Comprehensive Review

Prescription Opioid Abuse in Chronic Pain: An Updated Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse (Part 2)

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Chronic pain and prescription opioid abuse are extremely prevalent in the United States and worldwide. The consequences of opioid misuse can be life-threatening with significant morbidity and mortality, exacting a heavy toll on patients, physicians, and society. The risk for misuse of prescribed opioids is much higher in patients with chronic pain, especially those with concurrent substance use and /or mental health disorders. Several reasons can account for the occurrence of opioid abuse and misuse, including self-medication, use for reward, compulsive use related to addiction, and diversion for profit.

There is a need, therefore, for therapeutic approaches that balance treating chronic pain, while minimizing risks for opioid abuse, misuse, and diversion. Chronic opioid therapy for chronic non-cancer pain has seen a dramatic increase throughout the past 2 decades in conjunction with associated increases in the abuse of prescribed opioids and accidental opioid overdoses. Consequently, a validated screening instrument that provides an effective and rational method for selecting patients for opioid therapy, predicting risk, and identifying problems once they have arisen, could be of enormous benefit in clinical practice. An instrument as such has the potential to attenuate the risk of iatrogenic addiction. Despite the recent introduction of various screening strategies and instruments, no single test or instrument can reliably and accurately predict those patients unsuitable for opioid therapy or pinpoint those requiring heightened degrees of surveillance and monitoring throughout their therapy. Current opioid abuse screening tactics include assessing premorbid and comorbid substance abuse; assessing aberrant drug-related behaviors; stratification of risk factors; and utilizing opioid assessment screening tools. Several authors have contributed numerous screening tools and instruments to aid the assessment of appropriate opioid therapy. Additional essential measures include urine drug testing, prescription practice monitoring programs, opioid treatment agreements, and implementing universal precautions. Presently accepted recommendations consist of a combination of strategies designed to stratify risk, to identify and to understand aberrant drug-related behaviors, and to tailor treatments accordingly.

This manuscript, Part 2 of a 2 part update, builds on the 2012 opioid guidelines published in *Pain Physician*, and the 2016 guidelines released by the Centers for Disease Control and Prevention. It reviews screening, monitoring, and addressing opioid abuse and misuse in patients with chronic non-cancer pain.

Key words: Opioids, misuse, abuse, chronic pain, prevalence, risk assessment, risk management, drug monitoring, aberrant drug-related behavior

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4.0 Screening for Opioid Abuse Potential

A patient's risk of drug abuse must be assessed prior to the start of opioid therapy. The majority of risk-assessment tools revolve around previously discussed risk factors, as well as the presence of aberrant behaviors. While many screening tools have been developed specific to opioid risk assessment, none has

been fully validated across numerous populations and settings. There currently does not exist one single procedure or set of predictor variables capable of identifying patients with chronic pain who are "at-risk" for opioid misuse or abuse.

External sources of information, such as testing of biologic material (e.g., urine), interviews with spouses and family members, review of medical records, payer opioid prescription data, and prescription monitoring program input can be reliable sources that enhance the assessment and management of patients. Before starting opioid therapy, clinicians must take certain basic steps to prevent opioid abuse: distinguish individual opioid abuse risk factors; screen patients' potential for addiction and abuse during their initial visit; categorize patients in accordance with their level of risk and implement an appropriate level of monitoring; and refrain from judgments before a thorough assessment. Combining the above strategies with point of care urine drug testing (UDT) as a confirmatory tool have been shown to contribute significantly to the identification of inconsistencies (1).

4.1 Assess Pre- and Comorbid Substance Abuse

A small number of "at risk" patients with pain, who are opioid-naive and might potentially abuse their therapeutically appropriate opioid analgesics, can be identified by a clinical evaluation for substance use and psychopathology (2). Factors that have previously predicted abuse in one prospective study were age, past cocaine abuse (odds ratio [OR], 4.3), drug or driving under the influence (DUI) conviction (OR, 2.6), and past alcohol abuse (OR, 2.6) (3). Other indications of abuse potential may include daily nicotine use, illicit drug use in the past year, obesity, and long-term use of benzodiazepine and benzodiazepine-related drugs such as zolpidem (Ambien™), zaleplon (Sonata®), and eszopiclone (Lunesta®) (4,5) Related to this increased risk associated with concurrent benzodiazepine prescribing, health providers are strongly advised to avoid prescribing opioid pain medication to those patients using benzodiazepines (4). Dowell et al (4) recommend clinicians consider prescribing naloxone when there are present risk factors for opioid overdose (substance use disorder, higher opioid dosages: > 50 morphine milligram equivalents/d, concurrent benzodiazepine use).

Patients with a history of alcohol or cocaine abuse and alcohol or drug-related convictions require more intense assessment and follow-up for signs of misuse if opioids are prescribed. In addition, "at-risk" patients can be managed with prescriptions of small quantities of opioids meant to last for a few days, e.g., weekly prescriptions. Similarly, patients with comorbid psychiatric disorders and chronic non-cancer pain (CNCP) may benefit from a slower than normal titration of opioid doses, with the patient's mood and functioning closely monitored (6). Further recommended practices include prescribing less powerful medications such as noncontrolled prescription adjuvants when possible, and establishing a controlled substance agreement (pain contract) signed by the patient, a witness, and the practitioner (7).

4.2 Aberrant Drug-Related Behaviors

Because not all aberrant behaviors have the same origins or implications, it has been suggested that physicians must consider a differential diagnosis and tailor therapy accordingly (8). A review of data from opioid-tolerant patients participating in clinical studies of fentanyl buccal tablets for breakthrough pain revealed that 11% had aberrant behaviors related to fentanyl buccal tablets, and 6% had aberrant behaviors that were not (9).

Opioid misuse in and of itself may present in diverse, aberrant drug-related behaviors such as requests for early renewals, reports of lost or stolen prescriptions, observable intoxication or withdrawal, demanding behaviors, or failure to respond to treatment (10). Some patients may exhibit aberrant drug-related behaviors because of inadequate pain relief, including drug hoarding, escalating doses without physician approval, arguing combatively for more drugs, and other forms of noncompliance. Once appropriate pain relief has been established, these behaviors tend to abate. Among adolescents with a history of prescription opioid misuse, the most prevalent motives were "to relieve pain" (84.2%) and "to get high" (35.1%) (11). Forging prescriptions, stealing or borrowing drugs, frequently losing prescriptions, and resisting changes to medications, despite adverse effects, are more predictive of opioid misuse (12).

Prescription shoppers and patients with chronic nonmalignant pain problems are the main people comprising a limited but difficult group. The most sought-after drugs include opioids and benzodiazepines (13). Participants in a study by Morasco and Dobscha (13) with a positive history of substance use disorder reported borrowing medications from others at a significantly higher rate than those without a history of substance use disor-

der (OR = 6.62, 95% confidence interval [CI] = 1.4-30.7). This same patient group also requested early refills of pain medication more frequently than those without substance use disorder (OR = 3.86, 95% CI = 1.5-9.6).

4.3 Stratification of Risk Factors

The purpose of stratifying patients into risk categories is to determine the intensity and frequency of monitoring and clinical vigilance for all patients based on their risk of drug abuse. Risk stratification should not be used to deny pain treatment for high-risk patients. Every patient must be monitored to the minimal level, at the very least. Monitoring intensity should increase proportionately as the patient's risk level ascends from low to medium or high risk. Physicians must be empathetic, caring, and nonjudgmental, but also be willing to set and implement treatment boundaries. Hence, the physician is responsible for establishing realistic treatment goals for patients prior to treatment (4). If said treatment goals, at any point, become unattainable, the physician should strongly consider discontinuing opioid therapy as therapy should only be used when there is substantial improvement in pain and benefits outweigh risks (4). The clinician should remain aware, however, that recent research calls into question the efficacy of risk stratification, as no empirical evidence currently exists to support its use (14).

Low-risk patients do not exhibit past or present histories of personal or family substance use disorder (SUD). They also display no or a minimal co-occurring psychiatric disorder. A primary care provider may manage these patients. The level of monitoring would be routine follow-up (e.g., every 3 months) unless there is a change in pain, function, or mood, or evidence of misuse.

Moderate risk patients display either a past personal or family SUD history, as well as a moderate co-occurring psychiatric disorder. Patients in this category warrant co-management by specialists (addiction medicine or behavioral health specialists) and a primary care provider. Office visits should occur more frequently (monthly), and should consist of audits of their medical record (emergency department [ED] visits, doctor shopping), UDT, and pill counts until improvements in their risk status are seen.

High risk patients actively exhibit addiction or abuse disorders with either opioids or illicit drugs and/or display a co-occurring significant and unstable psychiatric disorder. These patients must be referred to interdisciplinary pain centers, an addictionologist, or a behavioral health center.

It is clear that all patients should receive monitoring. As patients' risk levels heighten from low to moderate or high risk, the magnitude of monitoring must increase proportionately. White et al (15) developed models using data from medical as well as prescription drug claims to distinguish patients at risk for prescription opioid abuse or misuse. Over a 12-month period, they concluded that abuse and misuse of prescription opioids were related to these factors: male gender; persons aged from 18 to 24 years old; patients that received 12 or more opioid prescriptions; early refills of opioid prescriptions; filling prescriptions from 3 or more pharmacies; escalating hospital visits; high numbers of outpatient psychiatric visits; increasing dosages of morphine; diagnoses of one of the following: nonopioid substance abuse, depression, posttraumatic stress disorder, and hepatitis.

To assist in the ongoing development of the patient-centered medical home model of care, which uses risk factor stratification and management, there has been an effort to embed into the electronic health record system a computerized decision support system based on expert consensus guidelines on chronic opioid therapy (COT) for CNCP. This support system would serve as a guide to decision-making when prescribing opioids (16).

4.4 Opioid Assessment Screening Tools

To help patients and providers navigate the challenges of COT and optimize therapy, the authors advise a strategy of frequent re-assessment of safety, efficacy, and misuse in patients on opioids to inform treatment decisions. To date, however, there is no widely accepted instrument or protocol to facilitate this monitoring strategy. Several opioid-specific screening tools are available for screening and monitoring of abuse. Many screening tools contain items on personal and family history of addiction and other risk factors such as age, sexual abuse, and psychological disease (17,18,19-39). The risk factors found in these tools are consistent with the literature on risk factors of opioid abuse, which suggest that younger age, anxiety, and depression are associated with greater risk for opioid misuse (40). Pain management claims several specialty-specific tools, while several other tools evaluate general addiction risk factors. A number of these tools are designed to aid in screening prior to starting COT, while others are useful for longer term monitoring of COT patients. A primary benefit of opioid assessment screening tools (OAST) such as the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) may be to

help clinicians identify the patients at low risk of addiction or misuse, and therefore use fewer resources to monitor them (6). OASTs exist in several formats, such as the Spanish SOAPP-R, which may be useful for clinicians who prescribe opioid therapy to patients whose preferred language is Spanish (41).

Passik and Weinreb (19) described a mnemonic for following relevant domains in patients with chronic pain on COT. The so-called 4 A's (analgesia, activities of daily living, adverse events, and aberrant drug-taking behaviors) reflect significant domains in monitoring these patients over time; however, it has not been validated in large studies (19). These instruments aid clinical decision making and, although they are strongly predictive of moderate to severe aberrant drug-related behaviors in patients who receive COT, they should not be viewed as necessarily diagnostically accurate (41). Several questionnaires are yet to be validated, and the psychometric properties of these instruments are considered to be weak (42). Selecting the proper tool requires the physician to have enough time, expertise of the available tools, and understanding of the clinical situation. Patients may encounter difficulties in format when completing and comprehending OASTs independently, such as reading comprehension and linguistic problems, and may in the end require assistance (19). The considerable length of other instruments renders them impractical for use in hectic clinical situations. Self-report tools may be manipulated by the patient, and substance abusers attempting to deceive health care providers may evade detection when using these instruments. Furthermore, aberrant behavior is not adequately explored by these tools while receiving treatment. With regard to feasibility, the main limitation was the length and respondent burden of the available instruments. As most opioid therapy is prescribed in general medical settings, monitoring must be brief to account for the reality of competing demands (43). The clinician should bear in mind that screening tools by themselves do not suffice to identify high risk patients, and a thorough personal and family history that includes substance abuse, psychiatric conditions, and sexual abuse should always be conducted irrespective of the use of screening instruments (44).

5.0 Monitoring Patients for Opioid Abuse

The pervasiveness of opioid abuse in the United States has necessitated that all patients receiving opioids for chronic pain be assessed frequently to assure the safety and efficacy of therapy. Current recommendations consist of intermittent adherence monitoring in order to identify any ongoing drug use and adverse effects related to therapy; justify ongoing treatment; evaluate compliance; investigate misuse and abuse; identify patient and physician responsibilities; and ensure sound and proper pain management (45,4,46). The frequency and intensity of monitoring are individualized and guided by risk stratification. Low risk patients receiving consistent opioid dosages may be monitored at 3 to 6 month intervals, while individuals at high risk of abuse require more frequent and focused monitoring. Routine monitoring sessions should include assessment and documentation of several factors, including the patient's severity of pain, psychological health, progression of treatment goals, ability to function, adverse effects, substance abuse and misuse, and any aberrant behavior related to drugs. External sources may be used to supplement information gleaned from monitoring sessions by providing data such as biological material tests (e.g., urine), family or caregiver interviews, medical record reviews, payer opioid prescriptions, and prescription monitoring program input; these sources and more can and should be utilized if helpful. Prescription Drug Monitoring Programs should also be used as a surveillance tool for those who are at high risk for abuse. Physicians should monitor inappropriate drug dosages, concurrent benzodiazepine use, and other dangerous combinations that increase the risk for overdose at regular intervals, ranging from every prescription to once every 3 months (4) .

Recent studies indicate that the implementation of prescription drug monitoring programs consisting of the aforementioned measures have helped to modestly ameliorate not only opioid abuse, but also excessive opioid prescribing (47,48). Nevertheless, adequate prescription monitoring mechanisms at the systems level remain inadequate or lacking. The detection of prescription drug misuse requires adept clinical skill and long-term observance of patients' behavioral patterns.

5.1 Screening Tools for Opioid Assessment

Numerous instruments have been designed to detect opioid therapy patients' aberrant drug-related behavior, but none have been adequately tested or are reliable and practical to administer to primary care patients receiving or being considered for long-term opioid therapy. Current screening tools generally consist of brief standardized questionnaires aimed at identifying putatively aberrant drug-related behaviors considered

predictive of addiction risk. Of note, these tools remain wholly unregulated by the Food and Drug Administration (FDA) or other authorities (49). Very little evidence exists pertaining to the prediction and identification of aberrant behaviors related to drugs; studies do not purvey standardized definitions of aberrant drug-related behaviors across the board and fail to recognize the severity of identified behaviors. Published questionnaires and protocols for interviews generally display quite frail psychometric properties and have yet to face scrutiny consistent with the practice of evidence-based medicine, unlike other accepted examination methods and protocols (50,51,52-55,56-58). What's more, methodological shortcomings limit the majority of studies evaluating these instruments (42).

Before beginning COT, one adequate screening tool with sufficiently high-quality deviation is the SOAPP-R, which may be implemented in combination with a thorough clinical assessment (59). It is suggested that OAST should be used, jointly with other measures, to guide and monitor therapy. Recommended screening tools with face and construct validity in addition to compelling content include the Pain Assessment and Documentation Tool and Current Opioid Misuse Measure (45). Guided by the "4 As," the Pain Assessment and Documentation Tool is yet another uncomplicated charting instrument developed to ensure regular long-term documentation over a variety of important domains (27,60).

Nine studies (n = 1,530) were evaluated by Chou et al (45,61) for screening tool correctness in detecting aberrant drug-related behaviors in CNCP patients on long-term therapy with opioids. Not a single investigator was blinded to the study results of the screening tools, and considerable discrepancies exist across the studies in regards to the type of aberrant drug-related behavior under examination. Out of the 9 studies, only 2 utilized the Pain Medication Questionnaire when dispensing evaluations. Eight instruments in total were studied: 2 were self-administered, interviewers proctored 4 of the instruments, and 2 studies failed to report the methodology behind their instrument. Only one study reported pain scores, and all of the investigations failed to document opioid dosages. One better-run study reported the use of the self-administered Current Opioid Misuse Measure to establish their instrument's diagnostic parameters, reporting a sensitivity of 0.75 (95% CI, 0.63-0.84) and specificity of 0.73 (95% CI, 0.65-0.80) (62). In a lower quality study, the interviewer-administered Addiction Behavior Checklist showed a sensitivity of 0.88 and specificity of 0.86 (35). Screening instruments in 4 studies showed poor diagnostic accuracy. Brown et al (63) set out to evaluate the potential for and incidence of aberrant drug-related behaviors among patients with chronic, moderate-to-severe pain in a primary care setting and to determine investigator compliance with the universal precautions approach to pain management and risk assessment. The study showed that although most patients in these primary care study centers were categorized as at least moderate risk for opioid misuse/abuse at baseline, there was an overall tendency for investigators to assign lower risk levels than those that were protocol-specified, thus suggesting a need for better understanding of factors influencing investigator decisions (63).

Atluri and Sudarshan (24) developed a tool to detect the risk of inappropriate use of prescription opioids in patients with chronic pain. The tool was developed for use in interventional pain management settings. Six clinical criteria were identified to predict opioid abuse:

1. Focus on opioids
2. Opioid overuse
3. Other substance abuse
4. Low functional status
5. Unclear etiology of pain
6. Exaggeration of pain.

Totaling the positive criteria establishes a score that ranges from 0 to 6; a score of 3 or more is predictive of abuse. A score above the 3 point cutoff is given to patients with a history of opioid misuse. A score of 3 or more, as reported by a retrospective study analyzing patients with CNCP receiving opioids, was indicative of abuse (OR 16.6; 95% CI: 8.3-33 and $P < 0.001$). These criteria formed the foundation of criteria utilized by Manchikanti et al (21) in a 500 patient prospective study. They revealed that one-fifth of patients in an interventional pain management setting (100 out of 500) had a history of drug abuse. The authors determined this was a cost-effective and reliable tool for screening drug abuse potential for interventional pain management that effectively predicted substance abuse but failed to sufficiently detect illicit drug use (25).

5.2 Urine Drug Testing

A noninvasive, inexpensive, and accurate monitoring strategy, urine screening is capable of detecting the majority of drugs for 1-3 days postexposure. Treatment compliance is confirmed by objective analysis by possible exposure of misuse and abuse of drugs in patients receiving treatment with opioids. Illicit drugs

like cocaine and heroin, as well as nonprescribed controlled substances are detectable by UDT (e.g., a patient prescribed oxycodone testing positive for hydromorphone). Self-reports of drug use, prescribed or illicit, by patients with chronic pain receiving opioids are frequently unreliable. Behavior monitoring alone for patients receiving treatment with opioids fails to identify potential problems revealed by UDT; one-fifth of patients purportedly adhering to their opioid regimen as prescribed by clinical experts tested positive for an illicit drug on urine screen (38,39).

In another practice, abnormal UDT results triggered referral to behavioral health and addiction medicine specialists in 40% of patients and assisted with detecting drug abuse or addiction in 19.6% of patients (64). Recommendations thereby maintain that routine urine drug screening should be employed in order to monitor patients receiving opioid therapy regardless of the presence or absence of signs of drug misuse. The proper practice of pain management must include UDT results as one facet of the complete clinical strategy, especially considering the occasional false-positive and false-negative. Furthermore, several compounds evade detection by standard urine screenings, necessitating the use of expensive and specific urine, hair, or blood tests (65). In spite of the wealth of data supporting urine screens, UDTs remain the exception, rather than the norm, in most opioid therapy monitoring programs.

A survey conducted at the 2008 American Congress of Pain Medicine uncovered extensive inconsistency behind attendees' motives for urine screening and criteria for testing; practitioners more often utilized urine screens in an effort to reveal undisclosed substances, and seldom employed them to assess opioid treatment compliance. A number of respondents never performed urine screens on patients receiving opioids. Two-thirds of respondents reported no formal training in the use of urine screens for patients receiving opioid therapy. The majority responded to performing random urine screens rather than scheduled ones, and limited protocols for urine testing existed (66).

Some respondents never tested the urine of their opioid patients, and about two-thirds of respondents had no formal training in urine testing of patients on opioid therapy. Most respondents did random, rather than scheduled, testing and few had any urine testing protocol (66). Christo et al (67) extensively reviewed the role of UDT in adherence monitoring and recommended an algorithmic approach based on well-controlled diagnostic accuracy trials (68,69).

Along with a more standardized approach to UDT implementation, there is also a glaring need to enhance the current methods for optimizing treatment after aberrant UDT results are obtained. In Morasco et al's (70) retrospective cohort study of 83 participants who were prescribed COT and had a UDT result that was positive for an illicit or nonprescribed substance, plans to modify treatment were documented in 69% of cases, with the most common treatment change after aberrant UDT results being the institution of more frequent UDTs, which occurred in 43% of cases. Clinicians documented plans to alter their opioid prescribing (e.g., demanding fills more frequently, altering doses of opioids, discontinuing opioids, or shifting to alternate opioids) in 52% of cases, but implemented these changes in only 24%. These results seemingly indicate that for the UDT to be of some utilitarian benefit in curtailing prescription opioid misuse, additional interventions and support measures to guide clinicians on how to tailor their clinical care for patients prescribed COT with subsequent aberrant UDT are needed (70).

5.3 Monitoring of Prescribing Practices

Passik and Kirsh (71) developed an original method of opioid prescribing named "in and out of the box" prescribing. These authors suggested that clinicians compare their own patterns of opioid prescribing to their peers' at regular intervals. "In the box" prescription patterns align comparably with the overall methods of the majority of opioid analgesic prescribing physicians, while "out of the box" methods vary considerably. "Out of the box" does not automatically disqualify it from proper practice; rather, sound reasoning must justify its use. This model is meant to notify physicians when their practice deviates from the mean, thereby influencing a decision to heighten documentation protocols. Areas that suggest "out of the box" prescribing include the type of pain condition where opioid use is controversial (e.g., headaches), an active psychiatric condition (e.g., depression, bipolar disorder, substance use and misuse disorders, disorders of impulse control), younger age, interaction with nonmedical users, as well as prescribing more than 180 mg/d of morphine equivalents. The upper dose limits for appropriate treatment of CNCP is recommended by consensus to lie between 180 to 200 mg morphine equivalents per day (45,72). It is suggested that the "out of the box" opioid therapy group should be carefully reevaluated for any change in their medical or social condition and/or a consultation with a pain specialist should be obtained to identify the fac-

tors that led to "out of box" prescribing. Some of the therapeutic strategies that may work include opioid rotation, multidrug therapy (nonsteroidal anti-inflammatory drugs [NSAIDs], anticonvulsants, antidepressants, topical analgesics), multimodal or multidisciplinary treatment with rehabilitation therapies (modalities, orthosis, exercises), behavioral interventions, injections and other interventional treatments, neuromodulatory treatments, and complementary and alternative medicine therapies (4,46,68,73-75,76,52-55,72,77-96). While this concept needs to be refined further, providers must recognize the fact that proper pain management must alleviate the patient's perception of pain while simultaneously allowing an increase in said patient's functional status. Multiple instances of inadequate pain control and/or a lack of improvement in ability to function warrant reconsideration of opioid analgesic therapy (72).

5.4 Payer Opioid Prescription Data

Requests for increases in opioid dosage by patients with CNCP should prompt a vigorous assessment of possible nonmedical motivations. Prescription databases and payer data checks, in concert with a thorough review of medical records, can be useful in identifying patients who receive larger than expected numbers of opioid prescriptions and the issues associated with larger prescription numbers. One rural family medicine practice's patient charts and payer opioid prescription data, reviewed retrospectively, uncovered individuals receiving 3 or more prescriptions (average 8.4; standard deviation [SD] = 5.5, range 3-28) from 2 or more providers (average 3.7; SD = 1.8, range 2-10) over a 6-month period. Compared to patients on opioids alone, those utilizing nonopioid medications for analgesia displayed 3.2 fewer prescriptions over a 6 month period and were significantly less inclined to receive 6 or more prescriptions (OR = 0.24, 95% CI = 0.08-0.73). Simultaneous nonopioid use for analgesia, an increasing number of providers, and an escalating dose of opioids best forecast the number of opioid prescriptions (97).

5.5 Prescription Drug Monitoring Programs

Prescription Drug Monitoring Programs (PDMPs) function to accumulate prescription drug data across states and monitor their movements (98,99). Three factors comprise these programs. Prescription data collection is the first; it displays the physicians and pharmacies responsible for each prescription. While the law mandates that pharmacies report this data, physicians are encouraged, but not required, to do so. A central repository fulfills the second component of a PDMP. Thirdly, adequate protocols must exist concerning the transmission of data from the central repository to the relevant authoritative agencies. Currently, 49 states, along with the District of Columbia and the US Territory of Guam have legislation authorizing the implementation of PDMPs (100). A variety of state agencies are involved with administering PDMPs in each individual state (law enforcement, professional licensing, departments of health, etc.), and as such, there is a significant difference in the manner and frequency with which the data are collected.

President George W. Bush signed into law the National All Schedules Prescription Electronic Reporting Act (NASPER) in 2005 which was created by the American Society of Interventional Pain Physicians and enacted by Congress (101). States are thereby required by this law to compile data on Schedule II, III, and IV drug prescriptions. Furthermore, states are mandated by this law to be capable of sharing data with each other. These measure allow for effective regulation of cross-border narcotic trafficking. At first, only Kentucky, Utah, and Idaho gave physicians access to programs able to monitor drug use. Currently, following the enactment of NASPER as well as funding from the Harold Rogers Prescription Drug Monitoring Program, multiple states are operating physician-friendly programs where pain physicians can identify the risk of overuse and abuse (98,99,101-105). Compliance has increased and drug abuse has fallen as a result of adherence monitoring (106-109).

5.6 Opioid Treatment Agreement

An opioid treatment agreement (OTA) is intended to relay information to patients concerning the risks and benefits of treatment with opioids, as well as establish a jointly agreed upon regimen, develop a relationship between provider and patient, enhance opioid treatment adherence via a documented therapy framework, and organize procedures in the case of problems. Frequently implemented in pain clinics, OTAs are reported to augment care by improving adherence to opioid therapy and reducing opioid analgesia misuse (106-119). Yet OTAs are controversial and questions are raised regarding their intent, elements, language and tone, readability, physician responsibility, and legal risk (110-113). Evidence to support the role of OTAs in decreasing the misuse of opioids is relatively weak; improvements to neither adherence, patient care, nor the rights of both patients and physicians have been

proven after the use of OTAs (112-114). One systematic review failed to reveal any high quality studies regarding opioid misuse outcomes in association with UDT and treatment agreements in patients with CNCP. Every study was observational and had a poor to fair grade; opioid misuse decreased slightly (7-23%) following a treatment agreement in the presence or absence of UDT (120). Suggestions from the Federation of State Medical Boards indicate the possibility of situations necessitating the implementation of a written OTA. Several states recommend and others require written OTAs. Physicians are advised to carefully inspect their individual state's policies concerning OTAs and controlled substances, and recognize the goals and procedures before developing and implementing an OTA.

In efforts to address the above mentioned shortcomings of OTAs, the FDA Safe Use Initiative recently convened a multi-disciplinary working group with outside experts to draft a patient-centered, model opioid treatment agreement named the Model Patient-Prescriber Agreement (model PPA). In a follow-up survey sent to FDA employees in the Center for Drug Evaluation and Research, the majority of the 209 respondents confirmed that the model PPA displayed a neutral tone (67.5%) as well as an easy to relatively easy understandability (90.4%). Participants in a usability study found that by and large, the model PPA would promote discussion between patient and provider, and that the subject matter thoroughly informed patients in a clear, easily understood manner. The results of these studies indicate that acceptable and usable opioid PPAs can be developed to serve a wide variety of stakeholders. A follow-up pilot study using the model PPA in medical facilities in the United States with patients is underway and will facilitate this determination (121).

5.7 Universal Precautions

The term "universal precautions" is derived from the infectious disease approach to potentially life-threatening infections which revolves around the understanding that, early on in treatment, it is nearly impossible to detect those patients infected with human immunodeficiency virus or hepatitis C virus. As a result, everyone is treated as potentially infected and the minimum appropriate level of precautions is applied to all patients. Similar to infectious disease, "at risk" patients are nearly impossible to detect in chronic pain management. Gourlay et al (116), in an effort to decrease stigma, contain risk, and enhance care for patients, proposed "universal precautions" for assessing and managing patients with chronic pain long term. Universal precautions are a unified step process including establishing a diagnosis and treating improvable etiologies as well as comorbid psychiatric syndromes; evaluation of psychological status in conjunction with addiction risk; causes including any comorbid psychiatric illness; psychological assessment including risk of addictive disorder; informed consent that includes anticipated benefits and foreseeable risks; a treatment agreement that describes the expectations and obligations of both patient and provider and also establishes appropriately set boundary limits to enable early identification and intervention around aberrant behavior; pre- and postintervention assessment of pain level and function; an appropriate trial of opioid therapy with or without adjunctive medications; reassessment of pain score and function; regular assessment of the "four A's" of pain medicine and affect; a periodic review of the pain diagnosis and comorbid conditions, including addictive disorders; and careful and thorough documentation to reduce medicolegal exposure and risk of regulatory sanction. A description of risk stratification based on a triage system was also included. Categorizing patients as low, medium, or high risk (Groups I, II, and III), made it possible to recommend to primary care practitioners those patients whom they might confidently manage on their own, co-manage with specialty support, or refer to specialty clinics with more experience and resources to tackle challenging cases (117-119,122,123). Reciprocal confidence and respect between provider and patient should form the foundation of universal precautions; both parties must commit to accomplishing attainable goals if the fight on both cancer and noncancer pain is to succeed.

A 10-point method for COT management is illustrated in Table 1 as described by Trescot et al (17) and Manchikanti et al (18).

6.0 Tackling Opioid Abuse and Diversion

Poisoning deaths account for the second most common cause of unintentional injury death for all ages in the United States, surpassed only by motor vehicle crashes (124). Opioids are safe medications for the treatment of acute and chronic pain if appropriately prescribed and monitored (125). However, over recent years the number of prescriptions filled for opioids has increased dramatically, and in the same proportion as the misuse, abuse, and diversion related to nonmedical opioid consumption (122,126,127).

Recently, pharmaceutical opioids have been considered the primary cause of overdose death in the United States (128). In 2011, the US Office of National Drug Control Policy addressed the pharmaceutical drug abuse epidemic by aiming to achieve a 15% reduction in illicit use of pharmaceutical opioids and a 15% reduction in overdose deaths over the next 5 years (129). According to the Centers for Disease Control and Prevention, the death rate related to prescription opioid poisoning has increased dramatically from 1.4 to 5.4 deaths per 100,000 persons from 1999 through 2010 (130). Furthermore, the number of visits to an ED requesting the nonmedical use of opioid prescriptions has notably increased from 172,738 in 2004 to 488,004 in 2011 (131).

As a result, the reduction of opioid diversion requires maximally effective tactics. To accomplish such goals, behavioral interventions, education, and monitoring must be incorporated into a tactical protocol (132,133). Preserving patient rights while combatting chronic pain demands rational research and focused education in order to reduce the disastrous influence of opioid abuse, overdose, and misuse.

Prescription drug monitoring programs do have the potential to attenuate diversion and abuse, but a shortage of funding on both the state and federal levels has curtailed their implementation (128). Innovative criminal justice policy changes, in association with a better understanding of drug users' concerns, may limit opioid-related adverse effects, specifically misuse, addiction, overdose, and death.

Table 1. *Ten-step process: An algorithmic approach for long-term opioid therapy in chronic pain.*

STEP I	Comprehensive initial evaluation
STEP II	Establish diagnosis ♦ X-rays, MRI, CT, neuro-physiologic studies ♦ Psychological evaluation ♦ Precision diagnostic interventions
STEP III	Establish medical necessity (lack of progress or as supplemental therapy) ♦ Physical diagnosis ♦ Therapeutic interventional pain management ♦ Physical modalities ♦ Behavior therapy
STEP IV	Assess risk-benefit ratio ♦ Treatment is beneficial
STEP V	Establish treatment goals
STEP VI	Obtain informed consent and agreement
STEP VII	Initial dose adjustment phase (up to 8-12 weeks) ♦ Start low dose ♦ Utilize opioids, NSAID's and adjuvants ♦ Discontinue • Lack of analgesia • Side effects • Lack of functional improvement
STEP VIII	Stable phase (stable – moderate doses) ♦ Monthly refills ♦ Assess for four A's • Analgesia • Activity • Aberrant behavior • Adverse effect ♦ Manage side effects
STEP IX	Adherence monitoring ♦ Prescription monitoring programs ♦ Random drug screens ♦ Pill counts
STEP X	Outcomes ♦ Successful – continue • Stable doses • Analgesia, activity • No abuse, side effects ♦ Failed – discontinue • Dose escalation • No analgesia • No activity • Abuse • Side effects • Non-compliance

6.1 Educating Patients and Providers

The need to treat pain is universal across medical specialties and primary care. In the United States chronic pain is reported by 30% of adults (aged 18 years or older) (134) which is evidence of the importance of this topic for patient care providers. Expert consensus guidelines have been adopted for pain management in many patient populations including elderly patients (135), patients with cancer (136), patients who have had surgery (18) (137), pain-related osteoarthritis (138), chronic low back pain (139), neuropathic pain (140), and cardiovascular pain (141). However, recent Canadian and US surveys based on undergraduate medical student curricula found that despite the high prevalence of opioids prescribed by US-trained doctors, medical schools provide inadequate training in pain management (142). Instructions in prescribing opioids are only accomplished by 30% of US medical schools, and 32% of Canadian medical programs (142,143). In addition, the mean number of hours devoted to undergraduate education in pain management is 11.1 hours per program in the United States (range, 1–31 hours) and 16 hours for Canadian medical schools (mean 16 hours, range 0–38) (142,143). Therefore, improving

medical school curricula is essential to not only improve pain management but also to ensure that clinicians in every avenue of pain management recognize the risk of adverse effects, abuse, and addiction with the medications they prescribe.

In 2005, the International Association for the Study of Pain published the third edition of its *Core Curriculum for Recommendations for Professional Education in Pain*; several universities have implemented pilot programs based on this curriculum (144). The formal assessment of outcomes, however, revealed only humble improvements in physician knowledge of the fundamentals of chronic pain and its treatment. Improving medical school curricula is the most effective long-term solution to this situation (145). Guidance is required for physicians to approach the problems of analgesic abuse and diversion, and curricula can aid by teaching universal precautions for monitoring patients receiving opioids. Controlled substance agreements that describe appropriate opioid regimens, expectations for opioid therapy, and protocols in the event of noncompliance are a necessary component of every prescriber's plan. Appropriate pain management training for young physicians should incorporate the necessary steps and appropriate timing to refer patients to pain specialists. The complexity of pain management calls for awareness by physicians when clinical scenarios exceed the scope of their skill. Preparing medical students to recognize such clinical situations may indeed be among the most important aspects of undergraduate training (145).

Physician education should be focused on considering a patient's risk for opioid misuse before initiating opioid therapy; recognizing that a patient is misusing and/or diverting prescribed medications; and understanding the variation in the abuse potential of different opioid medications currently on the market. Other strategies for providers include changing behavior and practice patterns, saying "no" to unreasonable patient demands, and adopting a universal precaution approach toward all patients prescribed drugs of addiction (146). In a recent Canadian study it was shown that physicians markedly reduced the quantities of opioids they prescribed after medical regulators referred them to a 2-day opioid-prescribing course. Educational methods included didactic presentations and case discussions. The course itself did not lead to significant additional reductions; however, a subgroup of physicians who prescribed high quantities of opioids might have responded to what was taught in the course (147). Therefore, interventions targeted at physicians who prescribe opioids more frequently are an important public health priority because overdose deaths are concentrated in patients of high prescribers of opioids.

Multiple factors are implicated in opioid misuse, abuse, and diversion. Among adolescents and young adult patients these include a patient's past or current mental health diagnosis (148), history of sexual abuse (149), previous substance abuse (150), or substance abuse by the patient's immediate family (151) or peer group (148). Likewise, in the adult population, the concurrent opioid use (2 or more opioids) in prescribed opioid therapy significantly increases the risks of aberrant opioid-associated behavior (152). In order to restrain opioid abuse but at the same time provide appropriate treatment for patients with pain, the patients need to be educated in the areas of safeguarding medications, disposing unused medications, and understanding the consequences of manipulating physicians and selling their medications (153).

The physician encounter that leads to a prescription for acute pain is an important teachable moment when patients and their families can be educated about their medications, side effects, and potential interactions. However, a lack of time limits the physician's ability to achieve this goal, especially in the ED (154). For example, studies of discharge instructions indicate that few patients (< 20%) are aware of what to do with unused medication (155,156). Sharing of unused opioid pills is common among patients (157,158). This contributes to diversion rates as high as 29% in young adults and college students (159).

Utah's Department of Health in 2008 added 12 questions to their state's Behavioral Risk Factor Surveillance System survey in an effort to elucidate the methods behind their residents' pursuit and use of prescription pain drugs. The results of said survey detected an estimated 20.8% of adults 18 or over in Utah had been prescribed opioid analgesics during the prior 12 months, with 3.2% of those patients admitting to taking larger and more frequent doses of their prescribed medications than their doctor recommended. Leftover medications were reported by 72.0%, and of those, 71.0% kept the drugs. Approximately 1.8% of all adults reported using prescription opioids that had not been prescribed to them.

In 2009 the Utah Department of Health released guidelines intended to diminish disability, morbidity, and mortality caused by prescription drugs like opioids. Included in these guidelines were recommendations for providers to instruct patients with resolved pain symp-

toms on the proper disposal of unused medications, as well as suggestions for prescribers to limit the amount of doses to the typical duration of severe, opioid-requiring pain for each patient's particular condition (117).

6.2 Behavioral Interventions

Patients with chronic pain who are noncompliant with prescribed opioids are commonly dismissed from medical practice. This situation is not optimal because these patients then seek treatment by going to multiple hospitals or engage in illegal activity. The end result is that individuals continue to experience poorly controlled pain and the problem of abuse and diversion remain persistent in the community (160). A randomized study was conducted by Jamison et al (161) to evaluate the benefits of close monitoring and cognitive behavioral motivational counseling in improving adherence among patients with non-cancer back pain at high risk of opioid abuse and misuse. This encouraging trial revealed the importance of motivational counseling, monthly urinary screens, and opioid adherence checklists when evaluating patients considered at high-risk for opioid misuse (161). As a result, the actual standard of care for long-term opioid therapy must include regular monitoring, a comprehensive assessment with a thorough history, a physical examination, and a mandatory opioid agreement with the patient. Individuals at increased risk of opioid misuse may benefit from more frequent visits, urine toxicology screens, use of adherence checklists, motivational counseling and pill counts (44). However, even with the recent improvement in opioid misuse and abuse detection and control, greater attention must be required on risk screening in order to mitigate the misuse of the prescribed opioids (162).

6.3 Managing Pain in Patients with Substance Abuse

Comorbidities are common among those who abuse prescription opioids: 85% or more suffer chronic pain, 55% or more have mental disorders, about 40% to 56% have concurrent alcohol dependence, and 60% or more are nicotine dependent. Additionally, patients who use illegally obtained or prescribed opioids in an effort to reconcile underlying mental health disorders may be classified as chemically coping. This condition may be considered in the middle of spectrum between frank addiction and regimen adherence. They have a tendency to focus on the pharmacologic treatment of pain and disregard nonpharmacological options for pain control (e.g., physical therapist or psychiatrist). These patients tend to utilize medications in nonprescribed manners. This may include self-medication, either by using medications when under stress as a coping mechanism, or by simply escalating their dose without consulting a physician. Although chemical copers comprise approximately 35% of patients with chronic pain, this group is not adequately studied in the literature. Abuse deterrent formulations may not be of significant benefit in this scenario; rather, these patients require psychotherapy to treat opioid misuse problems and their associated mental health conditions (163).

Patients at high risk for prescription opioid misuse who have histories positive for SUD are more likely to report pain and impairment, suffer from depression symptoms, and have current SUD compared to low risk patients. Adjusted analyses have found a significant association between prescription opioid misuse risk and pain catastrophizing (164).

Significant differences exist in opioid prescribing practices across prescriber specialties, and this may be reflective of differing norms concerning the appropriateness of opioids for the control of chronic pain (165). However, physicians of all specialties are universally "reluctant" to prescribe opioids to patients with CNCP and a history of substance abuse for fear of addiction, misuse, or diversion of the medications. In one study, individual interviews and focus groups were conducted with general practitioners, addiction specialists, pain specialists, and rheumatologists. A large number of participants expressed "distrust" that such patients indeed suffer from "genuine pain," which led to many patients being treated as guilty until proven innocent. Previous encounters with manipulative "drug seekers" provokes this negative regard towards these patients, and as a result pain continues to be undertreated in them. Several "red flags" may help alert physicians to potential prescription abuse and diversion, including doctor shopping, losing prescriptions, and early requests for prescription refills. Physicians reported different management approaches and stricter prescribing regimes for patients with a history of substance abuse to limit the potential of addiction, misuse, and diversion. Examples of poor pain management were described where drug users had been undertreated as a result of negative attitudes or the inexperience of staff (118).

Outcomes in the high risk for opioid misuse population may be improved by several methods such as universal precautions for all patients, interdisciplinary pain management, and special attention to their struc-

ture of care (119). Uncoordinated care remains one of the primary impediments to effective treatment of opioid dependence. Relapse episodes and the myriad of comorbidities to manage continue to challenge physicians as well. Considering that pain medication abusers consume significantly more health resources than nonabusers, coordination of care becomes essential for treating patients with pain. For instance, pain medication abusers present at the ED 2.3 times more frequently and are hospitalized 6.7 times more often than nonabusers. Integrated approaches to the treatment of substance abuse and pain are now being incorporated by managed care organizations, as they have come to the realization that the entire patient must be treated, and that alternative and behavioral treatments may significantly benefit the patient in addition to pharmacological therapy. Patterns of abuse are now easier to recognize thanks to the utilization of pharmacy claims data via prescription drug monitoring programs, which may be used to alert physicians to potential problems. The treatment of chronic pain necessitates the use of risk-minimizing strategies in regards to opioid dependence, and those physicians directly treating opioid dependence must optimize outcomes by implementing relevant policies. Such policies may include pain contracts, pill counts, random drug urine screenings, and establishing goals of therapy while re-evaluating patients intermittently during their treatment. Additionally, practitioners must prepare ahead of time by establishing a plan in case a patient relapses. Successfully managing patients with pain or opioid dependence requires that physicians, employers, and managed care organizations integrate their approaches into a careful, coordinated team effort (165). In addition to pharmacotherapy, behavior modification and strategies like screening, pain contracts, and prescription drug monitoring programs remain essential elements for a positive outcome (167).

6.4 Abuse Deterrent Formulations

Drug manufacturers are now developing abuse-deterrent formulations (ADFs) with the aim of either making opioid analgesics less attractive for nonoral abuse or increasing the consequences of abuse, ultimately to minimize the abuse of opioids among recreational reward-seekers (122,168). The majority of opioid abusers manipulate tablets in order to expedite intranasal, oral, or intravenous administration of the drug, while nonabusing patients tend to consume intact tablets. Several strategies have been employed by pharmaceutical companies to dissuade opioid abuse such as prevention of tablet tampering, integrating physical barriers (e.g., crush resistance), or enclosing compounds designed to render tablets noxious, inert, or unusable when altered. Much like the "magic bullet" theory behind antibiotic advancements (kill the bacteria without harming the patient), the goal of opioid analgesic reformulation is to provide a substance that is innocuous to the compliant patient but extremely difficult for the abuser to tamper with or misuse (169,170).

In January 2013, the FDA issued a draft guidance document to assist the pharmaceutical industry in developing new formulations of opioid drugs with ADF properties. The document explains the FDA's current thinking about studies designed to demonstrate ADF properties of a given formulation, how studies will be evaluated, and labeling claims that may be proposed based on study results (17). Approaches concerning ADFs currently approved for distribution include: physical/chemical barriers that confer resistance to crushing, combinations of opioid agonists/antagonists, the incorporation of aversive ingredients into opioid tablets, the use of prodrugs, and the implementation of drug delivery systems inherently difficult to manipulate by opioid abusers such as subcutaneous implants, depot injectable formulations, beads within a capsule, and erodible matrix technologies (171-173).

In 2010, the FDA approved the osmotic extended-release oral delivery system (OROS) of hydromorphone (Exalgo®, Mallinckrodt, Dublin, Ireland) for the treatment of moderate-to-severe pain in patients who are opioid-tolerant and who require around-the-clock analgesia (174). The abuse potential of OROS hydromorphone ER (extended release) was compared to IR (immediate release) by a study that revealed the ER formulation's delayed onset of positive drug effects combined with an escalated onset of negative effects lowered its abuse potential among patients with a history of recreational opioid use. The OROS hydromorphone ER tablet also contains a hard outer shell to protect it from manipulation by chewing or biting, further decreasing its abuse potential. Moreover, 24 hours of water immersion renders only 50% of the active ingredient recoverable, and milling leaves only 30% recoverable (172,175). An additional preparation creates a sequestered core of naltrexone within a small sphere of ER morphine sulfate (Embeda, Pfizer Inc., New York, NY). If crushed, the capsule releases naltrexone, thereby weakening any morphine-induced effects and increases in efficacy or decreases in abuse or misuse

potential have not as of yet been demonstrated (164).

The FDA in April of 2013 approved a reformulated OxyContin® (oxycodone hydrochloride controlled-release, Purdue Pharma, Stamford, CT) tablets (67). The federal agency determined that the reformulated product displayed abuse-deterrent properties because the tablet was more difficult to crush, break, or dissolve than the original OxyContin formulation. In addition, the physical and chemical properties of the reformulated product were expected to make the product difficult to inject and to reduce abuse via snorting (176).

One of the salient observations from the extended-release oxycodone (Purdue Pharma) post-marketing epidemiology program was that the introduction of the ADF reformulation was associated with an increased abuse of other single entity opioid analgesics including: IR oxycodone, generic ER oxycodone, and ER oxymorphone. These results are consistent with reports of patients preferring heroin or other opioid analgesics to reformulated extended-release oxycodone (120). Taken together, these data suggest that a ballooning effect is operative, in which reformulated extended-release oxycodone is being substituted with opioid analgesics more amenable to tampering and are indicative of the need for consistent application of ADF criteria to maximize the public health impact of this technology. Nevertheless, it is encouraging that the rates of abuse, misuse and accidental exposure associated with extended-release oxycodone have continued to decrease since the introduction of the reformulation, suggesting that a novel method to circumvent the ADF properties of the reformulated tablet has not become widespread. Although the development of various ADF methodologies will not likely be sufficient to prevent nonmedical opioid abuse, it must be part of a comprehensive effort that includes educational, governmental, and community endeavors such as risk evaluation and mitigation strategies (REMS) and state prescription drug monitoring and overdose prevention programs to effectively promote the safe use of opioid analgesics for the relief of chronic pain (177).

Cicero et al (178) recently utilized data from the ongoing Survey of Key Informants' Patients program, part of the Research Abuse, Diversion and Addiction Related Surveillance (RADARS) system that collects and analyzes postmarketing data on misuse and diversion of prescription opioid analgesics and heroin in order to investigate the initial abrupt fall in OxyContin abuse and considerable amount of abuse that has endured since 2012 (178). Their study reveals that the introduction of reformulated OxyContin in January 2009 significantly decreased the levels of past-month abuse when measured in June 2009 (45.1% [95% CI, 41.2%-49.1%]). However, levels remained elevated at 26.0% (95% CI, 23.6%-28.4%) when measured from July through December 2012; $P<.001$; $\chi 2=230.83$). This stagnation owed in large part to an influx of other opioids, such as heroin. Patients engaging in past-month abuse remained elevated from 2012-2014 at 25-30% of the study sample (95% CI, 23.7%-29.6%). The 88 study participants endorsing pre-ADF and ADF OxyContin can be attributed to 3 phenomena: a transition from nonoral routes of administration to oral use (38 participants [43%]); successful efforts to defeat the ADF mechanism leading to a continuation of inhaled or injected use (30 participants [34%]); and exclusive use of the oral route independent of formulation type (20 participants [23%]). It thusly appears that abuse-deterrent formulations can thoroughly curtail abuse, but the extent of their eradicative capabilities is limited by significant and persistent levels of abuse. (178). Nevertheless, these formulations are important innovations and warrant further study to assess their appropriate role as analgesics (179,180). Reducing physician concerns about potential misuse and abuse of opioids through additional education in pain management and dissemination of information about the potential benefits and availability of tamper resistant formulations should influence physicians' attitudes about and the adoption of tamper resistant formulations (181).

The FDA approved in October 2013 Zohydro™ (Zogenix, San Diego, CA), a single-entity, long-acting hydrocodone product (182). The approval was at best controversial (183,184). The controversy is based on the FDA's decision to approve it despite the recommendation of an FDA-appointed scientific advisory panel, which voted 11 to 2 against the approval of Zohydro. Multiple consumer safety organizations, health care agencies, addiction treatment providers, community-based drug and alcohol prevention programs, professional organizations, and other groups on the frontline of the opioid addiction epidemic have expressed concern and criticized the FDA's decision (185-191). In addition, the US Senate and House of Representatives, and various state attorneys general raised serious concerns about the approval of Zohydro. These concerns led to hearings in Congress along with multiple lawsuits and corrective legislation being discussed (170,192-194). However, supporters of Zohydro contend that this drug is necessary and essential to manage chronic pain and

improve functional status (186,187). Zohydro was reformulated in 2015 and designed to be abuse resistant, marking another step in the battle against opioid abuse utilizing BeadTek™, a technology that turns the drug into a viscous gel if it is crushed and dissolved in liquids or solvents. The products added are polyethylene oxide and povidone.

In 2014, the FDA approved Hysingla® ER (Purdue Pharma, Stamford, CT), another extended-release hydrocodone product. Hysingla tablets are extremely difficult to crush, to break, or to dissolve and cannot be easily prepared for injection because they form a thick gel. Hysingla uses a RESISTEC platform for extended-release solid oral dosage formulations, which uses unique polymer and processing which confers tablet hardness and viscosity when dissolved in aqueous solutions. However, these products are only expected to reduce, not completely eliminate, abuse.

To sum, certain forms of abuse, especially those involving tablet manipulation, may be incrementally improved by ADFs. Oral abuse remains far more prevalent however, and as a result it is necessary for clinicians to strictly follow the best-practice guidelines when prescribing opioids, including stratification of patients by risk level, intermittent monitoring and reassessment of patients for abuse and misuse potential, and counseling patients with information as to the risks of their medications. ADFs by themselves cannot and will not completely eradicate abuse, misuse, and diversion. They provide an additional obstacle to abusers, but clinicians should refrain from overconfidently prescribing these medications. No single formulation is intended to or indeed capable of annihilating every form of misuse and abuse. With this in mind, prescribers should not necessarily consider these products as the preferred agents for every scenario once they become available in clinical practice. Thorough patient evaluation and identification of abuse and misuse risk factors must be enforced and optimized prior to the initiation of abuse-deterrent and tamper-resistant formulations. Adequate measures for screening and monitoring must be implemented before these formulations may be considered for patients at high risk of misuse, abuse, and diversion (195).

There is no single treatment modality capable of addressing misuse, abuse, and diversion in chronic or acute pain; a multifaceted approach involving tamper-resistant opioid formulations, accurate assessments of patient risk, adequate funding for and referral to centers for addiction treatment, improved utilization of PDMPs, and heightened recognition of prescription opioid abuse is needed (196). Due to the variety of individuals exposed to opioids, an array of populations must be examined using multiple study designs in order to properly assess the abuse-deterrent potential of an opioid formulation. Any research conducted on abuse deterrence needs to incorporate studies that evaluate: abuse liability; the likelihood that opioid abusers will find methods to circumvent the deterrent properties of the formulation; randomized clinical trials calculating misuse and abuse in patients with pain who display both low and high risk of abuse; and postmarketing epidemiological studies (197).

6.5 Postmarketing Surveillance

Drugs acting upon the central nervous system require uniquely stringent surveillance due to their potential for misuse, abuse, and diversion. Behavior characteristics of these issues is often concealed, and for that reason many countries have implemented postmarketing surveillance systems in an effort to monitor for prescription drug abuse (198). In the United States, the approval and postmarketing surveillance is performed by the FDA, but similar agencies perform these functions in other countries (199,200). A postmarketing surveillance system for prescription drugs abused in the United States should include product-specific information that is accurate, immediately available, and geographically specific and includes all areas of the country.

The RADARS System is a national surveillance system that monitors the abuse, misuse, and diversion of prescription opioids. This program offer multiple perspectives on prescription drug abuse through the use of 7 unique programs that collect and report data on a quarterly basis, with geographic specificity (3-digit ZIP code level) throughout the United States (201).

Based on RADARS data, Dasgupta et al (202) published the importance of postmarketing surveillance of methadone and buprenorphine in the United States. The safety profile of buprenorphine seems superior to that of methadone in standard outpatient medicine settings. Nevertheless, certain scenarios exist during the treatment of pain and opioid addiction that call for the use of both drugs, and investigation should continue into their respective risks and benefits (202). Most producers of branded opioid analgesic products have created systems that measure abuse from multiple vantage points: criminal justice, treatment professionals, susceptible patient populations, and acute health events. In the past, the US government has not established similar requirements for the same products

produced by generic manufacturers. However, the FDA Amendments Act of 2007 includes generic opioid analgesic products by requiring that all products containing potent opioid drugs perform rigorous surveillance and risk management. While the FDA has developed general risk management guidance, more specific analyses are needed to improve surveillance methodology for drugs abused, misused, and diverted (203).

6.6 Regulatory Measures

The White House in April 2011 announced a plan to curb prescription drug abuse called "Epidemic: Responding to America's Prescription Drug Abuse Crisis." The key elements of the plan are: expansion of state based prescription drug monitoring programs; recommending convenient and environmentally responsible ways to remove unused medications from homes; supporting education for patients and health care providers; and reducing the number of "pill mills," and doctor-shopping through law enforcement. In concert with the White House plan, the FDA announced a new risk reduction program, called REMS, for all extended-release and long-acting opioid analgesics. The new REMS concentrates on educating physicians about proper pain management, patient selection, other requirements, and improving patient awareness regarding the safe use of opioid analgesics (204). As part of the plan, the FDA directed manufacturers of certain extended-release opioids and methadone to give patients educational materials, including a medication guide that uses consumer-friendly language to explain safe use and disposal. The FDA has directed makers of opioid analgesics to work together and develop a single system of implementing the REMS strategies. Physician training, patient counseling, and other risk reduction measures developed by opioid manufacturers as part of REMS are taking a firmer hold, in particular the role of abuse-deterrent agents within opioid products. They soon will become a standard for the various brand names of opioid products, e.g. oxycodone, morphine, hydromorphone, oxymorphone, methadone, transdermal fentanyl, and transdermal buprenorphine. At this time physician training is not mandatory under the REMS plan. Other federal agencies are working to get Congress to link mandatory opioid physician training to the already required Drug Enforcement Administration registration number needed to prescribe controlled substances. The FDA will also require risk management to include a way to determine if the education programs are helping to reduce problems associated with long-acting and extended-release opioids, while allowing patients who need opioids to obtain them (205).

6.7 Emerging Treatments

The opioid analgesics that are currently available exert their analgesic activity by binding to opioid receptors in the central nervous system (CNS). Centrally mediated opioid analgesia is accompanied by other CNS-mediated side effects such as respiratory depression, nausea, cognitive disturbances, tolerance, and addiction. At the heart of the issue of opioid misuse is the role of opioid systems in the reward circuitry, and the adaptive processes associated with repetitive opioid use that manifest during withdrawal. An opioid drug that retains analgesic efficacy without the centrally mediated rewarding effects of μ-opioids would be the "holy grail" for opioid research. Research is directed at developing opioid drugs with reduced deleterious side effects. Several alternatives are being investigated, such as combining μ-opioids with CB1 cannabinoid receptor antagonists or NK1 neurokinin receptor antagonists. Another alternative that holds promise is the development of peripherally acting opioid agonists without centrally mediated effects. Experimental and clinical research has revealed the existence of peripheral opioid receptors on neuronal and non-neuronal tissues (206,207). These peripherally restricted opioid receptors are activated by endogenous and exogenous opioid ligands and have a potent analgesic effect as demonstrated in experimental models of inflammatory pain (208-211). Peripherally acting opioid analgesics do not cross the blood-brain barrier and are therefore devoid of the common side effects that accompany centrally acting opioid analgesics. In the future, these drugs can potentially play a major role in providing optimal pain control and simultaneously curbing drug abuse. Emerging pharmacological insights into opioid receptors forecast the development of opioid-based analgesics with much improved safety profiles, decreased addiction, and possibly diminished opponent processes. Furthermore, knowledge of the circuitry and molecules responsible for nociception and pain transmission continues to increase; as it develops, novel therapeutic foci are revealed that will perhaps spawn efficient analgesics to be used either as monotherapy or in conjunction with present opioid therapies (212).

In efforts to counteract the wide range of side effects that may reduce patient quality of life and lead to reduced compliance with treatment, novel opioid formulations such as tapentadol have recently come to

the market with the aim of providing potent analgesia with reduced gastrointestinal and CNS side effects. Tapentadol is a centrally acting analgesic with 2 mechanisms of action, μ-opioid receptor agonism at spinal and supraspinal sites and norepinephrine reuptake inhibition in the spinal cord (213). It is available in an extended-release formulation for the management of chronic pain and has been associated with better gastrointestinal tolerability and compliance with therapy than oxycodone controlled-release which suggests that tapentadol ER may be a better option for the long-term management of chronic pain (214).

Another novel approach is the personalized medicine approach to opioid analgesic prescribing. At present there are insufficient data for deriving quantitative algorithms to achieve this goal based on individual patient phenotypes or genotypes. Pre-prescription identification of those patients likely to benefit from opioid therapy, i.e., with minimal side effects and low risk of abuse, lacks a well-validated, objective process. The concept of data-based personalized opioid prescribing has been proposed as a potential identification strategy. Multiple predictive elements may comprise such algorithms, including genetics, cerebral function and structure, distinct neurotransmitter pathways, and phenotypic traits peculiar to the patient such as gender, negative affect, and sensitivity to pain. Current knowledge lacks the depth of understanding needed to construct an adequate and efficient quantitative analgesic-prescribing algorithm. However, responder subtype analyses made practical by the large numbers of patients with chronic pain in proposed collaborative patient-based pain registries, in conjunction with follow-up validation of randomized controlled trials, may eventually permit development of clinically useful analgesic-prescribing algorithms (215).

Given the current knowledge of the psychoneuroimmunological effects of SUDs, immunotherapies to treat SUDs and the neuropsychiatric effects of SUDs pose a promising new direction for addiction treatment. Indeed, in a thorough and up-to-date review, Litten et al (216) provided a list of molecular targets and representative compounds that are currently being tested (preclinically and/ or clinically) in substance use and other drug use disorders. Included in this list of targets is neuroimmune modulation. Although not yet FDA approved or available to the public, anti-addiction vaccines are currently the most developed immunotherapeutic approach to addiction. Anti-addiction vaccines are designed to attract antibodies to a substance so that it is too large to pass through the blood brain barrier, effectively blocking its CNS action and rewarding effect (217-220). To date, vaccines have been developed against nicotine, morphine/heroin, cocaine, and methamphetamine, and an array of compounds are undergoing clinical trials or are in preclinical development (218-220). While this approach has clear potential benefit in terms of relapse prevention, a major limitation is likely to be that polysubstance use is highly prevalent (and perhaps the norm) within addiction populations. It is not feasible to vaccinate against all addictive substances (and perhaps contraindicated since many abused substances, such as morphine, also have approved medical indications), and many individuals will seek out and use alternative substances when their preferred substance is no longer effective.

In summary, researchers and clinicians continue to investigate this complex issue of substance use disorders and chronic pain with the goal to create a more individualized, safer approach for our patients with chronic pain. Society will require all stakeholders, patients, clinicians, scientists, governmental policy makers, pharmaceutical companies, and emerging technology manufacturers to play a role in the successful management of chronic non-cancer pain while minimizing opioid abuse.

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