REPORT 2 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (I-08)
Improving Medical Practice and Patient/Family Education to Reverse the Epidemic of Nonmedical Prescription Drug Use and Addiction
(Resolution 813, I-07)
(Reference Committee K)

EXECUTIVE SUMMARY

Objective: To review data on the nonmedical use of prescription controlled substances in the United States, especially as it pertains to youths and young adults and to note programs or organizations that have devoted resources to educating parents about the nonmedical use of prescription drugs by teens. The report also summarizes information on the clinical use of opioid analgesics and benzodiazepine-type compounds and their long-term safety and effectiveness, including the potential for misuse, and briefly notes methods or tools that have been developed to ensure appropriate patient selection and minimize the risk of substance misuse or diversion when these drugs are prescribed for therapeutic purposes.

Methods: English-language reports on studies using human subjects were selected from a MEDLINE search of the literature from 1966 to March 2008. Additional articles were identified by manual review of the references cited in these publications. Web sites of the Substance Abuse and Mental Health Services Administration, American Society of Addiction Medicine, American Psychiatric Association, American Academy of Pain Medicine, National Center on Addiction and Substance Abuse at Columbia University, Partnership for a Drug America, the White House Office on National Drug Control Policy, and the College on Problems of Drug Dependence were searched for relevant publications.

Results: Opioid therapy can relieve pain and improve mood and functioning on a long-term basis in a subset of patients with chronic pain. Screening for a patient's predisposition to and patterns of prior drug misuse/addiction is an important consideration in the safe and effective use of opioid analgesics in patients with chronic noncancer pain. Aberrant behaviors and substance use disorders, including addiction, appear to be less of a problem in chronic pain patients without a current or past history of alcohol/illicit drug use or substance misuse/addiction. In outpatients, benzodiazepines are used primarily for the treatment of anxiety and sleep disorders, and as muscle relaxants. Most benzodiazepine use is intermittent, relatively brief, and for symptom relief. Physiological dependence on benzodiazepines can develop with therapeutic doses. Misuse of benzodiazepines generally involves either deliberate misuse by individuals who use benzodiazepines for their euphoriant effects; use to enhance the effects of opioids, including methadone; use to temper the effects of cocaine or other stimulants; use to alleviate withdrawal or abstinence syndromes for various substances; or use to augment the effects of alcohol. Stimulants are used primarily in the treatment of attention deficit hyperactivity disorder in children and adults, as appetite suppressants, and in patients with narcolepsy.

Conclusion: Several stakeholders have responsibilities for maintaining a clinical practice environment that is conducive to the appropriate use of controlled substance in treating both acute and chronic conditions, while minimizing inappropriate use and diversion of these substances for nonmedical use. Approaches involve prudent patient selection and clinical practice; prevention programs, including minimizing diversion and reducing demand with prevention program for those at risk; and education for all those involved. Physicians are in an important position to educate and influence patients regarding safe practices associated with the use and home storage of prescription drug supplies. The report's recommendations propose relevant organized medicine and physician activities.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 2 - I-08

Subject: Improving Medical Practice and Patient/Family Education to Reverse the Epidemic of Nonmedical Prescription Drug Use and Addiction (Resolution 813, I-07)

Presented by: Carolyn B. Robinowitz, MD, Chair

Referred to: Reference Committee K (Lynne M. Kirk, MD, Chair)

Resolution 813 (I-07), "Improving Medical Practice and Patient/Family Education to Reverse the Epidemic of Prescription Drug Misuse and Addiction," introduced by the American Society of Addiction Medicine and referred by the House of Delegates, asked:

> That our American Medical Association collaborate with the American Academy of Pain Medicine, the American Society of Addiction Medicine, the American Psychiatric Association, the American College of Emergency Medicine, and others, to develop continuing medical education curricula aimed at reducing the epidemic of misuse of and addiction to controlled substances, especially by youth;
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> That our AMA encourage the Accreditation Council for Graduate Medical Education and the [Association of American Medical Colleges] to incorporate appropriate curricula into graduate and undergraduate medical education aimed at minimizing the incidence of unauthorized/non-medical use of opioids, opioid receptor agonists, benzodiazepines, and benzodiazepine receptor agonists;
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> That our AMA encourage medical specialty societies to develop practice guidelines and performance measures that would increase the likelihood of safe medical practice and targeted patient education around topics such as: (a) any practitioner writing a prescription for an opioid, an opioid receptor agonist, a benzodiazepine, or a benzodiazepine receptor agonist would document that they have screened for addiction before writing a prescription, by asking simple questions such as "Have you ever had a problem with or received treatment for addiction to or withdrawal from alcohol or other drugs?" or "Do you have a family history of alcohol or other drug addiction?"; (b) any practitioner writing a prescription for an opioid, an opioid receptor agonist, a benzodiazepine, or a benzodiazepine receptor agonist would document that they have educated their patient that there is the potential for the development of tolerance, withdrawal, or addiction with the use of the therapeutic agent; (c) any practitioner writing a prescription for an opioid, an opioid receptor agonist, a benzodiazepine, or a benzodiazepine receptor agonist would document that they have educated their patient about the risk of youth or others diverting to their own use left-over supplies of the therapeutic agent; (d) any practitioner writing a

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Action of the AMA House of Delegates 2008 Interim Meeting: Council on Science and Public Health Report 2 Recommendations Adopted, and Remainder of Report Filed.

prescription for an opioid, an opioid receptor agonist, a benzodiazepine, or a benzodiazepine receptor agonist would document that they have advised their patient to protect controlled substances supplies from unintended use by others, such as by using lock boxes or medicine cabinet locks akin to the way many persons use kitchen or bathroom cabinet locks to prevent unintentional or otherwise harmful use of home solvents or cleansers by infants or teens; (e) any practitioner writing a prescription for an opioid, an opioid receptor agonist, a benzodiazepine, or a benzodiazepine receptor agonist would document that they have educated their patient to protect controlled substances supplies from unintended use by others, such as by advising the patient to safely dispose of any unused supplies rather than keeping them in the home as an unwitting supply of agents for use by teenagers; (f) any practitioner writing prescriptions for an opioid, an opioid receptor agonist, a benzodiazepine, or a benzodiazepine receptor agonist for medium-to-long term plans of care, document their intended strategy for safe and effective opioid or sedative-hypnotic discontinuation when the need for further medical treatment with such an agonist is no longer present; and

That our AMA collaborate with the federal Centers for Substance Abuse Prevention and Substance Abuse Treatment to develop any reasonable and prospectively-effective strategy to actively involve physicians as being "a part of the solution" to the epidemic of unauthorized/non-medical use of controlled substances.

Resolution 813 focuses on the appropriate clinical use of opioid analgesics and benzodiazepine-type drugs; recent trends indicating a surge in the nonmedical use of such agents; the potential for development of substance use disorders or addiction when these agents are used on a long-term basis; and the need for appropriate dialogue with patients and education on the benefits and risks of these drugs, including the potential for diversion by family members. With respect to the 4th Resolve, both Centers are located within the Department of Health and Human Services Substance Abuse and Mental Health Services Administration (SAMHSA). The Center for Substance Abuse Prevention "works with [s]tates and communities to develop comprehensive prevention systems that create healthy communities." The Center for Substance Abuse Treatment "promotes the quality and availability of community-based substance abuse treatment services for individuals and families who need them" and works with states and community-based groups to "improve and expand existing substance abuse treatment services under the Substance Abuse Prevention and Treatment Block Grant Program."

This Council previously reviewed the use of opioids for chronic noncancer pain, and as part of a larger report, their use in treating neuropathic pain.[1,2] Other reports also have been developed by our AMA on issues related to appropriate pain management and the use of opioid analgesics in recent years.[3-5] The Council also notes that Report 11-A-07 of the Council on Medical Education, "The Status of Education in Substance Use Disorders in America's Medical Schools and Residency Programs,"[6] addresses the 2nd Resolve of Resolution 813 (I-07); therefore, this issue is not further discussed in this report.

This report reviews data on the nonmedical use of prescription drugs in the United States, including stimulants, especially as it pertains to youths and young adults and notes programs or organizations that have devoted resources to educating parents about the nonmedical use of prescription drugs by teens. The report also summarizes information on the clinical use of opioid analgesics and benzodiazepine-type compounds and their long-term safety and effectiveness, including the potential for misuse, and briefly notes methods or tools that have been developed to ensure

appropriate patient selection and minimize the risk of substance misuse or diversion when these drugs are prescribed for therapeutic purposes. Council on Science and Public Health (CSAPH) Report 8-A-08, "Substance Use and Substance Use Disorders," provides further information on the terminology and criteria applicable to the field of substance use disorders.[7]

Methods

English-language reports on studies using human subjects were selected from a MEDLINE search of the literature from 1966 to March 2008 using the terms "opioid-related disorders/diagnosis/epidemiology/*prevention & control," "*pain/drug therapy," and "*substance abuse/detection." Additionally, the terms "analgesics, opioid," OR "benzodiazepines" were used in combination with "*administration and dosage," "therapeutic use," "treatment outcome," "adverse effects," "physician's practice patterns," "addiction," "abuse," and "dependence." Additional articles were identified by manual review of the references cited in these publications. Web sites of the SAMHSA, American Society of Addiction Medicine, American Psychiatric Association, American Academy of Pain Medicine, National Center on Addiction and Substance Abuse at Columbia University, Partnership for a Drug Free America, White House Office of National Drug Control Policy, and the College on Problems of Drug Dependence were searched for relevant publications.

Trends in the Nonmedical Use of Controlled Substances

Multiple surveys on the nonmedical use of prescription drugs, emergency department visits related to prescription controlled substances, admission to treatment facilities for substance dependence, retail sales of controlled substances, and unintentional deaths due to prescription controlled substances have steadily risen over the last 15 years. Behaviors associated with the nonmedical use of prescription drugs are highly comorbid with other psychiatric disorders.[8]

Population Surveys. The National Survey on Drug Use and Health (NSDUH) showed that nonmedical use of psychotherapeutics in the past year in persons aged 12 years and older increased to 16.3 million or 6.6% of the U.S. population in 2006 (up from 2.9% in 1996); opioid analgesics accounted for 80% of the total.[9] Prescription psychotherapeutic agents covered in this survey include opioid analgesics, tranquilizers, stimulants, and sedatives. Nearly 7 million persons, or 2.8% of the U.S. population aged 12 years and older, used prescription-type psychotherapeutic drugs nonmedically in the past month in 2006. The nonmedical use of opioid analgesics increased significantly from 4.4 million users in 2002 to 5.2 million individuals in 2006, with the largest increase occurring in persons aged 18 to 25 years.

In 2006, 2.6 million persons aged 12 years or older used psychotherapeutics nonmedically for the first time, including opioid analgesics (2.2 million), tranquilizers (1.1 million), stimulants (845,000), and sedatives (267,000). Overall, youths and young adults report misusing these opioids more often than all other illicit drugs combined, except marijuana. Adolescents and young adults constitute the majority of first-time nonmedical users of prescription opioids. NSDUH excludes individuals not in "households" and therefore probably underestimates population nonmedical drug use.[10]

Similarly, the 2007 Monitoring the Future Survey (MTF), while showing an overall lower use of illicit drugs and alcohol in America's youth, found that the nonmedical use of prescription opioids remains elevated.[11] MTF surveys school-based youth, and does not capture dropouts, a group that has elevated rates of nonmedical drug use. A recent survey conducted by the Partnership for a Drug

Free America indicated that nearly 20% of teens reported misusing pain medications, stimulants, or tranquilizers that were not prescribed to them.[12]

Emergency Room Visits. The Drug Abuse Warning Network (DAWN) receives reports of emergency department (ED) episodes involving the nonmedical use of legal drugs. Nearly 600,000 U.S. ED visits in 2005 involved the nonmedical use of prescription or over-the-counter pharmaceuticals or dietary supplements, an increase of 21% from 2004. Visits increased 33% for stimulants, 24% for opioid analgesics (most commonly hydrocodone, oxycodone, and methadone), and 19% for benzodiazepines. Compared with 1995, ED visits attributable to opioid analgesics have increased 200% and those attributable to benzodiazepines have increased ~140%.[13-15] These data cannot be used to identify whether the drugs were obtained from a legitimate prescription, as opposed to other sources, and DAWN does not discriminate between visits associated with suicide attempts and inadvertent overdoses or adverse events.[10] Also, individuals can re-enter this database on multiple occasions and be counted as additional cases.

Treatment Facilities. Data on problems with substance dependence emanate from the Treatment Episode Data Set (TEDS) report, which provides information on the demographic and substance abuse characteristics of annual admissions to treatment for alcohol and drug dependence in facilities that report to individual state administrative data systems. TEDS admissions for primary misuse of opiates other than heroin increased from 1% of all admissions in 1995 to ~4% in 2005.[16] This database provides evidence that substance dependence or addiction to prescription opioids is increasing, but because it includes only treatment facilities that receive state funding, it cannot be used to estimate the prevalence of substance misuse/dependence in the general population.[10]

Retail Sales. Large increases in retail sales of stimulants and opioid analgesics have been recorded by the Drug Enforcement Administration (DEA) Office of Diversion Control over the last decade (Table 1).[17] Hydrocodone-combination products are the most commonly prescribed medication in the United States. More than 110 million prescriptions were issued in 2007, far exceeding the number of prescriptions for the second and third most prescribed medications—cholesterol-lowering atorvastatin, with about 63 million prescriptions, and the antibiotic amoxicillin, with about 52 million prescriptions.[18]

Other Consequences. Unintentional drug poisoning mortality rates increased 18% per year from 1990 to 2002.[19] Between 1999 and 2002, the number of opioid analgesic poisonings recorded on death certificates increased 91%.[20] Whether these figures can be directly linked with pain management practices is highly questionable.[21]

Sources of Prescription Drugs Used for Nonmedical Purposes

Typically, opioids and benzodiazepines are not diverted by patients who actually use them therapeutically for pain relief or treatment of symptomatic anxiety or insomnia. However, drug diversion can occur anywhere along a line from the manufacturer/wholesale distributor to the prescriber, hospital or retail pharmacy, or the patient. The actual contribution that poor prescribing practices or fraudulent activity on the part of prescribers makes to the supply of diverted controlled substances is unknown. Based on NSDUH, drugs used for nommedical purposes are obtained for free or taken or purchased from friends or relatives two-thirds of the time.[9] Eighty percent of individuals who received drugs for free believed their source obtained the prescription from a single prescriber. Depending on the age group, 18% or more individuals reporting nonmedical use obtained their prescription from a single prescriber; however, less than 3% reported “doctor

shopping" to obtain controlled substances. Figures derived from NSDUH are relevant for a portion of the "supply" side of prescription drugs for nonmedical use, but offer no information about the motives for such use.

The vast majority of stimulants are prescribed for the treatment of attention deficit hyperactivity disorder (ADHD). The Council recently examined the clinical use of stimulants in the treatment of ADHD, and noted the increase in stimulant prescriptions that has occurred over the last 15 years (CSAPH Report 10, A-07). A recent systematic review examined the nonmedical use and diversion of stimulants prescribed for ADHD.[22] Most information on this subject has been gleaned from school-based surveys and/or interviews. Teens and college-age students use these substances to maintain alertness, as an aid in studying, for their mood elevating/stimulant effects, or for experimentation.[23] Youth with ADHD who are being treated with stimulants are commonly approached to provide, sell, or trade their prescription medication; a smaller subset of patients with ADHD misuse their own medication.[22,24,25] The majority of those who engage in nonmedical use or diversion of stimulants have comorbid substance use disorders.[25,26] Poor medication compliance, diversion, and nonmedical use of stimulants also are relatively common among adult ADHD patients.[27]

Physicians generally believe the three main mechanisms of diversion to be "doctor shopping," patient deception, and forgery or altered prescriptions.[28] Among individuals seeking admission to substance use treatment programs for OxyContin® addiction, 78% of subjects reported the drug had not been prescribed for them, and a similar percentage reported prior treatment for a substance use disorder.[29]

In addition to outright prescription fraud, thefts from the distribution chain and access to illegal online pharmacies are important sources of controlled substances diverted into the illicit market.[30] Sources of fraudulent prescriptions include legitimate prescription pads that are stolen from physicians' offices, alteration of original prescriptions, and computer-generated prescription pads or fictitious prescriptions. The National Center on Addiction and Substance Abuse at Columbia University, in an update of a previous report, identified 159 Internet sites selling prescription opioids, sedative-hypnotics, and stimulants during a one-week period in 2008; 85% of these sites did not require a valid prescription (i.e., either they explicitly stated that no prescription was needed, made no mention of a prescription [47%], or offered on "online consultation" in lieu of a prescription [38%]).[31]

When the illicit marketplace and subgroups of users are examined, numerous sources of diversion are revealed, including prescribers and pharmacists; parents, relatives, and friends; "doctor shopping"; leftover medications; personal visits to non-US countries; burglaries; and "sneak thefts."[32]

Improving Patient/Family Education. The discussion above regarding common sources for the nomedical use of prescription drugs, particularly among youth, and the increasing trends for such use, highlight the need for a more direct approach to address this problem. Both the Partnership for a Drug Free America and the White House Office of National Drug Control Policy (ONDCP) have devoted significant resources to educating prescribers, parents, and the public about the realities of nonmedical prescription drug use. Our AMA has partnered with both organizations to help with their messaging. The Partnership has developed a FactSheet for parents, as well as a more comprehensive Toolkit; informative and instructive videos for download also are available (www.drugfree.org). The ONDCP has several resources available for combating nonmedical prescription drug use, including educational reports and "open letters" for both school professionals

and prescribers that can be downloaded and customized to help educate parents on this issue (www.theantidrug.com/resources/teen-rx.aspx). Prescribers can assist by reinforcing the message that patients (and especially parents) should make sure that their prescriptions for controlled substances are monitored and are kept in a safe place.

Clinical Use of Opioid Analgesics

Pharmacology. Opioid analgesics act at stereospecific receptors (*mu, kappa, delta*) within the central nervous system to reduce transmission of pain impulses at spinal and supraspinal levels, and affect the emotional response to pain at higher centers. Clinically relevant analgesics are predominately *mu* receptor agonists and include morphine (immediate- and sustained-release), codeine (alone or combined with acetaminophen), fentanyl (transdermal, oromucosal delivery), hydrocodone (opioid constituent in Vicodin®, Lortab®), oxycodone (opioid constituent in Percodan®, OxyContin®), hydromorphone (Dilaudid®), levorphanol (Levo-Dromoran®), and methadone.

Prescriptions for Opioids. Within the last two decades, advocacy efforts have succeeded in establishing a practice environment more conducive to managing acute nociceptive pain in patients suffering from cancer, terminal illness, and human immunodeficiency virus infection. Practice guidelines issued by national authorities, improvements in state pain policies, and ethical imperatives also have contributed, along with requirements for hospitals to document, monitor, and adequately treat acute pain. Prescriptions for opioid analgesics have increased substantially over the last decade, with more prescriptions being written for indications that do not involve cancer or terminal illness. Additionally, prescriber demographics have shifted for some products (e.g., OxyContin®, methadone).

Pain Management. Because adequate doses of opioid analgesics are highly effective in the treatment of acute nociceptive pain, and long-term opioid maintenance therapy of patients with opioid addiction can be accomplished safely, substantial interest developed in the potential clinical use of opioids for chronic noncancer pain.

Numerous randomized controlled clinical trials have demonstrated the ability of opioids to reduce pain intensity in patients with various chronic pain conditions (e.g., back and neck pain, osteoarthritis, rheumatoid arthritis, regional soft tissue pain syndromes)[1,33-41] and various neuropathic pain syndromes, although larger doses may be required in the latter.[2,41-48] Improvement in function and quality of life may be less consistent. Generally, these trials were relatively short (2 to 8 weeks, although some lasted 16 to 32 weeks) and utilized daily doses equivalent to ≤180 mg of morphine. More recently, the safety and efficacy of extended/sustained-release formulations of oxycodone, morphine, or oxymorphone have been demonstrated in patients with back pain or osteoarthritis.[49-52]

Potent opioids (e.g., morphine, oxycodone) are more effective than less potent derivatives (e.g., codeine, propoxyphene, tramadol), especially compared with nonsteroidal anti-inflammatory drugs (NSAIDs) and tricyclic antidepressants. However, approximately 1 in 3 patients discontinues therapy because of inadequate pain relief or adverse effects within the first several weeks, mostly constipation and nausea.[53,54] Other adverse effects associated with long-term therapy that can be problematic include suppression of the hypothalamic pituitary adrenal axis and hypothalamic pituitary gonadal axis, and possibly immunosuppressive effects.[55] Mechanisms associated with failed analgesia and adverse outcomes include opioid tolerance and opioid-induced abnormal pain

sensitivity or hyperalgesia.[56] The need for increased opioid doses during long-term therapy may be the result of pharmacologic tolerance, disease progression, or the phenomenon of opioid-induced abnormal pain sensitivity or hyperalgesia. In the latter cases, detoxification from high-dose opioids may improve pain management.[57,58]

Long-term Use. Although results of short-term randomized trials were encouraging, questions began to be raised about the efficacy of long-term opioid use in such patients. Because long-term randomized trials are not feasible, most evidence has been obtained from open label extension studies (that tend to be enriched with opioid responders), and survey data. For example, a population-based survey in Denmark of patients with chronic pain of more than 6 months' duration found that opioid usage was associated with concurrent moderate to severe pain, poor self-reported health, unemployment, higher use of the health care system, and poor quality of life.[59] Another open label, uncontrolled, registry study involving patients who previously participated in controlled trials of controlled-release oxycodone for osteoarthritis, diabetic neuropathy or low back pain, and who continued to require opioid analgesia for moderate to severe pain found that only 18% of patients remained on therapy after 3 years, with a modest need for dose escalation.[60]

Systematic reviews and meta-analyses have been conducted to gain better insight into the question of long-term effectiveness.[61-64] Results of these analyses also have been mixed, because they either combined trials of nociceptive and neuropathic pain, combined trials involving weak (or ineffective) regimens with more potent opioids, and used various definitions or criteria to identify emergent substance use problems. In general, these reviews indicate that opioid therapy relieves pain and improves mood and functioning on a long-term basis in a minority of patients with chronic pain. Discontinuation due to adverse events (nausea, constipation, and somnolence) or insufficient pain relief is common, and a subset of patients is identified with substance use disorders or aberrant drug taking behaviors during therapy (see below).

Pain Management versus Substance Use Disorders and Addiction

There is widespread agreement that a "balanced approach" to the clinical use of prescription opioids is needed so that risk management strategies and diversion control do not interfere with appropriate use of opioids to relieve pain and suffering.[10] As noted in CSAPH Report 8-A-08, vulnerability to developing a substance use disorder is based on interplay of the characteristics of the substance (ie, reinforcing properties); substance availability and cost; genes; environmental influences; social interactions; developmental history and experiences; and other host factors, including the presence of other psychiatric disorders.[7]

Patients with chronic pain frequently experience comorbid mood, anxiety, or somatization disorders; the presence of these disorders increases the risk that patients also will exhibit substance use disorders or aberrant drug taking behaviors.[65,66] According to the most recent National Epidemiologic Survey on Alcohol and Related Conditions data, 18% to 20% of the U.S. population with a substance use disorder have a co-occurring independent anxiety or mood disorder. Similarly, more individuals with substance use disorders have an alcohol use disorder and *vice versa.*

Substance Use Disorders/Addiction Associated with Therapeutic Exposure to Opioids

Subpopulations who misuse prescription opioids generally include the following: (1) individuals who use illicit opioids (e.g., heroin) and who turn to prescription opioids when their supply of illicit drugs is compromised; (2) polysubstance users, who use opioids within their framework of substance use (and some individuals with a primary opioid use disorder); and (3) patients with chronic pain who develop an opioid substance use disorder *de novo* after initial exposure to opioids in the course of legitimate treatment.[10] During short-term treatment for nociceptive pain, substance use disorders or addiction virtually never arise *de novo*.[67] In one of the first case series reporting on the use of opioids in chronic noncancer pain, substance misuse occurred in 2 of 38 patients (~5%), both of whom had a prior history of such misuse.[68] These low rates of potential substance misuse were generally accepted until problems with prescription opioids began to be reported anew in epidemiologic studies, and clinical observations involving patients treated with opioids on a long-term basis suggested larger problems.[69]

A systematic review published in 1992 concluded that the occurrence of substance use disorders in chronic pain patients treated with opioid analgesics approached 19%.[70] Subsequently, other reports suggested significant rates of substance misuse in these patients. A problem in adequately evaluating this issue is the lack of diagnostic criteria that are applicable to the pain management setting. That is, many of the criteria for diagnosis of substance abuse or substance dependence in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) IV-TR (and previously DSM III)[71] are commonplace occurrences in patients with chronic noncancer pain treated therapeutically with long-term opioids (or could easily manifest in patients with inadequately controlled pain), and therefore do not signal a substance use disorder *per se*.

DSM IV-TR does not use the term "addiction." Addiction is defined as "a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving." Once again, some of these criteria could easily manifest in patients with inadequately controlled pain and have nothing to do with addictive illness.

Consequently, while some investigators have relied on DSM criteria, many others have created various definitions and thresholds to identify substance use disorders or addiction in patients with chronic pain treated with opioids (i.e., physician subjective evaluation, occurrence of steady or unexplained dose escalation, "drug craving," early refills, lost prescriptions, "drug seeking behavior," multiple prescription sources, or positive urine/toxicology screening). Accordingly, the reported rates of substance use problems in studies involving chronic pain patients have varied widely from 0% to 50%.[72] In attempts to provide some clarity, alternate criteria for evaluating the presence of a substance use disorder/addiction or aberrant drug-taking behaviors in patients treated with opioids have been developed (Tables 2-4).[73-75]

Furthermore, a high percentage of patients presenting to interventional pain management settings are already taking opioids, and a proportion test positive for illicit drugs (23%) or have positive urine tests for opioids despite denying current use (12%).[76] A high rate of positive urine drug tests occurs in patients maintained on chronic opioid therapy; 21% to 45% of such patients have positive urine screens, defined as the presence of an illicit drug or an additional nonprescribed controlled medication in the urine, or the absence of the prescribed opioid.[77-79] A recent evidence-based review of the available studies (n=41) on the development of substance abuse/addiction and

aberrant drug-related behaviors in patients with chronic noncancer pain who were being treated with long-term opioid therapy determined that the substance abuse/addiction rate was 3.27% and aberrant drug-taking behavior occurred in 11.5% of patients. These conditions were rare (0.19% and 0.59%, respectively) in individuals with no previous or current history of abuse/addiction.[80] However, in concert with the findings noted above, in urine toxicology groupings, 20% of patients either had no prescribed opioid in the urine and/or a nonprescribed opioid in the urine, and 14% had illicit drugs in the urine.

Screening and Monitoring/Adherence

Based on the above findings, screening for a patient's predisposition to and patterns of prior drug misuse/addiction is an important consideration in the safe and effective use of opioid analgesics in patients with chronic noncancer pain. A multitude of screening tests for stratifying risk of aberrant drug related behaviors or substance use disorders/addiction have been developed, including adaptation of tests originally developed for alcohol screening (e.g., CAGE, Short Michigan Screening Test). These approaches attempt to identify patients who may not be suitable candidates for long-term therapy, or who may require stricter adherence monitoring. Current approaches have been recently reviewed and some of the more common tools are noted in Table 5.[56,72,81-89]

Adherence Monitoring. Direct approaches to monitoring adherence to therapy are urine drug testing and prescription monitoring programs; the latter approach was recently evaluated in Board of Trustees Report 8 (A-08), "Prescription Drug Monitoring to Prevent Abuse of Controlled Substances."[3] Urine drug testing assists in evaluating patients' compliance with prescribed regimens of controlled substances, and detects the misuse of other prescribed drugs or illicit substances.

Controlled Substances Agreement. Controlled substance agreements are another tool to foster appropriate management when opioids are used in patients with chronic noncancer pain. These agreements clarify parameters of treatment; explicate patient and physician responsibility; inform patients of expectations and role(s); and, address potential consequences if these obligations and responsibilities are not upheld. A sample agreement is available from the American Academy of Pain Medicine.

Opioid Risk Management. Summary guidelines previously offered by this Council for a prudent approach to prescribing opioids for chronic pain and implementing the necessary controls to minimize opioid misuse and diversion are still relevant (Table 6).[1] Patient compliance can be improved by combining the use of screening tests, urine testing, and treatment agreements. Also, because a substantial percentage of chronic noncancer pain patients evaluated in multidisciplinary treatment programs are already taking opioid medication, the prescription of opioids to such patients is influenced to a large degree by the patient's pain behavior (nonverbal communication of pain, distress, and suffering). These programs, and most pain treatment specialists, endorse an approach that utilizes opioids as an adjunct within a comprehensive treatment strategy that employs behavioral interventions in combination with other modalities to improve patients' coping and functional status.

Benzodiazepines

Pharmacology. Benzodiazepine binding sites are part of a macromolecular complex comprising the receptor for gamma-aminobutyric acid (GABA), the most common inhibitory neurotransmitter in

the human central nervous system. Benzodiazepines facilitate GABA-ergic neurotransmission and potentiate postsynaptic inhibition by allosterically increasing the affinity of $GABA_A$ receptors for GABA and increasing the amount of chloride current generated by $GABA_A$ receptor activation. Zolpidem (a nonbenzodiazepine) acts in a similar fashion as a benzodiazepine receptor agonist, and other drugs (zopiclone, eszopiclone, zalpelon) have binding domains located close to or allosterically coupled to benzodiazepine receptors. Benzodiazepines differ primarily in their potency and pharmacokinetics. Although tolerance develops to the sedative and psychomotor effects of benzodiazepines, anxiolytic effects appear to be maintained in the absence of dose escalation.[90,91]

Adverse drug events include short-term, long-term, and discontinuation-related events (see below). Studies on the association between long-term benzodiazepine use and brain abnormalities have yielded conflicting results. Such therapy does not result in detectable structural abnormalities;[92] impairments in certain cognitive domains (ie, visuospatial ability, speed of mental processing, and verbal learning) may be evident, but these also could be attributable to the presence of anxiety disorders themselves.[93,94] Long-term use may cause daytime somnolence, blunted reflexes, memory impairment, and an increased risk of falls and hip fractures in the elderly, as well as substance dependence or addiction (see below).

Historical Overview. Benzodiazepines became widely available in the 1960s and soon replaced other drugs for the treatment of generalized anxiety and sleep disorders, based on their rapid onset of action, margin of safety, and lower risk of tolerance and dependence. In the 1980s, high potency benzodiazepines were found to be more effective than other drugs for panic disorder. In the 1990s, selective serotonin reuptake inhibitors gained a place in the treatment of anxiety disorders, thereby affecting the clinical use of benzodiazepines for these conditions.[95] During this entire period, benzodiazepines were the cornerstone of treatment for insomnia. Although the benzodiazepines are still prescribed, the benzodiazepine receptor agonists and modulators (zolpiden, zopiclone, eszopiclone, zaleplon) are now the most highly prescribed treatments for insomnia. Except for these newer treatments of insomnia, much of the primary literature on the clinical uses of benzodiazepines was established 20 to 30 years ago.

The state of knowledge on the first 30 years of benzodiazepine usage was evaluated in a Task Force Report of the American Psychiatric Association (APA) in 1990.[96] Most of the conclusions in this report remain valid today:

- Most benzodiazepine use is intermittent, relatively brief, and for symptom relief.
- Long-term users are more often older, have chronic physical as well as psychiatric illness, experience psychological distress, and report that the drug is therapeutic.
- A small percentage of patients use therapeutic doses for self-medication of symptoms.
- Physiological dependence on benzodiazepines can develop with therapeutic doses; the degree of dependence and intensity of withdrawal symptoms are influenced by the dose, duration of treatment, abruptness of discontinuation (or taper schedule), and the pharmacokinetic properties of the individual agent.
- Symptoms expressed after discontinuation of, or between doses during, long-term therapy may reflect withdrawal, rebound effects, or recurrence of illness.
- Sedation, cerebellar dysfunction (motor incoordination, vertigo), psychomotor retardation (i.e., drowsiness, poor concentration, mental confusion) and memory impairment are the most common side effects.

- With long-term use, risks of chronic toxicity, including cognitive impairment, physiological dependence and discontinuation symptoms, exist.
- Benzodiazepines do not strongly reinforce their own use. When abuse does occur, it is usually among individuals who are also misusing other drugs or alcohol.

The APA Task Force Report was not able to consider emerging data on the use of certain high potency and shorter acting benzodiazepines, and the benzodiazepine receptor agonists had not yet been developed. However, most of the findings of this Task Force were reaffirmed by an expert international consensus panel in 1999.[97]

Current Patterns of Use

As noted above in the Trends section, tranquilizers and sedatives represent classes of psychotherapeutic substances that are subject to nonmedical use. Such use has increased in recent years, but not to the extent described for opioid analgesics. Several benzodiazepines or receptor site agonists are among the top 200 prescribed drugs in the United States, most commonly the hypnotics zolpidem, zolpidem CR, and eszopiclone, and the high potency anxiolytic benzodiazepines alprazolam, lorazepam, and clonazepam.[18]

Benzodiazepine receptor agonists and modulators have largely replaced the benzodiazepines for the treatment of insomnia. Zolpidem CR and eszopiclone (Lunesta®) are labeled for the treatment of chronic insomnia. Behaviorally, these drugs generate sedative effects at lower doses than other typical benzodiazepines (i.e., anxiolytic, muscle relaxant, anticonvulsant) and thus are asserted to have a lower risk of misuse, tolerance, dependence, and residual effects compared with benzodiazepines, although rebound insomnia occurs following discontinuation and prolonged high dose usage has been reported.[98-104]

Clinical Use

Anxiety disorders are chronic illnesses that impair daily functioning.[105] They can be difficult to treat and are associated with significant morbidity and mortality.[106-109] Benzodiazepines can be useful in the treatment of generalized anxiety disorder, panic disorder and/or agoraphobia, social phobia, performance anxiety, anxiety due to a general medical condition, and possibly substance-induced anxiety disorders. Long-term therapeutic users rarely escalate their doses.[110-112] However, when long term therapy is required, selective serotonin reuptake inhibitors may be preferred.

Benzodiazepine receptor agonists/modulators and certain benzodiazepines are marketed for the treatment of insomnia. Benzodiazepines also are used in the management of alcohol withdrawal, seizure disorders, skeletal muscle spasms, and in larger doses for spasticity and as preanesthetic medication for the induction of sedation or amnesia prior to certain procedures.

Concerns about the use of benzodiazepines in patients with alcohol use disorders have been expressed, but one prospective study of long-term users, some of whom had co-existing alcohol use disorders found that the dosage of benzodiazepines remained stable, and little association existed between benzodiazepine use and the onset of a new alcohol use disorder.[113] An early study on this topic found that 94% of recently detoxified alcoholic patients who were prescribed benzodiazepines as needed for anxiety reported the medication to be helpful in staying sober over a 1-year period; 1 in 7 ended up taking the benzodiazepine daily.[114] Another study of patients referred for treatment of benzodiazepine dependence found that 40% of such individuals had a

prior history of alcohol abuse or dependence, but the pattern of long-term benzodiazepine use was one of low daily doses, with attempts to decrease the dose or stop taking the medication.[115]

Benzodiazepine Use, Nonmedical Use, and Dependence

Despite the relatively positive findings of the APA Task Force Report, concerns about the substance dependence/addiction liability of benzodiazepines continue to be expressed. Some patients who begin a therapeutic trial of benzodiazepines for an anxiety or sleep disorder eventually escalate their dosage or take the drug for a longer period than intended[116-120]; however, benzodiazepines are rarely the preferred drug of abuse. An estimated 80% of benzodiazepine abuse is part of polydrug abuse, most commonly with opioids.[121] Benzodiazepine-type drugs do not display the direct reinforcing properties typical of other substances that are commonly misused (e.g., opioids, alcohol, cocaine, amphetamine); however, their reinforcing properties are more apparent in subjects with histories of drug or alcohol misuse, or in patients with anxiety or sleep disorders.[122-127] Rapid-onset benzodiazepines are more reinforcing and those with a shorter duration of action may have a higher potential for misuse potential because of the need for frequent dosing to mitigate withdrawal symptoms.[128] Therefore, the misuse of benzodiazepines generally involves one of the following: (1) deliberate misuse by individuals who use benzodiazepines for their euphoriant effects; (2) use to enhance the effects of opioids, including methadone; (3) use to temper the effects of cocaine or other stimulants; (4) use to alleviate withdrawal or abstinence syndromes for various substances; or (5) use to augment the effects of alcohol.

Long-term therapeutic use may cause physical dependence, but if this development is not associated with aberrant drug seeking behavior, it does not constitute addiction. Development of physical dependence is closely related to the dose used and the duration of use. It does not imply misuse or loss of benefit, but rather a need for tapering of treatment at discontinuation.[91] The vast majority of individuals with a high degree of benzodiazepine dependence also misuse other psychoactive substances and have significant psychiatric comorbidity (major depression, panic disorder, generalized anxiety disorder, personality disorders).[129-131]

Discontinuation/Withdrawal Symptoms. Attempts at withdrawing benzodiazepines may cause anticipatory anxiety, rebound insomnia, irritability, and other symptoms that perpetuate a spiral of dependency and abuse.[132] Pseudowithdrawal is a psychological or subjective withdrawal that occurs as a result of a patient's apprehension about discontinuing medication.[133] A significant percentage of long-term users may be reticent or fearful of attempting drug holidays.[134] In patients who experience withdrawal, the most significant factor is duration of treatment plus the dose and rate of tapering.[135] Certain withdrawal symptoms (ie, nervousness, difficulty sleeping, agitation, irritability, difficulty concentrating) may mimic an anxiety disorder, but mitigate with time, whereas a recurrence of anxiety persists and may worsen. In some cases, anxiety symptoms may "rebound" above the baseline intensity existing before therapy. Other withdrawal symptoms (depending on severity) may include sensory hypersensitivity, tinnitus, perceptual changes, tremors, and in more severe cases, myoclonic jerking or seizures. Not all long-term users taking therapeutic doses exhibit withdrawal symptoms on discontinuation; when they occur, withdrawal symptoms can be managed by gradual tapering.[136-138] Brief intervention combined with institution of a tapering schedule is effective in promoting discontinuation or significant lowering (~50%) of daily dosages in long-term users.[139,140]

One-half to two-thirds of patients with benzodiazepine dependence can be successfully tapered in the short term, and about half of these remain benzodiazepine free.[141] More predictive of success

are: offering a tapering program, lower daily dosage at discontinuation starting point, patient self-initiated dosage reduction, less severe dependence, and lack of alcohol misuse.

Long-term Users. In individuals with no previous history of substance misuse, long-term prospective studies and epidemiologic surveys have found that the majority of patients not only rarely escalate their dosage, but tend to decrease the required dosage over time.[110-112,141] Long-term benzodiazepine users are generally older, have comorbid mental health disorders and/or suffer from chronic diseases, report a lower perceived health status, and use more avoidance coping behavior compared with short-term users.[142,143] Initial benzodiazepine prescriptions to older adults are typically intended for the treatment of anxiety or insomnia. A significant minority develops a pattern of long-term use, raising concerns about tolerance and dependence.[144] From a safety perspective, several issues require assessment when a decision is made to prescribe a sleep medication, including next day residual effects and the potential for abuse, tolerance, and dependence. In many elderly patients, the benefits of these drugs may not justify the increased risks of falls and cognitive impairment, particularly if the patient has pre-existing risk factors for cognition or psychomotor dysfunction.[145] Although not necessarily recommended, in some patient populations receiving care in mental health settings, up to one-third of patients with depression also may receive prescriptions for benzodiazepines.[146] However, even very long-term users can successfully discontinue or substantially reduce their use of medication with supervised tapering and/or cognitive behavioral therapy.[147]

Clinical Guidance

The APA Task Force Report noted that before prescribing benzodiazepines, physicians should[92]:

- Assess the potential therapeutic benefit versus long-term risk of dependency and likelihood of discontinuation symptoms, and potential toxicity.
- Evaluate patients for current or past alcohol or other drug dependence.
- Understand that the risks of cognitive impairment, physical dependence, and discontinuation symptoms are all more likely with high doses; duration of therapy >4 months; advanced age; current or prior history of substance dependence; and use of higher potency, shorter half-life benzodiazepines.
- Understand that for some patients, the benefits of ongoing treatment with benzodiazepines clearly outweigh the risks; typically these are patients with demonstrable persistent anxiety as a component of medical illness that cannot otherwise be treated.
- Appreciate that long-term nightly use of benzodiazepines for treatment of insomnia is probably not warranted for most patients and may be especially hazardous in the elderly; however, some elderly patients can sleep only with the assistance of a benzodiazepine.

Summary. Physicians should "use the lowest benzodiazepine doses that are therapeutic and treat for the shortest duration of time as indicated by the patient's condition; ongoing daily maintenance treatment should be decided on a case-by-case basis, and they should regularly reevaluate these patients in order to ensure that continued use is therapeutic and warranted. Special caution should be taken when benzodiazepines are prescribed to the elderly or to those with a current or prior history of substance abuse or dependence."[92]

Physicians also should "discuss the goals and limitations of benzodiazepine therapy with the patients, including the meaning of physical dependence and its implication; adopt a dynamic stance to treatment designed to determine the lowest effective dose and a plan for discontinuation; and

reevaluate the need for treatment in the short term and over the long term with intermittent structured attempts to taper the drug."[91]

CONCLUSION

Several stakeholders have responsibilities for maintaining a clinical practice environment that is conducive to the appropriate use of controlled substances in treating both acute and chronic conditions, while minimizing inappropriate use and diversion of these substances for nonmedical use. These stakeholders include various federal agencies (Food and Drug Administration, DEA, National Institute on Drug Abuse, Substance Abuse and Mental Health Services Administration), state medical boards, physicians and other health care professionals, patients and their families, and the pharmaceutical industry. Approaches involve prudent patient selection and clinical practice, prevention programs including minimizing diversion and reducing demand with prevention programs for those at risk, and education of all those involved. The recommendations below propose relevant organized medicine and physician activities.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following recommendations be adopted in lieu of Resolution 813 (I-07), and that the remainder of this report be filed:

1. That our American Medical Association (AMA) collaborate with relevant medical specialty societies to develop continuing medical education curricula aimed at reducing the epidemic of misuse of and addiction to prescription controlled substances, especially by youth. (Directive to Take Action)

2. That our AMA encourage medical specialty societies to develop practice guidelines and performance measures that would increase the likelihood of safe and effective clinical use of prescription controlled substances, especially psychostimulants, benzodiazepines and benzodiazepines receptor agonists, and opioid analgesics. (Directive to Take Action)

3. That our AMA encourage physicians to become aware of resources on the nonmedical use of prescription controlled substances that can assist in actively engaging patients, and especially parents, on the benefits and risks of such treatment, and the need to safeguard and monitor prescriptions for controlled substances, with the intent of reducing access and diversion by family members and friends. (Directive to Take Action)

4. That our AMA consult with relevant agencies on potential strategies to actively involve physicians in being "a part of the solution" to the epidemic of unauthorized/nonmedical use of prescription controlled substances. (Directive to Take Action)

5. That our AMA support research on: (a) firmly identifying sources of diverted prescription controlled substances so that solutions can be advanced; and (b) issues relevant to the long-term use of prescription controlled substances. (Directive to Take Action)

Fiscal Note: $3,000.

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Table 1. Retail Sales of Opioid Medications and Stimulants (Grams of Medication)

Substance	1997	2002	2006	% Change
Amphetamine base	1,345,338	5,050,056	7,759,292	576%
Methylphenidate	8,029,771	11,099,677	15,895,770	198%
Codeine	22,242,049	20,284,867	16,955,450	-24%
Oxycodone	3,732,637	20,533,350	34,632,256	928%
Hydrocodone	8,072,700	17,769.369	28,229.679	350%
Meperidine	2,382,762	2,609,324	2,530,510	7%
Methadone	397,189	2,328,286	5,986,487	1507%
Morphine	4,378,578	7,995,001	14,679,305	335%
Fentanyl base	55,484	204,450	380,129	686%

Table 2. Criteria for Problematic Opioid Use[69]

1. The patient displays an overwhelming focus on opiate issues during pain clinic visits that occupies a significant proportion of the pain clinic visit and impedes progress with other issues regarding the patient's pain. This behavior must persist beyond the third clinic treatment session.

2. The patient has a pattern of early refills (3 or more) or escalating drug use in the absence of an acute change in his or her medical condition.

3. The patient generates multiple telephone calls or visits to the administrative office to request more opiates, requests early refills, or has problems associated with the opiate prescription. A patient may qualify with fewer visits if he or she creates a disturbance with the office staff.

4. There is a pattern of prescription problems for a variety of reasons that may include lost medications, spilled medications, or stolen medications.

5. The patient has supplemental sources of opiates obtained from multiple providers, emergency rooms, or illegal sources.

Table 3. Drug Use Behaviors Relatively More Predictive and Less Predictive of Addiction[70]

More Predictive	Less Predictive
• Selling prescription drugs • Prescription forgery • Stealing or "borrowing" drugs from others • Injecting oral formulations • Obtaining prescription drugs from nonmedical sources • Concurrent abuse of alcohol or illicit drugs • Multiple dose escalation or other noncompliance with therapy despite warnings • Multiple episodes of prescription "loss" • Repeatedly seeking prescriptions from other clinicians or from emergency rooms without informing prescriber or after warnings to desist • Evidence of deterioration in the ability to function at work, in the family, or socially that appears to be related to drug use • Repeated resistance to changes in therapy despite clear evidence of adverse physical or psychological effects from the drug	• Aggressive complaining about the need for more drugs • Drug hoarding during periods of reduced symptoms • Requesting specific drugs • Openly acquiring similar drugs from other medical sources • Unsanctioned dose escalation or other noncompliance with therapy on 1 or 2 occasions • Unapproved use of the drug to treat another symptom • Reporting psychic effects not intended by the clinician • Resistance to a change in therapy associated with "tolerable" adverse effects with expressions of anxiety related to the return of severe symptoms

Table 4. Patterns Suggesting Addiction in Chronic Pain Paients[71]

Adverse consequences/harm due to use

- Intoxicated/somnolent/sedated
- Declining activity
- Irritable/anxious/labile mood
- Increasing sleep disturbance
- Increasing pain complaints
- Increasing relationship dysfunction

Impaired control over use/Compulsive use

- Reports lost or stolen prescriptions or medications
- Frequent early renewal requests
- Urgent calls or unscheduled visits
- Abusing other drugs or alcohol
- Cannot produce medications on request
- Withdrawal noted at clinic visits
- Observers report overuse or sporadic use

Preoccupation with use due to craving

- Frequently misses appointment unless opioid renewal expected
- Does not try nonopioid treatments
- Cannot tolerate most medications
- Requests medications with high reward
- No relief with anything except opioids

Table 5. Screening for Risk of Opioid Misuse

Test	Number of Items	Description
Prescription opioid checklist[69]	Five (see Table 3) behaviors observable in the clinic setting	Prescription abuse checklist to by used by physicians; patients meeting ≥3 criteria are misusers
Prescription drug use questionnaire[78]	42-item questionnaire evaluating 6 domains	Structured interview completed by physician
Screening toll for addiction risk (STAR)[79]	14 true and false questions	Completed by patient
Pain Assessment and Documentation Tool (PADT)[80]	Assesses 4 domains	Completed by physician
Pain Medication Questionnaire (PMQ)[81]	26-item self-report instrument to assess risk for aberrant drug related behaviors	Completed by patient
Screener and Opioid Assessment for Patients with Pain (SOAPP)[82]	24-item questionnaire designed to assess risk for aberrant drug-related behaviors	Completed by patient
Opioid Risk Tool (ORT)[83]	10 yes/no questions	Completed by patient
Scoring System to Predict Outcome (DIRE)[84]	Assesses 4 domains (diagnosis, intractability, risk, efficacy)	Completed by physician

Table 6. Elements of Various Guidelines on the Use of Opioids in Chronic Pain[1]

Evaluation of the Patient—History and Physical Examination

- Obtain a pain history and assess impact of pain on social, occupational, physical, and psychological function
- Review previous diagnostic studies, other consultations/opinions, and previous surgical and medical interventions.
- Review medical, psychiatric and substance abuse history and assess coexisting diseases or conditions.
- Conduct a directed physical examination

Treatment Plan and Objectives

- Establish working diagnosis and medical indication for treatment with opioids
- Outline measurable outcome objectives (eg, pain control, activities of daily living, functional improvement)
- Provide informed consent on the risks and benefits associated with opioids.
- Discuss the conditions under which opioids will be prescribed and possibly discontinued

The use of a single prescribing source and pharmacy should be encouraged where practical. Some practitioners may employ a written agreement that specifies conditions of prescribing, including use of urine toxicology, and the conditions under which the prescribing may be terminated such as evidence of misuse. The latter may include repeated loss or theft of medication, unsanctioned escalation of dosage, acquisition of opioids from other sources despite adequate treatment, or other aberrant behaviors.

Periodic Review

- Assess the safety and efficacy of treatment (eg, subjective pain ratings, functional changes, quality of life, opioid side effects)
- Assess for compliance and evidence of medication misuse
- Reassess the nature of the pain complaint to confirm that opioid therapy is still warranted

With regard to the treatment plan and periodic review, a therapeutic trial of sufficient duration (several weeks) for initial dose titration, with frequent reviews and efficacy assessment to establish the value of opioid therapy, is recommended. The regularly scheduled administration of pure opioid agonists with a long duration of action may be more effective than pain contingent use alone.

Consultation

- Referral to a specialist in pain medicine may be warranted depending on the expertise of the practitioner and the complexity of the problem
- Referral to an addiction specialist is often indicated for patients with a history of addiction or substance use disorder.
- Referral to a psychiatrist or psychologist may be indicated in cases with significant psychiatric comorbidity or behavioral influences.

Documentation. Accurate, complete, and contemporary medical records should be maintained. Additionally, specific documentation is warranted on:

- Evaluation
- Diagnoses, including the reason for opioid prescribing if not readily obvious from the diagnoses
- All prescriptions written
- Overall pain management plan
- Consultations received
- Written patient instructions, consents, or agreements
- Periodic review of patient status, including outcome assessments that support continued prescription of opioids