Perspectives on Opioid Analgesics for Pain Management

OPTIMIZING THE BENEFITS WHILE MINIMIZING THE RISKS
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TUFTS HEALTH CARE INSTITUTE PROGRAM ON OPIOID RISK MANAGEMENT
Perspectives on Opioids for Pain Management: Optimizing the Benefits, while Minimizing the Risks

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Introduction

When the Tufts Health Care Institute (THCI) Program on Opioid Risk Management began its work in 2005, the United States was five years into the prescription opioid epidemic. While the benefits of prescription opioid medications for managing chronic pain were clear, associated risks of addiction, abuse and divergence had emerged and were growing rapidly. The earliest documented cases of prescription opioid abuse were identified in Maine around 2000; by 2005, opioid abuse had already devastated communities across the country.

At that time, there was no comprehensive approach to understanding the nature of the problem and designing potential interventions. Professionals from multiple sectors and perspectives—including clinicians, government agencies and pharmaceutical manufacturers—were in desperate need of information and guidance. Yet it was a situation akin to the parable of the blind men touching an elephant. Stakeholders understood their piece of the issue, without being able to connect the pieces, comprehend the overall nature of the problem, and envision systematic responses to it.

Recognizing the need to bring together multiple stakeholders so that they could fully explore the issues related to abuse and diversion, the THCI Program on Opioid Risk Management organized and conducted 16 summit meetings between 2005 and 2012. To our knowledge, this Program has been the only academic forum that provided a neutral environment where experts from multiple disciplines could come together to review and learn about the nature of the prescription opioid abuse epidemic, gather data to analyze the problem, and identify potential solutions.

The summit meetings were based on an intervention-oriented paradigm. That is, in order to impact the complex issues related to prescription opioid abuse and diversion, first we aimed to create an understanding of the issues. Next, we strived to offer solutions that could be used by a variety of organizations and professionals. Finally, we focused on how to monitor and measure the impact of interventions, to ensure that they are implemented effectively. An emphasis on practical, effective intervention permeated all our thinking and activities.

The Program has also played a critical role in the development of a network of individuals and organizations focused on safe prescription opioid use. While in the past many experts with a passion for this issue worked in isolation, our summit meetings created a breeding ground for individuals to become ongoing collaborators, both in follow-up to the meetings, and in planning new initiatives. One of the most gratifying outcomes of the Program is the many seeds that were planted at our meetings, which have grown into a variety of new programs and initiatives. It is not uncommon to see ideas and materials that were developed at our summits become widely disseminated in the field, and part of the common, contemporary understanding of prescription opioid abuse.

Over recent years, we have witnessed many positive developments in the battle to curb opioid abuse and diversion. For example:

- The Office of National Drug Control Policy (ONDCP) has shown increasing concern about opioid safety and published a Prescription Drug Abuse Prevention Plan in 2011.
- Federal Agencies—including the Food and Drug Administration (FDA), Drug Enforcement Administration (DEA), Substance Abuse and Mental Health Services Administration (SAMHSA), National Institute on Drug Abuse (NIDA), and Centers for Disease Control (CDC)—have become stalwart proponents for taking action to make opioid prescribing safer, and to prevent abuse and diversion.
Pharmaceutical companies have taken action to improve the safety of prescription opioid medications and continue to pursue even safer medications.

Professionals and members of the public have become increasingly aware of prescription opioid abuse, with articles appearing almost daily in professional journals and the popular press.

Academic research has increased, with more funding opportunities to support this work.

Prescription monitoring programs (PMPs) have been established in most states, and a center of excellence in prescription monitoring was established at Brandeis University.

At the same time, despite increased and widespread awareness of the problem, much remains to be understood and implemented. The following are important priorities:

- Many promising interventions—such as lock boxes, use of PMP data, and patient monitoring—are not yet adequately studied or deployed.

- Further identification of effective interventions is needed, especially community-based interventions. As they are implemented, they should be evaluated to understand their long-term impact.

- More work is needed by public and private payers to implement policies that support safe prescription opioid use.

- Development is needed of both pain treatments with no abuse potential and effective abuse-deterrent formulations.

- Drug manufacturers, as part of the Risk Evaluation and Mitigation Strategies (REMS) process, are now required to develop prescriber educational materials and initiatives, but much is yet to be known about how to train clinicians effectively on safe prescribing.

- Increased public education is needed for people at all ages, from youth to the elderly.

- While some new research funding has become available, much more is needed.

In sum, today, we are in a different place than we were when the THCI Program on Opioid Risk Management began. While there is still much work to be done, we conclude this Program having accomplished a great deal. We have helped to identify and understand this multi-faceted problem, convened the many stakeholders who can help address it, raised awareness, sparked collaborations, and planted seeds for the work that is still needed—in science and research, education and training, and development and evaluation of interventions.

The support and participation of many organizations and individuals have brought us to this point in the quest for safe, effective use of prescription opioids. On behalf of all of us involved in the management of this Program, we appreciate the generosity and participation of the funders who have supported our work over the years. We would also like to acknowledge the passion and knowledge of the expert faculty who collaborated in our summit meetings. Finally, we are grateful to the close to 400 individuals who participated in our meetings and helped develop the analyses and recommendations laid out in these pages.

Nathaniel Katz, MD, MS
Program Director
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Program on Opioid Risk Management
Description of the Tufts Health Care Institute Program on Opioid Risk Management

In 2005, Tufts Health Care Institute (THCI) established the Program on Opioid Risk Management to address the public health crises of prescription opioid abuse and diversion. The mission of the Program is to address challenges in the development and utilization of opioid analgesics, by engaging a multidisciplinary group of stakeholders to focus on optimizing the benefits of opioids for pain management, while minimizing their risks, including abuse and diversion.

SUMMIT MEETING DESIGN AND TOPICS
The mainstay of the Program’s activities has been its high-level summit meetings. These meetings were attended by representatives from government regulatory agencies, academic and research institutions, health care delivery organizations, pain and addiction specialists, insurers, community-based organizations, law enforcement, the pharmaceutical industry, medical laboratories, and others. Each meeting was limited to approximately 50 invited participants, in order to maximize interactivity and the exchange of ideas.

The framework of each summit included didactic presentations by experts in the field, interactive discussions, and breakout groups, in which participants developed recommendations on strategies to address key issues. Many of the expert presenters remained involved in the Program over the years, providing guidance on meeting topics and participating as contributing authors of publications resulting from meetings.

The Program hosted 16 summit meetings, addressing a broad range of topics.

1. Perspectives of Major Stakeholders on Opioid Risk Management, March 2005
2. Development of Abuse-Resistant Opioid Formulations, October 2005
5. Responding to Signals of Opioid Abuse and Diversion, March 2007
6. Understanding Types of Opioid Abusers, September 2007
7. Sources of Diverted Prescription Opioids, March 2008
8. The Role of Urine Drug Monitoring in Pain Management, June 2008
10. Prescription Monitoring Research Update, April 2009
11. Risk Evaluation and Mitigation Strategies for Prescription Opioids, July 2009
12. The Role of Dentists in Preventing Opioid Abuse, March 2010
13. Prescription Opioid Abuse: Challenges and Opportunities for Payers, June 2010

DELIVERABLES
Several manuscripts stemming from summit meetings have been published in professional, peer-reviewed journals.


Other THCI Program on Opioid Risk Management projects include:

• A case-controlled study of risk factors for developing prescription opioid addiction, 2007

• Citizen petition to the Food and Drug Administration (FDA) to publish a guidance for industry on development of abuse-deterrent formulations of prescription opioid products, 2008

• Testimony at the Commonwealth of Massachusetts OxyContin and Heroin Commission, 2009

• Survey of prescription opioid prescribing patterns of dentists in West Virginia, 2010

• Submission of REMS summit meeting recommendations to the FDA, in preparation for its Drug Safety and Risk Management Advisory Committee Meeting, July 2010
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Information presented at the THCI Program on Opioid Risk Management summit meetings is the opinion of the individual faculty member, and does not reflect the opinion of the National Institute on Drug Abuse, National Institute of Health, the Department of Health and Human Services, any other federal agency, or the U.S. Government.

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An increase in prescription opioid abuse and diversion is an important consequence of the greater availability of opioids to address the widespread problem of undertreated pain. Opioid risk management refers to efforts to minimize the harms associated with opioid therapy while maintaining appropriate access to effective pain treatment. Management of these linked public health issues requires a coordinated effort among stakeholders at the federal, state, industry, practitioner, and patient levels.

The Tufts Health Care Institute (THCI) Program on Opioid Risk Management convened this summit meeting to a) identify key stakeholders involved in opioid risk management and their responsibilities in this area; and b) summarize approaches currently used to monitor and address prescription opioid abuse and diversion.

FEDERAL AGENCIES’ RESPONSIBILITIES
The Food and Drug Administration (FDA) regulates the approval of new drugs for marketing based on efficacy and safety data, including their potential for abuse. The FDA is also responsible for reviewing drug labeling and promotional materials of new drugs for consistency with approved labeling. For drugs posing a high risk of abuse and diversion, the FDA oversees the risk management strategies and educational activities that the drug’s sponsor must put in place to reduce these risks. The Drug Enforcement Administration (DEA) regulates the production and distribution of drugs with potential for abuse, termed controlled substances, by a) setting production quotas; b) regulating prescribers, pharmacies, manufacturers, distributors, importers, and researchers; and c) playing a role in law enforcement activities to curb drug abuse and diversion. The DEA, working with the FDA, schedules controlled substances, which are placed on one of five schedules based on their medical usefulness and potential for abuse. The FDA and DEA work closely on opioid risk management, with the FDA focused on clinical issues and the DEA focused on law enforcement approaches. The White House Office of National Drug Control Policy establishes policies, priorities, and objectives for the nation’s drug control program. The Substance Abuse and Mental Health Services Administration (SAMHSA) provides surveillance of drug abuse and supervises addiction treatment services. The National Institute on Drug Abuse (NIDA) supports drug abuse research and the transfer of scientific data to policy makers, practitioners, and the public.

STATES’ RESPONSIBILITIES
Neither the DEA nor the FDA have the authority to regulate clinical practice or prescribing decisions made by clinicians. This responsibility lies with state agencies. State medical boards can promote safe opioid prescribing by developing guidelines, regulations, and policies related to the use of controlled substances. Recognizing the need for consistent state policies nationally, the Federation of State Medical Boards developed uniform clinical guidelines for pain management, including appropriate use of opioid analgesics. Many states have also implemented electronic prescription monitoring programs (PMPs) to curb “doctor shopping” and diversion.

HEALTH CARE PROVIDERS’ RESPONSIBILITIES
Health care providers have the daunting task of balancing effective pain treatment with the risks of prescription opioid abuse. They are responsible for using prudent approaches to prescribing and implementing controls to minimize abuse and diversion. They can do this by implementing “universal precautions” when treating patients with prescription opioids, including: conducting a complete diagnostic evaluation of pain; screening for risk of opioid abuse and co-morbid psychological conditions; using medication agreements; using urine drug testing; and monitoring routinely for signs of abuse. If aberrant behavior surfaces, the provider is responsible for evaluating whether this behavior indicates opioid abuse, and for actively managing the problem.
HEALTH CARE PAYERS’ RESPONSIBILITIES

Payers can influence utilization of opioids with a number of strategies. These include: establishing formulary restrictions and tiered co-pays; requiring prior authorization for sustained-release opioids unless prescribed by a specialist; imposing quantity limits for dispensing; and reviewing claims to detect patterns of abuse.

PHARMACEUTICAL INDUSTRY’S RESPONSIBILITIES

The pharmaceutical industry has product liability responsibilities for reducing the risk of abuse and diversion. The FDA is authorized to provide industry guidance on risk management activities, and has established guidance documents for industry on: conducting pre-marketing risk assessments; developing and implementing Risk Evaluation and Mitigation Strategies (REMS); and performing post-marketing pharmacovigilance and pharmacoepidemiologic assessments.

IDENTIFYING PRESCRIPTION OPIOID ABUSE AND DIVERSION

Several information systems are used to track abuse and diversion in different populations. These include:

- Monitoring the Future, which annually surveys adolescents and young adults;
- SAMHSA’s National Survey on Drug Use and Health, the largest community-based survey;
- SAMHSA’s Drug Abuse and Warning Network, a surveillance system that monitors drug-related visits to hospital emergency departments and drug-related deaths;
- The FDA’s Adverse Event Reporting System, a passive surveillance system that captures serious adverse drug reactions;
- The Treatment Episode Data Set, which monitors patients entering addiction treatment programs; and
- The Medicaid Abuse Drug Audit System, a computer program that is used to review Medicaid prescriptions of controlled substances to track unusual prescribing.

Only a few systems can detect diversion. State PMPs can detect doctor shoppers. The Automation of Reports and Consolidated Orders System, operated by the DEA, monitors distribution of controlled substances and can be used to identify diversion.

INTERVENTIONS FOR PRESCRIPTION OPIOID ABUSE AND DIVERSION

A range of interventions is currently used to curb opioid abuse and diversion. One key area is educational programs for prescribers, pharmacists, patients, and the community. The FDA, SAMHSA, and pharmaceutical companies have all developed such educational programs. Many pharmaceutical manufacturers are working on development of abuse-deterrent formulations, to reduce the risk of extraction of opioids from prescriptions for the purpose of abuse or diversion. Many pain societies are focused on developing guidelines for effective management of chronic pain and the safe prescribing of opioids. Other programs, such as the DEA’s Pharmacy Theft Prevention Program, RxPATROL, and PMPs, are designed to prevent theft of prescriptions and doctor shopping.

Participation in the THCI Program on Opioid Risk Management afforded me an opportunity to share real-life struggles with prescription drug abuse that Operation UNITE witnesses daily throughout southern and eastern Kentucky. As one of the first regions to experience this epidemic, our families and communities continue to be hit hard. The Program gave us the opportunity to share Operation UNITE’s holistic vision and describe the multi-stakeholder collaborations that we have formed. It also provided us the opportunity to meet individuals from across the nation who understand the need to balance treating legitimate pain patients while stopping unethical prescribers and illegal prescription pill traffickers. The THCI Program has enabled us to think more strategically about the need to educate prescribers and pharmacy providers about the impact of prescription drug abuse.

Karen Kelly, President and CEO, Operation UNITE

Participation in the THCI Program on Opioid Risk Management afforded me an opportunity to share real-life struggles with prescription drug abuse that Operation UNITE witnesses daily throughout southern and eastern Kentucky. As one of the first regions to experience this epidemic, our families and communities continue to be hit hard. The Program gave us the opportunity to share Operation UNITE’s holistic vision and describe the multi-stakeholder collaborations that we have formed. It also provided us the opportunity to meet individuals from across the nation who understand the need to balance treating legitimate pain patients while stopping unethical prescribers and illegal prescription pill traffickers. The THCI Program has enabled us to think more strategically about the need to educate prescribers and pharmacy providers about the impact of prescription drug abuse.

Karen Kelly, President and CEO, Operation UNITE
Development of Abuse-Resistant Opioid Formulations

OCTOBER 2005 :: Unrelieved pain and prescription opioid abuse are inextricably interconnected public health problems. The development of abuse-deterrent formulations (ADFs) of prescription opioids is among the most important balanced risk management approaches to improving access to pain relieving treatment, while decreasing opioid abuse. Successful development of ADFs requires: defined subtypes of abusers; technical product development; accepted scientific methods to measure differences in abuse liability; standards for product labeling; and guidelines for promotion.

The purpose of this Tufts Health Care Institute Program on Opioid Risk Management summit meeting was to a) define subtypes of prescription opioid abusers; b) outline elements of a pathway for development of abuse-deterrent opioids; c) explore approaches to developing ADFs and methods of assessing abuse liability; and d) discuss implications for clinical utilization.

SUBTYPES OF PRESCRIPTION OPIOID ABUSE

Several distinct types of prescription opioid abusers can be discerned, including “hard core” addicts, polydrug abusers, rave abusers, recreational abusers, inexperienced abusers, and patient abusers. Different approaches to abuse resistance will be required in different circumstances. For example, approaches that prevent or deter intravenous injection will have no impact on abusers who chew or swallow the products intact. The types of prescription opioid abuse easiest to address with ADFs may not be the most important from a public health standpoint. Research is needed to validate the subtypes of abuse and characterize their phenomenology.

APPROACHES TO ABUSE-DETERRENT FORMULATIONS

ADFs are intended to be resistant to: chewing; crushing (for intranasal abuse); dissolving (for intravenous abuse); and conversion from slow onset to rapid onset formulation (e.g., accelerated extraction with alcohol) leading to “dose dumping” and risk of overdose. Various approaches have been tried by pharmaceutical companies, including development of the following: inherently less euphorogenic analgesics, inherent dual mechanism analgesics, agonist-antagonist combinations, aversive ingredients, prodrugs, non-injectable or non-tamperable formulations, smart dispensing devices, and depot formulations/devices. Patients, physicians, payers, and regulators should be aware that no product will be fully abuse-proof.

REGULATORY ISSUES

The Food and Drug Administration (FDA) encourages the development and clinical utilization of abuse-resistant prescription opioids in a manner consistent with regulatory obligations, including labeling that is scientifically accurate and evidence-based. Summaries of scientific data from abuse liability studies may be placed on the label, and promotion of this information is permissible. Beyond abuse liability studies, the FDA may require that large epidemiologic studies with years of real-world data be conducted to monitor diversion, abuse, and associated complications in the community. The FDA also requires studying the potential impact of re-formulation on the safety or efficacy of the product for its intended population.

ASSESSMENT OF ABUSE DETERRENCE

Tampering, or extractability, can be defined as “manipulating a pharmaceutical dosage form to change its drug delivery performance in a way not specified or intended by the manufacturer.” Tampering is distinguished from abuse in that the latter can occur without the former (for instance, by taking larger quantities of the intact form). There are currently no industry standards for the assessment of tampering and extractability. More work is needed to develop standards around testing and interpretation of extractability, including issues related to alcohol interactions.

CONTROLLED HUMAN USE LIABILITY STUDIES

Testing potentially addictive medications in clinical pharmacology studies has long been part of the evaluation of abuse liability. Human abuse liability studies can provide relevant information for the drug label, help define approved use, help identify potential market advantages, and assist in shaping the risk management program. [Note: Subsequent to this summit the FDA introduced a blueprint for the elements of a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of extended-release and long-acting opioid analgesics outweigh the risks. Liability studies may help inform clinicians of one aspect of the risks associated with prescribing such agents.] Phenomena that can be detected in such studies include: aversive effects, prodrugs, antagonist effects, dose-response of active and antagonist compounds, solubility, and absorption. One study will not answer all questions due to diversity of patient populations, types of abuse, and routes of administration. Improvement of the methods used in abuse liability studies is needed, particularly for studies assessing pain and prescription opioid abuse.

Clinical trials have generally not been a source of systematically collected information about abuse liability. This is due to a lack of validated methods, particularly outcome measures for abuse; a lack of constructs and diagnostic criteria; and the exclusion of high-risk patients from trials, resulting in a low event rate. When abuse-related data have been collected, passive methods were employed (e.g., spontaneous reports of abuse-related events, loss of drug supply) and data were interpreted without scientific consensus around appropriate methods and interpretation. Despite these limitations, important information on abuse liability can and should be gathered prospectively during the drug development process. Clinical trials including high-risk patients should be conducted, and the rate of abuse calculated using a time-to-exit approach, where exit is based on evidence of abuse. Also, trials that directly assess the “attractiveness” of products to abusers should be useful to assess abuse liability pre-market.

POTENTIAL OUTCOME MEASURES

Epidemiologic studies are viewed as the gold standard for making explicit claims about the abuse rate of a product in the community. However, no such studies on prescription opioid abuse have been published, and there are no consensus methods for conducting or interpreting such studies. Further work is needed to determine the goals, methods, and interpretation of epidemiologic studies, and their labeling implications.

Surveillance may be defined as the ongoing systematic collection, analysis, and interpretation of outcome-specific data for use in the planning, implementation, and evaluation of public health practice. Although there are many databases and surveillance systems for monitoring drug abuse, no system exists that provides timely and scientifically valid and timely estimates of abuse rates of specific products in a manner that is useful for public health surveillance. The development of such surveillance methods is necessary to reduce under-treated pain and prescription opioid abuse.

CLINICAL UTILIZATION

Meeting participants shared the vision that ultimately all prescription opioids will be abuse-deterrent, but they recognize that there are obstacles in realizing that vision. Ideally, ADFs with no new safety or efficacy issues should be prescribed to all patients appropriate for this treatment with opioids. However, reimbursement may be an issue since ADFs are likely to be more expensive than generic opioids. Because of this, it is likely that ADFs will be initially prescribed only to high-risk patients. Prescribing decisions will depend on the specific patient situation and the safety, efficacy, and abuse-resistance properties of the product.
Best Practices in Opioid Risk Management

SEPTEMBER 2006 :: Prescription opioids can provide great benefits to patients suffering from chronic pain, but they carry a high risk of being abused or diverted. Comprehensive opioid risk management programs provide a mechanism for balancing the benefits and risks associated with opioid analgesic therapy. Opioid risk management programs should include pre- and post-marketing risk assessments, patient and physician education initiatives, and tight supply chain controls. This summit meeting explored and examined these issues.

IMPROVEMENT OF PRE-MARKET RISK ASSESSMENT METHODS

Abuse liability studies are a cornerstone of pre-market assessment of a new drug or formulation. These studies are often conducted with drug abusers or addicts, and are not necessarily predictive of abuse in chronic pain patients. These studies also should be conducted with chronic pain patients to have better predictive validity. Additionally, there is currently no reliable method for collecting and evaluating abuse-related events in clinical trials.

EFFECTIVE USE OF POST-MARKETING SURVEILLANCE

Surveillance of abuse-related events began in the early 2000s; it was not until 2006 that the data were first used to find ‘hot spots’ of abuse and to help target interventions. More recently, post-marketing surveillance data have been used to design nationwide interventions to curb prescription opioid abuse. These developments shifted the paradigm of surveillance from an observational tool to a means of constructing specific interventions for the types of problems detected.

TRAINING FOR PRESCRIBERS ON SAFE PRESCRIBING PRACTICES

The standard approach to clinician education—passively receiving information from resources such as brochures, articles, and seminars—to promote best practices in opioid prescribing has not fundamentally changed prescribers’ practices. Clinician education should shift from passive to active training approaches that enable clinicians to develop practical skills and change their behavior. Methods for evaluating changes in clinicians’ behaviors should also be put in place.

ENHANCED PATIENT AND CONSUMER EDUCATION

To date, most prescriber guidelines require prescribers to educate patients on safe opioid use. To support this goal, various consumer and community education programs have been developed. Nevertheless, a lack of systematic application of these guidelines along with insufficient community education programs remains a problem.

INVOLVEMENT OF PAYERS IN OPIOID RISK MANAGEMENT

Payer organizations are an important stakeholder. Payers can support opioid risk management by mandating clinician training on safe opioid prescribing; encouraging patient education by clinicians; and supporting and reimbursing the use of non-opioid pharmacotherapy and non-pharmacotherapeutic approaches to the treatment of pain.

QUANTIFYING THE EFFECTIVENESS OF RISK EVALUATION AND MITIGATION STRATEGIES

The Food and Drug Administration mandates that pharmaceutical companies that develop medications with potential for abuse must implement a set of post-marketing strategies, known as Risk Evaluation and Mitigation Strategies (REMS), aimed at minimizing a medication’s abuse in the real world. These strategies include education of prescribers, pharmacists, patients, and the community, as well as surveillance and interventions. In order to evaluate the effectiveness of these strategies, REMS should include both quantifiable objectives and methods to evaluate these objectives.
NOVEMBER 2006 :: The development and marketing of abuse-deterrent formulations (ADFs) for prescription opioids is crucial to decreasing prescription opioid abuse while improving appropriate access to analgesic medications. This approach is supported by the Food and Drug Administration (FDA). The Tufts Health Care Institute Program on Opioid Risk Management convened this summit meeting to develop recommendations on the type of support and guidance needed from the FDA and Congress for the development of ADFs.

OBTAINING FDA AND CONGRESSIONAL SUPPORT FOR THE DEVELOPMENT OF ABUSE-DETERRENT FORMULATIONS

The FDA has authority to stimulate development and commercialization of ADFs by granting incentives such as guidance, protocol assistance for pivotal clinical trials, Fast Track status and Priority Review for new drug applications, and meaningful labeling. A citizen petition could help persuade the FDA to produce a guidance document for the development of proprietary and generic opioid ADFs. The petition could request removal of older, more abused formulations from the market once an ADF is approved. Additional incentives requiring congressional legislation could include: a) marketing exclusivity; b) extension of the 3-year non-patent exclusivity period to 5 years; c) guaranteed reimbursement of ADFs; d) tax credits/incentives for clinical trials and surveillance studies to cover such costs; e) provisional scheduling for ADFs; and f) potential differential scheduling (post-market) with the Drug Enforcement Administration.

BENCH-TOP ASSESSMENT OF EXTRACTABILITY

In general, because multiple types of opioid formulations exist, there is no one-size-fits-all set of standards for assessing ADFs. Sponsors should report on the product solubility in readily available solvents, the volatility of the opioid in the formulation, the impact of physical manipulations (crushing, varying temperature to accelerate delivery, using physical stress, or microwaving) and the sophistication of procedures required to extract the active ingredient. The amount of aversive components or antagonists that carry through the extraction should be sufficient to deter abuse. An explicit claim could be made that the product has been formulated to resist tampering by certain techniques, although this would need negotiation with the FDA.

PRE CLINICAL ABUSE LIABILITY TESTING OF ABUSE-DETERRENT FORMULATIONS

Pre-clinical studies should include testing of opioid antagonist-containing ADFs for physical dependence, decreased euphoria, or withdrawal; testing for single dose substitution (preventing withdrawal from a reference analgesic like morphine); evaluating reinforcing effects (whether animal self-administers); and drug discrimination (differentiating between reference compound and ADF).

ANALGESIC CLINICAL TRIALS FOR MEASURING ABUSE LIABILITY

Trials for primary approval demonstrate the safety and efficacy of the ADF as an analgesic. For reformulated opioids, a single randomized control trial for efficacy is generally sufficient. Pharmacokinetic data are sufficient if the new formulation and the parent product are bioequivalent, but if an added ingredient alters bioequivalency or may compromise safety/efficacy of the product, then new efficacy trials are needed. New products require safety trials.

For trials to support ADF-type claims, outcome measures related to abuse include patient self-report of drug use; use of aberrant behavior checklists by physicians; urine toxicology results; prescription monitoring program data; “ambiguous medication handling events;” and patient questionnaires.

HUMAN ABUSE LIABILITY TESTING

Information on detecting abuse liability signals for known chemical entities can be found in the literature. Standard abuse liability studies should aim at determining whether a) the untampered/tampered ADF produces less euphoria than a tampered/untampered comparator; b) abuse-deterrent ingredients are effective; and c) the prodrugs have the desired pharmacokinetic-pharmacodynamic (PK-PD) profile.
Product PK, route of administration, study population, self-administration, relative cost of tampering, and level of expertise needed to modify the drug should be addressed. Potential claims would address drug liking (lower for drug X than for control drug Y) and effects of self-administration (lower for drug X than for drug Z).

ALCOHOL INTERACTION HUMAN STUDIES

Studies on the potential interactions between ADFs and co-administration of alcohol should include PD measures. These studies can be useful in establishing the clinical importance of in vitro interactions with alcohol. For ADFs, ethanol effects on all active components must be considered. The proposed ADF guidance document should specify criteria for which in vitro studies require an in vivo study; when PK-PD findings are not clinically significant; when they reveal a clinically meaningful protective effect of the ADF if taken with alcohol; and what magnitude of an alcohol effect defeats the abuse-deterrent properties of the ADF. Necessary controls should be spelled out. Conditions for conducting PK-PD alcohol interaction studies for formulations by generic companies should also be specified. Conclusions drawn from PK-PD studies must be related to data on actual patterns of alcohol consumption and specific medication use, in order to anticipate the public health importance of any interaction risk.

The following two kinds of labels may be possible. An existing class label warning could be used, similar to the current label for immediate release morphine, e.g., “Warning: Should be used with great caution in a reduced dosage in patients receiving central nervous system suppressants, including alcohol.” Alternatively, an enhanced or boxed warning risk “Label Option B” could be used, e.g., “Patients must not consume alcoholic beverages or prescription or non-prescription medications containing alcohol while on this product. Co-ingestion of alcohol with product X may result in increased plasma levels and a potentially fatal dose of component Y.”

EPIDEMIOLOGIC STUDIES

Post-approval labels could say “Product X is associated with a lower prevalence of abuse than other formulations with the same active ingredients,” or “Product X is associated with lower prevalence of IV administration than other formulations containing the same active ingredients.” Several types of studies could be conducted to support these claims, as noted below.

- Epidemiologic studies focused on:
  - comparators using the active ingredient and other drugs in the same schedule and in the target schedule for the ADF;
  - indicators of abuse, addiction, diversion, and active surveillance for adverse events and efficacy; and
  - populations with known abuse risk factors, comorbidities, and pharmacogenomic variations;
- A condition-based registry study (e.g., for chronic pain);
- Retrospective studies in street populations;
- Studies of physicians (as a sentinel population and as a source of information about drug access and reactions);
- Diversion studies; and
- Studies of surveillance systems.

To support the overall conclusions that product X is less abused intravenously or is less abused overall, a large, multi-year registry study would be needed, including two comparators in a different schedule than the drug (e.g., oxycodone versus hydrocodone), and some measures of diversion and of the onset of abuse patterns in the patient population.

Documenting lower abuse potential across a wider population implies a long-term study, which may be unacceptable to the sponsor because of the expiration of exclusivity. The length of the study and whether it could begin pre-marketing could be negotiated with the FDA.
Responding to Signals of Prescription Opioid Abuse and Diversion

MARCH 2007 :: In response to public health concerns about prescription opioid abuse, the Food and Drug Administration (FDA) mandated that pharmaceutical companies put in place risk management programs aimed at preventing, detecting, and reducing opioid abuse while maintaining appropriate access to opioid therapy. Risk management programs use surveillance methods to monitor for signs of abuse in the real world. These methods include signal detection (detecting the signs of abuse); field investigation (characterizing the nature of signals and potential interventions); and intervention (deploying measures to mitigate the signals).

The Tufts Health Care Institute Program on Opioid Risk Management convened this summit meeting to
- outline methods to detect signals of prescription opioid abuse;
- discuss existing signal assessment studies and ensuing interventions and identify gaps in knowledge; and
- articulate key policy considerations.

SIGNAL MANAGEMENT: DETECTION, PRIORITIZATION, ASSESSMENT

Signals, often based on statistically significant deviations from baseline expectations, indicate that something unexpected is occurring. Pharmacovigilance uses traditional information sources (e.g., health care providers, patients, pharmacists, sales/field representatives, media reports, published literature) to detect signals. It may also draw on other sources to gauge abuse or diversion, such as:

- The Internet, including drug sale sites, social media web sites, user blogs, chat rooms, and listservs, such as National Association of Drug Diversion Investigations (NADDI) or RxPatrol;
- Federal, state, and local law enforcement;
- National and local media reports;
- Federal surveys, such as Drug Abuse Warning Network (DAWN), National Survey on Drug Use and Health (NSDUH), and Monitoring the Future;
- Poison control centers, from data collected by Treatment Episode Data Set (TEDS), Researched Abuse Diversion and Addiction-Related Surveillance (RADARS), and Addiction Severity Index–Multimedia Version;
- Drug abuse treatment programs, from TEDS and RADARS data;
- Regulatory boards; and
- Key informants, such as methadone maintenance specialists, pain management specialists, other health care professionals, patients in treatment programs, and pain patients.

Signals may be of various types: sentinel events, sustained shifts, one-time or long-term spikes, linear or non-linear trends, or cyclical changes. They may have specific attributes—formal or informal; qualitative or quantitative; verifiable or unverifiable; passive or active; timely or delayed; from single or multiple sources; and geographically specific or widely distributed.

Potential signal data are best channeled into a central database, monitored by a team that verifies accuracy and triages the information. An assessment is relayed to a multidisciplinary advisory group with drug safety, epidemiology, regulatory, legal, and clinical expertise, which makes decisions on the next step. Actions that may be taken could be intervention, investigation, or further monitoring.

Interpretation of signals is best done by multiple stakeholders seeking a common solution. Signal attributes are used to prioritize and triage incoming data, assessing the seriousness
of the problem in relation to public health and safety. Multiple signals are integrated and assessed, based on source reliability, signal types, and decisions about data dissemination. A “levels framework,” where levels in which abuse occurs are hierarchically organized by environment (i.e., by state, county, city, school, family, individual) is convenient for cataloguing information and establishing where eventual interventions should be targeted.

**SIGNAL ASSESSMENT**

Three approaches for signal assessment are described here:

*Rapid assessments*, completed in approximately 10 months (or in approximately 3 weeks if an ultra-rapid assessment is needed) build on existing data to characterize the nature and extent of problems in a specific location. Quantitative surveys, key informant interviews, focus groups, direct observations, intercept interviewing, and ethnography are applied, using a SWAT team approach that employs drug abuse specialists to gather information.

*The field research process* enables pattern recognition from large, product-specific data repositories on abuse and diversion maintained by the sponsor. Field researchers confirm signal indications, and then relay data to an inter-departmental group with drug safety, pharmacovigilance, and legal expertise. The company responds to actionable assessments by educating patients and prescribers about drug use and safe storage, and/or by mobilizing additional stakeholders.

*Post-marketing surveillance* involves review of all data sources (e.g., NSDUH, forensic laboratory information systems, FDA adverse effect reports, DAWN Live), patient interviews upon entry into treatment programs, data from snowball sampling, ethnographic studies to follow-up signals, physician surveys, and monitoring of Internet newsgroups (e.g., NADDI, Rx News). Advisory groups determine the need for further action. If a signal is confirmed, staged assessments are used to phase in more intensive procedures, including background examination of media reports and existing data, interviews with key informants, focus groups with patients in treatment programs, observations and intercept interviews, large scale use of rapid assessment, and on-going ethnographic studies.

**INTERVENTIONS**

Rational choice of interventions aimed at mitigating risk relies on results of detailed signal analyses described above. Clarification of stakeholder roles and responsibilities is important for designing effective approaches. Manufacturers have a clear responsibility for devising product safety-related solutions (e.g., product safety inserts, medication guides) in parallel with education. Interventions by the pharmaceutical industry include development of abuse-deterrent formulations; retraining of sales representatives; introduction of restrictions for off-label marketing; education of clinicians prescribing a high volume; and use of local and national media.

Some signals may transcend individual products and require broader interventions. These could include implementing prescription monitoring programs at the state level to reduce doctor shopping; educating patients and families to lock medications, reduce access, and safely dispose of unused medication; and providing school-based interventions and programs.

Summit meeting participants discussed a framework that includes prioritizing and assessing signals, and endorsed development of policies based on collaboration with related stakeholders. Public domain sharing of experience with signal management processes that are already implemented by some companies is essential. The results of the assessments should be matched to an appropriate and cost-effective intervention. More attention is needed to devising ways for evaluating outcomes of such interventions.
Understanding the Types of Opioid Abusers

SEPTEMBER 2007 :: Prescription opioid abuse is a public health problem with multifaceted ramifications. For example, physicians’ concerns about the potential for patient dependence, abuse, misuse, and diversion of opioid medications, as well as regulatory sanctions, may deter them from prescribing opioid analgesics. As a result, some patients may be hindered in having appropriate access to prescription opioids for treatment of pain. The ramifications of prescription opioid abuse are perceived differently by other stakeholder groups such as government agencies, non-government organizations, law enforcement, pharmaceutical companies, health care payers, professional medical societies, and academia. None of these groups alone is equipped to address the entire problem.

The Tufts Health Care Institute Program on Opioid Risk Management convened this summit meeting to consider whether the use of a typology of abusers could help minimize the risk of abuse and diversion, while fostering safe utilization of prescription opioid analgesics. The purpose of the meeting was to: a) discuss how subtyping is used in treatment of other substance abuse and psychiatric disorders, and b) identify gaps in knowledge about subtyping related to prescription opioid abuse.

USE OF SUBTYPING

The use of typologies, or the differentiation of groups that share one or more common characteristics, can be an effective approach for classifying relatively homogenous groups, or subtypes. When applied to psychiatric and substance use disorders, subtyping is an abstract category organized according to a conceptual, theoretical or clinical principle. The primary purpose of subtyping in this case is to improve diagnostic classification and make the most efficient use of clinical services. Approaches to typology can be univariate—based on a single variable such as gender, age of onset, family history, personality profile, or psychotherapy—or multivariate, based on a combination of factors. Identification of specified, homogenous subgroups may advance research in areas such as etiology and genetics, prevention, interventions, behavioral treatments, health services research, and pharmacotherapeutics. The product of subgroup analysis can provide a better understanding of outcomes that may facilitate treatment matching, or can help predict the course and prognosis of the substance abuse disorder.

THE NEED FOR BETTER UNDERSTANDING OF SUBTYPES RELATED TO PRESCRIPTION OPIOID ABUSE

The summit meeting highlighted the utility of looking at more refined typological methods used to delineate subtypes of alcoholics. When dealing with opioid addiction specifically, the need for valid and reliable screening instruments is critical, to facilitate better detection of prescription opioid abuse.

Epidemiological methods, while temporally informative, have not fully identified subtypes with different patterns of high risk of prescription opioid use. When used to identify subgroups and subtypes, epidemiologic research may be able to assist general practitioners and mental health professionals to better identify the most prominent symptoms and the subgroup of users more prone to developing an opioid analgesic addiction. Currently, the majority of opioid subtypes discussed are based on clinical observations, and there is a great deal of overlap across these groups.

Sharpening the boundaries of the current understanding of subtypes will help clinicians weigh risks versus benefits when deciding whether to prescribe long-term opioid therapy, determining the appropriate level of monitoring, and providing tailored interventions. Classification based on opioid poisonings provides a unique research endpoint; however, it is comprised of diverse at-risk populations. Looking to the future, genetic research holds unique promise to identify individuals at highest risk, although it may not help identify the social characteristics of abusers.
Sources of Diverted Prescription Opioids

MARCH 2008 :: A significant portion of prescription opioid abuse occurs as a result of diversion, the transfer of prescription medication from lawful to unlawful distribution or possession. In addition to the legal concerns that diversion raises, it has become an important public health problem. The Tufts Health Care Institute Program on Opioid Risk Management convened this summit meeting to a) develop the study of diversion as a science; b) identify gaps in understanding about diversion of prescription opioids and strategies to address these gaps; and c) discuss interventions to reduce diversion and ways to maximize their effectiveness.

FORMS OF PRESCRIPTION OPIOID DIVERSION

Primary prescription opioid diversion occurs directly from the supply chain. Methods include theft from manufacturers, distributors, hospitals, clinics, physician offices, and pharmacies; prescription forgery; script doctors and pill mills; doctor shopping; theft from patients’ homes; and patients selling their medication. Secondary diversion includes buying or trading medication from a dealer, friends or family members.

SOURCES OF DATA ON DIVERSION

Quantifying prescription opioid diversion is difficult, and has been done primarily in an anecdotal fashion. Quantitative data sources for diversion include law enforcement monitoring, such as the Drug Enforcement Administration (DEA) Form 106, which reports theft from the supply chain; RxPatrol, a system of passive reporting of pharmacy robberies; the National Forensic Laboratory Information System, which compiles drug seizure data; and the Federal Bureau of Investigation’s data on diversion arrests. Other data sources include prescription monitoring programs (PMPs), which can detect doctor shopping, and the National Survey on Drug Use and Health (NSDUH), which measures drug use in the general population. Unfortunately, each type of data offers only a piece of the picture, and integrating these data to develop a meaningful picture is nearly impossible. As a result, there is an urgent need to create a systematic method to collect quantifiable diversion data.

PREVALENCE OF DIVERSION

Some analyses have shown that diversion from the supply chain represents a small portion (0.1%) of the controlled substances traveling through it. However, this represents a large volume of medication, estimated at 5.7 million doses. NSDUH data have shown that most diversion occurs post-prescription. The majority of prescription opioid abusers obtain these medications directly through a physician’s prescription or from family members or friends who were prescribed the medication by a physician. This underscores the important role of prescribers in curbing diversion, and the need to engage them.

PREVENTING, DETECTING, AND COMBATING DIVERSION

Methods to prevent diversion should recognize that diversion depends on drug availability, demand, intent, opportunity, and market conditions, such as price. Approaches to preventing and combating prescription opioid diversion include:

- Educating and training physicians to detect diversion by regularly monitoring patients and performing urine drug tests;
- Educating patients on locking medication at home and properly disposing of unused doses;
- Imposing strict limitations on the dispensing of certain prescription opioids;
- Analyzing PMP data to detect doctor shoppers;
- Conducting surveillance;
• Passing laws that prevent Internet sales of prescription opioids without consulting a physician;

• Developing abuse-deterrent opioid formulations;

• Putting in place law enforcement teams specifically dedicated to tackle diversion of prescription opioids;

• Adopting new tracking technologies;

• Improving the accuracy of theft reports (DEA Form 106) by using online reporting;

• Combining the DEA Form 106 with state reports; and

• Uniformly enforcing existing regulations in all states.

None of these approaches alone can fully resolve the complex problem of prescription opioid diversion. However, they have been shown to be effective, and in combination, have the potential to have greatly increased impact.
Prescription opioids may be effective for select patients in alleviating persistent pain and increasing function. But physicians who treat chronic pain patients should be aware of the possibility of misuse and abuse of prescription opioids medications by their patients. Detecting prescription opioid abuse is possible from patient self-reporting (e.g., questionnaires) and behavioral evaluations. However, the former can be unreliable if patients do not report honestly, and the latter are often difficult to interpret as valid indicators of abuse.

The use of urine drug monitoring (UDM) in the clinical setting was initiated in the 1990s in response to the dramatic rise in prescription opioid abuse. UDM has grown as a component of pain management in primary and specialty care settings because it can screen for the presence of prescribed medications, reflecting treatment compliance, and non-prescribed medications, suggesting self-medication or abuse. Nevertheless, many physicians are uneducated about UDM and how to incorporate it into their practice.

The Tufts Health Care Institute Program on Opioid Risk Management convened this summit meeting to a) review the utility and technical aspects of UDM and the challenges of interpreting UDM results within the therapeutic context; b) develop preliminary guidelines for the use of UDM in pain management; and c) discuss related payer issues.

**Analytical Methods Used in UDM**

In response to legal challenges and to problems in early use of UDM by the U.S. military, strict guidelines for sample collection, chain-of-custody, standardization of test procedures, quality control, and review of results by certified scientists have been developed.

Several methods can be used to collect biological samples.

- **Blood** testing is the most accurate method, but it is invasive. Most drugs are rapidly cleared from the blood, though some assays detect metabolites that have half-lives longer than the parent drug. Testing is performed on the unbound fraction.

- **Urine** is the biological sample of choice, because collection is non-invasive and large volumes can be obtained. Tests for cocaine, amphetamines, opioids, marijuana, and benzodiazepines in urine are relatively inexpensive, and false positives are rare. For most drugs, detection time averages 1-5 days. However, the potential for sample-tampering (e.g., substitution, dilution) should be considered when using urine.

- **Saliva** (oral fluid) is non-invasive, samples are less vulnerable to tampering, and drug concentrations in saliva accurately reflect blood levels. However, on-site kits for benzodiazepines/marijuana in saliva are not reliable.

- **Hair** samples are appropriate when testing for chronic use; drugs typically appear in hair 6-8 days after use. However, hair testing is costly and time-consuming, samples are susceptible to contamination, and relationships between dosage, ingestion time, and drug levels are not reliable.

Two methods of testing and result interpretation are available.

- **Immunoassays** are relatively inexpensive and not labor-intensive. These tests are used for initial screening tests and to distinguish negative from presumptive positive samples.

- **Gas chromatography/mass spectroscopy** (single stage or tandem) are used for confirmatory testing and identification of specific drugs/metabolites. These tests are highly specific and reliable, but expensive and labor-intensive. Expertise is required to interpret test results, especially for certain classes of drugs. Physicians should seek the help of trained laboratory personnel to correctly interpret unexpected results.
URINE DRUG MONITORING IN CLINICAL PAIN PRACTICE

UDM should be used as a consensual diagnostic test, as a component of an opioid agreement, when utilizing a “universal precautions” approach for assessing and treating chronic pain patients. It enables the physician to document compliance with a treatment plan, and to preserve trust and mutual respect with the patient. Testing should be done for all new patients in a pain practice who are being treated with a controlled substance. UDM practices vary; some practitioners advocate testing all patients at all visits and others advocate two or three random tests throughout the year.

The absence of a prescribed drug in test results may indicate diversion, unsanctioned treatment interruption due to intolerable adverse effects, running out of medication due to earlier overuse to treat unresolved pain, or misuse (e.g., taking medication PRN instead of around the clock). The presence of a non-prescribed medication may indicate drug abuse, self-medicating, or an attempt to treat unresolved pain with other analgesic medications acquired without a prescription. A physician should discuss unexpected results with his or her patient in an open, non-judgmental dialogue in order to accurately identify the problem, try to understand the patient’s motivation behind the behavior, and devise an appropriate response.

OUTCOME STUDIES AND CLINICAL RESEARCH GAPS

Decisions about administering UDM in the therapeutic setting are motivated by a variety of factors, including the need to monitor compliance, or identify and mitigate abuse and diversion by patients; however, there are few systematic outcome studies on this topic. A number of studies suggest that UDM is more effective at detecting aberrant drug-taking behavior than relying on patient self-report or behavioral monitoring by the treating physician. Limited high-quality evidence suggests an improvement in clinical outcomes when UDM is employed. Future research is needed to address gaps in the following key areas: investigating clinical outcomes of UDM; understanding current UDM practices in the management of chronic pain; and evaluating strategies for implementing UDM in chronic pain management.

PAYER ISSUES

Random drug testing in schools, the military, and the workplace is paid for by the Department of Education or local schools, the military, and employers, respectively. However, payment policies of third party payers for UDM in medical practice vary according to a number of factors. These include whether physicians are addiction-certified and where they practice (e.g., a pain clinic, substance abuse treatment center, hospital-based clinic, or hospital emergency room). Policies related to prior authorization requirements also vary. Reimbursement for Medicaid patients varies by state, and payment under Medicare remains a challenge. Incorporating UDM in clinical practice—considered a standard procedure for safe prescribing of opioids—will not be accomplished without appropriate reimbursement.
Co-ingestion of Alcohol with Prescription Opioids

NOVEMBER 2008 :: Enhanced access to prescription opioids has led to a marked increase in their non-medical use. There has also been a parallel rise in the number of Americans who abuse or depend on alcohol (estimated at 8.5% of the population in 2001-2002). Because of potential serious adverse effects resulting from alcohol and prescription opioid co-ingestion, package inserts for most opioid medications carry warnings against this practice. However, very few studies have examined alcohol and prescription opioid co-ingestion.

The Tufts Health Care Institute Program on Opioid Risk Management convened this summit meeting to a) discuss the epidemiology and magnitude of alcohol and prescription opioid co-ingestion; b) review the pharmacology underlying alcohol-opioid interactions; and c) identify methods to curb co-ingestion.

EPIDEMIOLOGY OF ALCOHOL AND PRESCRIPTION OPIOID CO-INGESTION

Data from medical examiners show an upward trend in fatalities resulting from alcohol and prescription opioid co-ingestion. Significantly more individuals call poison control centers due to co-ingestion than due to alcohol or prescription opioids alone. The majority of adolescents and young adults who used prescription opioids non-medically in the past year reported ingesting them with alcohol, and co-ingestion with prescription opioids is more prevalent than with any other scheduled medication class. The vast majority of people with an opioid abuse or opioid addiction disorder also have an alcohol abuse or alcohol addiction disorder. Individuals with a pre-existing alcohol use disorder are about 20 times more likely to develop an opioid use disorder than those without alcohol problems, and non-medical use of opioids increases with the severity of alcohol consumption. These facts suggest that alcohol and opioid use disorders are highly co-morbid.

PHARMACOLOGY OF ALCOHOL-OPIOID INTERACTIONS

In some extended-release formulations, alcohol can induce the rapid release of a large dose of the active ingredient (referred to as dose dumping), potentially leading to an overdose. Physiologically, the dangers of co-ingestion come from the interaction between alcohol and opioids at various levels. Alcohol can alter the pharmacokinetic profile of opioids by increasing their absorption and decreasing their metabolism, in turn increasing their pharmacological effect. Both alcohol and opioids are respiratory depressants, and co-ingestion can result in fatal respiratory depression. In addition, alcohol induces a large release of beta-endorphin in the reward/reinforcement centers of the brain, potentiating the reward response triggered by opioids. Individual variations in opioid treatment responses and in the susceptibility to opioid and alcohol abuse disorders are believed to be due to polymorphism in the expression and function of mu-opioid receptors and variation in liver metabolic pathways.

POTENTIAL SOLUTIONS TO CURB ALCOHOL AND PRESCRIPTION OPIOID CO-INGESTION

Epidemiologic data support the case for public education and training at the community level as well as in schools and colleges. Furthermore, these data strengthen the case for a shift of focus from incarceration of abusers to prevention and treatment. Because many abusers obtain opioids directly from physicians or from friends or family members who have been prescribed the medications, there is an urgent need to educate physicians to apply a “universal precautions” approach to all patients using opioids.
This includes a) evaluating patients' risk for opioid and alcohol use disorders; b) making consistent use of urine drug monitoring to detect misuse, abuse, and diversion of opioids and co-ingestion with alcohol; and c) educating patients on safety issues (e.g., the potentially fatal dangers of co-ingestion, and the importance of locking medications and never sharing medications). If co-ingestion is identified, causes—e.g., misuse, self-medication of mood and sleep disorders, abuse, or addiction—should be identified to plan the appropriate response. This might include education, a change in treatment plan, or substance abuse treatment.

Pharmaceutical companies and regulatory agencies have undertaken some efforts to limit co-ingestion. Package inserts for most opioid medications carry warnings in the medication guide about co-ingestion with alcohol. Old extended-release formulations that produced alcohol-related dose dumping have been taken off the market, and all new extended-release formulations are tested for dose dumping before approval. Pharmaceutical companies are looking at approaches that can specifically mitigate the effects of co-ingestion, including use of naltrexone, which blocks the effects of opioids and reduces the reinforcing effects of alcohol; incorporation of a prodrug; and use of an aversive agent that would be released upon alcohol consumption.
Prescription monitoring programs (PMPs) provide an important intervention for addressing prescription opioid abuse and diversion. PMPs have two overarching goals: to increase public safety by deterring diversion and fraud, and to improve public health by supporting safe prescribing. PMPs aim to address these in parallel. Toward this end, PMPs can identify individuals with problems of abuse, addiction, or diversion (e.g., through doctor shopping or pharmacy shopping) and point to instances of inappropriate or criminal prescribing or dispensing on the part of the prescribers.

The Tufts Health Care Institute Program on Opioid Risk Management convened this summit meeting to a) provide an update on the evidence base for prescription monitoring as a public health intervention; b) describe key methodological requirements for conducting valid prescription monitoring research; and c) explore future directions in prescription monitoring research.

STATE AND FEDERAL PRESCRIPTION MONITORING PROGRAMS

At the time of this meeting, PMPs were operational in 32 states, and legislation was under consideration in four more. [Since this summit meeting, PMPs have become operational in additional states.] At the federal level, funding was appropriated in 2009 for two programs. The Hal Rogers Prescription Drug Monitoring Program, created in 2001 and administered by the Department of Justice, had $7 million appropriated for 2009-2010. The National All Schedules Prescribing Electronic Reporting program (NASPER), a formula grant with the mission of approaching prescription monitoring from the public health standpoint, had $2 million appropriated for the year.

DATA COLLECTION AND ACCESS

Both programs permit disclosure of prescription monitoring data to health care providers and encourage use of the data to identify and treat patients at risk for substance abuse. The Hal Rogers Program permits states to have considerable flexibility in the drug schedules they choose to monitor, in providing access to PMP data, and in the methodologies they use to collect, share and transmit data. NASPER funding, in contrast, mandates the collection of prescription data for Schedule II-IV drugs and the sharing of information among states to help curb diversion across state lines. However, a lack of homogeneity across states with regard to data collection and access makes comparison and analysis of information from different states a challenge. Because of this, new regulations are being put in place to facilitate interstate sharing of information in order to prevent and detect abuse and diversion of controlled substances across state lines.

PHYSICIAN USE OF PRESCRIPTION MONITORING DATA

Physicians can use prescription monitoring reports as a tool to identify doctor shopping by identifying patients with overlapping prescriptions for similar drugs. Prescription monitoring should be used as part of a multi-faceted risk management program, in conjunction with patient screening for aberrant behaviors, risk stratification, compliance monitoring, patient education, and use of abuse-deterrent formulations when possible. Physicians utilizing prescription monitoring data should be alert to the challenges of balancing privacy, data security, and state and federal regulations of prescribing practice.
THE PUBLIC HEALTH IMPACT OF PRESCRIPTION MONITORING

The use of serialized, government-issued prescription pads for prescribing Schedule II controlled substances has curbed prescription form tampering and fraud. Moving to electronic prescriptions should further limit tampering. Introduction of PMPs is also correlated with decreased pharmacy and doctor shopping, and higher rates of admissions to substance abuse treatment programs.

Prescription monitoring has a potential adverse impact if physicians change their prescribing practices to substitute non-Schedule II drugs in cases where a controlled substance was the better choice. Such potentially inappropriate prescribing has generated much debate, since prescription monitoring is not meant to hinder prescribing opioids for legitimate medical purposes. While descriptive and quantitative empirical studies confirm that prescription monitoring is associated with a decrease in prescribing and use of controlled substances, the extent to which a substitution effect contributes to this reduction has yet to be established.

Collectively, empirical studies indicate a positive influence of PMPs on abuse and diversion. At the same time, evaluations have been published, pointing to an urgent need for further work to evaluate these programs.

ALLAYING FEARS ABOUT PRESCRIPTION MONITORING

Apprehension about prescription monitoring is based on misperceptions about its potential impact on health care. These misperceptions include the following:

*Prescription monitoring incurs high costs.* In reality, prescription monitoring in most states is estimated to cost less than $1 million per year, while achieving much greater savings in health care and societal costs.

*Compliance with PMP requirements is time-consuming for pharmacists.* In fact, data required for prescription monitoring are the same as those already recorded by pharmacists. Little additional time is required by pharmacists to consolidate the data and submit it to the PMP. Increased homogeneity in data collection across states and implementation of electronic prescribing should further facilitate efficient reporting.

Although more data are necessary to fully assess the impact of prescription monitoring on public health, PMPs seem to have a positive impact on curbing doctor and pharmacy shopping. The implementation of PMPs in all states and improvement in data sharing methods among states are likely to improve their overall efficiency. A range of improvements should be implemented, including allowing easy electronic access by physicians and facilitating reporting by pharmacists upon dispensing. The use of prescription monitoring needs to be carefully balanced with the protection of privacy and the availability of prescription medications for legitimate treatment.

*PMPs, with their associated bureaucratic requirements and law enforcement activities, have a chilling effect on appropriate use of prescription opioids for pain.* While this may have occurred in earlier years, overall prescribing of opioid analgesics continues to increase, even in states using electronic PMPs.

Prescription monitoring violates HIPAA. HIPAA permits sharing of protected health information, but the regulations set specific requirements for such disclosures. Sharing of prescription monitoring information is subject to these requirements. Programs mandate that prescription monitoring data must be shredded by physicians after use and cannot be disclosed.
JULY 2009 :: Under the Food and Drug Administration Amendment Act of 2007 (FDAAA 2007), pharmaceutical companies are required to continue post-market monitoring of certain prescription drugs to ensure that the benefits of these drugs outweigh the risks. They are required to do this by developing Risk Evaluation and Mitigation Strategies (REMS), which can include mandatory certification of patients, prescribers, and pharmacists, and an outcome assessment for each REMS solution. Upon establishing this regulation, the FDA provided little specific guidance on how to develop a REMS that incorporates a rational intervention for preventing prescription opioid abuse, while still maintaining adequate appropriate patient access to these analgesics. Although some REMS are already in place, there is a critical need for REMS that are effective in addressing the growing number of overdose deaths due to prescription opioid abuse.

The Tufts Health Care Institute Program on Opioid Risk Management convened this summit meeting to a) identify critical components of a REMS solution and propose strategies to improve REMS effectiveness; b) discuss how root cause analysis (RCA) can be applied to developing REMS solutions; and c) identify strategies for using results of an RCA to change prescriber, pharmacy, and patient behavior.

ROOT CAUSE ANALYSIS OF OPIOID-RELATED FATALITIES

A number of industries (e.g., the airline, nuclear power, and chemical industries) use RCA to understand the underlying reasons for serious accidents and to reduce the risks of future mishaps. An RCA consists of unraveling causal pathways that lead to a disastrous event, in order to design appropriate solutions that radically alter its likelihood of recurrence. An RCA should be coherent and data-driven. Summit meeting participants recognized the need for developing similar, comprehensive analyses of the causes of prescription opioid abuse. These studies should focus on overdose deaths and other possible indicators of opioid abuse, such as pediatric exposure, addiction and diversion. Developing a comprehensive RCA for overdose fatalities related to prescription opioid abuse will take time; a provisional RCA should suffice in the short term.

Three levels of response should be considered when analyzing a serious accident, with the intent of reducing the probability of recurrence. Level 1 considers the events or accident mechanism, which are the physical events that lead to the disaster, though they may not necessarily be the root cause. Level 2 refers to the workplace conditions. Level 3 encompasses systemic factors, which address broader issues such as how much feedback exists in the system and how comfortable employees (including managers) are about speaking up regarding possible risks. An RCA asserts that essential change must occur at Level 3 in order to radically alter the risk of recurrence.

Developing a comprehensive RCA for overdose fatalities related to prescription opioid abuse is difficult, since little has been published on the causes of this many-faceted problem. Capturing data is a prerequisite for developing an effective REMS. Who are the people who are dying? Are they patients or non-patients? Where do they get their medication? Do they live in urban or rural areas? Have they seen a doctor in the past year, and if so, what kind? What induced them to start taking the medication? For patients, was there a therapeutic error of some type? What were the individual-level risk factors for overdose? What were the environmental risk factors? A preliminary RCA, even if all these data are not available, will help to update the general understanding of the problem. It can help to build collaborative relationships at the systemic level, allowing stakeholders to learn together while continuing to collect data and analyze trends.
An etiologic assessment of prescription opioid abuse involves looking at three aspects of the problem: how opioid use and abuse begin; why potentially fatal opioid exposures occur; and why these exposures become fatal. The etiology of abuse should be considered in two populations—patients needing pain management, and non-patients in the community—because the initial factors that lead to opioid abuse in these populations are likely to be very different.

EVALUATION OF PROGRAM ELEMENTS AND OF THE OVERALL PROGRAM

The evaluation of a mitigation program and its elements should encompass multiple aspects of the REMS solution. Examples are: technical (whether the program does what it is supposed to do), performance (whether physicians order adequate urine tests, whether patients lock up their medications), clinical (whether patients are treated for their condition, whether patients abuse their medications), and epidemiological (whether overdose deaths decrease).

SYSTEMIC CHANGES LINKED TO THE ROOT CAUSE ANALYSIS

These changes should focus on altering specific prescriber, pharmacist, and patient behaviors. Changes should be established within the framework of commonly used methods for setting performance improvement objectives. Targeted behaviors should be within the critical paths of RCA, and tactics for altering such behaviors should encompass workflow solutions.

BEHAVIOR CHANGE THROUGH EFFECTIVE USE OF PHARMACY SYSTEMS

The vast majority of prescriptions in the U.S. are transacted electronically, through a switching company that links pharmacies to payers for the purpose of insurance verification. This infrastructure provides a cost-effective opportunity to support behavior change for physicians, patients, and pharmacists in a manner that does not burden the health care system. Switching technology can be used to automatically verify whether a specific prescriber, patient, or pharmacist has completed training in safe opioid use as a “safe use condition” for dispensing the medication. Such technologies have the potential to meet one goal of REMS, with respect to supporting automated verification of stakeholder training at the point of dispensing.

Overall, summit meeting participants agreed that rational REMS solutions to curb overdose deaths related to prescription opioid abuse can be drafted based on a preliminary RCA. At the same time, there is an urgent need for a comprehensive RCA of overdose deaths related to prescription opioid abuse, and this should be a high priority for funding organizations.

Things that I learned from the THCI Program on Opioid Risk Management that still make me think are:

- the cost of prescription opioid abuse to insurers; and
- the fact that the number of prescriptions and doses of opioids has increased and the number of addicted persons has increased, yet pain is still not relieved.

Adele D. Audet, RPH
Assistant Director, Drug Control Program
Massachusetts Department of Public Health
The Role of Dentists in Preventing Opioid Abuse

MARCH 2010 :: The most frequently abused prescription opioids are immediate-release (IR) hydrocodone-containing preparations, IR oxycodone-containing preparations, and other IR opioids (codeine, propoxyphene). Individuals who abuse prescription opioids most often obtain them from prescriptions from physicians or dentists, or from family members or friends.

This Tufts Health Care Institute (THCI) Program on Opioid Risk Management summit meeting was convened to a) review data on the role of dentists in opioid prescribing and in the prevention of prescription opioid abuse; b) define a research agenda on the role of dentists in these areas; and c) discuss recommendations for dentists on safe and effective use of opioids in dental practice.

THE ROLE OF DENTISTS

The top specialties prescribing IR opioids in the U.S. are family medicine (approximately 15% of prescriptions), followed by dentistry and internal medicine (approximately 12% of prescriptions each). An estimated 1 to 1.5 billion doses of IR opioid products are prescribed by dentists annually. Because the prescription opioid epidemic largely involves IR opioid products, it follows that dentists may be writing opioid prescriptions that are being ingested in the context of non-medical use or abuse.

PRESCRIBING PRACTICES FOR ACUTE DENTAL PAIN

A survey of dental prescribing practices among oral surgeons following third molar extraction — the most common dental surgical procedure, usually in healthy young adults with a mean age of 20 years — found that on average, they performed 53 cases per month. This extrapolates to 3.5 million per year in the U.S., not including those done by general dental practitioners. In 80% of these cases, general anesthesia or deep sedation was utilized. The preferred peripherally-acting postoperative analgesic was ibuprofen (73.5%), but 85% of oral surgeons almost always prescribe a centrally-acting opioid analgesic, the most common being hydrocodone/acetaminophen (APAP) (64%). This means that 3.5 million individuals, often young adults, may have their first exposure to opioids and anesthetics when receiving dental care. On average, 20 tablets of hydrocodone/APAP were prescribed to each patient, with instructions in 96% of cases to take as needed for pain.

In 2010, the THCI Program on Opioid Risk Management collaborated on a statewide survey of West Virginia (WV) dentists, to study their prescribing patterns and knowledge of prescription opioid abuse and diversion. Survey results showed that:

- 88% of dentists prescribed opioids in the past year, and 12% dispensed opioid analgesics from their office.
- Among those who prescribed opioids, the most frequently prescribed IR opioid was hydrocodone/ APAP (73%).
- The most common supply of opioids post-surgery was 20 doses or a 3-day supply.
- The most frequently prescribed non-opioid analgesics were non-steroidal anti-inflammatory drugs (NSAIDs) (55%), followed by APAP (35%).
• 90% of dentists wrote or called in up to 25 IR opioid prescriptions per week.
• 36% of dentists expected patients to have leftover drugs.
• 36% of dentists did not ask new patients if they had a history of substance abuse.
• 76% of dentists estimated that up to 20% of their patients had substance abuse problems.
• 79% of dentists were aware of the WV Board of Pharmacy Controlled Substance Monitoring Program, but 77% used it fewer than 25 times in the previous year.
• 58% believed they were the victims of prescription fraud or theft. The most common methods were fake pain symptoms (43%), claims that a prescription was stolen (28%), forged prescriptions (14%), and altered pill quantities (14%).

The survey suggested the need to educate dentists on the composition and pharmacokinetics of analgesics; the use of NSAIDs as first-line agents in the appropriate population; the need for assessment of drug and alcohol abuse at intake and ongoing; the use of guidelines for treating patients with drug and alcohol addiction; the importance of providing information to patients about proper disposal of unused medication; and the utility of state prescription monitoring program (PMP) data.

EVIDENCE FOR THE USE OF ANALGESICS IN DENTAL PAIN
There are multiple randomized, controlled trials of analgesics in dentistry, because a key, pivotal model for an acute pain analgesic medication required by the FDA is third molar extraction. Typically, 95% of patients have moderate to severe pain after third molar extraction. NSAIDs at optimal doses are superior in efficacy to single-entity opioids, are at least as efficacious as optimal doses of peripheral-opioid combination drugs, and have a more favorable side effect profile than opioids. NSAIDs should be considered as first line drugs in most cases of postsurgical dental pain. The use of preemptive NSAIDs and long-acting local anesthetics also appear to delay the onset of post-surgical dental pain.

PAIN MANAGEMENT IN THE CHEMICALLY DEPENDENT DENTAL PATIENT
With at least a 10% incidence of substance abuse in the general population, dentists can expect to encounter patients with substance abuse issues in their practice. Dental professionals must learn to recognize these individuals and establish practices to manage their acute pain appropriately. They should consult with these patients’ primary care physicians and collaborate with their families if a controlled substance is necessary. Informed consent and strict parameters for treatment are essential. Medical practice has established standards of care that can be adapted by the dental profession. Tools such as PMPs should be utilized. It is unclear how urine drug monitoring can be incorporated into general dental practice.

CHRONIC OPIOID THERAPY IN DENTISTRY
Dentists have a role in managing some types of chronic orofacial pain. They should recognize the complexities of treating chronic pain patients with long-term opioids, and use universal precautions, including assessing the patient’s risk of abuse; using PMPs and questionnaires; selecting an appropriate treatment; writing an informed consent and treatment agreement; and regularly monitoring the patient for compliance. An exit strategy is needed to terminate opioid therapy, when appropriate.

CONTROLLED SUBSTANCE REGULATIONS
Some state dental boards have developed advisories regarding appropriate use of controlled substances to manage pain in dentistry. Dentists are accountable for acquiring the knowledge and skills to practice in accordance with accepted standards of care for pain management, and they should understand applicable federal and state regulations regarding the prescribing and administration of controlled substances.

SCREENING FOR SUBSTANCE ABUSE
Community dentists, who see patients frequently and develop long-term relationships with them, have an important role in screening patients for prescription opioid abuse. Dental hygienists, who spend the most time with patients, should integrate screening tools into their practice, with the dentist interpreting and discussing the results when necessary. Dentists should collaborate with patients’ primary care doctors and develop protocols to refer patients to substance abuse treatment centers, so that a process will be in place if needed.
Prescription Opioid Abuse: Challenges and Opportunities for Payers

JUNE 2010 :: It has been estimated that nearly 2.5 million individuals initiate non-medical use of prescription opioids each year. Much of the cost of prescription opioid abuse and its health care consequences is paid for by private and public health insurers. Individuals who abuse prescription opioids or sell them illegally often obtain them by diverting prescriptions that have been paid for by insurance companies or government programs. In addition to the costs of the drugs, people who abuse prescription opioids incur much higher medical costs than non-abusers due to the serious health consequences of opioid addiction.

A Tufts Health Care Institute Program on Opioid Risk Management summit meeting was convened to a) develop an understanding of payers’ perspectives on prescription opioid abuse and diversion, and b) develop recommendations for payer-based approaches to decrease health consequences and costs associated with prescription opioid abuse.

SCOPE OF THE PROBLEM

Prescription drug costs represent about 10% of U.S. health care spending, and the share borne by payers has increased significantly in recent years. Payers incur 75% of prescription costs (47% by private payers and 28% by government). The number of total opioid prescriptions rose by over 200% between 1992 and 2002, with frequently abused hydrocodone and oxycodone posting nearly 400% increases. Opioid abuse and diversion is costly to payers. The overall medical and prescription costs associated with opioid addiction and diversion have been estimated at $72.5 billion annually for public and private payers.

In addition to the direct costs to health insurers, prescription opioid abuse has an impact on other types of insurers. Automobile, property, and workers compensation insurers face increased costs for accident, property damage, and worker compensation claims. These may stem from individuals driving while impaired or engaging in other risky behavior, and from fraudulent claims designed to finance the purchase of illegal prescriptions.

RISK MANAGEMENT SOLUTIONS FOR PAYERS

Health care payers can implement risk management solutions that will help reduce prescription opioid abuse and its associated costs, while ensuring that patients with pain are able to obtain access to opioid analgesics.

Internal policies. A number of payers have implemented processes that can help to limit misuse of prescription opioids. Formulary controls that limit reimbursement can help ensure that higher risk opioids are not prescribed, or that they are limited only to patients with appropriate diagnoses. Claims review procedures can be designed to question potentially inappropriate prescriptions, and to flag prescriptions that are coming from primary care providers, rather than specialists. Individuals who are suspected of doctor shopping can be “locked-in” to use of a single pharmacy or a single prescriber.

While it may be useful, claims matching can be difficult to institute because many claims databases do not interface with one another. It is important that payers develop procedures for handling potential fraud cases that allow for individualized consideration of each case, including clinical oversight to ensure that patients and providers are not mistakenly penalized when they are using and prescribing opioids appropriately.

External policies. Clinical research on prescription opioid abuse has shown that clinicians can employ a number of strategies to limit the risks associated with prescribing these medications. This research has led to guidelines, such as those released by the American Pain Society and the American Academy of Pain Medicine, that recommend use
of universal precautions. Payers can limit their own risk by promoting and supporting the use of these precautions among health care providers.

**Patient screening.** A wide range of risk factors for prescription opioid abuse have been identified, including age, gender, family history, presence of a major psychiatric disorder, and a history of aberrant behaviors. Payers can promote patient screening by, first, encouraging practitioners to use some of the many screening tools that are available for this purpose and, secondly, reimbursing for the time involved.

**Use of Prescription Monitoring Programs.** Data from prescription monitoring programs (PMPs) can be used to identify individuals engaged in abuse or diversion. Payers can facilitate use of PMP data through technology, and they can encourage, or even require, prescribers to check the PMP before prescribing controlled substances. As health IT evolves, payers can link the PMP to electronic prescribing tools or to pharmacy computers at the time of dispensing. Payers can use PMP data to investigate if prescribing patterns fit within the standard of care in a community, and to identify geographic areas where doctor shopping and adverse outcomes are higher than average and warrant closer surveillance.

**Patient education and communication.** Current guidelines recommend use of counseling, informed consent, and treatment agreements with patients receiving prescription opioids. Patient education is time-consuming, and is not likely to occur unless time-efficient and effective approaches are developed and implemented. Supportive reimbursement policies by payers could also have a facilitating role.

**SBIRT, or Screening, Brief Intervention, and Referral to Treatment.** SBIRT provides a comprehensive approach to identifying those at risk for substance abuse disorders and providing early intervention in the community setting. Patients are screened for substance abuse problems, then provided with a brief intervention or treatment (for low to moderate risk cases) or referred to specialists (for high risk cases). Use of SBIRT is associated with reduced substance abuse, fewer emergency room visits, and fewer hospital days. Several large studies have suggested that it is cost-effective for payers. Payers can support use of SBIRT by aligning reimbursement and training policies with the services required to follow this method.

**Coordinated care.** It has been suggested that patients with chronic pain, like other chronic conditions, would benefit from care that conforms to the American Academy of Family Physicians’ Patient Centered Medical Home Model. Payers can encourage this type of care by providing information technology support and by participating in health information exchanges that promote carefully coordinated care. Such care is more effective for the patient, and it controls costs by reducing or eliminating duplicate tests and treatments.

**Physician education.** Physicians need appropriate training if they are to implement risk management strategies, universal precautions, and effective opioid abuse treatment in their practices, particularly since little is taught about pain in medical school or post-graduate training. Considerable data from the Veterans Administration and other clinical settings show that intensive, one-on-one, longitudinal programs, which teach physicians how to prescribe opioids safely and provide continued support of long-term practice improvements, can be highly successful at changing physician behavior in this area. Payers who invest in such training for their physicians are likely to see reduced costs and improved member health.

Many health care payers are unaware of the toll of prescription opioid abuse and diversion on the health of their members and on their bottom lines. Strategies discussed at this summit meeting can be used by private and public payers to manage these risks.

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*My participation in the Tufts Health Care Institute Program on Opioid Risk Management helped me to differentiate risk management practices from good clinical care practices. Participating in the Program also advanced our work with prescription monitoring programs (PMPs). We are now following through on tracking how a number of opioid treatment programs are using PMP databases to improve patient care.*

*Mark W. Parrino, MPA, President*

*American Association for the Treatment of Opioid Dependence*
Advancing Safe Opioid Prescribing Through Prescriber Training and Behavior Change

MARCH 2011 :: Prescription opioid abuse and addiction is a significant challenge to the medical profession. Professional organizations, government agencies, and other stakeholders have spent substantial time and effort developing guidelines and recommendations for best practices in opioid prescribing, pain management, and diagnosis and treatment of addiction. The ultimate purpose of these guidelines is to ensure that individuals with chronic pain receive the medications they need, while minimizing the risks of misuse and addiction. However, the benefits of these guidelines are only realized to the extent that they are understood, embraced, and adopted on a large scale by the medical community that oversees the use of these medications.

The Tufts Health Care Institute Program on Opioid Risk Management convened this summit meeting to a) identify the limitations of traditional approaches to medical education in changing prescriber behavior; b) explore how the field of implementation science can be applied to behavior change for safe opioid prescribing; and c) discuss innovative approaches to prescriber training, including use of computer-based simulation.

USE OF IMPLEMENTATION SCIENCE

Many studies have described the low rates at which even relatively simple guidelines are adopted by physicians, other caregivers, and medical organizations as a whole. Efforts to disseminate innovations such as new opioid prescribing guidelines are most efficient when they lead to widespread diffusion, which can be defined as the process by which an innovation is spread among members of a social system, such as a health care organization or a physician group. Factors that can affect diffusion include the attributes of the innovation, opinions of potential adopters, parameters of the social network, and the desired timing. Successful, widespread adoption of an innovation requires adoption by key individuals, who then influence others to follow their lead.

Implementation science has identified four phases in the process of disseminating an innovation. Pre-implementation consists of developing a greater understanding of the problem. Multiple methods and resources can be used, including field observation, review of patient charts, one-on-one interviews, and focus groups. An outcome of pre-implementation can be the formation of an advisory body of various stakeholders, leaders, and experts who will assess the problem, develop a plan, and oversee the implementation process. The redesign and implementation phases are intended to develop and implement programs that promote best practices based on pre-implementation findings and preliminary planning. Typically these phases progress from small to large scale—i.e., from pilot projects, to small efficacy trials, to large effectiveness trials—with the ultimate goal of a system-wide deployment of best practices. Implementation science recognizes two types of evaluation. Formative evaluation aims at improving programs or interventions as they are being designed and/or implemented, while summative evaluation assesses the efficacy and outcomes of an intervention after it has been completed.

EXAMPLES OF SYSTEM CHANGES TO IMPROVE OPIOID PRESCRIBING

One goal of the meeting was to review the effectiveness of existing approaches to changing clinician behavior. Speakers from eight organizations presented examples of programs that they have implemented with some success:

- **Operation Unite**, a community program that encompasses youth and community education programs, drug and alcohol treatment programs, law enforcement strategies, use of drug courts, and other interventions in eastern Kentucky to reduce prescription drug related overdoses.

- The Veterans Administration’s **pain care agreements program**, which helps physicians document pain and assess opioid benefit and risk for patients.
The Tufts Health Care Institute Program on Opioid Risk Management is a recognized leader in the field, and is regarded by regulatory agencies as an important source for advice and information on key public health issues related to prescription drug abuse.

The Program has been invaluable to me, as it focused on many aspects of prescription drug abuse, including discussion of possible solutions, such as risk management, physician education and training, patient education, and development of abuse-deterrent products. The Program has also been helpful in facilitating stakeholder contacts, and has helped me to understand the role of opioid prescribing in dentistry and the role of insurance companies in health care delivery.

Multi-stakeholder collaboration has been one of the best features of the Program, with participants invariably covering a broad array of populations and disciplines. Participants have included high school students in drug abuse treatment, representatives from the Drug Enforcement Administration and other law enforcement agencies, pain and addiction experts, and other key opinion leaders.

It has been, for me, a tremendous educational experience.

Michael Klein, PhD, Director, Controlled Substance Staff, FDA

• New York State’s tamper resistant prescription pad program, which requires that all prescriptions are dispensed on official forms, practitioners and facilities are registered, and all controlled substance prescriptions are reported to state authorities.

• Utah’s academic detailing program, which educates health care providers on safe prescribing of opioids.

• New Hampshire’s Medical Society Opioid Prescribing Improvement Project, which uses an interdisciplinary, non-academic process to provide recommendations on pain management and prevention of opioid abuse.

• Massachusetts’ implementation of the Screening, Brief Intervention, Referral to Treatment (SBIRT), a brief screening method that primary care practitioners can use to screen patients for opioid misuse or risk of misuse, intervene when misuse is suspected, and refer individuals for treatment if necessary.

• The Opioid Compliance Study at Brigham and Women’s Hospital in Boston, which identifies high risk individuals and randomizes them to receive either conventional care or close monitoring.

• Massachusetts Naloxone Distribution Program, which provides education on overdose prevention and treatment, and distributes doses of Naloxone for use in emergencies.

COMPUTER-BASED SIMULATION TRAINING FOR CLINICIANS

Computer simulation allows modeling of real or hypothetical situations in order to impart skills that are important for mastering a practical task or a specific environment. Computer simulation training can solve problems, such as lack of access to live training programs, and it can provide exposure to infrequent but important scenarios. Development of virtual patients and virtual situations may be useful for teaching physicians to handle complex psychological or behavioral conditions, and for improving patient communication and diagnostic skills. Some computer-based learning programs have already been implemented in medical training, but the effectiveness of these approaches has not been fully evaluated.

Summit meeting participants concluded that the principles of implementation science, together with the application of computer-based simulation, have the potential to greatly improve opioid prescribing and reduce the toll of prescription opioid abuse and addiction on patients, their families, and society.

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Summit meeting participants concluded that the principles of implementation science, together with the application of computer-based simulation, have the potential to greatly improve opioid prescribing and reduce the toll of prescription opioid abuse and addiction on patients, their families, and society.
Many individuals who abuse prescription opioids are first exposed to opioids during treatment for chronic pain, resulting in substantial overlap between the chronic pain and substance abuse patient populations. These circumstances have created a need for the convergence of clinical skills between practitioners who address chronic pain and those who address substance abuse, in order to treat both conditions simultaneously. Effective management of these patients requires the ability to recognize individuals who are at high risk for addiction; identify patients who are currently misusing opioids; provide appropriate treatment or referrals to patients who become addicted; and continue to manage chronic pain in patients who are addicted to opioids or other substances.

The Tufts Health Care Institute Program on Opioid Risk Management convened a summit meeting to a) review available evidence on the uses of pharmacotherapies to treat prescription opioid addiction and current best practices for the management of chronic pain in addicted individuals; and b) develop a clinical update of pharmacology for treatment of pain in patients with opioid addiction.

**PHARMACOTHERAPEUTIC APPROACHES TO PRESCRIPTION OPIOID ABUSE AND ADDICTION**

Three medications have been approved to treat prescription opioid abuse and addiction. The opioid agonists methadone and buprenorphine are prescribed for opioid maintenance patients. A third drug, naltrexone, an opioid antagonist, is prescribed for those patients wishing to abstain from opioid use. Until recently, federal laws prohibited physicians from prescribing opioids for maintenance treatment except under highly controlled conditions in clinics. In 2000, the Drug Addiction Treatment Act expanded the ability of physicians to prescribe opioids for opioid addiction, allowing office-based treatment with FDA-approved medications for maintenance or detoxification, including prescription of Schedule III opioids. Under the Act, physicians are required to obtain specific credentials, and are limited in the number of patients they can treat.

Methadone is a full opioid receptor (OR) agonist. Although patients may now be able to obtain prescriptions for methadone at their primary care physician’s office, some patients prefer, and may do better in, a more structured clinic environment.

Naltrexone is an OR antagonist. Although oral naltrexone can be highly effective in motivated patients, it often has a poor outcome due to non-compliance. It does not treat pain. Further, patients may try to overcome the antagonist properties of naltrexone by taking large quantities of opioids, resulting in a high potential for opioid overdose. Sustained release formulations of naltrexone, such as Depotrex or Vivitrol, can improve compliance and may be a good choice for patients with milder opioid abuse disorders, but are unlikely to help patients who need an opioid for treatment of chronic pain.

Buprenorphine is a partial OR agonist. Buprenorphine is thought to be less liable to abuse than other synthetic opioids, has less overdose risk compared to full agonists, and carries fewer withdrawal symptoms. Buprenorphine is available as a monotherapy (Subutex) and in combination with the abuse-deterrent compound naloxone (Suboxone). In the general population, buprenorphine treatment success has been associated with older age, presence of depression, lack of prior treatment, and abuse of prescription opioids by an oral/sublingual route rather than injection. Chronic
pain patients were as likely as non-chronic pain patients to succeed in treatment, and many experienced significant pain improvement.

To date, it is unknown how to choose between buprenorphine, methadone, and particularly naltrexone, where there are very little data for specific types of patients. Further research is needed to determine the most effective addiction treatment for specific patient subgroups.

**BUPRENORPHINE AND METHADONE AS PAIN THERAPIES**

A 7-day buprenorphine transdermal patch is approved to manage moderate to severe chronic pain in patients who require continuous opioid analgesia. Buprenorphine has a relatively good safety profile but its half-life is highly variable, and it induces withdrawal symptoms when discontinued. Methadone is also an effective analgesic, and may be more effective than other opioids when treating neuropathic pain. However its pharmacokinetic profile is unpredictable, making it potentially dangerous and it can lead to fatal overdoses even when taken as prescribed. Significant clinical experience and careful monitoring is needed to use methadone safely for pain relief.

**THE POTENTIAL FOR ABUSE OF BUPRENORPHINE AND METHADONE**

Because these compounds are agonists, they have the potential for abuse; in fact, abuse of these drugs is prevalent. Methadone is the third most common opioid, after oxycodone and hydrocodone, to be confiscated in drug seizures, and there has been a considerable increase in recent years in the rate of abuse and fatal overdoses related to it.

**MANAGEMENT OF PATIENTS WITH CHRONIC PAIN AND SUBSTANCE ABUSE DISORDERS**

Managing pain in patients who are being treated for addiction requires careful coordination with the addiction treatment program. Patients on methadone maintenance who have chronic pain can be treated with opioids (either a supplemental dose of methadone or an additional alternate opioid), but must be monitored very closely due to the risk of diversion. In patients on buprenorphine maintenance, buprenorphine should be given every 6-8 hours to treat opioid dependence and pain at the same time. In patients being treated with naltrexone, non-opioid pain relievers are the main option.

Managing addiction in pain patients requires an integrated team approach that involves the primary care physician or pain specialist and a substance abuse treatment specialist. Psychological counseling, cognitive behavioral therapy, urine drug monitoring and supervision are important to ensure treatment success.

**FUTURE PHARMACOTHERAPEUTIC APPROACHES FOR OPIOID-ADDICTED INDIVIDUALS**

*Probuphine* is a subcutaneously implantable 6-month buprenorphine formulation intended to reduce the risk of diversion and improve patient compliance. *Buprenorphine film* is a child-resistant buprenorphine formulation that reduces the risk of accidental exposure. *Lofexidine* is an alpha-2-adrenergic receptor agonist related to clonidine that is used for opioid detoxification because it suppresses acute symptoms of withdrawal. *Vivitrol* is an injectable, extended release form of naltrexone given once a month; it was approved in 2010 for the treatment of addiction to heroin or opioid analgesics. *Ibudilast* is a novel agent, still in development, which enhances morphine analgesia, reduces opioid tolerance, and suppresses opioid withdrawal symptoms.

**REGULATORY ASPECTS OF DEVELOPING NEW MEDICATIONS FOR OPIOID ADDICTION**

Most studies of new pain medications for registration with the FDA exclude patients with substance abuse disorders, even though these individuals make up 15%–40% of the chronic pain patient population. There is a high public health need for therapies that are approved for use and shown to be effective in patients with both chronic pain and substance abuse disorders.

Pharmaceutical companies might be motivated to perform studies in these dual diagnosis patients if they are able to seek a dual indication—for pain and co-morbid addiction—for new medications. A potential regulatory pathway exists in that current FDA guidance strongly encourages the use of narrow sub-populations of patients in drug development, encouraging studies focused on individuals with specific genetic characteristics, for example, or differences in drug metabolism. Companies may be able to test therapies that have already been approved for one indication in a sub-population with a specific co-morbidity—for example, chronic pain patients who have developed addiction, or patients with addiction who require pharmacotherapy for pain.
Pain has recently been described by the Institute of Medicine as a $635 billion problem that affects over 100 million Americans (“Relieving Pain in America,” 2012). Prescription opioid abuse claims over 15,000 lives annually, with its own costs approaching $100 billion. Complications associated with non-steroidal anti-inflammatory drugs result in high morbidity and mortality.

Looking back the epidemic of morphine abuse and addiction at the turn of the 20th century prompted the U.S. government to launch a research program, located ultimately at the National Institutes of Health (NIH), which sought to develop non-addictive, effective pain medications. The federally funded NIH analgesics development program was set up as a “three-legged stool,” with the major components being a medicinal chemistry center, an animal testing center, and a human testing center.

While the program did not find one perfect medication, it accomplished a great deal including the development of most of the opioids and opioid antagonists used in modern medicine—methadone, levo-alpha-acetyl-methadol (LAAM), buprenorphine, tramadol, naloxone, naltrexone, and fentanyl. These medications have greatly strengthened the practice of medicine today, and have improved and saved many lives by enabling more effective treatment of pain, substance abuse, and opioid overdose. Despite the current epidemic of morbidity and mortality associated with analgesic medication use, the NIH analgesics development program was shut down in 2008, due to lack of funding for drug testing.

The Tufts Health Care Institute Program on Opioid Risk Management convened this summit meeting to a) articulate the need for safer analgesic medications; and b) develop recommendations to address this need, drawing on lessons learned from the NIH Medicines Development Program.

**THE URGENT NEED FOR CONTINUED DEVELOPMENT**

While the pharmaceutical industry is eager to develop and commercialize better analgesics, most of its efforts have been targeted at reformulating existing analgesics to make them more convenient or less “abusable.” Only a few pharmaceutical companies are currently developing analgesics targeting mechanisms or pathways that are not related to the opioid receptors, such as the FAAH enzyme or the cannabinoid receptors. Although this effort may bear fruit in the long-term, it is not sufficient in the context of the current epidemic of prescription opioid abuse and the associated morbidity and mortality. Currently, the NIH budget devoted to chronic pain research represents less than 2% of the total NIH budget, and only one-tenth of the NIH neuroscience budget.

Summit meeting participants unanimously agreed that the NIH analgesics development program should be revived as soon as possible. Potential components of the revived program could include:

- Refunding a network of laboratories to focus on medicinal chemistry;
- Refunding animal testing facilities with a focus on developing more predictive animal models of pain and addiction; and
- Setting up a small network of clinical research sites to rapidly and inexpensively screen compounds for analgesic activity and abuse potential.
This program will need to fit into NIH’s current structure, but it should have a strong, independent, and dedicated leadership focused exclusively on the goals of this program, in order to maintain its mission and focus despite shifts in NIH priorities and activities.

RECENT AND FUTURE DEVELOPMENTS

Recent developments hold great promise for opioid pharmacology. One such development is the landmark 2012 crystallization of the opioid receptor and ligands that target mu receptor heterodimers which may lack the side effects of tolerance and dependence. Other recent discoveries include non-opioid analgesics with powerful analgesic capabilities in animals and humans. Opportunities now exist to develop better, more targeted analgesics. Summit meeting participants agreed that the time is right to revive the NIH drug testing program to take full advantage of these new discoveries.

The Tufts Health Care Institute Program on Opioid Risk Management has had a positive impact on our work by giving us a more complete picture of the problem. Our exposure on this issue had been limited to professionals in the insurance industry and law enforcement. The Program introduced us to several issues we had previously not explored, including the science behind prescription drug addiction and the difficulty medical professionals have in detecting and treating this addiction.

In the last two years, there have been several new initiatives and programs created, some of which originated from THCI Program meetings. I continue to have contact with several professionals and organizations I met through the Program.

Dennis Jay, Executive Director
Coalition Against Insurance Fraud
Organizations Represented at the Tufts Health Care Institute Program on Opioid Risk Management Summit Meetings, 2005-2012

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COMMUNITY-BASED ORGANIZATIONS
Join Together
Learn to Cope
North Shore Recovery High School
Operation Unite

FEDERAL AGENCIES
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Food and Drug Administration (FDA)
Office of National Drug Control Policy (ONDCP)
National Center for Posttraumatic Stress Disorder (NCPSD)
National Institute on Alcohol Abuse and Alcoholism (NIAAA)
National Institute on Drug Abuse (NIDA)
National Institute of Neurological Disorders and Stroke (NINDS)
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TUFTS HEALTH CARE INSTITUTE

Tufts Health Care Institute (THCI), founded jointly by Tufts University School of Medicine and Tufts Health Plan, is a leading not-for-profit educational organization, serving health professionals and health care delivery systems. The Institute’s mission is to help physicians and other health care professionals deliver high quality, cost-effective, evidence-based, and patient-centered care—essential goals for health reform.

In support of this mission, THCI conducts courses, seminars and conferences, both in the classroom and online, on topics related to improving quality, cost-effectiveness and patient satisfaction. THCI staff have deep content knowledge in these domains, and are expert in developing, organizing, disseminating and evaluating customized educational resources and programs. The Institute employs active learning techniques in order to increase practitioner competence, skills and performance, with the ultimate goal of improving patient outcomes.

The Institute also convenes summit meetings, with leaders and content experts from multiple perspectives, to examine defined health system problems and propose solutions. Following these meetings, THCI disseminates proceedings and reports. Past summits have addressed such issues as Collaboration in a Competitive Health Care Market, and Breaking New Ground in Employee Wellness. Since 2005, THCI has sponsored and organized the Program on Opioid Risk Management. THCI is structured to partner with and leverage other major contributors in the health care arena—including professional development providers; health care delivery systems; local, state and federal agencies; and national health care professional associations—to promote high quality, cost-effective delivery of care for patients and to optimize the allocation of health care resources for populations.

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To access a downloadable version of this publication, visit the THCI Program on Opioid Risk Management website, at http://www.thci.org/opioid/. This site also provides details and references for each of the THCI Program on Opioid Risk Management’s 16 summit meetings.

NATHANIEL P. KATZ, MD, MS,
PRESIDENT AND CEO, ANALGESIC SOLUTIONS

Nathaniel P. Katz, MD, MS, is President and Chief Executive Officer of Analgesic Solutions, a research, education, and consulting firm exclusively focused on pain therapeutics. Dr. Katz is also Adjunct Assistant Professor of Anesthesia at Tufts University School of Medicine. After completing his neurology residency at Tufts-New England Medical Center, he entered a pain management fellowship in the Department of Anesthesia at Brigham & Women’s Hospital in 1990 and was later appointed staff neurologist in the Pain Management Center. Dr. Katz subsequently founded the Pain & Symptom Management Program at Dana-Farber Cancer Institute and the Pain Trials Center (a clinical analgesics research unit) at Brigham & Women’s Hospital. He remained director of both until 2001. From 2000-2004, Dr. Katz served as Chair of the Advisory Committee, Anesthesia, Critical Care, and Addiction Products Division, U.S. Food and Drug Administration, during which time he completed a Master’s of Science degree in Biostatistics at Columbia University. Dr. Katz is active in shaping public policy to reduce prescription opioid fraud and abuse, having served as a consultant to the Office of National Drug Policy and other government agencies.

Dr. Katz’s interests include clinical research methods, analgesic clinical trials, opioids for chronic pain, opioids and addiction, neuropathic pain, cancer pain, and new methods for advancing prescription monitoring. He has completed numerous clinical trials of treatments for pain, both industry-initiated and investigator-initiated, involving pharmaceuticals, non-pharmaceutical analgesics, and devices, and has also conducted studies related to opioids, pain, and addiction. He is an active member of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) and has been a co-author on several IMMPACT guidelines. Dr. Katz has over 60 publications in peer-reviewed journals and numerous presentations at scientific congresses. He has served as an Associate Editor at the Clinical Journal of Pain and Associate Editor (Pain) for the Encyclopedia of Neurological Sciences, and has overseen many local and national educational programs on pain management.
Abbreviations

ADF
Abuse-deterrent Formulation

AERS
Adverse Event Reporting System – is now FAERS
(FDA Adverse Event Reporting System)

APAP
Acetaminophen, used especially when combined with a prescription drug (e.g., hydrocodone/APAP)

DAWN
Drug Abuse Warning Network

DEA
Drug Enforcement Administration

FDA
U.S. Food and Drug Administration

FDAAA 2007
Food and Drug Administration Amendments Act of 2007

IR
Immediate Release

LAAM
Levo-alpha-acetyl-methadol, a synthetic opioid used in the treatment of opioid addiction

MTF
Monitoring the Future

NADDI
National Association of Drug Diversion Investigators

NASPER
National All Schedules Prescription Electronic Reporting Act

NIDA
National Institute on Drug Abuse

NIH
National Institutes of Health

NSAID
Nonsteroidal anti-inflammatory drug

NSDUH
National Survey on Drug Use and Health

PK-PD
Pharmacokinetic/Pharmacodynamic

PMP
Prescription Monitoring Program

RADARS
Researched Abuse Diversion and Addiction-Related Surveillance

RCA
Root Cause Analysis

REMS
Risk Evaluation and Mitigation Strategies

SAMHSA
Substance Abuse and Mental Health Services Administration

SBIRT
Screening, Brief Intervention, and Referral to Treatment

TEDS
Treatment Episode Data Set

THCI
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UDM
Urine Drug Monitoring