

Focus Article

Approaches to Improve Pain Relief While Minimizing Opioid Abuse Liability

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Abstract: Two strategies should greatly improve pain management while minimizing opioid abuse. The first strategy involves the systematic implementation in every clinical practice of “universal precautions,” a set of procedures that help physicians implement opioid therapy in a safe and controlled manner. These procedures include: 1) carefully assessing the patient’s risk for opioid abuse; 2) selecting the most appropriate opioid therapy; 3) regularly monitoring the patient to evaluate the efficacy and tolerability of the treatment and to detect possible aberrant behaviors; and 4) mapping out solutions if abuse and/or addiction is detected, or in case of treatment failure. The second strategy involves the use of opioid formulations designed to deter or prevent product tampering and abuse. Results of clinical trials of new formulations of existing opioids (including oxycodone, morphine, and hydromorphone) suggest the potential for reduced abuse liability and, if approved, will be evaluated after launch for reduced real-world abuse. Integration of these formulations in clinical practices based on universal precautions should help further minimize the risk of opioid abuse while fostering appropriate prescribing to patients with indications for opioid therapy.

Perspective: *Undertreated pain and prescription opioid abuse remain important public health problems. In the absence of strong empirical evidence, common sense dictates that a universal-precautions approach—a systematic and easily adopted process that clinicians can quickly put into practice—is advised to promote safe opioid prescribing. Abuse- and tamper-resistant opioid formulations are emerging tools that may enhance safe opioid prescribing; further research and postmarketing analysis will clarify their utility and role in clinical practice.*

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Key words: Pain, opioid analgesics, universal precautions, abuse resistance, abuse deterrence.

Balanced use of opioid analgesics as a component of pain management has become a very difficult task for many physicians and is fraught with controversy. The increase in prescription opioids abuse has been shown to correlate with their increase in use,¹⁴ leading some to believe that opioids are prescribed too widely. Others believe that prescription opioids are underused due to overly cautious concerns of abuse and addiction, thus depriving patients of 1 potentially effective option for pain relief.^{5,35} We believe that the systematic application of universal precautions are effective tools to help the clinician simplify and

navigate the complexities of pain management and provide the best available means to have a meaningful impact on reducing prescription opioid abuse. Coupled with the application of universal precautions as principles of practice to reduce opioid abuse and diversion is the emerging pharmaco-technology of novel formulations designed to deter abuse of the products. Several formulations are currently under development and FDA review, and should be available in the near future. Although the use of abuse-deterrent or tamper-resistant formulations can potentially help minimize the risk of prescription opioid abuse, they will not be a substitute for good clinical practice. We proffer that for the full benefit of these new formulations to be realized, clinicians should have a firm foundation in universal precautions.

In the present article, we review: 1) the definitions of abuse and related terms; 2) the incidence and

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Table 1. Definitions

TERM	DEFINITION
Misuse ^{25,36}	The term <i>misuse</i> is problematic, as it is used by some as an overarching term for all prescription opioid-related problems, including abuse; herein we use the term <i>misuse</i> more specifically, to denote problems not arising from euphoria-seeking behavior, and consistently with its use in the poisoning literature; thus we define it as “ <i>the use of a medication (with therapeutic intent) other than as directed or as indicated, whether willful or unintentional, and whether harm results or not.</i> ”
Abuse ^{25,36}	<i>Abuse</i> is another problematic term, as it is used in the DSM to denote a specific psychiatric diagnosis within substance use disorders; here, we use it more broadly to indicate any use in the context of euphoria-seeking behavior. Thus, we define it as “ <i>any use of an illegal drug or the intentional self-administration of a medication for a nonmedical purpose such as altering one’s state of consciousness, eg, ‘getting high.’</i> ”
Aberrant Behavior ^{25,36}	<i>Aberrant behavior</i> has been used in various ways. These can range from mildly problematic behaviors such as “hoarding” medications to be able to use extra doses during times of more severe pain (consistent with <i>misuse</i> as defined above) to felonious acts such as selling medications. For the purposes of our discussion we will define it as “ <i>any medication-related behaviors that depart from strict adherence to the prescribed plan of care.</i> ”
Addiction ¹	<i>Addiction is a primary, chronic neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestation; behavioral characteristics include 1 or more of the following: impaired control over drug use; compulsive use; continued use despite harm; craving.</i>
Pseudoaddiction ^{25,36}	<i>Pseudoaddiction is a condition in which patients with undertreated pain exhibit certain aberrant behaviors (eg, doctor shopping) in an attempt to obtain adequate management of their pain; this often occurs in patients with undertreated pain. Although these behaviors may mimic those associated with true addiction, they resolve with adequate pain control.</i>
Dependence ^{25,36}	<i>Physical dependence is the state of pharmacological adaptation manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, or administration of an antagonist. The term dependence is commonly conflated with addiction, although it represents a distinctly different phenomenon. Although all addicts may experience dependence, all those who experience dependence are not addicts.</i>
Tolerance ^{25,36}	<i>Tolerance is the state of adaptation in which exposure to a given dose of a drug induces biologic changes that result in diminution of 1 or more of the drug’s effects over time. Alternatively, escalating doses of a drug are required over time to maintain a given level of effect.</i>

consequences of prescription opioid abuse and related phenomena; 3) the challenges in detecting abuse; 4) the universal precautions that aim at minimizing the risk of abuse; and 5) the rationale behind the design of abuse-deterrent and abuse-resistant formulations and their development status.

Definitions

There is an absence of consensus on definitions for some of the terms related to the nonmedical opioid use of prescription opioids, and the definitions proposed in the Diagnostic Statistical Manual of Mental Disorders (DSM) can be misleading and problematic when used in the context of pain care. Thus, for the sake of clarity, and to develop the theme of this paper, we provide definitions in Table 1 for misuse, abuse, aberrant behavior, addiction, pseudoaddiction, dependence, and tolerance.

The Incidence and Impact of Prescription Opioid Abuse

Various studies using different measures have shown that prescription opioid abuse is a widespread problem that has serious consequences. A recent study from the Substance Abuse and Mental Health Services Administration³⁹ reported that 5.2 million Americans (2.1% of the US population) used prescription pain relievers (most of which are opioids) nonmedically in the past month,

and 1.7 million (.7%) people met criteria for “abuse or dependence” of prescription pain relievers in the past year. The study also showed that 2.1 million persons initiated nonmedical prescription pain reliever use in the past year, which is similar to the number of new initiates for marijuana (2.1 million) or cigarettes (2.2 million).³⁰ A 2007 survey titled “Monitoring the Future” was conducted on 48,500 students and revealed that approximately 1 in every 10 (9.6%) high school seniors used Vicodin (hydrocodone) and 1 out of 20 (5.3%) used Oxycontin nonmedically in the past year.²⁰

Evidence has also shown that prescription opioid abuse results in substantial morbidity and mortality. In 2006, drug-related visits to emergency departments (EDs) that were due to prescription opioids (hydrocodone, oxycodone, and methadone) amounted to approximately 170,000.³⁸ Admissions to substance abuse treatment centers due to opioids other than heroin have more than quadrupled in the past 10 years (from approximately 16,000 in 1995 to 75,000 in 2006).⁴⁰ In 2004, the rate of deaths due to unintentional or undetermined poisoning with opioid analgesics in the US was 2.96 per 100,000 population, exceeding the rate of deaths associated with cocaine and heroin.³³

The rise in prescription opioid abuse has increased concurrently with increasing prescriptions of opioids.¹⁴ In the early 2000s, the number of ED visits due to prescription opioids rose linearly with the availability of opioids,⁴⁴ and there was a linear relationship between drug poisoning mortality and opioid analgesic sales.³²

Table 2. Universal Precautions Tools for Safe Opioid Prescribing

1. Assess
 - Initial Patient Assessment (by clinician and patient self report)^{4,41}
 - Mental Health Screening²
 - Structured Patient Outcome Assessment^{31,45}
 - Urine Toxicology¹⁶
 - Prescription Monitoring Report²²
2. Triage
 - Triage Tool¹⁷
3. Manage³⁰
 - Patient Treatment Agreement
 - Opioid Analgesics for Chronic Pain in Adults
 - Structured Brief Intervention and Referral to Treatment
 - Exit Tool

It is unknown whether the availability of prescription opioids has caused increases in abuse and mortality; the very fact that more prescription opioids are available highlights the need to educate patients on proper storage and disposal.

The main sources of prescription opioids for abuse reported by nonmedical users derive directly or indirectly from physicians. Among persons aged 12 or older who used pain relievers nonmedically in the last year (in 2007), 18.1% indicated that they obtained the drug from 1 doctor and 56.5% obtained the drug from a friend or relative for free, while very few in this general community-based survey obtained the drugs from drug dealers/strangers or internet pharmacies (4.1% and .5%, respectively).³⁷ Overall, 27% of oxycodone addicts at a psychiatric facility reported obtaining their prescriptions from their doctor;¹⁸ in another study, 31% of oxycodone extended-release addicts admitted for detoxification reported that they initially obtained the drug legitimately by prescription, usually for complaints of back pain.³⁴ No conclusions can be drawn from these data about the relationship between pain, opioid treatment, and addiction; only that those with a diagnosis of opioid addiction frequently obtain opioid prescriptions from physicians under the pretext of pain. In addition, admission to a treatment center for addiction does not always mean the patient actually was addicted. In some instances, patients are only dependent but due to environmental pressure they are admitted for detoxification.

Prescription opioid abuse also has a significant cost to society. Birnbaum et al³ calculated that the total cost (in 2005 dollars) of prescription opioid abuse is approximately \$8.6 billion, with workplace costs representing \$4.5 billion, healthcare costs \$2.6 billion, and criminal justice system costs \$1.4 billion.

Although these data are limited by the fact that it is not always possible to determine whether the drugs are misused or abused (as the terms are often used interchangeably in these reports) and whether the misuse/abuse is done by patients or nonpatients, they clearly show the important impact of illicit prescription opioid use in our society. Most troubling is that physicians, in good-faith efforts to relieve pain, are a major source of

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prescription opioids that sustain this growing societal problem.²⁸

Universal Precautions Can Help Optimize Treatment While Minimizing Abuse

Complex epidemiological, societal, clinical, and personal factors are involved in prescription opioid abuse, making it difficult for physicians to predict and detect abuse when it occurs. Moreover, only 1 out of 5 physicians has had training in identifying potential diversion of prescription medications.²⁹ Because informal judgment (“gut feeling”) about a patient’s risk of abuse is prone to error, it is imperative that simple universal precautions be systematically applied to every patient considered for opioid therapy. Developing such a system will add objectivity to decision-making, reducing barriers to undertreatment while reducing abuse.

Universal precautions (summarized in Table 2) are a systematic set of procedures and tools that: 1) aid the physician in gathering relevant information; 2) help the physician interpret the information collected; and 3) provide a roadmap for making responsible decisions based on the information collected.

Universal precautions should help the clinician make the most reasonable decisions based on the information at hand with the goal of relieving suffering for patients with legitimate indications for opioid therapy while reducing the risk of abuse.¹⁷ For this strategy to be effective, universal precautions need to be applied to each and every patient eligible for long-term opioid therapy.

Universal precautions should be viewed as a method to optimize therapy. Some clinicians who were unaware of the dangers of abuse or not trained to detect abuse and diversion may prescribe fewer opioids by applying universal precautions. On the other hand, other physicians may end up prescribing more opioids relative to their previous practices because they feel more confident and in control.

Measures of Universal Precautions

Involving the Office Staff

Universal precautions should be viewed as a practice-wide system. A first step is preparing the office staff to ensure that the appropriate administrative infrastructure is in place and the staff is trained to perform a few simple but important tasks. Tamper-resistant and copy-proof prescription pads without the prescriber’s DEA registration number should be available at all times, so office staff should routinely check availability of these pads and ensure an adequate supply is always available. Charts of patients on long-term opioid therapy should be tagged. Tagging should be done discretely so that patient confidentiality is preserved. Each day, 1 office staff member should review incoming appointments, identify patients on long-term opioid therapy, and ensure that the chart contains necessary assessment tools and questionnaires (described below)

Table 3. Recognizing Nonmedical Users of Prescription Drugs*COMMON CHARACTERISTICS OF THE NONMEDICAL USER OF PRESCRIPTION DRUGS:*

- Unusual behavior in the waiting room
- Assertive personality, often demanding immediate action
- Unusual appearance—extremes of either slovenliness or being overdressed
- May show unusual knowledge of controlled substances and/or gives medical history with textbook symptoms or gives evasive or vague answers to questions regarding medical history
- Reluctant or unwilling to provide reference information; usually has no regular doctor and often no health insurance
- Will often request a specific controlled drug and is reluctant to try a different drug
- Generally has no interest in diagnosis
- Fails to keep appointments for further diagnostic tests or refuses to see another practitioner for consultation
- May exaggerate medical problems and/or simulate symptoms
- May exhibit mood disturbances, suicidal thoughts, lack of impulse control, thought disorders, and/or sexual dysfunction
- Cutaneous signs of drug abuse: skin tracks and related scars on the neck, axilla, forearm, wrist, foot, and ankle; such marks are usually multiple, hyper-pigmented and linear; new lesions may be inflamed; shows signs of “pop” scars from subcutaneous injections

MODUS OPERANDI OFTEN USED BY THE DRUG-SEEKING PATIENT INCLUDE:

- Must be seen right away
- Wants an appointment toward end of office hours
- Calls or comes in after regular hours
- States he/she is traveling through town, visiting friends or relatives (does not have a permanent address)
- Feigns physical problems, such as abdominal or back pain, kidney stone, or migraine headache in an effort to obtain narcotic drugs
- Feigns psychological problems, such as anxiety, insomnia, fatigue, or depression in an effort to obtain stimulants or antidepressants
- States that non-narcotic analgesics do not work or that he/she is allergic to them
- Contends to be a patient of a practitioner who is currently unavailable or will not give the name of a primary or reference physician
- States that a prescription has been lost or stolen and needs replacing
- Deceives the practitioner, such as by requesting refills more often than originally prescribed
- Pressures the practitioner by eliciting sympathy or guilt or by direct threats
- Utilizes a child or an elderly person when seeking methylphenidate or pain medication

(Source: Drug Enforcement Agency, 1999⁷)

that the practice has chosen to use to support universal precautions. If electronic medical record systems are in use, be sure to enable and/or utilize automatic dosing safeguards (if available) that alert the physician when there are frequent opioid prescriptions for an individual patient.

Assessing the Patient Before Treatment to Determine the Patient's Risk of Substance Abuse

A highly confounding situation that physicians face is to distinguish recreational nonmedical users seeking opioid medication for the sole purpose of abuse (see Table 3) from patients who are at high risk of substance abuse but with a legitimate medical need for analgesia.⁴ To sort out these populations, physicians routinely managing patients with chronic pain should perform systematic assessments to risk-stratify patients¹⁷ (Table 4) to identify patients with chronic pain conditions with a low risk of abuse; chronic pain patients with moderate or higher risks for abuse; or individuals seeking opioids for nonanalgesic purposes.

Past medical records should be obtained whenever possible on a patient not known to the practice. Sometimes phone calls to past treating physicians can be helpful to corroborate the patient's history. Clinically, a detailed pain history, physical examination, and corroborating laboratory/imaging studies should be

obtained to determine the cause of pain and, if possible, mechanism-specific treatments. Sleep (and sleep-related respiratory risk), psychiatric history, functional capacities, and social circumstances are of paramount concern in the management of patients who may warrant long-term therapy with controlled substances. A thorough medication history is imperative, including a determination of whether the patient is opioid-tolerant. Additionally, patients should be evaluated to determine whether they have a history of substance abuse and/or are currently abusing drugs, and for aberrant behaviors consistent with abuse if they are to be placed on chronic opioid therapy. This evaluation should involve: 1) analyzing the patient's behavior; 2) determining the patient's history of substance abuse; 3) performing a physical examination; 4) performing urine toxicology¹⁶ (if deemed pertinent); and 5) obtaining the patient's prescription monitoring report (PMR), if available (not all states have prescription monitoring programs)⁸ (Table 2). These initial assessments allow the physician to rate the overall patient's risk of substance abuse using a Triage Tool (see example in Table 4), which provides guidance on how to manage various levels of risk.¹⁵

Monitoring the Patient Throughout the Treatment

To prevent problematic behaviors and detect signs of abuse, addiction, or pseudoaddiction, the physician should monitor the patient regularly throughout the

Table 4. The Triage Tool

RISK LEVEL	CHARACTERISTICS	MANAGEMENT*
1- Low	<ul style="list-style-type: none"> No history of substance abuse; minimal if any risk factors 	<ul style="list-style-type: none"> Can be managed by PCP If aberrant behaviors are observed, consider increasing risk category
2- Medium	<ul style="list-style-type: none"> Past history of substance abuse (not prescription opioid abuse); significant risk factors† Patient previously assigned to low risk exhibiting aberrant behaviors 	<ul style="list-style-type: none"> Comanage patient with addiction and/or pain specialists If aberrant behaviors are observed or persist, consider assigning to high-risk category
3- High	<ul style="list-style-type: none"> Active substance abuse problem; history of prescription opioid abuse Patient previously assigned to medium risk exhibiting aberrant behaviors 	<ul style="list-style-type: none"> Opioids may not be appropriate—switch to nonopioid therapy Consult with or refer to specialists who manage patients with comorbid pain and addictive disorders Continue to manage patient's medical care including pain relief and monitor specialized care

*Choosing between management options is on a case-by-case basis and depends on a variety of parameters. Careful clinical judgment is required.

†Turk et al⁴² recently reviewed risk factors for abuse. Strong risk factors (predictors) of prescription opioid abuse were a personal history of illicit drug and alcohol abuse. Several variables have been identified as "mixed predictors," meaning they were found to be significant in some studies but not others: male sex; a history of an anxiety disorder; a history of prescription drug abuse; and race (nonwhite). Other variables have not been extensively examined but, when they were evaluated, they were positive predictors: a family history of drug and illicit drug abuse; a history of childhood sexual abuse; a history of DUIs or drug convictions; lost or stolen prescriptions; and using supplemental sources to obtain opioids.

treatment. Monitoring treatment efficacy, tolerability, and compliance can also help the physician distinguish between addiction and pseudoaddiction. Monitoring should include: 1) urine toxicology (twice a year or randomly for most patients with aberrant behaviors), including detection of the prescribed drug (to assess compliance) and typical illicit drugs (Table 4); 2) prescription monitoring reports (PMRs) (annually or when aberrant behaviors are detected) to detect doctor shopping, multiple pharmacy use, and early refills; 3) pill count (at each visit) for high-risk patients to monitor compliance; and 4) a patient-assessment questionnaire to evaluate the efficacy and tolerability of the treatment by assessing pain levels, functioning, and adverse effects.

With all the information collected, the physician will be able to assess the patient's therapeutic response to treatment (ie, are therapeutic goals being met?), drug-related adverse events, and the patient's adherence to the treatment plan. Using the Triage Tool (Table 4), the physician will be able to reassess the patient risk of abuse and decide whether to continue or stop the treatment. If aberrant behavior is suspected, the physician should evaluate in depth its seriousness and whether it represents misuse, abuse, or early signs of addiction. Based upon this analysis, intervention may include: 1) give the patient a warning, reinforce the treatment agreement, and continue the same treatment regimen; 2) same as #1 but adjust the treatment regimen (eg, increase frequency of visits); 3) discontinue opioid therapy (see exit strategy below; without discharging the patient from their practice); or 4) refer the patient to a pain/addiction specialist for consultation or to assume care (with or without discontinuing opioid therapy).

Opioid therapy should be terminated (by carefully tapering the opioid dose) for: 1) patients who are persistently noncompliant with their medications despite efforts in treatment management; 2) patients who have not responded to opioid therapy despite appropriate opioid rotation; and 3) patients who have intolerable

side effects. Some patients respond poorly to opioids, even with appropriate titration. This has led some clinicians to chase the pain with very large doses of opioids without providing any significant benefit. Therefore, it is essential to monitor the patient closely and to discontinue opioid therapy when the benefit doesn't exceed the potential harm of opioid therapy. Physicians who become aware that their patients are involved in selling their drugs, distributing them to others for illicit use, or forging prescriptions are not obligated to report these acts to the appropriate authorities,⁷ but continuing to prescribe to patients under these circumstances constitutes a criminal breach of the Controlled Substances Act.⁶

Specific Tools for Implementing Universal Precautions

Behavioral Analysis

Although analysis of large datasets shows that certain demographic groups are more likely to be nonmedical users of prescription opioids, the differences between groups are actually small, and applying this information to an individual may lead to erroneous "profiling," because there are nearly as many exceptions as there are rules. Thus, clinicians are advised not to make snap judgments about a particular patient's risk based on age, gender, race, disease state, or the community in which they live. More useful are behaviors that span demographic differences and tend to be signs of a potential problem (Table 3). These may include displaying a sophisticated knowledge of pain medications, having an assertive personality, or making adamant demands for a particular drug, displaying no interest in diagnosis, unusual or erratic behavior in the waiting room, failure to show up for follow-up appointments, and a pattern of doctor shopping are also red flags that may signal a problem (Table 3).⁷ However, no individual behavior is an absolute indicator of drug abuse, and analyzing a patient

behavior should be performed with great circumspection and care. For instance, distinguishing pseudoaddiction (see definitions) from real addiction can be difficult and may take some time. If unsure, the physician should consult with or refer the patients to a pain specialist. If a drug-seeking behavior is identified (see criteria on Table 2), the physician may confront the patient and, depending on the response, may refer the patient to substance abuse treatment or to law enforcement (Table 3).

History of Substance Abuse

The physician should collect past and present patient and family history of substance abuse and mental illnesses. This information is collected both in a subjective and objective manner, when possible. For instance, a questionnaire (Table 2) should be used to ask the patient whether he/she is using illicit drugs. An objective examination of the patient for signs of drug abuse (eg, needle scars) may prove useful, though positive findings tend to be uncommon.

Urine Toxicology

Many nonmedical drug users are very proficient at masking overt signs of abuse. In a study of patients on long-term opioid therapy who had no aberrant behaviors suggestive of abuse, urine toxicology revealed a high rate of positive urine toxicology.²⁶ Thus, urine drug monitoring provides an important adjunct to the identification of individuals using illicit and nonprescribed drugs, or prescribed drugs from another source. For consistency of results, urine toxicology should be performed using the same laboratories, as methods among laboratories may differ. To minimize variability, it is recommended that the physician use the same laboratory for all tests for all patients.

While the presence of nonprescribed opioids may denote opioid misuse or abuse, the absence of prescribed opioids may be a sign of lack of adherence (perhaps due to unacceptable side effects, suboptimal efficacy, or hoarding for future use), bingeing, or diversion, all of which require intervention. Thus, urine toxicology should aim at detecting not only the typical set of illegal drugs (cocaine, heroin, marijuana, and methamphetamine) but also a standard set of prescription opioid and nonopioid drugs (eg, codeine, morphine, methadone, hydrocodone, hydromorphone, oxycodone, oxymorphone, fentanyl, buprenorphine, and benzodiazepines), as well as all other opioid medications the patient is currently taking. A "no threshold" level of detection should be specified to increase likelihood of detecting prescribed medications. It is important to know drug metabolites to prevent egregious misunderstandings. For instance, hydromorphone is a metabolite of hydrocodone, morphine is a metabolite of codeine, and oxymorphone is a metabolite of oxycodone. These metabolites would be expected to show up in the urine of patients prescribed hydrocodone, codeine, or oxycodone.

Physicians should consider urine drug tests (UDTs) for most patients annually but certainly when there are suspicious behaviors. The physician should also consult with

the laboratory to correctly interpret any inconsistent results since some false positives may occur. Any inconsistent result should be discussed with the patient. The patient's explanation to an abnormal UDT should be considered in determining how to manage the finding. Each finding may dictate a different response.

Prescription Monitoring Report

To avoid being deceived by "doctor shoppers" and potential nonmedical users, the physician should obtain a PMR, if available. Prescription monitoring programs are in place in most states to monitor the prescription of scheduled drugs, including prescription opioids. Physicians may obtain PMRs by contacting their state's Health Department. The PMR lists the physicians and pharmacies that have prescribed or dispensed opioid medications to a patient in the past and thus are primarily used to detect doctor shoppers. PMRs include prescription details such as drug name, dose, and number of days of supply for all prior and current opioid medications. PMRs should be interpreted with caution as they may contain errors; for instance, a prescription may be attributed to the wrong individual, or may be missing from a report. Thus, PMR data revealing unexpected prescriptions or questionable activity should be verified (by contacting the other prescribing physicians) before taking action.

Questionable motives (eg, doctor shopping, abuse, or diversion) are often suggested when a patient has obtained prescription opioids from several prescribers and several pharmacies.²³ There is currently no consensus as to what threshold number of prescribers and pharmacies indicate inappropriate behavior. A low threshold such as ≥ 2 doctors and ≥ 2 pharmacies is likely to identify most doctor shoppers, but will most likely include many patients who have appropriate behavior; a patient may have used ≥ 2 doctors and ≥ 2 pharmacies because he/she has moved, has seen different doctors in different settings (eg, physician's office, hospital, clinic), has various conditions or interventions (eg, cancer, back pain, surgery) managed or performed by different physicians. A high threshold such as ≥ 10 prescribers and ≥ 10 pharmacies is likely to indicate inappropriate behavior in most if not all cases, but will probably miss cases of inappropriate behavior (high specificity, low sensitivity). According to experienced clinicians, the use of ≥ 4 doctors and ≥ 4 pharmacies is an acceptable indicator for inappropriate behavior.²³ Notwithstanding these arbitrary limits, the most useful approach is to inquire about any other prescriptions written for controlled substances (especially opioids) and determine the merits of those on an individual basis. The PMR should be interpreted in the context of a complete patient assessment, including the patient's history of substance abuse, physical examination, a follow-up assessment, urine toxicology, evidence of early refills, pill counts, review of outside medical records, consultation with other physicians who prescribed opioid medication to the patient, consultation with a pain specialist, and interviews with significant others (spouse, family). Depending on the case,

Table 5. ARFs and ADFs in Clinical Development; Status as of April 2009

TRADE NAME	OPIOID	COMPANY	DESIGN/RATIONALE	DATA SUMMARY/CLINICAL STATUS
ARFs (use physical barriers to resist tampering)				
New OxyContin	Oxycodone	Purdue	Hard plastic polymer rendering the tablet difficult to crush or dissolve	Presented to FDA in May 2008. Was not approved for the market
Remoxy	Oxycodone	Pain Therapeutics & King Pharmaceuticals	Highly viscous liquid intended to resist crushing, dissolution, injection or inhalation	NDA submitted in June 2008
COL-003	Oxycodone	Collegium Pharmaceuticals	Waxy excipient reported to resist chewing, crushing, and boiling	No published study
ADFs (use chemical barriers to deter abuse)				
Embeda	Morphine	King Pharmaceuticals	Contains sequestered naltrexone (an opioid antagonist); naltrexone is released when product is crushed, blunting the effects of morphine	Intact Embeda: -Provides similar levels of morphine than morphine sulfate -Provides undetectable naltrexone levels -Has low C _{max} and long T _{max} for morphine Crushed Embeda: -Releases naltrexone and morphine in vivo -Has high C _{max} and short T _{max} for morphine but is less desirable than morphine sulfate because naltrexone blunts morphine euphorogenic effects
ELI-216	Oxycodone	Elite Pharmaceuticals	Contains sequestered naltrexone (an opioid antagonist); naltrexone is released when product is crushed, blunting the effects of morphine	Crushed ELI-216 induces less euphoria than crushed ER oxycodone because naltrexone blunts the euphoria of oxycodone
Formulations that are both TRF and ADF				
Acurox	Oxycodone	King Pharmaceuticals	Contains an aversive agent (niacin) that causes unpleasant effects when injected, inhaled, or taken orally in high doses	Swallowing excess product causes unpleasant effects, ie, flushing Converts to a viscous gel in common solvents

Abbreviations: ADF, abuse deterrent formulations; TRF, tampering-resistant formulations.

options of action include consulting with or referring the patient to a pain specialist, continuing treatment under very strict monitoring, discontinuing opioid treatment (switching to nonopioid therapy), or referring the patient to law enforcement.

Abuse-Resistant and Abuse-Deterrent Formulations (ARFs and ADFs)

Rationale for ARFs and ADFs

New opioid formulations designed to deter or prevent medication abuse and/or tampering have been recently developed. When prescribed in the context of universal precautions, these formulations should provide an additional barrier to prescription opioid abuse. These formu-

lations may be categorized according to their design. ARFs use a physical barrier (resisting alterations) that makes it difficult to tamper with or extract the core opioid, or renders the tampered tablets unsuitable for injecting or snorting. ADFs deter misuse or abuse by pharmacologically modifying the formulation ("chemical deterrent") such as adding another compound that decreases or prevents reward or induces an aversive effect. For instance, some ADFs contain aversive agents (eg, niacin) that will cause an unpleasant reaction if taken in high doses, even if the formulation is not tampered with; other formulations use an antagonist (eg, naltrexone) that cancels the active drug's effect if the formulation is tampered with.

Table 5 summarizes the various formulations in development with their rationales and development status.

Formulations in Development

Several ARFs (also referred to as tamper-resistant formulations) and ADFs are in late phase of clinical development and may soon become available to physicians. The formulations described below are in phase 3 of development.

New OxyContin formulation

Purdue Pharmaceuticals is developing a new formulation of OxyContin that uses a hard polymer.¹¹ This renders the tablet difficult to crush or grind and to dissolve in common solvents even if milled mechanically. Even if breaking the tablet is achieved, tablet fragments retain some controlled-release properties. Also, hydration of tablet fragments results in a viscous gel that inhibits extraction of the active ingredient for injection. The formulation was presented to the FDA on May 7, 2008 but has not yet received market approval.¹² No studies on this formulation's abuse-resistance properties have yet been published or presented in a peer-reviewed setting.

Remoxy

Pain Therapeutics and King Pharmaceuticals are developing Remoxy, a long-acting formulation of oxycodone contained in a highly viscous liquid formulation matrix. The capsule is intended to resist abuse by crushing, freezing and crushing, or by dissolving in water, alcohol, or other common liquids. The gel is a viscous mass of sucrose acetate isobutyrate, like taffy, that is difficult to snort or inject.⁴³ No studies on this formulation's abuse/tamper-resistant properties have been published or presented in a peer-reviewed setting but a randomized phase-3 efficacy trial in moderate-to-severe osteoarthritis showed Remoxy provided superior pain relief over placebo.¹³ A New Drug Application (NDA) was submitted for Remoxy on June 10, 2008. The FDA requested additional nonclinical data for their review.

COL-003

Collegium Pharmaceutical is developing COL-003, an extended-release formulation of oxycodone. Particles of oxycodone are formulated in a waxy excipient base (DETERx technology) and encapsulated. Crushing/chewing COL-003 reduces particle size, but the formulation retains its sustained-release properties. The pharmacokinetics of intact COL-003 are similar to that of OxyContin. Moreover, chewed COL-003 particles display pharmacokinetics characteristics similar to that of the intact product. In addition, COL-003 does not provide a fast and high level of drug in the bloodstream,¹⁰ which many researchers believe would make the chewed particles less appealing to reward-seeking nonmedical users.

ALO-01/Embeda

King Pharmaceuticals is developing ALO-01/Embeda, an extended-release formulation of morphine combined with sequestered naltrexone, a morphine antagonist. ALO-01 comes as a capsule filled with pellets, each containing a naltrexone core surrounded by morphine. The principle of the ALO-01 formulation is that when intact

ALO-01 is ingested orally, morphine is absorbed but no or little naltrexone is released because naltrexone is sequestered by a nonporous membrane. But if ALO-01 is crushed and ingested orally or snorted (or crushed, dissolved, and injected), naltrexone is released and counteracts the euphoric effects of morphine.²¹

Several studies have been conducted to demonstrate the abuse-deterrent properties of ALO-01. The first study showed that ALO-01 and extended-release morphine provide similar levels of morphine and that most patients receiving intact ALO-01 have undetectable levels of naltrexone.²⁴ Another clinical study demonstrated that crushing and ingesting the ALO-01 capsules yields concentrations of plasma naltrexone similar to that of immediate-release naltrexone,¹⁹ which demonstrated that naltrexone is successfully released when the capsule is altered. A third study evaluating the pharmacokinetics and abuse liability of ALO-01 compared with morphine showed that ingestion of crushed ALO-01 capsules results in plasma morphine pharmacokinetics similar to that of oral IR morphine. The study also showed that intact or crushed ALO-01 capsules are significantly less desirable to recreational opioid users than immediate-release morphine. A multicenter randomized trial in moderate-to-severe osteoarthritis showed ALO-01 was as effective as an active comparator in relieving pain.²⁴ An NDA was submitted for ALO-01 capsules on June 30, 2008.

ELI-216

Elite Pharmaceuticals is developing ELI-216, an extended-release formulation of oxycodone containing sequestered naltrexone. ELI-216 is similar in design to ALO-01 except that in ELI-216 capsules oxycodone and naltrexone are in separate pellets. Because the naltrexone pellets are nonporous, naltrexone is not released when the capsule is ingested whole (intact); naltrexone is only released when the capsule or pellets are crushed. Elite has conducted a study that successfully demonstrated the euphoria-blocking effects of ELI-216: subjects (n = 17) dosed with crushed ELI-216 reported a much lower level of euphoria during the first 3 hours than those dosed with crushed oxycodone hydrochloride extended-release capsules (average peak euphoria: <10 vs 71 [0–100-mm scale], respectively).⁹ Elite Pharmaceuticals is currently conducting a phase-3 study to evaluate the safety and efficacy of ELI-216 in patients with osteoarthritis.

Acurox

Acurox is an immediate-release formulation of oxycodone containing niacin. Niacin causes unpleasant effects such as flushing, itching, and sweating. The formulation is designed to cause these unpleasant effects if an excess number of tablets is swallowed, but to result in no unpleasant effects at the recommended dose.²⁷ The formulation is designed to convert to a viscous gel (making it less desirable for injection or snorting) when subjected to common solvents. No data on this formulation have been published or presented in a peer-reviewed setting.

Conclusion

The undertreatment of pain is a crucial public health problem confounded by the problem of opioid abuse. We submit that it is possible to safely expand the use of opioid therapy to patients whose pain need to be managed while reversing the trend of prescription opioid abuse by systematically implementing universal precautions in routine clinical practice. As new tools such as ARFs and ADFs become available, these can be smoothly integrated into practice as an added component of universal precautions. While it may be impossible to prevent all abuse or diversion, the absence of any systematic approach to risk management in day-to-day practice has detrimental effects on legitimate patients and the public health at large.

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The universal-precautions approach needs to be tested prospectively to determine its effectiveness and limitations, but the magnitude of the dual problems of undertreated pain and prescription opioid abuse demand immediate attention, and we as a society cannot afford to wait to adopt such a sensible and actionable strategy.

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