt. Sinai University School of Medicine affiliates.

Likewise, illegal purchase of opioids plays only a small role in the non-medical use of opioids. Only 4.3 percent of those using opioids for non-medical purposes got the pain relievers from a stranger, and 0.4 percent bought them on the Internet, according to results from a 2008 U.S. Department of Health and Human Services study.¹⁷ Among persons 12 years old or older in 2007-2008 who used pain relievers non-medically in the past year, 55.9 percent got the drug most recently from a friend or relative for free, and 14.3 percent bought or stole them from a friend or family member, while an additional 18 percent reported they got the drug from a single doctor.

Non-Medical Use of Opioids: Acquisition Sources
88% report getting pain relievers from a friend, relative, or a single physician



- 70% report getting pain relievers from a friend or relative
- 18% report abusing the drug prescribed by a single physician

National Survey on Drug Use & Health 2008

The Role of Prescribers in Opioid Safety

Just as the field of pain medicine encompasses a wide variety of patients with acute, chronic, malignant (cancer-related), and other forms of pain, so are the pain treatment services provided by a wide variety of prescribers. These prescribers may include primary care physicians, anesthesiologists, physical medicine and rehabilitation physicians, pain medicine subspecialists, neurologists, psychiatrists, nurse practitioners, physician assistants, and other specialties.

Most opioids, however, are not prescribed by specialists. In fact, about 44 percent of the prescriptions for ER and LA opioids in 2009 were given by primary care (27 percent) and internal medicine (17 percent) physicians, according to SDI, a Plymouth Meeting, Penn.-based healthcare market insight and analytics firm.¹⁸ This trend prevails despite—or perhaps because of—the relatively insignificant time spent on pain management throughout the course of their training and education. Only three percent of medical schools have a separate required course on pain management and four percent require a course on end-of life care.¹⁹

Historically, there has been a lack of training, particularly for primary care physicians, about how to prudently evaluate candidates for opioid therapy, initiate and adjust therapy, and recognize signs suggestive of aberrant drug behaviors or addictive disorders. Current continuing medical education (CME) and continuing education (CE) programs on the topic remain fragmented and inconsistent.

On top of this, prescribers, patients and consumers often inadvertently increase the risk of harm from medication use. Informational errors in prescribing that add risk can occur when a prescriber has incomplete access to or does not effectively use existing information about the drug, the patient or the condition. For instance, prescribing a very high-potency opioid analgesic indicated for use only in opioid-tolerant individuals to a patient who is not opioid tolerant could lead to respiratory depression or even death.²⁰

One study showed that the number of overdose deaths could have been prevented by changes in prescribing practices, specifically by better risk assessment.²¹ Some of the overdose deaths were among patients suffering from depression or substance abuse that should have received substantial education and close oversight.

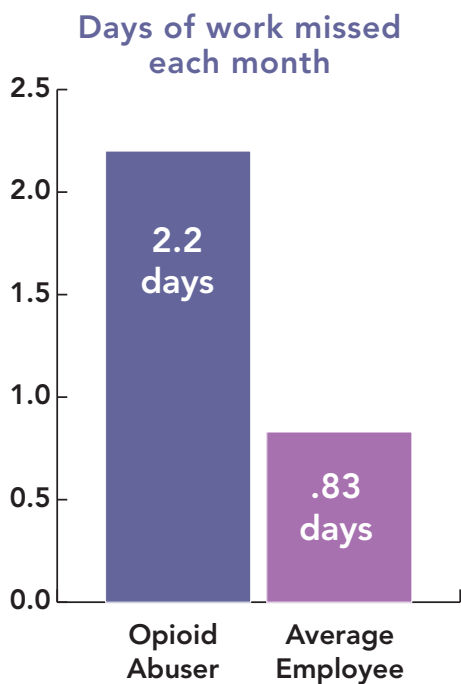
The lack of clear, consistent education and information has contributed to misuse, abuse and overdose in opioid use and, as a result, provides a significant opportunity to improve patient safety. Improved education would not only decrease the risk to patients, but also offer prescribers a clearer understanding of appropriate use and the ability to demonstrate compliance with training, thereby reducing concerns about being unfairly or falsely targeted by drug enforcement officials.

The Consequences and Costs of Opioid Misuse and Abuse

Opioid misuse and abuse carries staggering social and economic costs. Pain medication overdose deaths have risen significantly over the years to become the second leading cause of unintentional injury death, just behind motor vehicle injuries, according to a CDC study completed in 2010.²² For deaths attributed to drugs, the most common drug categories are cocaine, heroin and opioid prescription drugs. According to the study, deaths involving opioids increased 62.5 percent from 1999 to 2004.²³ By 2006, data showed that prescription opioids were involved in more overdose deaths than heroin and cocaine combined.²⁴

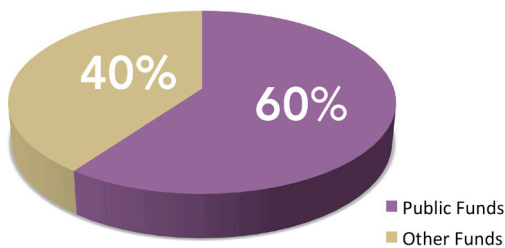
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The economic costs of opioid misuse and abuse are equally high. According to the National Survey on Drug Use and Health (NSDUH), conducted annually by the Substance Abuse and Mental Health Services Administration (SAMHSA), patients who report personal opioid abuse miss more than 2.2 days of work each month, compared with the 0.83 days per month missed by the average employee.²⁵ One study estimated the total cost for opioid abuse in 2001 was \$8.6 billion, including direct healthcare costs of \$2.6 billion and lost productivity of \$4.6 billion.²⁶



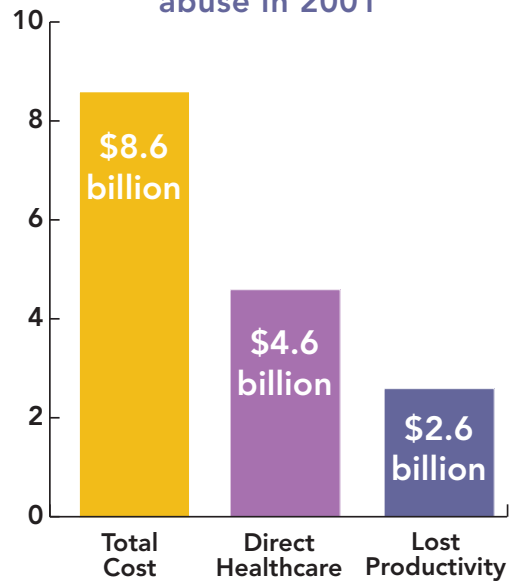
Ruetsch C. Empirical View of Opioid Dependence. *J Manag Care Pharm.* 2010;16(1-b):S9-S13.

Percent of hospital costs related to opioid overdoses paid for with public funds



Healthcare Utilization Project (HCUP). Agency for Healthcare Research and Quality. <http://www.ahrq.gov/data/hcup/>. Accessed Aug. 18, 2010.

Total cost for opioid abuse in 2001



Birnbaum HG, White AG, Reynolds JL, Greenburg PE, Zhang M, Vallow S, et al. Estimated costs of prescription opioid analgesic abuse in the U.S. in 2001; *Clin J Pain* 2006;22:667-76.8.

Opioid abusers are associated with mean annual direct healthcare costs that are 8.7 times higher than those of non-abusers (\$15,884 versus \$1,830).²⁷ On average, hospital inpatient costs accounted for 46 percent (\$7,239) and physician-outpatient costs accounted for 31 percent (\$5,000) of opioid abusers' healthcare costs compared with 17 percent (\$310) and 50 percent (\$906), respectively, for non-abusers.²⁸ Hospital stays from an unintentional overdose of opioids and sedatives jumped 37 percent between 1999 and 2006, and intentional overdoses of these drugs skyrocketed by 130 percent in that time.²⁹

This higher rate of serious adverse outcomes among opioids results in significant financial costs not just to the affected individuals and their families but to society as a whole. About 60 percent of the hospital costs related to opioid overdoses are paid for with public funds. In 2007, opioid overdoses led to nearly 30,000 hospital visits and the cost of these visits was over \$700 million, the majority of which was paid for by Medicare or Medicaid.³⁰

Targeting Drug Abuse and its Effects on Prescribers

Given the rising economic and societal toll of the misuse and abuse of opioids, it is not surprising that there is an increasing demand for stricter enforcement of how these drugs are prescribed and distributed.

The U.S. Drug Enforcement Administration (DEA) has investigated doctors who they suspect are inappropriately prescribing hundreds of millions of dollars of drugs that are contributing to an epidemic of abuse, crime and death. A 2005 Cato Institute Policy Analysis argues that the government has gone too far in “waging an aggressive, intemperate, unjustified war on pain doctors.”³¹

Whether drug enforcement authorities have gone too far or not, clearly this trend has affected how prescribers treat pain. As indicated previously, up to half of doctors said fear of investigation affected how they treated chronic pain, and some doctors have been frightened out of pain management altogether, according to the report.³²

A 2001 study of California doctors found that 40 percent of primary care physicians said fear of investigation affected how they treated chronic pain.³³ In a survey by the California Academy of Family Physicians, Dr. Paul Grossman says, “If a clinician has the slightest inkling that a patient presenting with severe pain has an ulterior motive for wanting pain control interventions, the clinical encounter becomes a ‘no win’ scenario from the clinician’s perspective. If he prescribes an opiate, he’ll be staring at the ceiling in the middle of the night wondering if the opiate is being sold on the street. If the clinician doesn’t ... wondering if he caused a patient to needlessly endure ongoing pain.”³⁴

In states where regulatory bodies aggressively monitor physicians’ prescribing habits, there is even more reluctance among doctors to adequately treat pain.³⁵ Pain specialists have been sued both for overmedicating and under treatment of their patients’ pain.

Dr. Thomas Stinson, an anesthesiologist in Medford, Mass., told *TIME* magazine in 2005 that he closed his then 20-year practice to new pain patients, “It is impossible to be sure that a patient is not diverting any of his medication. I fear I might be targeted.”³⁶

Thus, prescribers are faced with the dilemma of how to safely incorporate opioids into treatment plans that maximize the possibility of successful pain control while minimizing the risk of misuse, abuse or diversion. The dilemma is heightened for primary care physicians who shoulder most of the burden of pain management, despite having received little specific training in pain medicine or substance abuse, and generally being constrained to increasingly brief visits for evaluating and managing complex problems.

Prescribers who prescribe opioids to treat pain are often caught between their professional obligation to relieve suffering and their desire to avoid contributing to the public health problem of prescription drug abuse. The challenge is to curtail the inappropriate use and diversion of prescription opioids while ensuring their availability to benefit legitimate patients.

In order to prescribe opioids safely and effectively as the number and types of these medications increase, prescribers need to better understand the risk factors which may increase the likelihood for abuse of opioids, such as history of substance abuse, young age, history of preadolescent sexual abuse, mental disease, social patterns of drug use and psychological stress. Knowing in advance whether a patient carries one or more of these risk factors can assist the prescriber in monitoring the progress of treatment and prevent abuse.³⁷ The key to managing a patient’s opioid intake lies in screening for abuse potential and carefully monitoring the progress of treatment.

Balancing Safety, Access, and Choice through the Science of Patient Safety

The rise in recent years of the number of patients needing pain treatment amidst mounting concerns about abuse and misuse has led to the fundamental need to balance the challenges of safety, access and the prescriber's choice in prescribing pain medication.

In order to improve safety, the federal government continues to struggle with balancing competing interests – making affordable pain medications available to patients without unduly burdening the healthcare system, while curbing the inappropriate and sometimes illicit prescribing, dispensing and use of opioids. The DEA has attempted to address the problem by licensing healthcare professionals to prescribe controlled substances and regulating the availability of pain medications in interstate commerce through the use of quotas. The FDA has attempted to implement risk minimization action plans (RiskMAPs) that are intended to mitigate the identified risks of these medications. Neither approach seems to have been effective, as shown by the increase in non-medical use of opioids and related overdose deaths in the last decade.³⁸

Partially in response to these concerns, in 2007 Congress gave the FDA authority to require a REMS for new drugs, as well as for certain prescription drug products already on the market, to ensure the benefits of the drug outweigh the associated risks. The legislation emphasizes that the goal of a REMS is to minimize the stated risks of a drug while, at the same time, avoiding impeding patient access to medications essential to treat painful diseases and conditions.

In February 2009, the FDA announced it will require a class-wide REMS program for LA and ER opioids, to include 24 prescription pain medications that contain fentanyl, hydromorphone, methadone, morphine, oxycodone and oxymorphone. Products approved after the announcement and before the execution of the class-wide REMS would be required to submit an “interim REMS” that would be adapted to the class-wide requirements when those became effective. The class-wide REMS for the LA and ER opioids would be the most far-reaching risk management program ever undertaken in the U.S., affecting 3.8 million patients, nearly one million prescribers and between 25 million and 30 million prescriptions a year.³⁹

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For stakeholders, the most contentious REMS component centers on the ability to appropriately and transparently monitor the medications without placing an undue burden on the healthcare system. Public comments from many professional and patient organizations have been highly critical of any FDA requirements for formal physician training certification and registries, and/or patient registries. Healthcare professionals believe formal certification is overly burdensome and will result in a lower number of prescribers who can treat chronic pain patients, putting additional pressure on pain specialists and reducing or eliminating access for poor or vulnerable people in pain, especially those living in rural areas.

Another unintended consequence of a class-wide REMS for both healthcare professionals and patients could be avoidance of ER opioids, leading to an inappropriate reliance on short-acting opioids that also carry similar risks and a minimal REMS program that simply consists of a standard class-wide Medication Guide. Called the “balloon effect,” this illustrates how putting regulatory pressure on one side of the pain medication spectrum (i.e., ER opioids) could result in expanded use on the other side of the spectrum, specifically IR opioids, which have minimal REMS requirements.

In fact, an Advisory Committee to the FDA recommended that the REMS should be applied to all opioids for this very reason.⁴⁰ Although recognizing that IR opioids also present serious risks to patients when not used properly, the FDA decided in its REMS proposal not to broaden its scope, arguing that LA and ER opioids posed a greater threat than IR opioids and that a REMS for all opioids would affect an even greater number of patients and create a much greater burden on the healthcare system.⁴¹

FDA’s Class-wide REMS Proposal Rejected by Advisory Committee

Based on extensive input from industry, physicians, patients and others, the FDA presented a proposed “Risk Evaluation and Mitigation Strategies (REMS) for Extended-Release and Long-Acting Opioid Analgesics” to the Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and The Drug Safety And Risk Management Advisory Committee in July 2010.

The proposed goal for the REMS was to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of LA and ER opioids, while maintaining patient access to these medications. This would be accomplished

by educating prescribers in appropriate patient selection, dosing, and patient monitoring, and by educating patients in the safe use, storage, and disposal of opioids, according to the FDA.

The proposed class-wide REMS required pharmaceutical companies to develop and ensure the distribution of a patient-friendly medication guide, prescriber and patient education programs, and an assessment process to determine the effectiveness of the REMS in reducing serious adverse outcomes from the misuse and abuse of opioids.

Specifically, the FDA proposed that sponsors (manufacturers) be required to develop an educational program that would educate prescribers about appropriate patient selection, dosing and patient monitoring. Prescribers also would be trained to counsel patients on the safe use, storage and disposal of opioids. Sponsors would be required to provide patient education sheets for prescribers to use in their interactions with patients. The content of these patient education sheets would be FDA approved.

The Advisory Committee rejected this class-wide REMS plan for ER and LA opioids, contending that the plan was too weak to safeguard against misuse and abuse of those products. The panel’s rejection of the FDA’s proposed REMS was not a rejection of the concept of a REMS, but demonstrated concern that the elements of the class-wide LA and ER opioids REMS did not go far enough – for instance, this panel recommended that the REMS should apply IR opioids as well as ER and LA opioids. The FDA will consider the recommendations of its Advisory Committee but is not bound by the panel’s recommendations in drafting a final version of its REMS plan for ER and LA opioids.

Concerns About What's Next: Registries, Mandatory Prescriber Education

If the FDA follows the advice of the Advisory Committee, a new REMS could be far more restrictive than the one proposed in July.

For instance, the committee expressed concerns that the FDA's REMS failed to include mandatory prescriber and patient education, which would be difficult to enforce without a registry system for prescribers and patients. In fact, the FDA considered proposing that the REMS require individual prescribers or patients to enroll in a REMS program with real-time verification of prescriber training at the pharmacy level, but decided against it "at this time."⁴² Numerous comments at the public meeting and in the docket stated that a REMS that employs a patient registration system would be overly burdensome and create a stigma for pain patients that could adversely affect their access to necessary medications, in addition to raising significant privacy concerns. Nearly four million patients are prescribed LA or ER opioids annually,⁴³ and enrolling so many patients in a registry would be an enormous undertaking with unpredictable effects on patient access. Many patients have expressed concerns that being forced to join a registry could compromise the privacy of their medical information, while healthcare professionals are generally opposed to the additional oversight and intrusion in their practice of medicine. For these reasons, the FDA proposed a limited REMS at the meeting with the expectation that it would carefully monitor the effects of the program and consider further steps if the limited REMS approach did not prove effective in curbing serious adverse outcomes resulting from inappropriate prescribing, abuse and misuse.

Some panelists called for Congress to develop legislation that would create a system in which prescriber training for opioids would be tied to DEA registration. But there is concern, even among FDA officials, that requiring a training program for opioid prescribers could result in physicians opting to no longer prescribe the medicines, leaving some patients without access to treatments for pain. The REMS statute requires the FDA to ensure that any restrictions the agency imposes does not create an undue burden on the healthcare system or society. Some experts warned the FDA that a requirement for individual prescriber registration and real-time verification of pharmacist training before filling an opioid prescription would likely cause some prescribers and pharmacies to "opt out" of the program, leading to potential adverse consequences to patients' access to pain medications. More than one million prescribers are registered with the DEA to prescribe opioids. About 700,000 of these prescribers prescribe LA and ER opioids. About 66,000 pharmacies are registered with DEA.⁴⁴ In the long term, linking the education to the existing DEA registration system would more efficiently ensure appropriate education of physicians, but legislation would be required.

Members of the American Society of Interventional Pain Physicians (ASIPP) want lawmakers to appropriate \$55 million over the next five years to fund a 2005 federal law called the National All Schedules Prescription Electronic Reporting (NASPER). NASPER would help states collect data on consumers who "doctor shop" and on physicians who over-prescribe or incorrectly prescribe pharmaceuticals.

To date, 41 states have prescription monitoring programs in place that can receive and distribute controlled substance prescription information to authorized users, according to ASIPP, although six are not operational.⁴⁵ The drugs that must be reported also vary depending on the state, as do other details, such as the mechanism for reporting, the mechanism for accessing the data, and who can access the data.⁴⁶ But many states do not meet NASPER standards — failing, for example, to monitor prescriptions electronically; only covering certain drug categories; or giving pharmacies more than seven days to submit information. In addition, only two states, Kentucky and Connecticut, are attempting to share information among states, which ASIPP says is necessary to prevent drugs abusers from stocking up on pills in states that have more lax standards.

While some argue that a national prescription monitoring program similar to those already in place in some states would be an alternative to a registry, others would counter that a prescription monitoring program is just a registry under a different name.⁴⁷

Going Beyond REMS: Covidien's Scientific Approach

Covidien has advocated implementation of a class-wide REMS program as a basic foundation, allowing flexibility to meet individual ER opioid product risks, and addressing legal and regulatory concerns associated with a “one-size-fits-all” class-wide REMS. Industry members must then, in Covidien's view, go a step further by developing safe-use educational and informational tools that reflect the specific risks and benefits associated with each product. At the July 2010 meeting, Herbert Neuman, MD, Vice President of Medical Affairs and Chief Medical Officer for Covidien Pharmaceuticals, told the FDA's Advisory Committee for REMS:

“We focus on mitigating the risks of our products. We support this philosophy with three pillars of effective safe use initiatives: collaboration, education and innovation. The FDA has proposed a REMS that is appropriate and well balanced to meet the needs of patient safety, access and choice. And that is an essential foundation. But the pharmaceutical industry must take responsibility for developing supplemental voluntary safe use programs tailored to the unique risk profiles of their products.”

That's the approach Covidien took in creating its REMS and voluntary safe use program for a recently approved ER opioid that was approved by the FDA in 2010. Specifically, Covidien applied a scientific approach to risk management, conducting an extensive Failure Mode and Effect Analysis, or FMEA, of its ER hydromorphone HCl medication use process. This evidence-based methodology addressed process failures – or what could go wrong when patients take the medication – as well as the corresponding causes, and identified a range of mitigating voluntary tools, beyond those required in the REMS, that were refined and validated by multiple stakeholder focus groups.⁴⁸

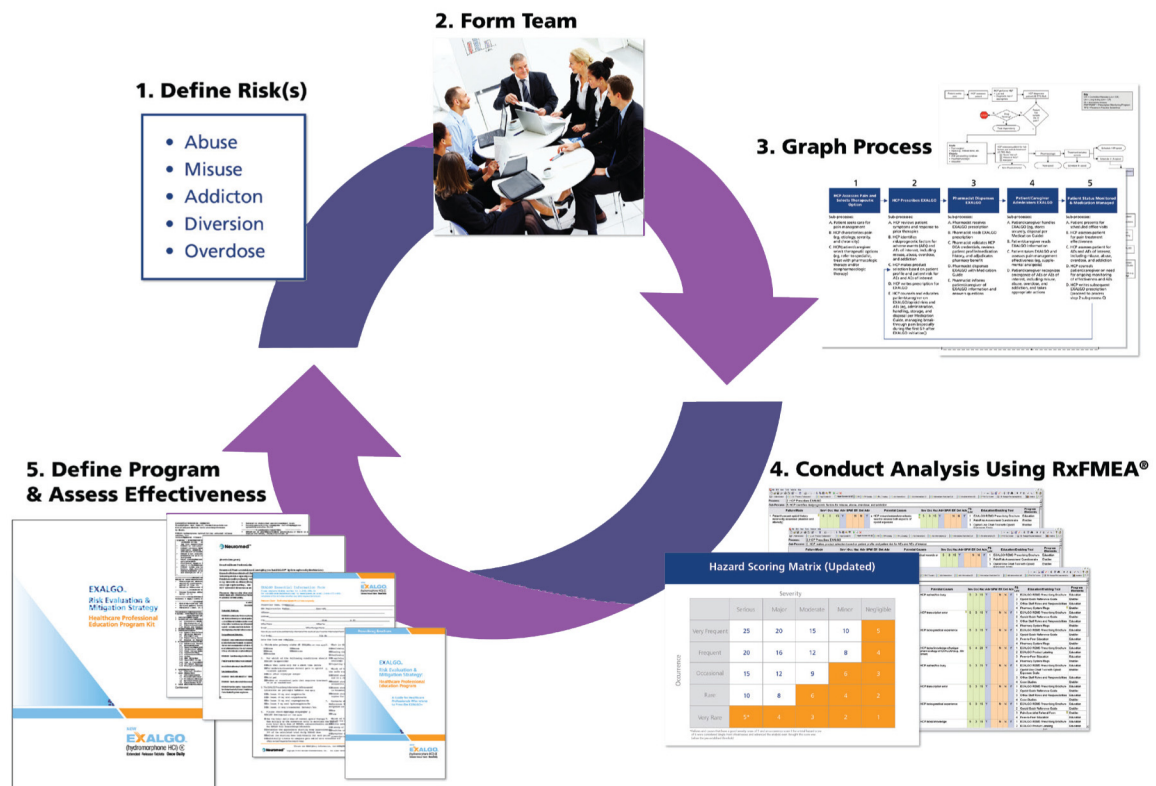
This evidence-based methodology also has been employed by governmental agencies, manufacturers and others, and is a valuable tool for improving patient safety.⁴⁹ For example, FMEA has been used by The Joint Commission and hospitals in reducing medication errors and improving patient care.^{50 51 52 53} RxFMEA® is a propriety software application (ParagonRx, Wilmington, Del.) enabling users to systematically identify, rank and define potential human factor and other failures related to pharmaceutical product use and specify interventions to address those failures.

By collaborating with experts and learning from pain treatment and risk management leaders, Covidien developed an overall risk mitigation program to meet and exceed the product's REMS objectives. Consistent with company priorities and values, their focus was to educate, collaborate and innovate to improve patient safety. A special effort was made to design and enact programs that preserve access for appropriate patients and avoid unnecessarily burdening prescribers, pharmacists and current or future patients. Most importantly, the mandated REMS was designed to ensure patients understand the need to take their medication exactly as directed by their prescriber, as well as understand the key safe use messages to reduce risk.

The FMEA process consists of a predetermined set of steps to assure a systematic and reproducible method of analysis (as depicted in the illustration below). A multidisciplinary team of more than 15

members thoroughly defined the medication use process for the ER opioid. The team then defined ways the steps in the process could fail and the underlying behaviors that could cause failure. Hazard scores for each potential failure were calculated on the possible and expected frequency and severity of the failure. The scores were used to prioritize each potential cause of failure, analyze the hazards that could lead to unsafe actions, determine interventions to mitigate potentially dangerous behaviors, and ensure multiple interventions address individual serious risks and promote effectiveness.⁵⁴ Interventions consist of educational programs and materials, and enabling tools. Metrics were defined to help measure how each intervention is accepted, understood, and used by the healthcare professionals and patients. Project briefs were created to aid in tool development and to specifically target particularly risky or dangerous behaviors.

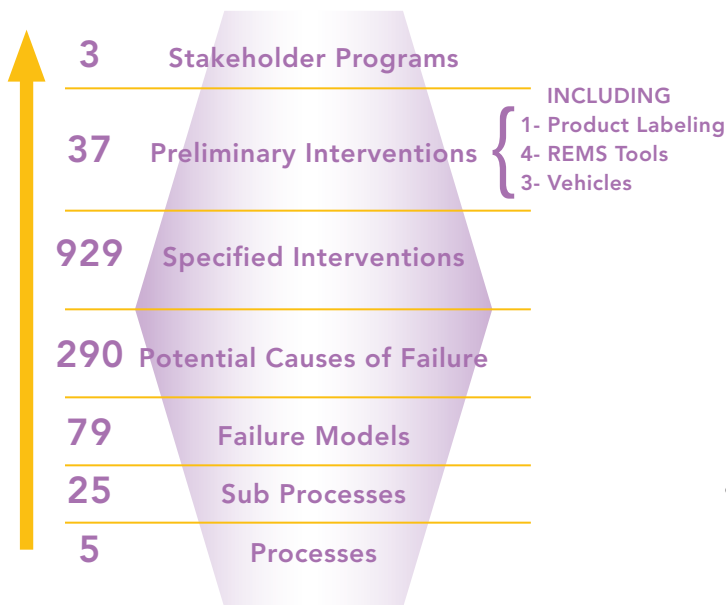
The RxFMEA® Process



Holman K, Mills S, Morelli A, et al. A Science-Based Approach to Responsible Risk Management for a Novel Long-Acting Opioid Analgesic [poster]. American Society of Pain Educators. September 2010.

A total of 30 processes and sub-processes were analyzed yielding 79 failure modes and 290 potential causes of failures. These failures led to 929 identified interventions, for which 37 preliminary tools were specified to be distributed through physician, pharmacy, and patient/caregiver programs. The process also identified the five tools required by the FDA as meeting the REMS objectives: Medication Guide, Dear Healthcare Professional Letter, Prescribing Guide, Dedicated REMS Web Site (www.EXALGOrems.com), and Full Prescribing Information (not limited to REMS). Results of the analysis are shown in the illustration below.

Results of Covidien Extended-Release Opioid Rx FMEA® Analysis



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This process provided the science-based “evidence for action” leading to the systematic identification, dissemination and use of the most appropriate set of tools to mitigate the risks identified by the highest hazard scores. As a result, the FDA-required tools were concluded to be necessary, but not sufficient, to mitigate

important patient safety risks – a gap in protecting patient safety that required additional tools. This focused effort led to the creation of important and impactful tools to be used by stakeholders; provided a solid foundation for future program redesign; will allow for a phased implementation of additional specified tools to address identified risks; and can be adapted for use based on real world experience and the results of program assessments.

Beyond Covidien’s administration of the REMS for its ER opioid, the FMEA process led to a number of additional valuable tools and processes, including:

- The REMS-required Essential Information Form, or EEIF, was designed to assess the education program currently in place, with the goal of 100 percent voluntary participation by prescribers. To ensure the highest return rate for the forms after sending an initial mailing to 60,000 potential prescribers (three times the FDA mandate), Covidien created a universal prescriber contact process. Far exceeding FDA requirements, this process consists of an ongoing call center that contacts every new prescriber who has yet to submit the completed EEIF, as well as encouragement to complete EEIFs by Covidien’s commercial team and medical science liaisons, as needed.
- A patient education tool, not required by the REMS, that exceeds the FDA’s patient education requirements and includes a brochure that provides guidance on the safe use and storage of the product with answers to many common questions, as well as a pain diary and introductory video.
- A dose alert timer placed on top of the pill bottle that sounds an alarm to remind patients when it is time for their next dose, meant to address unintended overdose and underuse.

Altogether, Covidien's safe use program deploys a much broader and deeper risk minimization offering than required by the FDA. Through a continuous improvement process, Covidien expects the combination of education and enabling tools will maximize the benefits and minimize the risks of this important class of medication. Covidien's internal oversight team is measuring the performance of the REMS, and an expert advisory board provides commentary and guidance on the effectiveness and need to refine current required and voluntary interventions. Covidien also plans ethnographic studies of experts in the field to identify innovative risk mitigation methods for a broader prescriber audience and to ensure as much as possible that patients properly use and store the medications in the safest and most effective way.

Broadening the Patient Safety Effort: Launching the C.A.R.E.S. Alliance

Assuring much-needed safety and appropriate access when it comes to powerful pain medications such as opioids is a task that is beyond any one company, professional group, patient advocacy organization or government agency. The continuous rise in prescription drug abuse, misuse, overdose and diversion is a complex problem, and no single intervention or stakeholder group can address every facet of the issue.

As a result, Covidien felt it important to share its discoveries and tools with all others grappling with these same issues. For example, much of the information included in its REMS prescriber educational program is general enough in scope and content that it could be included as part of a more comprehensive, "big picture" educational campaign regarding the diagnosis and treatment of both acute and chronic pain with a broad range of opioid analgesics that leverages both traditional and new communication vehicles.

Furthermore, restoring the balance among safety, access and choice requires collaboration among healthcare professionals, patients, patient advocacy organizations, healthcare professional associations, government agencies, industry organizations, pain advocates, anti-abuse groups, like-minded companies and pharmacy groups.

"If we are to help solve society's problems with drug abuse and pain, we need to take a look at the whole problem and find common ground," says Art Morelli, Vice President of Medical Affairs Operations at Covidien.

That's why Covidien created the C.A.R.E.S. Alliance, a multi-faceted approach with a mission of "collaboratively improving patient outcomes through innovative and scientific education." The Alliance, with guidance from patients themselves and experts in the fields of pain treatment and risk management, aims to improve patient and societal safety while ensuring patients suffering from pain still have access to needed medications.

The Alliance will offer more than 60 patient and health professional tools and resources – identified through the FMEA process used to validate its ER opioid REMS tools – free to patients and healthcare professionals via its new web site, www.caresalliance.org. Many of these tools involve providing the information and expertise to help healthcare professionals understand guidelines and best practices in the use of all types of opioid drugs to treat chronic pain; assess patient risk factors for misuse, abuse and addiction; and counsel patients and family about the risks of opioids and the importance of keeping them safe from other family members or outsiders.⁵⁵ In addition, the C.A.R.E.S. Alliance will help prescribers stratify patients for risk to determine those who can be adequately treated in the primary care setting, and those who should be co-managed with pain or addiction specialists or referred to the care of a pain specialist.

In addition, patient education tools are available via the C.A.R.E.S. Alliance web site. Patients are provided education about the risk of abuse in their household and appropriate medication use. The materials are designed to increase patients' comfort in their risk awareness so they may manage the risks accordingly in partnership with their healthcare professionals.

Ultimately the goal is better patient and societal outcomes, and the key to achieving that goal is to use a valid scientific method as a basis to evaluate the tools offered to patients and health professionals. In one of the multiple efforts to advance the science of safety, the C.A.R.E.S. Alliance is partnering with Dr. Peter Neumann on a project to "add science to REMS" by studying the history and effectiveness of risk communications to patients, in an effort to communicate more effectively with patients about their medication. Dr. Neumann is director of the Center for the Evaluation of Value and Risk in Health at the Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, and professor of Medicine at Tufts University School of Medicine.

Other efforts will follow, based on input received from the leaders in the field as to where harder, more scientific data and research is necessary to improve the science behind patient safety and opioid use.

"Collaborative efforts like the C.A.R.E.S. Alliance, based on solid, credible scientific evidence, will help make safe and effective pharmaceutical treatment a reality," says Aaron Gilson, MS, MSSW, PhD, of the Pain and Policy Studies Group at the University of Wisconsin, and a member of Covidien's REMS advisory board.

Conclusion: Advancing the Science of Patient Safety

Balancing the significant need to address and treat debilitating chronic pain in America with a growing crisis of abuse, misuse, overdose and addiction to prescription pain medications is complex. We must assure these powerful medicines are not used inappropriately, while we also support the tens of millions of Americans suffering from chronic pain. Appropriate access to treatments, including prescription pain medicines, will help improve their quality of life and, in many instances, will help assure they continue to lead productive, fulfilling lives.

Both the increased incidence in pain treatment and the growing problem of inappropriate opioid use have taken a huge toll on our society, ripping families apart, reducing work productivity and resulting in hospitalization and even death. Unfortunately, the goals of safety and access can be conflicting ones, and attempts to achieve one goal can come at the cost of attaining the other. By coming together to promote education and communication among prescribers, pharmacists and patients through the C.A.R.E.S. Alliance, both goals can be achieved.

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