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Tomorrow's Vision of Pain Management: A Continuum of Solutions to Minimize Opioid Misuse, Abuse, & Diversion

The Practitioner's Dilemma

Practitioners today find themselves caught in the midst of a national public health dilemma when managing patients with chronic pain. According to David B. Brushwood, RPh, JD, Professor of Pharmacy Health Care Administration, College of Pharmacy, University of Florida, Gainesville, FL, practitioners are struggling to balance both a therapeutic imperative that demands that they "always provide opioid analgesics and other controlled substances when they are appropriate for a patient," and a regulatory imperative, which insists that they "never provide opioid analgesics when they are inappropriate for a patient." Although an apparently simple concept, its implementation is complicated.

The reality of treating patients in clinical practice means that practitioners sometimes will mistakenly refuse treatment for responsible patients and at other times prescribe opioid analgesics inappropriately (Table 1). Regulators focus on eliminating the prescribing of opioids to those who would abuse or divert them. Professor Brushwood argued that reaching such a goal is impossible because practitioners inevitably will err at some point. Attempts to eradicate the prescribing of opioids to irresponsible patients can create a severe imbalance in pain management practice, and result instead in adequate pain care being withheld from responsible patients, which is equally egregious. The solution is to minimize the sum of the 2 errors through balance rather



than emphasize eliminating one bad decision over another.^{1,2} The only way to prevent all opioid abuse and diversion would be to eliminate all drug flow. "The goal should be not to eliminate but to minimize opioid abuse and diversion," concluded Professor Brushwood. ■

Table 1. Central Principle of Balance

| | | State of the World | |
|----------------------------------|--------------------------------------|------------------------------------|--|
| | | Patient is responsible opioid user | Patient is NOT responsible opioid user |
| Healthcare Professional Activity | Opioids are prescribed/dispensed | Good Decision | Bad Decision |
| | Opioids are NOT prescribed/dispensed | Bad Decision | Good Decision |

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Strategies to Minimize Risk of Opioid Misuse, Abuse, & Diversion

The fear of failing to uphold the imperative to never provide opioid analgesics when they are inappropriate for a patient drives the practice of pain management by many practitioners, according to Lynn R. Webster, MD, FACPM, FASAM, Medical Director of Lifetree Clinical Research and Pain Clinic, Salt Lake City, UT. The possibility that patients will abuse, become addicted to, or divert opioids is one of the greatest risks associated with prescribing opioids, he said. Ambiguous presentations of abuse and addiction vary widely among patients and complicate predicting who is likely to develop an opioid use disorder.

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Continuum of Aberrant Behaviors

Definitions of abuse and addiction do not fit neatly into a taxonomic hierarchy, but exist along a continuum of aberrant behaviors, ranging from none to egregious. “Clearly there are people who are addicted, and clearly there are people who have a substance use problem,” Dr Webster said, but where an abuser becomes an addict is not clearly demarcated. Patients who display an apparently aberrant behavior are not necessarily substance abusers, and all abusers are not necessarily addicted. However, he stressed that all addicted patients display aberrant behaviors when they are abusing their medication. In his pain management practice, approximately 40% of patients will display an aberrant behavior within a year of initiating opioid treatment, but Dr Webster reiterated that aberrant behaviors are not necessarily synonymous with abuse and addiction.³ About half of the patients who display aberrant behavior (20% of all patients) will meet the definition of abuse, and approximately 2% to 5% of all patients will be addicted.³ A combination of genetics, social/environmental issues, and drug properties contribute to the development of an opioid use disorder.⁴⁻⁹

Assessment of Risk

To better predict which patients are more likely to develop an opioid use disorder, practitioners should assess risk prior to prescribing opioids, with frequent reassessments during treatment. Many practitioners are reluctant to take a lengthy structured-interview approach, but several tools can help them discern which patients are more or less likely to develop an opioid use disorder.

Ambiguous presentations of abuse and addiction vary widely among patients.

The CAGE-AID (Adapted to Include Drugs) questionnaire is a popular assessment tool, according to Dr Webster, but false-positive results can occur.¹⁰ The first question asks, “Have you felt the need to Cut down on your alcohol or drug use?”¹⁰ However, it is not uncommon for pain patients who do not have an opioid use disorder to feel uncomfortable with or reluctant to take opioids.¹¹ The second question asks, “Have people Annoyed you by criticizing your use of alcohol or drugs?” This question also may falsely identify patients without an opioid use disorder because family or friends often do not approve of their opioid analgesic treatment for pain, and patients may be annoyed by their criticism. Again, the third question, “Have you ever felt bad or Guilty about your alcohol or drug use?” can easily apply to

pain patients adhering to their opioid treatment regimen who may nevertheless feel guilty about needing to take opioids for pain. The final question asks, “Have you ever needed an Eye-opener to steady your nerves or get rid of alcohol or drug after-effects?” Because many pain patients take an opioid at the start of their day, Dr Webster argues that this question, as well as the tool itself, is not helpful in determining whether a patient has or will develop an opioid use disorder.

The Screening Instrument for Substance Abuse Potential (SISAP) is another tool to screen for opioid use disorder. Developed from the National Alcohol and Drug Use Survey of approximately 9,900 people in Canada, common denominators identified among individuals with an opioid use disorder included age younger than 40 years, recent or past history of substance abuse, and alcohol consumption (men: ≥ 5 drinks/day or ≥ 17 drinks/week; women: ≥ 4 drinks/day or ≥ 13 drinks/week).¹²

Dr Webster recommends 2 tools to prospectively predict which patients will develop an opioid use disorder. The Screener and Opioid Assessment for Patients with Pain (SOAPP) assesses family and personal history of substance abuse; history of legal problems; craving prescription medication; nicotine dependence; and mood swings.¹³ During validation, age younger than 40 years and having abnormal urine drug test (UDT) results were common behaviors associated with high-risk patients. Dr Webster developed and routinely

Table 2. Universal Precautions in Pain Medicine¹⁹

1. Make a diagnosis with appropriate differential
2. Psychologic assessment including risk of addictive disorders
3. Informed consent
4. Treatment agreement
5. Pre- and post-intervention assessment of pain level and function
6. Appropriate trial of opioid therapy +/- adjunctive medication
7. Reassessment of pain score and level of function
8. Regularly assess the “Four A’s” of pain medicine
9. Periodically review pain diagnosis and comorbid conditions, including addictive disorders
10. Documentation

Gourlay D, et al. *Pain Med.* 2005;6:107-112.

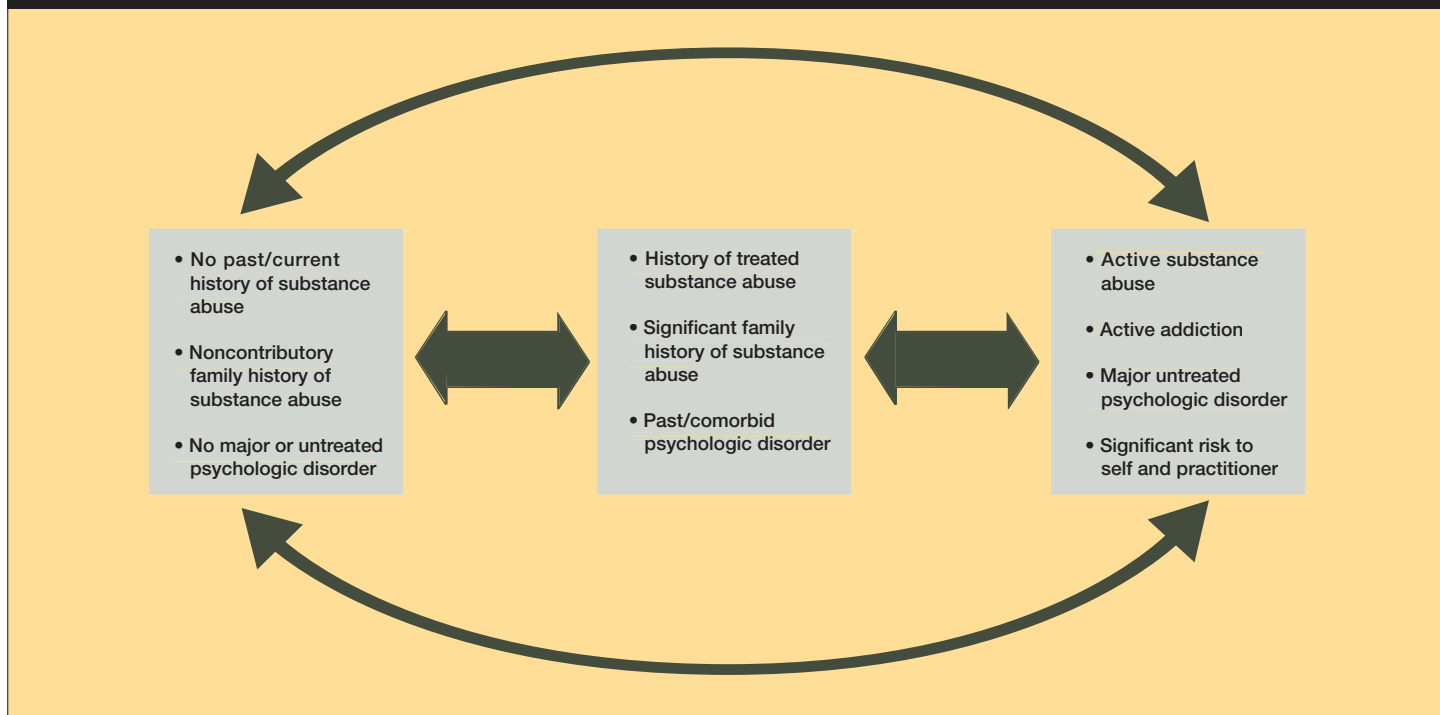
requires patients to complete the Opioid Risk Tool (ORT) prior to prescribing opioids.³ This patient-administered questionnaire asks about family and personal history of substance abuse (alcohol, illegal drugs, and prescription drugs); age (16-45 years); a history of preadolescent sexual abuse; and psychologic disease. The scores, weighted according to the patient’s gender, place patients in one of 3 categories: low, moderate, or high risk. During validation of the ORT, 94% of low-risk patients did not display any aberrant behavior within the first year of opioid treatment, but 91% of high-risk patients displayed multiple aberrant behaviors within the first 6 months of treatment, often in the first or second months.³ Dr Webster explained that a history of sexual abuse is highly predictive of an opioid use disorder because anxiety and post-traumatic stress disorders are common sequelae for which patients

may try to self-medicate with their opioids analgesics prescribed for pain.¹⁴

Despite their strong predictive values, screening tools do not predict or reveal every opioid use disorder. Studies have demonstrated that monitoring aberrant behaviors alone will fail to detect 50% of chronic pain patients using nonprescribed or illicit drugs.¹⁵ However, adherence monitoring with a controlled substance treatment agreement, periodic monitoring, periodic UDTs, pill counts, and education, when necessary, can reduce opioid abuse by 50%.^{16,17}

When using UDTs, it is important practitioners understand the limitations of different tests and what they are designed to detect. For example, most opiate immunoassays are designed to detect morphine and codeine and do not reliably detect semisynthetic and synthetic opioids—practitioners should contact the

Figure 1. Universal Precautions in Pain Medicine¹⁹



Gourlay D, et al. *Pain Med.* 2005;6:107-112.

testing laboratory to determine which tests to order for a particular patient.¹⁸ While practitioners should not wait for the appearance of aberrant behaviors to order a UDT, such tests are not necessary for every patient on every visit. Dr Webster recommends a “Universal Precautions” approach for initial evaluation, as well as vigilant reassessment to recognize the onset of an opioid use disorder, because patients can move along the continuum from one risk-group to another (Table 2, Figure 1).¹⁹ Three fundamental areas that influence patients’ probability of developing an opioid use disorder are environment, genetics, and drug properties.⁸

Environment

The level of stress in a chronic pain patient’s life can correlate with a higher risk of developing an opioid use disorder, although individual patients will have different thresholds for dealing with stress over time. Common stressors among chronic pain patients include inability to provide for family, inability to engage in sexual activity, and low self-esteem. Stressful factors may not result immediately in aberrant behavior, but unrelieved stress over a period of time is more likely to influence behavior, which can become increasingly egregious if left unchecked. In addition, environmental cues associated with drug abuse can also

induce a conditioned response (withdrawal or craving) in the absence of the drug.²⁰

Drug Properties

The rewarding or addictive properties of drugs that stimulate dopamine release in the limbic system can be measured using the abuse quotient ratio (C_{max}/T_{max} : the maximum concentration of a drug released in the shortest interval of time). Because reinforcement is related to the onset of action, rapid-onset drugs are more likely to be abused than those with slower onsets and slower declines.^{8,9,20} Therefore, when necessary, long-acting opioids are preferred for high-risk patients with pain; depending on the level of risk,

short-acting opioids for breakthrough pain may also need to be avoided.

The formulations of some modified-release opioids, designed to release drugs at a constant rate over an extended time, can be manipulated to accelerate release of the opioid (eg, crushing or chewing the drug and adding alcohol).^{9,21} Drugs ingested through injection, smoking, and inhalation have much more rapid onset than the oral route, but oral administration can still lead to behavioral reinforcement and addiction.⁸ While lipophilicity increases the passage of a drug through the blood-brain barrier, water solubility facilitates the injection of a drug, volatility favors the inhalation of drugs in vapor form, and heat resistance favors smoking the drug.²⁰

Genetic makeup is thought to influence patients' vulnerability to an opioid use disorder.

Genetics

Genetics can affect patients' vulnerability to an opioid use disorder, as well as their response to or perception of pain. Strains of laboratory rats have been used to demonstrate genetic vulnerability to pain sensitivity and/or addiction in animal models.²²⁻²⁵ Fischer 344 rats will reject a highly rewarding substance, while Lewis rats will display extreme drug-seeking behavior once exposed to a rewarding

substance. Sprague-Dawley rats display drug-neutral behavior under normal circumstances and behave like Fischer 344 rats, displaying apathy toward the drug. When multiple stressful factors are introduced, however, Sprague-Dawley rats respond similarly to Lewis rats, and tirelessly seek the rewarding drug.²⁶ Genetic makeup is likewise thought to influence patients' vulnerability to an opioid use disorder, with risks increasing in stressful environments.²⁷

Pharmacogenetic factors also contribute to interindividual variability in the response to opioids, both for analgesia and addictive behavior.²⁸⁻³² The response to an opioid depends on a combination of factors, including drug absorption, distribution, metabolism, and elimination, as well as mu-opioid receptor binding and signaling. Thus variation in the alleles of multiple candidate genes may potentially influence patients' response to opioids.^{29,30,33-36}

Although a majority of people respond similarly to a drug, that therapy could be inadequate for some groups or more likely to cause toxicity in others. An example of a highly polymorphic gene is CYP2D6, which is involved in the metabolism of many drugs, including the opioids codeine, hydrocodone, methadone, oxycodone, and tramadol.^{34,37,38} Allele combinations determine whether the CYP2D6 phenotype is a poor-, intermediate-, extensive-, or ultraextensive- metabolizer.^{34,39} Poor metabolizers may demonstrate an increased risk of drug-induced side effects

or a lack of therapeutic effect if a prodrug requires conversion to an active metabolite. For example, individuals with a polymorphism that disrupts normal CYP2D6 activity have a poor response to codeine, which requires CYP2D6 activity to metabolize the prodrug codeine to the active drug morphine.²⁹ Another example is CYP2D6 ultra-extensive metabolizers, who may have less success with methadone maintenance treatment for heroin addiction.^{40,41}

Reducing risk for an opioid use disorder requires a thorough initial assessment and vigilant ongoing monitoring.

Summary

Risk for an opioid use disorder can be predicted to some extent using available tools and knowledge. Reducing such risk requires a thorough initial assessment and vigilant ongoing monitoring. For some patients, the risk and harm from opioid therapy outweigh the benefits of the treatment, and tapering/discontinuing opioids may become necessary. Pain practitioners are becoming more sophisticated when selecting patients for treatment, tailoring opioid analgesic therapy to patients' individual risk factors, and modifying that therapy based upon the patients' behaviors. ■

Novel Opioid Diversion- & Abuse-Deterrent Solutions: A Paradigm Shift

Novel strategies are being developed to address the dual public health crises of prescription drug abuse and undertreated pain in the United States.^{42,43} It is important that measures to address prescription drug abuse are balanced, so as not to interfere with the legitimate treatment of pain. Some studies have correlated the increase in deaths from opioids with the increase in legitimate prescribing of opioid analgesics for pain, but there is no direct evidence that one is driving the other, and undertreated pain remains significant, explained Scott M. Fishman, MD, Chief of the Division of Pain Medicine and Professor of Anesthesiology, University of California, Davis, California.⁴³⁻⁴⁵

Abuse and Diversion of Controlled Substances

Abuse of pharmaceuticals is clearly increasing in the United States. Between 1992 and 2003, the number of Americans abusing controlled prescription drugs jumped by 94%—2 times the increase in the number of people abusing marijuana, 5 times the increase in those abusing cocaine, and 60 times the increase in heroin abuse.⁴⁶ The Drug Abuse Warning Network estimates that nearly 1.5 million

drug-related emergency department (ED) visits in 2005 were associated with drug abuse, of which 27% involved pharmaceuticals only (primarily central nervous system [CNS] and psychotherapeutic agents), 8% involved illicit drugs with pharmaceuticals, and 4% involved illicit drugs with pharmaceuticals and alcohol.⁴² The most frequent CNS agents in ED visits were opioid analgesics, among which hydrocodone, oxycodone, and methadone were most common.⁴² Hydrocodone is so frequently abused for a number of reasons, including its classification as a Schedule III controlled substance (while many other opioids are Schedule II) and being the most prescribed drug in the United States.⁴⁷

Prescription drug misuse in the United States has a tremendous impact on society. In 2003, 2.3 million teens ages 12 to 17 years (9.3%) admitted abusing a controlled prescription drug in the past year, 83% of whom abused opioids.⁴⁶ The rate of increase in prescription drug abuse among teens has grown at a faster pace than among adults.⁴⁶ For example, between 1992 and 2002, the number of new prescription opioid abusers ages 12 to 17 years increased by 542%,

compared with a 124% increase among those ages 18 years and over.⁴⁶ Abuse of controlled prescription drugs has also skyrocketed among students at US colleges.⁴⁸ From 1993 to 2005, the proportion of students who abused prescription opioid analgesics in the past month increased by 343%.⁴⁸

Almost 80% of state and local enforcement agencies report either high or moderate availability of diverted pharmaceuticals in their area.⁴⁹ Dialogue about prescription drug abuse in the United States focuses largely on inappropriate physician prescribing and patient misuse, but other important sources of diverted controlled prescription drugs include thefts (ie, armed robberies, night-break-ins, employee/customer pilferage) and loss (Figure 2).⁵⁰

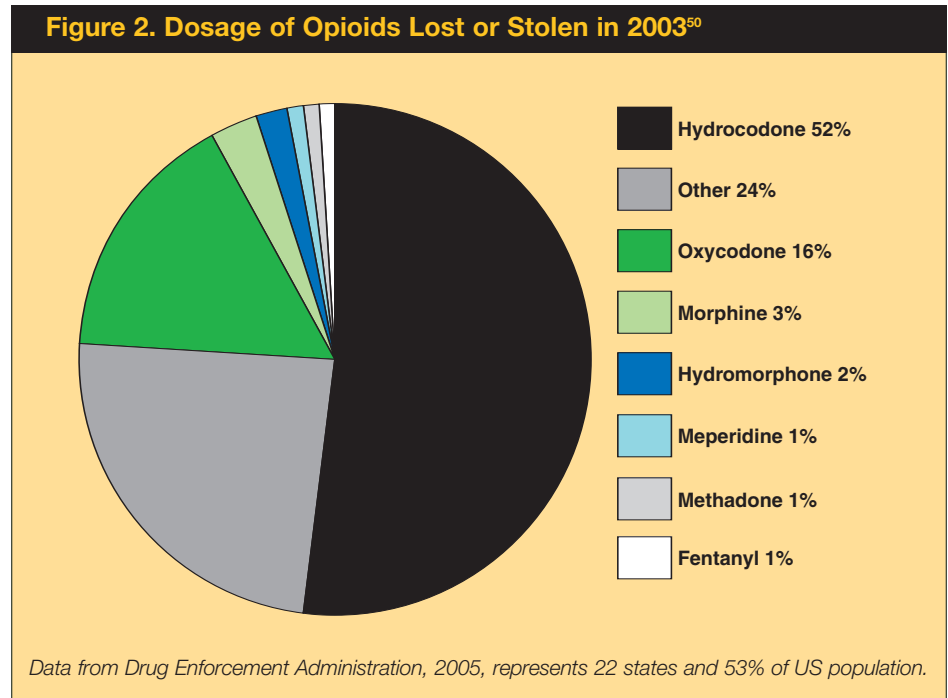
Opioid Diversion-Deterrent Technologies

Prescription Monitoring Programs

Prescription monitoring programs (PMPs) are designed to facilitate the collection, monitoring, and reporting of information on the prescribing and dispensing of controlled pharmaceuticals.⁵¹ PMPs have been available in some states for a number of years, and have used a multitude of strategies and technologies. “One of the big problems is that we don’t have a unified methodology,” explained Dr Fishman. As of June 2006, 32 states had enacted legislation requiring PMPs, and 16 additional states were proposing, preparing, or considering such

legislation.⁴⁹ The National All Schedules Prescription Electronic Reporting Act (NASPER), signed into law in 2005, provides federal grants for the establishment of a controlled substance PMP in each state, with communication between state programs, but NASPER is not a federal or national PMP.^{52,53} While such programs can assist states to identify diversion trends as they emerge and provide valuable information to clinicians to assist in patient management and reduce abuse or diversion, the primary purpose of most state programs has been to assist law enforcement in the identification of doctor shoppers and overprescribers.^{52,53}

There has been rapid growth in the production of reports by PMPs across the country.⁵⁴ The number of fulfilled requests increased by more than 700% from 108,961 in 2001 to an estimated 806,692 in 2006.⁵⁴ A survey of the 32 states with a PMP found that PMPs' ability to fulfill requests for data varies by the type of requester (law enforcement and regulatory agencies: 97%; prescribers, pharmacies/ pharmacists, and state attorneys general: 87%; researchers: 71%; patients: 58%).⁵⁴ However, many states that are permitted to share solicited and unsolicited information are not doing so presently (Figure 3).⁵⁴ PMPs' ability to fulfill requests at the federal level varies by the type of agency (eg, Drug Enforcement Administration [DEA]: 84%; Federal Bureau of Investigation: 81%; Federal Attorney General: 77%; US Food and



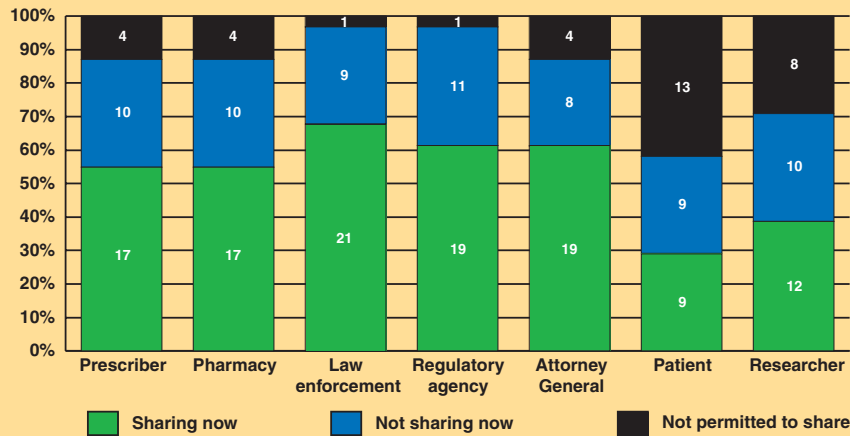
Joranson DE, Gilson AM. *J Pain Symptom Manage.* 2005;30:299-301.

Drug Administration [FDA]: 61%).⁵⁴

According to the DEA, individuals seeking diverted pharmaceuticals in states that have implemented PMPs have, in some cases, turned to traveling to nearby states that do not operate such programs to illegally obtain pharmaceuticals.⁴⁹ The White House National Drug Control Policy measured the effectiveness of PMPs through a simple statistic: in 2000, the 5 states with the lowest number of modified-release oxycodone prescriptions per capita had PMPs, and the 5 states with the highest number of such prescriptions per capita all lacked them.⁵¹ Dr Fishman questioned whether a reduction in prescribing should be the sole indicator of success for a PMP at a time when there is

a dual public health crisis of undertreated pain and prescription drug abuse. Following the introduction of PMPs in Idaho, New York, Rhode Island, and Texas, prescribing of Schedule II controlled substances fell by 50% or more;⁵⁵ in contrast, the proportion of Schedule III controlled substance prescriptions increased.⁵⁵ This “substitution effect” can interfere with pain relief when physicians, faced with barriers to prescribing a certain type of medication, will often prescribe around that barrier by selecting drugs that are perceived as less scrutinized, even if they are less efficacious.⁵⁵ Another example is California, which has a PMP program that requires triplicate prescriptions for Schedule II medications—however, only half of California physicians had triplicate

Figure 3. Intrastate Sharing Practices and Permissions: Solicited (N=32 States)⁵⁴



IJIS Institute. Consulting Engagement Report. PMP Committee Phase II PMIX Pilot Project Survey of State Prescription Monitoring Programs. IJIS Institute; 2007.

prescriptions issued to them;⁵⁵ “and those who had them were afraid to use them,” he said.

While state PMPs may assist clinicians in making appropriate treatment decisions, prevent them from becoming unwitting accessories to prescription drug abuse, and identify patients who may benefit from referral for treatment, they can also be barriers to care. Dr Fishman stressed that for PMPs to be useful clinically and to minimize concerns regarding regulatory scrutiny, the data should be mandated to be available to clinicians and should be administered through state agencies that regulate health care rather than law enforcement.⁵⁵ “Prescription monitoring has a great deal of potential, and I think in the next year we’re going to start seeing resolution of the problems,” he said.

Radio Frequency Identification

Implementation of Radio Frequency Identification (RFID) into pharmaceutical units or packaging could help deter the theft of drugs from the legitimate pharmaceutical supply chain.⁴⁹ Mandatory use of the RFID pedigree system for prescription drug shipments is under consideration by the FDA.⁴⁹ The resultant reduction in pharmaceutical diversion could be significant, as the quantity of pharmaceuticals diverted through theft from legitimate sources, particularly pharmacies, is approximately 6.8 million dosage units each year.⁴⁹ Furthermore, RFID will aid law enforcement in pharmaceutical diversion investigations through tracing sources of supply, recovering stolen shipments, and identifying vulnerable areas in the supply chain.⁴⁹

Opioid Abuse-Deterrent Technologies

Opioid analgesics, particularly modified-release preparations, can be tampered with in many ways.⁹ A prospective survey of prescription drug abusers entering a treatment facility found that the majority (80%) had altered the delivery system of the prescription drug by chewing, snorting, or intravenous administration.²¹ To counter this, new strategies and formulations are being developed to help prevent or deter abuse of prescription opioids (Table 3). Abuse-deterrent technologies include physical barriers, aversive components, and pharmacologic properties, or a combination of mechanisms (Figure 4).^{9,56-59}

Physical Design

Physical barriers are under development to make it difficult to crush, dissolve, or otherwise extract the full dose of drug from a formulation.⁵⁶ These can take the form of matrices, gels, beads, osmotic pumps, bioerodible hydrogels, implants, lock-out devices, and transdermal technologies.

Aversive Technology

Opioid formulations are making use of sequestered aversive or toxic components, which are only released if the formulation is crushed or otherwise tampered with.⁵⁶ Aversive components include opioid antagonists that counteract opioid effects, capsaicin (which produces a burning sensation), ipecac (an emetic that induces nausea and vomiting), and bitter-tasting agents. “Elements that would dissuade

Table 3. Abuse-Deterrent Opioid Formulations in Development

| Brand name | Generic name | Company | Development stage |
|------------|----------------------------------|---|-------------------|
| Oxytrex™ | Oxycodone IR + naltrexone | Pain Therapeutics, Inc. | Phase III |
| Remoxy™ | Oxycodone ER | King Pharmaceuticals, Inc./ Pain Therapeutics, Inc. | Phase III |
| Kadian® NT | Morphine sulfate ER + naltrexone | Alpharma Inc. | Phase III |
| OxyADF | Oxycodone IR | Acura Pharmaceuticals, Inc. | Phase II |
| NRP-290 | Hydrocodone prodrug | New River Pharmaceuticals Inc. | Phase I/II |
| ELI-216 | Oxycodone ER + naltrexone | Elite Pharmaceuticals, Inc. | Phase I |

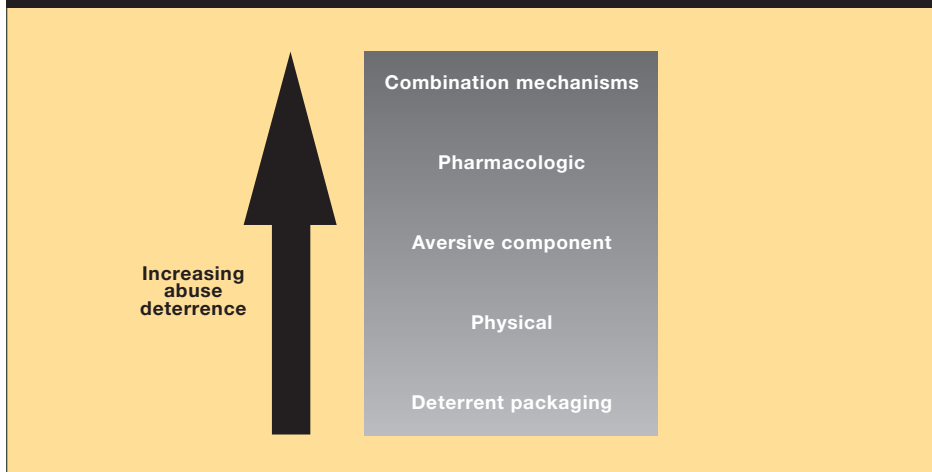
ER = extended release IR = immediate-release
 Gershell L, Goater JJ. *Nature Reviews Drug Discover* 5, 2006;5:889-890.

is not released,” said Dr Fishman, “But in the altered state [ie, if tampered with], the antagonist contaminates the product.”

Pharmacologic Properties

Pharmacologic formulations under development include prodrugs that require enzymatic cleavage in the gastrointestinal tract (first-pass metabolism) for the active metabolite to be produced.⁵⁶ The resulting slow release would be undesirable for someone abusing the opioid for recreational purposes.

Figure 4. Opioid Abuse-Deterrent Technologies



Conclusions

Following the introduction of such technologies, there is likely to be a new paradigm for clinical decision-making. Agents with the lowest potential for misuse will likely be selected as first-line agents, with other agents with high potential for misuse, abuse, and diversion being considered only if the first-line agent fails. However, many questions remain about these technologies, including short- and long-term analgesic efficacy, bioequivalence to existing products, the level of deterrence inferred (for the casual abuser vs determined abuser), the associated risk (particularly for patients who may have low risk for misuse), and how they will be viewed in the FDA approval process and for DEA scheduling. “Currently there is no abuse-proof formulation, and anything can and likely will be misused,” concluded Dr Fishman. “Determined abusers will abuse.” ■

someone from otherwise misusing the drugs,” explained Dr Fishman, but would pass unnoticed with normal, unaltered use.

One of the earliest abuse-deterrent opioids was developed in response to the reports of abuse of pentazocine with the antihistamine tripeleminamine (“Ts and Blues”) in the 1970s.⁶⁰ In response to this

abuse, the manufacturer introduced Talwin NX™, a combination of pentazocine with low-dose naloxone.⁵⁷ Pentazocine abuse declined following the reformulation, although it was not eliminated.⁵⁷ A number of opioid agonist-antagonist formulations are under consideration or in development.^{56,57} “In the unaltered state, the antagonist

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