Opioid Dependence: Managing the High Cost of Treatment Failure

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5. Strive to report subjects of current interest to managed specific off-label indication.

7. Subject all supplements to expert peer review.

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6. Seek and publish content that does not duplicate content care pharmacists and other managed care professionals.

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**Target Audience**

This activity has been developed for managed health care professionals, including pharmacists and physicians seeking innovative strategies for appropriate treatment and management of opioid dependence.

**Learning Objectives**

Upon completion of this continuing education program, learners will be able to:

1. State the epidemiology and burden associated with opioid dependence treatment.
2. Describe the economic and clinical impact of opioid treatment to managed care.
3. Review management strategies for opioid dependence treatment considering clinical, economic and humanistic factors.
4. Discuss communication methods and techniques for dialogue with treating physicians and other treatment providers to ensure the optimal care of patients undergoing opioid dependence treatment.

**Funding**

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Release date: February 1, 2010
Expiration date: January 31, 2011
Opioid Dependence: Managing the High Cost of Treatment Failure

Physicians

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Creative Educational Concepts, Inc. (CEC) and Lancer Solutions, LLC, on behalf of AMCP Horizons, LLC. CEC is accredited by the ACCME to provide CME for physicians.

CEC designates this educational activity for a maximum of 2.0 AMA PRA Category 1 Credits. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This CME/CE activity was planned and produced in accordance with ACCME Essential Areas and Policies.

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This knowledge-based activity has been assigned ACPE # 0245-9999-10-004-H01-P and will award 2.0 contact hours (0.20 CEUs) of continuing pharmacy education credit. CEC complies with the Criteria for Quality for continuing education programming.

Please address any medicine or pharmacy accreditation questions to the Provider of continuing education for this activity, Dana Frazier, Creative Educational Concepts, Inc., at 859.260.1717, or via email dfrazier@ceconcepts.net.

Type of Activity: Knowledge-Based

Term of Offering

This activity has a release date of February 1, 2010, and is valid for 1 year. Requests for credit must be received no later than January 31, 2011. Please refer to the enrollment form at the end of this activity for further instruction on continuing education credit.

Fee Information

There is no fee to participate in this educational activity.

Statement of Need

Drug abuse and dependence are on the rise. According to the 2007 National Survey on Drug Use and Health (NSDUH), an estimated 5.2 million persons aged 12 or older were current users of prescription pain relievers for nonmedical purposes. The burden of opioid dependence is influenced by a variety of factors, including recognition of dependence, a fear of being stigmatized, comorbid conditions, and other barriers interfering with treatment; for example, up to 47% of patients who seek treatment for opioid dependence have documented psychiatric comorbidities. Given the challenges in the terminology of addiction, a rise in abuse rates, and the difficulty of managing opioid dependence, it is important for managed care audiences to understand this problem. Communication between managed care professionals and network providers may prevent further growth in prescription pain reliever abuse rates and help to promote the proper use of opioids.

Original Presentation of This Learning Activity

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In this educational activity, Drs. Nicholls, Ruetsch, and Ms. Bragaw discuss a product (clonidine) that is not approved by the U.S. Food and Drug Administration (FDA) for the treatment of opioid withdrawal, and Dr. Jan discusses the class of antidepressants being used off-label for chronic pain.

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Introduction: Landscape of Opioid Dependence

Saira A. Jan, MS, PharmD

ABSTRACT

BACKGROUND: The use of opioids for chronic noncancer pain increased 222% from 1992 to 2002. Opioid dependence has also increased significantly, leading to a burden on patients, employers, insurers, society, and the entire health care system. It is imperative that opioid dependence is addressed and treated properly, in order to return patients to being productive participants in the workplace and society.

OBJECTIVE: To provide an overview of addiction, abuse, and dependence and identify risk factors for addiction.

SUMMARY: Studies have shown that intensive use of opioids is associated with increased utilization of costly health care services, prolonged disability, and continued use of opioids, leading to abuse and dependence in many patients. While identifying patients at risk for developing opioid dependence is difficult, there are many risk stratification tools now available to practitioners, including the Opioid Risk Tool (ORT) or Screener and Opioid Assessment for Patients with Pain (SOAPP). Understanding the differences between dependence, addiction, and tolerance is essential to managing patients on opioids.

CONCLUSION: It is imperative that patients be properly managed when being treated for pain. Physicians and employers have to be able to identify patients at risk for opioid abuse or exhibiting symptoms of opioid abuse and know how to address their needs.

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Drug abuse and dependence are on the rise. The widespread use of opioid analgesics for the treatment of chronic noncancer pain and for acute pain management began in the late 1980s. Between 1980 and 2000, there was an increase from 8% to 16% in the number of patients receiving opioids for chronic musculoskeletal pain and an increase in use from 8% to 11% for acute musculoskeletal pain. In 2002, reports show a 222% increase in the absolute number or prescriptions for opioid narcotics over the previous 10-year period.

Today, the most common method for treating chronic pain is with the use of prescription analgesics, including opioids. In the 1970s, chronic pain patients were encouraged by society to avoid opioids due to concerns that taking opioids invariably led to addiction. In the early 1980s, the pendulum shifted to widespread use of opioids, based on results of a small study (n = 20) showing chronic pain patients could benefit from pain control using opioids with little risk of developing dependence. Additionally, in the 1990s, a review article of several studies showed patients with neuropathic pain experienced relief from opioids.

Unfortunately, many patients continue to take opioids despite inadequate pain control. Patients on chronic narcotic pain medications generate higher costs of health care, have higher surgery rates, a greater level of disability, and higher rates of late opioid use. Late opioid use is defined as receiving ≥ 5 opioid prescriptions between 30 and 730 days after onset of pain, a quantity of prescriptions that is generally beyond what is considered appropriate for symptom control for an acute pain exacerbation. In a retrospective cohort study of 8,443 workers’ compensation claims for acute disabling lower back pain, looking at claims from January 1, 2002, and December 31, 2003, intensive use of opioids early in treatment was associated with worse long-term outcomes, increased use of costly medical services (including surgery), prolonged disability, and continued use of opioids.

One dilemma that arises with using opioids long term is that hyperalgesia (increased pain sensitivity), decreased libido and other hormonal effects, and depression may occur, as well as tolerance. Statistics have shown that at least 1 of these effects is experienced by 51% of all patients taking oral opioids. Another concern is the risk of dependence and addiction. For most of the twentieth century, opioid dependence has been problematic. A review of 24 studies (2,507 chronic pain patients) have shown that there is a 3.3% risk of developing addiction. While this percentage is low, it represents a large population that is hard to manage. Evaluating and re-evaluating patients who are at higher risk of developing addiction is something that all clinicians treating chronic pain patients treated with opioids should be performing on an ongoing basis.
As part of the Food and Drug Administration Amendments Act (FDAAA) of 2007, the U.S. Food and Drug Administration (FDA) may require risk evaluation and mitigation strategies (REMS). The purpose of REMS is to assure the safe use of prescription drugs. In the future, the FDAAA may require providers of health care to obtain certification or special training to prescribe certain prescriptions (such as opioids) and may also require pharmacies to be specially certified to dispense such medications. Additionally, they may require patients who use such medications to be enrolled in a registry or provide evidence of safe use conditions.

In response to such legislation and other legal concerns, many practitioners may shy away from prescribing opioid medications, resulting in undertreatment of pain. The proper management of pain may be affected by concerns over drug diversion, abuse, and addiction. Physicians should be utilizing current treatment guidelines and recommendations. Guidelines and recommendations for the treatment of chronic noncancer pain have been developed by the American Society of Interventional Pain Physicians, the American Chronic Pain Association, and joint guidelines by the American Pain Society and the American Academy of Pain Medicine that aim to best treat pain and reduce abuse and diversion. Guidelines have also been developed to manage patients with substance abuse disorders by the American Psychiatric Association and the Work Group on Substance Use Disorders. Current recommendations include having patients enter into pain management contracts, requiring routine random urine screenings and random pill counts, utilizing available tools to assess the risk of abuse, following proper prescribing practices, and re-evaluating therapy on an ongoing basis. If patients are carefully selected by their physician to receive opioids, nonopioid and nonpharmacological treatments are integrated into the care plan, and patients are assessed for their risk of abuse, proper pain management may be achievable while minimizing the risk of abuse and dependence.

In response to rising rates of opioid abuse and diversion, the FDA has issued black-box warnings on many opioids. Patients who are opioid naive should not be given medications such as extended-release oxycodone or fentanyl patches, lozenges, or buccal tablets. Misuse of products such as these may lead to increased rates of abuse and adverse events (including death). Many drug manufacturers are developing new formulations of opioids that have abuse deterrent properties such as controlled release mechanisms, agonist-antagonist combinations, and delivery devices with tamper resistant properties.

Addiction and abuse affects people of all ages and races. Addiction is similar to other chronic diseases such as diabetes and hypertension, though is rarely managed as such. Genetic studies over the last 10 years have provided evidence needed to define dependence as a chronic disease. Dependence is now beginning to be recognized as a brain disease with behavioral manifestations, as opposed to criminal behavior or a personality disorder. Continued abuse of drugs is not a voluntary behavior; drug abuse can take over a person's ability to wield self-control. Brain imaging studies on drug-addicted patients have revealed changes in areas of the brain responsible for decision making, judgment, memory, learning, and behavior control; these changes may explain the destructive and compulsive actions seen in addiction.

The Harrison Narcotic Act of 1914 allowed physicians to treat opioid dependence. However, the U.S. Supreme Court overturned that act in 1919 and ended office-based opioid treatment. Not until 2002 did office-based opioid treatment return when the FDA approved sublingual buprenorphine for the in-office treatment of opioid dependence. While methadone clinics were established in the mid-1970s, methadone for opioid dependence is not approved for office-based treatment; as such, patients must report to a methadone clinic for treatment.

Defining Dependence

Substance abuse problems often fall into 1 of 2 categories: dependence and abuse. Individuals with opioid dependence may continue to use opioids even knowing there is some deleterious effect from the use of the substance. Addiction and physical dependence are not the same. Any patient on opioids has the potential of developing physical dependence and may suffer withdrawal symptoms upon the discontinuation of the opioid. Due to conflicting definitions of addiction and dependence, a consensus document from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine was developed in 2001. The panel defined the following terms:

Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include 1 or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Addiction is comprised of 4 core elements (the 4 Cs): Compulsive use, inability to Control the quantity used, Craving the psychological drug effects, and Continued use of the drug despite its adverse effects. Some examples of compulsive use consist of preoccupation with taking the drug, stockpiling the drug, and utilizing multiple prescribers (“doctor shopping”) and/or pharmacies to obtain more of the drug. Inappropriate use also consists of selling the drugs to others or injecting/snorting drugs that were not designed to be consumed in that manner. Loss of control is when patients take their medication much more frequently or at higher doses than prescribed. Patients suffering from addiction may also experience a strong desire for the feeling
they experience when taking the drug (feeling “high”), not for pain relief.⁴

**Physical dependence** is a state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation of a drug, a rapid dose reduction, a decreasing blood level of the drug, and/or administration of an antagonist.⁵,²⁸ The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) published by the American Psychiatric Association states that a definite diagnosis of “dependence” requires that 3 or more of the following 6 characteristic features be experienced or exhibited:²⁸,³⁰

1. A strong desire or sense of compulsion to take the drug;
2. Difficulties in controlling drug-taking behavior in terms of its onset, termination, or levels of use;
3. A physiological withdrawal state when drug use is stopped or reduced, as evidenced by the characteristic withdrawal syndrome for the substance or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;
4. Evidence of tolerance, such that increased doses of the drug are required in order to achieve effects originally produced by lower doses;
5. Progressive neglect of alternative pleasures or interests because of drug use, increased amount of time necessary to obtain or take the drug or to recover from its effects; and
6. Persisting with drug use despite clear evidence of overtly harmful consequences, such as harm to the liver, depressive mood states, or impairment of cognitive functioning.

**Tolerance** is a state of adaptation in which exposure to a drug induces changes that result in a diminution of 1 or more of the drug’s effects over time.²⁸

**Pseudoaddiction** is another term that is used frequently. Pseudoaddiction refers to signs of addiction in patients whose addictive behaviors go away when their pain is brought under control.⁴ Examples of aberrant drug-related behaviors seen in pseudoaddiction include unauthorized dose escalation and hoarding of medications.⁶ Pseudoaddiction often occurs when a patient’s pain is poorly treated or undertreated. It is very hard to diagnose pseudoaddiction until the pain is brought under control, which is often hard to achieve.⁵ Certain patients may be misdiagnosed as addicts; to avoid this misdiagnosis, physicians should be educated about proper pain management strategies and be able to assess risk of addiction in their patients.²⁵

Many health care professionals have difficulty understanding the differences between these terms and definitions and how to adequately respond to these concepts.²⁰,³¹ Given this confusion in terminology, it is important for managed care professionals to use consistent definitions that resonate with providers in their network.

**Who Is At Risk for Developing Addiction?**

Risk stratification should be performed when starting patients on opioids for chronic noncancer pain to mitigate risks and enhance benefits of opioid use.¹⁵ Practitioners need to learn how to assess the risk of addiction and aberrant drug-related behavior to protect patients at-risk for developing dependence and to better treat patients who may be at lower risk. In addition to risk stratification, risk management should include use of prescription monitoring programs (if available), compliance monitoring, patient education, psychological screening and psychotherapy, and selection of abuse-deterrent formulations of narcotics when appropriate.³² As predisposition to addiction may be genetic, a family history and personal history of abuse of alcohol or illicit drugs should be obtained.²⁴

There are several tools available to physicians to assess risk of addiction, including:⁵,³³,³⁴

- CAGE (Cutting down, Annoyance by criticism, Guilty feeling, Eye-openers)
- CAGE Aid (CAGE adapted to include drugs)
- ORT (Opioid Risk Tool)
- PADT (Pain Assessment and Documentation Tool)
- SOAPP (Screener and Opioid Assessment for Patients with Pain Version 1)
- SOAPP-R (Revised Screener and Opioid Assessment for Patients with Pain)

Prior to beginning opioid therapy for chronic noncancer pain, patients should also have a psychological assessment to determine their coping skills, social and familial stressors, and prior history of substance abuse.²⁹,³² Risk factors for addiction are multi-factorial. There are environmental, social, biological, or genetic factors that may make an individual more susceptible to abuse and addiction of opioids.³² Genetics may account for between 40% and 60% risk of developing addiction.²⁴ Patients with coexisting mental disorders also experience a higher rate of risk of developing dependence than the general population.²⁴

**Conclusion**

Due to the increased utilization of costly health care services seen in opioid dependent patients, it is imperative that health care providers optimally manage their patients with chronic pain who require treatment with opioids.¹,²,³,¹⁰ Inadequate or inappropriate treatment may lead to prolonged disability and continued use of opioids and may increase the risk of abuse, dependence, and diversion.¹ While identifying patients at risk for developing opioid dependence is difficult, physicians should utilize risk stratification tools available to them to best manage their patients’ pain.⁶,¹¹


Empirical View of Opioid Dependence

Charles Ruetsch, PhD

ABSTRACT

BACKGROUND: The impact of opioid dependence on employers, managed care, and society is significant. Inappropriate use of narcotic analgesics leads to uncontrolled pain management, dependence, and may lead to patient deaths, creating a tremendous cost burden to the health care system.

OBJECTIVE: To provide an overview of the clinical and economic impact of treating opioid dependence on managed care, employers, and society.

SUMMARY: An estimated 6% to 15% of people in the United States abuse drugs, and approximately 20% of Americans report using prescription opioids for nonmedical use. This is associated with an annual cost of nearly half a trillion dollars, taking into account the medical, economic, social, and criminal impact of this abuse. A recent study showed that patients who abuse opioids generate mean annual direct health care costs 8.7 times higher than nonabusers. The National Survey on Drug Use and Health (NSDUH), conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA), found that patients who report opioid abuse miss more than 2.2 days of work monthly, compared with the 0.83 days per month reported for the average person. Presenteeism and productivity are also affected by misuse and dependence on opioids.

CONCLUSION: The costs associated with opioid dependence are significant. Physicians, employers, and managed care organizations must be proactive in appropriately diagnosing and treating patients who suffer from substance abuse disorders in order to lessen this economic burden.

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C hronic pain is typically defined as pain that lasts longer than the usual course of an acute disease, or beyond the time for an injury to heal when the injury is associated with a chronic pathological process causing chronic discomfort. It may also be defined as pain that is persistent and not responsive to routine pain control modalities. There is a role for the use of opioids in treating chronic pain. Due to changes in treatment philosophies, there has been a pendulum-like swing from under-prescribing opioids to overprescribing opioids. Over the past 20 years, there has been an increase in the use of opioids to treat both cancer-related and noncancer pain.

It is estimated that 6% to 15% of the U.S. population abuses drugs, and the abuse of illicit drugs and alcohol contributes to more than 100,000 deaths per year in the United States. Because of this, clinicians may be afraid to prescribe opioids to patients who truly need them for adequate pain control. This “opiophobia” may be due to the lack of training and education in pain management by physicians. Clinicians should be able to differentiate between natural physiological and pathological psychological dependence (addiction). Patients may be mislabeled as addicts and thus have their pain inappropriately managed. While this is beyond the scope of this supplement, it is an important topic and should be considered by managed care professionals when addressing the obstacles a pain management clinician faces.

Effect on Employers

Approximately 20% of Americans have used prescription analgesics for nonmedical purposes. Abuse and dependence on opioids adds an economic burden to employers and managed care providers. Policymakers, health professionals, and leaders in business are often unaware of the high costs associated with substance use disorders. Growing awareness of the issues surrounding substance abuse will benefit patients as well as employers and insurance providers. According to the National Survey on Drug Use and Health (NSDUH) survey, conducted annually by the Substance Abuse and Mental Health Services Administration (SAMHSA), patients who report opioid abuse miss more than 2.2 days of work monthly, compared with the 0.83 days per month missed by the average employee. Employers are starting to realize that patients often start on opioids for legitimate medical reasons but develop dependence due to mismanagement or other risks.

Impact on Society

Data for the NSDUH are collected yearly and include questions to assess the pervasiveness of substance abuse disorders over the previous 12 months. Each year, approximately 67,500 people are surveyed; questions are designed to examine the use of alcohol and illicit drugs, including the nonmedical use of prescription pain relievers. Criteria from the Diagnostic and Statistical Manual
of Mental Disorders, 4th edition (DSM-IV) are used to classify patients as physically dependent upon or abusing certain substances.7,8 The survey also assesses health and emotional disorders among patients who may be abusing or misusing drugs or alcohol. Patients are surveyed on substance use and abuse, tolerance, withdrawal, attempts to reduce use that were unsuccessful, problems at work, home, school, or within their family, or dealings with others, physical danger, and legal trouble resulting from substance use.7

In 2007, 13.3% of respondents (equivalent to 33 million people) to the NSDUH survey reported having used prescription pain relievers nonmedically (i.e., without a prescription, more often or in greater amounts than prescribed, or using for a reason other than prescribed by the physician) in their lifetime.7,9 About 8% of respondents aged 12 and older (equivalent to 19.9 million people) reported being current illicit drug users (defined as use during the month prior to the survey). Illicit drugs include nonmedically used psychotherapeutics (including opioid analgesics), cocaine, heroin, hallucinogens, and inhalants. Of the 19.9 million Americans estimated to use illicit substances, 5.2 million (approximately 1 in 4) used prescription pain relievers nonmedically within the past month. The report states “this was higher than the estimated 4.4 million in 2002, but the difference between the rates in 2002 and 2007 (1.9% and 2.1% of the U.S. population, respectively) was not statistically significant. However, the rate was higher in 2007 (2.1%) than in 2004 (1.8%).”7 In contrast, the number of current heroin users decreased from 0.14% to 0.06% of the population (338,000 to 153,000 people) between 2006 and 2007.”7 (Figure 1).

The prevalence of current (past month) nonmedical use of prescription pain relievers is similar for males (2.5%) and females (2.8%). Illicit drug use is seen in all racial groups. The group with the lowest prevalence is Asians (7.2%), and the group with the highest prevalence are multiracial individuals (22.1%).7

Large numbers of people misuse prescription opioids, or purchase them illegally on the street; the most commonly misused prescription opioids are oxycodone and codeine. While representing only 4.6% of the world’s population, Americans consume 80% of the worldwide opioid supply, including 99% of the hydrocodone supply and 66% of illegal drugs.10 Among patients who reported using prescription analgesics nonmedically within the past 12 months, 56.5% said they received the drug from a friend or relative for free, and 81% of these friends or relatives obtained the prescription analgesic from a single doctor. In addition, 18% of patients using nonmedically reported obtaining a prescription directly from a single doctor, 4.1% reported buying the substance from a stranger or drug dealer, and 0.5% bought the drug over the Internet.7

The NSDUH survey also assesses initiation of, or first-time, substance use. In 2007, approximately 2.7 million people aged 12 or older used an illicit drug for the first time. The categories of illicit drug use with largest number of past year initiates were marijuana and nonmedically used pain relievers, at 2.1 million reported in each category.7 Information on first-time use is valuable to researchers and policy makers, as these measures are often indicators of patterns of substance use, and can be used to assess the effectiveness of prevention programs currently in place. The mean age when patients initiated illicit drug use was 18 years old, with 60.1% of patients younger than 18 years old. The average age of first-time users of nonmedical use of pain medications was 21.2 years old.7 Another study done by the Partnership for a Drug-Free America found nearly 1 in 5 teens (19% or 4.5 million) reported abusing prescription medications to get high; 1 in 10 teens (10% or 2.4 million) reported abusing cough medicine to get high.11

The substance abuse treatment profile is equally complicated. Of those people who were treated for substance abuse during 2007, 17.3% reported that they were being treated for prescription pain reliever abuse. More than half of those treated utilized two or more sources of payment.12 Private insurance contributed to part of the payment for 34.9% of those patients. Medicare paid for 19.7%; Medicaid 18.2%; self-pay as part of payment 53.3%; funds from family 19.6%, and 26.3% reported using public assistance other than Medicaid.7

The Centers for Disease Control and Prevention recently reported that the inappropriate use of the opioid fentanyl led to the deaths of more than 1,000 people between April 2005 and March 2007.5,13,14 Further, between 1999 and 2005, deaths from

![Nonmedical Use of Psychotherapeutic Drugs Within the Past Month Among Persons Aged 12 or Older: 2002-2007](image-url)

* denotes that the difference between this estimate and the 2007 estimate is statistically significant at the 0.05 level.

Source: Substance Abuse and Mental Health Services Administration, Office of Applied Studies (2008). Results from the 2007 National Survey on Drug Use and Health: national findings. NSDUH Series H-34. DHHS publication no. SMA 08-4343.7
unintentional drug poisonings (including prescription opioid analgesics) doubled to 22,448.13 Absenteeism, presenteeism, and productivity are all affected by abuse of opioids. Patients who abuse opioids tend to miss work more frequently and are less productive while at work.3,15

### Diagnosing Dependence

In addition to the 6 criteria listed in the DSM-IV for determining dependence, a seventh criterion of withdrawal (defined by the patient experiencing withdrawal symptoms such as difficulty sleeping, cramps, tremor) was added for the purpose of the NSDUH survey for patients on pain relievers, cocaine, heroin, sedatives, stimulants, and alcohol.7

Patients were defined as abusing substances (as opposed to being dependent upon them) if they met 1 or more of the following criteria:

1. serious problems at work, home, or school due to using the substance
2. regularly using the substance and then performing a task that may put the patient in physical danger
3. repeatedly getting into trouble with the law after using the substance
4. use of the substance led to problems with friends or family, though continuing to use the substance knowing that it caused those problems7

According to the NSDUH survey, 9% of respondents (equivalent to 22.3 million Americans) were classified with substance abuse or dependence based on DSM-IV criteria in 2007. Of those, 1.7 million were abusing or dependent on prescription analgesics (opioids).7 The survey also identified treatment need as receiving treatment at a facility (such as rehabilitation or mental health center), inpatient hospitalization, or having a substance use disorder. The survey estimated a need for treatment for alcohol or illicit drug use in 23.3 million Americans aged 12 or older. Of these 23.3 million Americans, 20.8 million did not receive treatment. Of those 20.8 million, 1.3 million said they felt they needed treatment for their illicit drug or alcohol use, with 28.5% saying they made an effort to get treatment and 71.5% reporting they made no effort.7

Data from the Drug Enforcement Administration (DEA) illustrates the staggering increase in use of opioids from 1997.16 Figure 2 is derived from the DEA’s Automation of Reports and Consolidated Orders System (ARCOS), which monitors the flow of Controlled Substances from their point of manufacture through commercial distribution channels to point of sale or distribution at the dispensing/retail level—hospitals, retail pharmacies, practitioners, mid-level practitioners, and teaching institutions.16 For example, total oxycodone use in grams per 100,000 U.S. population increased from 1,668 grams in 1997 to 13,333 grams in
In addition to the increased use of opioids, the Centers for Disease Control and Prevention also reported a 62.5% increase in opioid deaths between 1999 to 2004.18,19,20

Burden and Cost
The presence of chronic pain is prevalent in 2% to 40% (median 15%) of the adult population, with 48% reporting back pain as the source of their chronic pain.1 While the duration and chronicity of chronic pain is controversial, some studies show that chronic low-back pain and neck pain lasting 5 years or longer after the initial occurrence is seen in up to 60% of adult and pediatric patients.21 It has been estimated that patients with back pain cost health care approximately 60% more than patients without back pain ($3,498 vs. $2,178).1 The American Society of Interventional Pain Physicians (ASIPP) further estimates that the cost of treatment for patients with chronic noncancer pain is higher than the costs to treat cancer, AIDS, and coronary artery disease combined in the United States, citing failed back surgeries and continued care (including prescription pain relievers) leading to increased cost.1

Nearly half a trillion dollars are spent in the United States yearly on expenses associated with medical, economic, social, and criminal impact caused by the use and abuse of addictive substances (including opioid pain medications, illicit drugs, alcohol, and nicotine).3 A 2005 study by White et al. found that opioid abusers are associated with 8.7 times higher mean annual direct health care cost than nonabusers ($15,884 versus $1,830, respectively, P<0.01).22 The study also found that hospital inpatient and physician-outpatient costs accounted for 46% ($7,239) and 31% ($5,000) of opioid abusers’ health care costs compared with 17% ($310) and 50% ($906), respectively, for non-abusers. Opioid abusers generated drug costs that were more than 5 times higher than costs for non-abusers ($2,034 versus $386, respectively, P<0.01). Costs are significantly higher when the comorbidity of depression is taken into account. Even when the study used a matched control of depressed patients, the average health care costs of opioid abusers were 1.8 times higher than the average health care costs of depressed patients.22 It has been observed that 39% to 47% of patients who seek treatment for opioid dependence have documented psychiatric comorbidities.23 Opioid users also have a higher rate of depression compared with nonusers (16% vs. 6%).24,25,26

Several barriers to treatment exist. A 2005 Drug Abuse Warning Network (DAWN) report examined emergency room admissions for nonmedical use of prescription drugs and found that 33% of these admissions were due to opioids or opioid combinations.27 This figure may be underestimated due to the stigma attached to opioid dependence, a stigma that can be so overwhelming that every year thousands of patients choose to continue using opioids rather than risk possible exposure by receiving treatment. In addition to stigma, other reasons for not receiving treatment were found in the NSDUH report, including the patient was not ready to stop using (38.7%), the patient had no health coverage and could not afford cost (31.1%), a possible negative effect on employment (11.6%), patient not knowing where to go for treatment (11.6%), and patient concern that receiving treatment might cause neighbors/community to have negative opinion (11.1%).28

Effect on Managed Care
Mean annual direct health care costs for opioid abusers can be more than 8 times higher than for nonabusers ($15,884 versus $1,830, respectively, P<0.01),29 highlighting the importance of finding cost-effective medications for the treatment of opioid dependence. The real-world direct drug cost of buprenorphine/naloxone in 2010 is about $250 per prescription, more than 10 times the direct drug cost of methadone.30 However, it is possible that buprenorphine is cost-effective compared with methadone for the treatment of opioid dependence when all of the cost factors are considered including the costs of dispensing, counseling, toxicology screens, and administrative and capital costs.31 Cost savings may be derived from treatment adherence, and lower utilization of health care services/counseling that are realized in subsequent years may contribute enough to offset the direct drug cost of buprenorphine/naloxone.

Conclusion
Abuse and dependence upon opioids, including prescription analgesics and heroin, affect not only the individual’s health, but also add to the financial burden of their families, employers, and health insurance carrier. For both health reasons and financial burden, it is imperative that opioid dependent people get the treatment that they need.1,17,19 Physicians and payers can help opioid dependent individuals, their families, and the health of their practices and managed care organizations by appropriate screening and treatment of opioid dependency.

REFERENCES
Empirical View of Opioid Dependence


Opioid Dependence Treatment and Guidelines

Lance Nicholls, PharmD; Lisa Bragaw, RPh; Charles Ruetsch, PhD

ABSTRACT

BACKGROUND: In response to the growing incidence of opioid dependence, guidelines have been created, and new treatments are being developed to assist physicians in treating dependence and withdrawal of opioids.

OBJECTIVE: To review treatment modalities and guidelines utilized in opioid dependence.

SUMMARY: Guidelines for the treatment of opioid dependence have been developed by organizations such as the American Society of Interventional Pain Physicians (ASIPP) and the American Psychiatric Association (APA). Current guidelines recommend comprehensive treatment with pharmacological agents such as methadone, buprenorphine, or buprenorphine combined with naloxone as well as psychosocial therapy. These guidelines stress the need for an integrated approach to treatment. Office-based opioid treatment is currently being utilized to treat opioid dependent patients in a physician’s office setting with buprenorphine/naloxone replacement therapy as an alternative to entering patients into a methadone clinic. These office-based programs offer a breakthrough in access to care for dependent patients.

CONCLUSION: Physicians need to be aware of and adhere to currently accepted guidelines and recommendations for treating opioid dependent patients, including integrating psychosocial treatments and behavior modification strategies for optimal results. Clinicians must be educated on the new treatment modalities and regulations surrounding the use of these therapies.

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In response to the increased incidence of opioid abuse, the large degree of variance in patterns for prescribing opioids, and the many different medical specialties involved in treating patients with chronic pain, the American Society of Interventional Pain Physicians (ASIPP) has developed guidelines to help direct physicians who are treating chronic noncancer pain with opioids to better improve the treatment of these patients and reduce the rate of drug diversion. ASIPP notes that these guidelines are not intended to be a standard of care, as the body of evidence surrounding opioid use and misuse is constantly changing.1,2 Physicians should be encouraged to develop and establish care plans for each of their patients based on that patients needs and risk factors.1,2

Wherever the treatment location or circumstances, some guidelines have suggested criteria to consider when treating opioid dependence. The following criteria were developed by the American Society of Addiction Medicine (ASAM) to consider in the treatment of dependence:3

1. acute intoxication and/or withdrawal potential
2. biomedical conditions and complications
3. emotional, behavioral, or cognitive conditions and complications
4. readiness to change
5. relapse, continued use, or continued problem potential
6. recovery/living environment

The American Psychiatric Association (APA) guideline identified the following 3 treatment modalities to be effective strategies for managing opioid dependence and withdrawal. (Please also refer to Table 1).4,5

1. opioid substitution with methadone or buprenorphine, followed by a gradual taper
2. abrupt opioid discontinuation with the use of clonidine to suppress withdrawal symptoms
3. clonidine-naltrexone detoxification

Anesthesia-assisted rapid opioid detoxification is no longer recommended due to a high incidence of adverse events (including severe pulmonary edema and aspiration pneumonia) that do not outweigh the benefit of treatment.6,7

The APA guideline stresses that psychosocial treatments are an essential component of a comprehensive treatment program. As one of the recommended psychosocial treatments, the guideline indicates that the community reinforcement approach (CRA) has been effective in alcohol dependence and, in theory, may help with opioid dependence. The basis of CRA is that patients with substance use disorders (SUD) lack positive reinforcement in their environment regarding finding activities that are pleasurable when sober, and that reinforcers for substance use may perpetuate SUD. CRA is geared at providing alternative positive reinforcers and rewarding community and familial involvement. Friends and family members serve to reinforce positive behaviors
and promote a sober lifestyle in order to enable the patient to remain abstinent. Patients in CRA programs are also provided with job counseling and training, marriage counseling, and incentives like vouchers for recreation or food to promote and reward sober behaviors.6

### Treatment Modalities

#### Treatment for Acute Opioid Intoxication

Mild to moderate acute opioid intoxication does not usually require treatment, but a severe opioid overdose requires emergency medical management to treat respiratory depression induced by naloxone.5,8 Once acute symptoms are resolved, patients should be treated for opioid withdrawal and enrolled in a long-term treatment plan or program.8

**Clonidine.** Clonidine is generally considered a safe, non-narcotic medication used to help patients withdraw from opioids. It is a centrally acting alpha-2 adrenergic agonist and works to minimize the noradrenergic hyperactivity seen in opioid withdrawal.5,6 Clonidine is not currently approved as a treatment for opioid withdrawal in the United States but has been studied in other countries extensively.8 For opioid withdrawal, clonidine is typically dosed at 0.1 mg to 0.3 mg orally up to every 6 hours.4,5,6 The use of clonidine in opioid withdrawal is limited because of its hypotensive and sedative adverse effects. It also does not manage withdrawal symptoms such as cravings and general malaise.9 One benefit of clonidine is that it does not produce tolerance or dependence like opioid medications and can be immediately given with naltrexone (an opioid antagonist) if warranted.6

Contraindications to clonidine use include renal dysfunction, cardiac disorders, and hypotension.6 Clonidine-assisted opioid detoxification is typically done in the inpatient setting, so physicians can best monitor the patient. If treatment is going to be administered in the outpatient setting, it is generally recommended that it should be under the guidance of experienced staff and that patients should not be given more than a 3-day supply of medication.6

Some clinicians will rapidly withdraw patients from opioids using a combination of clonidine and naltrexone. The patient is pretreated with clonidine to avoid some of the abrupt withdrawal symptoms caused by the naltrexone. This regimen is sometimes used to transition patients into narcotic antagonist therapy.6

**Naltrexone.** Naltrexone is a mu-receptor antagonist. It also antagonizes the kappa-receptor, and weakly antagonizes the delta-receptor. The mu- and kappa-receptors are responsible for analgesia, sedation, respiratory depression, euphoria, and dependence. Stimulation at the delta receptor provides analgesia and possibly psychomimetic and dysphoric effects. Naltrexone’s active metabolite is 6-ß-naltrexol, which provides the opioid antagonism.1 When used in conjunction with clonidine for opioid withdrawal, naltrexone is usually dosed between 50 mg and 100 mg daily and can also be dosed 3 times weekly.4,5,6

Patients given clonidine and naltrexone must be monitored closely throughout the withdrawal process, especially during the first 8 hours of therapy, due to the potential severe withdrawal symptoms and risk of hypotension.6

#### Opioid Substitution Therapies

Methadone or buprenorphine maintenance therapy is appropriate for use in patients who have a history of dependence lasting more than 1 year.8 Methadone replacement therapy became the first treatment modality for opioid dependence, and its use became widely available in the late 1960s.10 Buprenorphine is a newer treatment modality that became available for office-based opioid treatment in 2000.11

**Methadone.** The use of methadone in opioid dependence dates back to 1950, when oral methadone was being used by U.S. Public Health Service hospitals in the treatment of opioid abstinence syndrome. In 1968, in response to the rising rates of heroin addiction, Drs. Marie Nyswander and Vincent Dole began research that led to the use of once daily dosing of methadone to prevent symptoms of opioid withdrawal and craving.10,12

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**TABLE 1 Common Medications for Opioid Dependence**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Action</th>
<th>Indication</th>
<th>Dosage</th>
<th>Frequency</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>Partial opioid agonist</td>
<td>Withdrawal &amp; maintenance</td>
<td>2-32 mg sublingual</td>
<td>Daily or 3 times per week</td>
<td>Respiratory depression, headache, constipation</td>
</tr>
<tr>
<td>Clonidine</td>
<td>α2-adrenergic antagonist</td>
<td>Withdrawal</td>
<td>0.1-0.3 mg orally</td>
<td>Every 6 hours</td>
<td>Bradycardia, hypotension, dry mouth, drowsiness</td>
</tr>
<tr>
<td>Levomethadyl acetate</td>
<td>Opioid agonist</td>
<td>Maintenance</td>
<td>25-100 mg orally</td>
<td>3 times per week</td>
<td>QT prolongation, Constipation</td>
</tr>
<tr>
<td>Methadone</td>
<td>Opioid agonist</td>
<td>Withdrawal &amp; maintenance</td>
<td>20-100 mg orally</td>
<td>Daily</td>
<td>Constipation, respiratory depression, dizziness, nausea, sedation</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Opioid antagonist</td>
<td>Withdrawal &amp; maintenance</td>
<td>50-100 mg orally</td>
<td>Daily or 3 times per week</td>
<td>Anxiety, nausea, myalgia</td>
</tr>
</tbody>
</table>

Adapted from: Fiellin DA, O’Connor PG. Office-based treatment of opioid-dependent patients. New Eng J Med. 2002;347:817-23. 4 Lexi-Comp (Lexi-Drugs, comp + specialties) [computer program]. Lexi-Comp; Mar 28, 2009. 5 For more information, please refer to the prescribing information for these drugs.
Though originally developed in 1939, methadone was not widely used as a pain reliever until World War II, possibly because initial doses were too high which resulted in intolerable adverse effects. In 1947, Eli Lilly bought the commercial rights for methadone for $1 and coined the brand name “Dolophine” from the Latin words “dolor” (pain) and “finis” (end).

By 1971, an estimated 25,000 patients were enrolled in a methadone maintenance treatment (MMT) program. Following the enactment of federal regulations (21 CFR Part 291) in 1972 and the Narcotic Addict Treatment Act of 1974, methadone use became restricted to a closed system requiring that doctors and pharmacies be registered to provide methadone treatment (regardless of the indication), resulting in the creation of federal- and state-licensed methadone clinics. In 1976, the American Pharmaceutical Association (now known as the American Pharmacists Association) won a lawsuit to allow pharmacies to dispense methadone solely for treatment of pain, not to treat dependence. Currently, methadone for the use of outpatient maintenance and detoxification may only be provided by Opioid Treatment Programs (OTP) certified by the Federal Substance Abuse and Mental Health Services Administration (SAMHSA) and registered by the Drug Enforcement Administration (DEA).

However, exceptions may be made to allow a patient to continue with methadone maintenance treatment if admitted to the hospital for conditions other than opioid dependence and requires temporary methadone maintenance during the hospital stay (in accordance with 21 CFR 1306.07(c)).

**Pharmacology of Methadone.** Methadone hydrochloride is available commercially in 5 mg and 10 mg scored tablets and should be stored at controlled room temperature. Methadone is an opioid receptor agonist at the mu-receptor. It is also an antagonist at the N-methyl-D-aspartate (NMDA) receptor. The commercial drug is a synthetic racemic mixture. The R isomer (R-methadone) is believed to be responsible for its analgesic properties, while the S isomer (L-methadone) is the NMDA antagonist and may be responsible for toxicities, including prolonged QTc (corrected QT interval). The NMDA antagonism is beneficial in severe neuropathic and “opioid-resistant” pain. The NMDA receptor mediates opioid tolerance, thus antagonism at this receptor may reverse opioid tolerance. The S-isomer inhibits the reuptake of norepinephrine and serotonin as well.

The bioavailability of methadone following oral administration is highly variable and ranges from 36% to 100%, with peak plasma concentrations being reached between 1 to 7.5 hours. It is a highly lipophilic drug which binds predominantly to a1-acid glycoprotein. It is 85% to 90% protein bound in plasma. Metabolism is primarily via N-demethylation to the inactive metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), which is excreted in the urine. Methadone is primarily metabolized by CYP3A4 and secondarily by CYP2D6. It is also metabolized through CYP2B6, CYP2C19, CYP2C9. Therefore, enzyme inducers such as carbamazepine, nevirapine, phenobarbital, phenytoin, rifampin, saquinavir, and St John's Wort may decrease levels of methadone, which could potentiate withdrawal symptoms. Inhibitors of these enzymes, such as macrolide antibiotics (such as erythromycin), ketoconazole, fluvoxamine, clopidogrel, itraconazole, halofantrine, sertraline, and ticlopidine may increase methadone levels, enhancing its effects and toxicities.

Patients should be counseled to notify their physicians about any over-the-counter or herbal products they are taking to assess for interactions. Clinicians should be advised to evaluate each patient’s medication list to identify potential drug interactions and evaluate response to therapy before adjusting methadone dosages.

The half-life is highly variable, ranging from 8 to 59 hours, and is thought to be due to a bi-exponential model. The initial decline in plasma levels occurs within 2 to 3 hours, followed by the terminal phase of 15 to 60 hours. The analgesic effects of methadone are typically much shorter than its half-life. Analgesic dosing every 8 hours may lead to drug accumulation and potential adverse effects such as Torsades de Pointes.

Methadone is indicated by the U.S. Food and Drug Administration (FDA) for the treatment of moderate to severe pain that is unresponsive to non-narcotic pain medications, for the detoxification of opioid addiction, and for maintenance treatment of opioid dependence in conjunction with social and medical services. It is contraindicated in patients with respiratory depression, acute bronchial asthma, or hypercarbia (high blood levels of carbon dioxide). The peak respiratory depression caused by methadone persists longer than its analgesic action, especially in the initial dosing period. Therefore, iatrogenic overdose is often seen during the initiation of treatment or when titrating methadone doses. A black-box warning has been added to the prescribing information stating the risk of cardiac and respiratory-related deaths after the initiation of methadone treatment. Clinicians are strongly advised to review and understand the pharmacokinetics of methadone when initiating therapy and converting patients to methadone from other opioid analgesics. Careful attention is required especially at the initiation of treatment and when titrating doses. Most cases of respiratory depression, QT prolongation, and cardiac arrhythmias (including Torsades de Pointes) have occurred in patients on high doses of methadone, but these adverse events have been observed in doses used for maintenance of opioid dependence as well.

Patients who are concomitantly on other opioids, benzodiazepines, other sedatives, and other CNS depressants are at increased risk of respiratory depression, hypotension, sedation, or coma. Due to the potential risks of prolonging the QT interval, caution should be used when co-administering other agents with known risk of QT prolongation, including some neuroleptics, tricyclic antidepressants, and calcium channel blockers.

As a Schedule II narcotic, methadone has an abuse potential similar to morphine and carries the risk of misuse, abuse, or
criminal diversion. Physicians should be aware of tools used to assess risk of abuse in order to best treat patients who require methadone for the management of pain. Abuse and misuse of methadone increases patients' risk for overdose and death, especially when consumed concurrently with alcohol and other substances such as benzodiazepines. Tolerance and physical dependence are commonly seen during chronic therapy, and methadone treatment should not be stopped abruptly. Withdrawal symptoms of methadone consist of restlessness, yawning, perspiration, myalgia, chills, lacrimation, anxiety, irritability, joint pain, weakness, abdominal cramps, nausea, vomiting, diarrhea, hypertension, and increased respiratory or heart rate.

For management of opioid dependence and detoxification, the treatment standards cited in 42 CFR Section 8.12 for methadone administration should be followed. Medication-assisted methadone treatment usually lasts at least 12 months and can continue for 2 years or more. The length of treatment usually depends on individual patient needs, accounting for past instability (past dysfunction related to work, relationships, and behavior) and chronicity (length of opioid misuse/abuse and previous response to treatment). The typical initial dose is 20-30 mg once daily and should not exceed 30 mg; this dose is usually sufficient to suppress withdrawal symptoms. The typical maintenance dose range is 80-120 mg per day, with dosing adjustments being made over the first week based on withdrawal symptoms.

Patients may choose short-term detoxification (a shorter period of withdrawal under medical supervision) or opt for maintenance treatment. When and if patients are ready to taper off methadone after a prolonged period of maintenance, it should be under medical supervision. Dose reductions should be less than 10% of the maintenance dose and there should be a period of 10 to 14 days between dose reductions. Patients should be monitored for signs of relapse when withdrawing from methadone maintenance treatment. Common side effects of methadone are similar to other opioids and include constipation, dizziness, sedation, lightheadedness, nausea and vomiting; less common side effects include itching, dry mouth, headache, weakness, and hypotension. Patients should be informed of the risk of addiction and abuse associated with methadone use, as well as contraindications and side effects, including signs and symptoms of respiratory depression and cardiac problems potentially associated with methadone use. A baseline and follow-up ECG may be warranted. Patients should be educated to prevent theft and misuse and advised to avoid illicit drugs and alcohol. Patients should be encouraged to seek other services, such as psychological counseling and pain management for their underlying pain condition.

Office-Based Opioid Treatment

Treatment for opioid dependence has different approaches such as pharmacologic, psychosocial or behavioral counseling and other options. Office-based opioid treatment evolved after passage of the Drug Addiction Treatment Act of 2000 (DATA 2000), allowing physicians to use some Schedule III-IV drugs such as buprenorphine and combinations thereof. Physicians who wish to treat opioid dependence with buprenorphine and buprenorphine/naloxone in their offices must qualify for a waiver under DATA 2000 by meeting 1 or more of the following criteria in addition to holding a valid and current state medical license and DEA registration number:

- subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties
- addiction certification from the American Society of Addiction Medicine
- subspecialty board certification in addiction medicine from the American Osteopathic Association
- completion of at least 8 hours of training with respect to the treatment and management of opioid-addicted patients, sponsored by an organization authorized in the DATA 2000 legislation, or by another organization that the Secretary of the Department of Health and Human Services deems appropriate
- has participated as an investigator in clinical trials leading to the approval of a Schedule III, IV, or I narcotic drug for maintenance or detoxification treatment

The DEA will issue qualified physicians a second DEA number beginning with an “X” after the physician has notified the Center for Substance Abuse Treatment (CSAT) that they have met the above criteria. When the program first started, physicians were limited to treating only 30 patients; however, in 2007, that limit was raised, allowing physicians to treat up to 100 patients for opioid dependence.

Buprenorphine and Naloxone Replacement Therapy—Pharmacology and Pharmacokinetics

Buprenorphine is a partial mu-receptor agonist and an antagonist at the kappa-receptor. Buprenorphine has a high affinity for the mu-receptor, but at low efficacy, thus exhibiting opioid agonist activity and producing a dose-related response, but producing no additional effect beyond a certain point (it has a ceiling effect with regards to opioid response). A ceiling effect is where the analgesic effect plateaus and no additional benefit is seen by increasing the dose, but an increase in the adverse opioid effects is anticipated. The activity expressed at the kappa-receptor provides analgesic activity, and also provides benefits for use in opioid deterrence, maintenance, and detoxification. Also, because of the partial activation of the mu-receptor, patients are less likely to abuse buprenorphine. The high affinity for the mu-receptor coupled with the slow rate of disassociation from the receptor may block the effects of other opioids by displacing those other agents from the receptor. However, this same action may cause withdrawal symptoms in patients who have consumed opioids recently. For this reason, patients are typically initiated on buprenorphine or buprenorphine/naloxone therapy under medical supervision and...
after they have already started to exhibit signs and symptoms of withdrawal, with the goal of transitioning the patient from a state of physical dependence on opioids to an opioid-free state, while aiming to minimize withdrawal symptoms in the patient.\textsuperscript{18}

Naloxone is a competitive antagonist at the mu- and kappa-receptors, though it exhibits most of its action at the mu-receptor.\textsuperscript{1,13} The bioavailability after oral and sublingual dosing is low, but parenteral administration leads to a rapid onset of action leading to rapid reversal of opioid effects. It is added as an abuse deterrent; adding naloxone to buprenorphine reverses the opioid effects if a patient were to crush and inject buprenorphine/naloxone.\textsuperscript{1,13} Buprenorphine is roughly 96% protein bound to alpha-and beta-globulin, while naloxone is about 45% bound primarily to albumin. Buprenorphine is metabolized by glucoronidation and by N-dealkylation via the cytochrome P450 3A4 isoenzyme to the active metabolite norbuprenorphine. Norbuprenorphine may also undergo further glucoronidation. Naloxone is metabolized by direct glucoronidation to naloxone 3-glucoronide and by N-dealkylation.\textsuperscript{11} The mean elimination half-life of buprenorphine and naloxone is 37 hours and 1.1 hours, respectively.\textsuperscript{11}

Buprenorphine undergoes significant first-pass metabolism, yet due to high lipid solubility, has excellent sublingual bioavailability, with an onset of action being seen within 30 to 60 minutes, and peak effect between 90 and 100 minutes.\textsuperscript{13} Approximately two-thirds of buprenorphine is eliminated in the feces, the remaining third is excreted in the urine. Because of the extensive hepatic metabolism of both buprenorphine and naloxone, dosage adjustments should be considered in patients with decreased liver function, and patients should be monitored for signs and symptoms of opioid withdrawal due to the potential for elevated levels of naloxone. No dosage adjustments are required for renal failure.\textsuperscript{1,13}

Due to the metabolism through the CYP 3A4 isoenzyme, patients receiving agents that are CYP 3A4 inhibitors (azole antifungals, macrolide antibiotics, and HIV protease inhibitors) should be closely monitored, and dose adjustments may need to be made. Additionally, patients receiving a concomitant CYP 3A4 inducer (phenobarbital, carbamazepine, phenytoin, and rifampin) should also be monitored, and dose adjustments may need to be made.\textsuperscript{3} As buprenorphine can alter the level of liver enzymes, liver function should be monitored periodically depending upon any recent symptoms or history of hepatitis.\textsuperscript{20}

Buprenorphine is available as 2 mg and 8 mg sublingual tablets as a single agent, and in combination with naloxone, in 2 mg buprenorphine/0.5 mg naloxone or 8 mg buprenorphine/2 mg naloxone sublingual tablets.\textsuperscript{11} The single agent is primarily used in the initial phase of detoxification from long-acting opioids (methadone, sustained-release morphine, or sustained-release oxycodone), as the naloxone may precipitate withdrawal symptoms in the beginning of replacement therapy in patients withdrawing from these agents.\textsuperscript{3} The sublingual buprenorphine and sublingual buprenorphine/naloxone are only approved dosage forms of buprenorphine for office-based opioid treatment.\textsuperscript{13}

The typical dose range for buprenorphine is 2-32 mg per day, with the average dose being 16 mg, where 96% of opioid receptor coverage is achieved. The most common side effects include constipation and nonspecific headache.\textsuperscript{11}

**Phases of Office-Based Opioid Treatment**

With regards to buprenorphine, there are 3 phases in treating the patient. They are induction, stabilization, and maintenance.\textsuperscript{18} During the induction phase, patients must be experiencing mild withdrawal symptoms and to have avoided opiates for at least 6 hours.\textsuperscript{3} Clinicians can use the Clinical Opiate Withdrawal Scale (COWS) or the Adjective Rating Scale for Withdrawal (ARSW) to determine withdrawal status.\textsuperscript{9} The goal of this phase is to determine the minimum dose of buprenorphine required to prevent further withdrawal symptoms, reduce cravings, and provide minimal adverse effects.\textsuperscript{18} When patients are no longer experiencing withdrawal symptoms, they have entered the stabilization phase of treatment. At this time, patients should be following up frequently with their physicians, and dose adjustments may be needed to obtain levels adequate to reduce cravings, yet minimize adverse drug effects.\textsuperscript{18,19} This phase typically lasts one to two months.\textsuperscript{19}

The maintenance phase is the longest phase of treatment. Medication-assisted buprenorphine treatment usually lasts at least 6 months and can continue for 2 years or more. Similar to methadone treatment, the length of buprenorphine treatment usually depends on individual patient needs considering past instability (past dysfunction related to work, relationships, and behavior) and chronicity (length of opioid misuse/abuse and previous response to treatment).\textsuperscript{20} If the patient regularly has negative urine toxicology screens and receives a stable dose of buprenorphine, the doctor may extend the intervals between visits to up to 30 days.\textsuperscript{18} During the maintenance stage, psychosocial and family issues must be addressed to help the patient be successful in avoiding opioids and managing dependence.\textsuperscript{18}

**Methadone Versus Buprenorphine Replacement Therapy**

Helm et al.\textsuperscript{13} reviewed several studies including a randomized, double blind, parallel group study conducted by Johnson et al. that found buprenorphine (16 to 32 mg) to be as effective as high-dose methadone (60 to 100 mg) in reducing opioid use in short-term maintenance (at 17 weeks) compared with low-dose methadone (20 mg per day).\textsuperscript{21} In 2003, Mattick et al. determined that both buprenorphine and methadone are effective in opioid dependence treatment.\textsuperscript{22} A total of 405 opioid dependent individuals (as defined by DSM-IV criteria) were randomized into 2 treatment groups. One group received sublingual buprenorphine, while the other received oral methadone. A flexible dosing schedule was utilized, individualized to the patient’s needs in each arm of the study. Minimum and maximum doses of therapy were 2 mg/32 mg for buprenorphine and 20 mg/150 mg for methadone,
The outcomes measured were retention in treatment, negative urine samples, and measures of illicit drug use and risk behavior utilizing the Opiate Treatment Index and Symptom Checklist. Social functioning, physical and mental status were also evaluated. Over the 13-week trial period, 54.8% of patients completed the trial. The trial did not find a statistically significant difference between treatments in the percentage of patients retained for the full 13 weeks of treatment (59% of the methadone group vs. 50% of the buprenorphine group; \( P = 0.061 \)).^{13,22}

The American Academy of Family Physicians (AAFP) has issued clinical recommendations based on the Strength of Recommendation Taxonomy (SORT) evidence rating system.\(^{23}\) The strength of SORT evidence ratings are ranked as A, B, or C ratings. An A rating is given when there is “consistent, good quality patient-oriented evidence,” a B rating is assigned where there is “inconsistent or limited quality patient-oriented evidence,” and a C rating denotes “consensus, disease-oriented evidence, usual practice, expert opinion, or case series.” The AAFP clinical recommendations state that “buprenorphine should be used to effectively manage opioid dependence” and have assigned an A rating for this recommendation.\(^{19}\)

Marsch et al. conducted a study of opioid-dependent adolescents to evaluate the relative efficacy of both buprenorphine- and clonidine-assisted withdrawal. Both medications were provided with 3 times weekly behavioral counseling and incentives contingent on opiate abstinence during the detoxification. A greater number of adolescents who received buprenorphine remained in treatment (72% versus 39%, \( P < 0.05 \)), and achieved markedly greater levels of abstinence from opioids (determined by negative urine tests) compared with those receiving clonidine (64% vs. 32%; \( P = 0.01 \)).^{15,20}

Effective alternatives to long waiting lists for entry into methadone maintenance treatment have been studied.\(^{27}\) Schwartz et al. compared the effectiveness of interim methadone maintenance (i.e., consisting of an individually determined methadone dose and emergency counseling only for up to 120 days) with that of the usual waiting list condition and found that interim methadone maintenance resulted in a substantial increase in the likelihood of entry into comprehensive treatment.\(^{27}\)

Adherence and persistence to treatment protocols are also very low. A retrospective drug use evaluation was conducted on patients receiving buprenorphine-naloxone in a managed care population.\(^{28}\) Persistence was determined by examining prescription claims data and defined as a gap of 30 days or less between expected refill date and the actual refill date. A total of 84 patients met study inclusion criteria; among these patients, the study found persistence rates of 47.6% at 1 month, 27.4% at 6 months, and 20.2% at 12 months. Utilization of opioids decreased by 18.8% from the pre-treatment to post-treatment period (1.49 opioid prescriptions PMPM vs. 1.21 opioid prescriptions PMPM; \( P = 0.031 \)). The actual drug cost of opioids including buprenorphine-naloxone appeared to be 26.9% lower ($156.24 PPM in the post period compared with $213.74 PPM in the pre period, but the difference was not statistically significant (\( P = 0.254 \)). Currently no studies have evaluated gaps in therapy greater than one month, which may indicate relapse and restarts of treatment, so it is challenging to identify true rates of relapse.\(^{28}\) Results showed that almost one-half (47.5%) of patients requiring opioid detoxification did not receive prescription opioids through an outpatient pharmacy during the 6-month period preceding opioid detoxification, suggesting that patients in need of buprenorphine-naloxone therapy obtain opioids illicitly, or use other illicit drugs, such as heroin. It is difficult to evaluate true cost savings of therapy as administrative claims databases do not capture the cost of illicit opioid use.\(^{28}\) In a retrospective chart review, Cadiero et al. reported that patients had an average of 3.4 prior substance use treatments prior to receiving induction of buprenorphine.\(^{29}\)

One recent study found the cost of providing 1 month of treatment per patient was $147 in methadone clinic treatments, $220 in methadone office treatments, and $336 buprenorphine office treatments (\( P < 0.001 \)).\(^{30}\) Mean monthly medication cost was $93, $86, and $257, respectively (\( P < 0.001 \)). The cost to patients was $92, $63, and $38, respectively (\( P = 0.102 \)), demonstrating that while the overall cost of buprenorphine is higher, the cost to the patient for buprenorphine therapy is lower.\(^{30}\) Another analysis of 259 published articles of economic evaluations of treating opiate dependence found that most studies used narrow treatment perspectives and surrogate outcome measures, concluding that the quantity and quality of economic evaluations are limited, evidence on cost-effectiveness of psychosocially-assisted pharmacotherapy is virtually nonexistent, and that most economic evaluations of treatment options are limited in terms of the range of costs and benefits considered.\(^{31}\)
## Conclusion

Office-based treatment programs are a breakthrough in access to care for patients who find it difficult to attend an outpatient program daily and who are not able to travel long distances to obtain treatment. These programs also allow for better integration of health care needs for patients and thus serve to improve the quality of care provided. Buprenorphine and buprenorphine/naloxone have a better safety profile in cases of overdosing than methadone and can be given every 2 to 3 days as tolerated rather than every day as is the case for methadone. Prescriptions can be filled at the local pharmacy rather than visiting a clinic daily.6,11

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Patient Perspective, Complexities, and Challenges in Managed Care

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ABSTRACT

BACKGROUND: Lack of coordination of care is one of the largest obstacles involved with treating opioid dependence. Physicians also face the challenges of managing comorbidities and dealing with relapse.

OBJECTIVE: To examine the clinical, economic, and humanistic factors involved in treating opioid dependence.

SUMMARY: Despite the extensive utilization of narcotic analgesics, pain is often uncontrolled. Effective pain management and coordination of care is essential in treating pain patients, as patients who abuse pain medications consume more health care resources than nonabusers. Patients who abuse are 2.3 times more likely to present at the emergency department and 6.7 times more likely to be hospitalized than nonabusers. Managed care organizations are now incorporating integrated approaches to treating pain and substance abuse disorders, realizing that patients must be looked at as a whole, considering alternative and behavioral therapies in addition to pharmacological treatments. They are also able to assess patterns of abuse using pharmacy claims data and alert physicians to potential problems by making use of prescription monitoring programs. Physicians who treat chronic pain must utilize strategies to minimize the risk of developing dependence on opioids, and practitioners treating opioid dependence must employ policies to optimize outcomes. Such strategies include developing pain contracts; performing random urine screenings and pill counts; and setting goals of therapy and re-evaluating patients throughout treatment. Plans must be in place in the event of relapse, as well.

CONCLUSION: In order to be successful in managing opioid dependence, physicians, employers, and managed care organizations must work together to provide an integrated approach to treatment.

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DISCLOSURES

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Lack of Coordination of Care. The lack of coordination of care in chronic pain treatment is critical. Often a primary care physician is prescribing opioids, but the patient may see other practitioners who also prescribe pain medications. The traditional approach of opioid management within a managed care organization (MCO) has been to look at medical and pharmacy claims data and try to identify multiple prescribers and multiple pharmacies for a patient receiving opioids. Many patients with drug-seeking behaviors will go to multiple pharmacies, often paying cash for their opioids, in order to obtain more medication or to avoid being caught going to multiple prescribers (“doctor shopping”). If the claims are not being billed to the MCO or pharmacy benefit managers (PBM), it is much more difficult to be tracked, as MCOs can only report on the prescriptions for which they are being billed. If a MCO identifies a patient going to multiple prescribers and pharmacies, they may limit the patient to 1 pharmacy, or notify the prescribing physicians. MCOs collaborate with PBMs to perform drug utilization reviews, individual profile reviews, and perform reviews for fraud and abuse. MCOs and PBMs may also look closely at high cost members—those members who utilize the top 10% of resources. However, the problem with opioid dependence is much larger than just cost. Patients who have substance abuse disorders utilize substantially more health care resources than nonabusers. For example, they are 6.7 times more likely than nonabusers to be hospitalized, and 2.3 times more likely to utilize the emergency department. Emergency department (ED) physicians, like other health care providers, often struggle to distinguish patients with legitimate pain from those reporting pain fraudulently to obtain narcotic prescriptions for abuse or diversion, as pain is principally subjective. There is also a disconnect in tracking patients who utilize the ED for obtaining pain medications, as they are not identified on prescription monitoring programs set up by the MCOs. The medications dispensed in the hospital or ED are billed through the patient’s medical benefit, not the prescription benefit.

Several organizations are now incorporating an integrated approach to chronic pain management, including looking at patients as a whole (including a behavioral component), implementing management programs for existing disease-state conditions, and developing programs to manage individual patients as a whole. Physicians need to continue to monitor their patients, both for pain and for aberrant drug-related behavior. Formal opioid treatment agreements between the physician and the patient should be in place so the patient knows what is acceptable and expected of them, while protecting the physician as well. Contracts such as these help keep the lines of communication open.

Aberrant Drug-Related Behaviors. Aberrant drug-related behaviors cover a broad spectrum, from aggressively seeking medications and increasing dosages without physician approval to injecting or snorting medications intended for oral use and illegal activities such as selling drugs. The more aberrant the behavior, the higher the risk of developing addiction. Risk tools described earlier in this supplement for assessing aberrant behavior should be utilized. To reduce or avoid the risk of abuse, physicians must implement adherence monitoring programs. Studies have shown that monitoring compliance with random pill counts, for example, and random urine screening results in noteworthy reductions in utilization of illicit drugs.

Fishbain et al. performed an evidenced-based review of studies of abuse, addiction, and aberrant drug-related behavior seen in patients with chronic pain and taking oral opioid medications. Among 5 studies of chronic pain patients (n = 15,442), the average percentage of aberrant drug-related behaviors (as determined by urine toxicology screening) was 20.4%. It was noted that aberrant drug-related behaviors were identified at a higher rate by urine toxicology screenings than by observation of patient behavior (20.4% vs. 11.5%). The 11.5% was determined by a review of 17 studies (n = 2,466 chronic pain patients) that identified aberrant drug-related behavior through observation alone. These results further emphasize the need for doctors to perform routine urine screenings on their opioid patients. Patients should know at the beginning of treatment that these tests will be done, and that they are for their benefit, similar to how diabetics test their blood sugar to make sure they are staying on track with their therapy.

Primary care physicians should be educated on when a patient needs to be referred to a pain management specialist. Likewise, if a pain management specialist has identified an issue, he/she should know when to refer the patient to appropriate resources or services.

Management of Comorbidities. Psychiatric disorders are commonly seen in patients with opioid dependence. Opioid dependence is commonly characterized by frequent relapse and results in social and health consequences, including unemployment, criminal behaviors, and blood-borne infections (HIV) from injecting opioids illicitly using dirty or shared needles. A recent non-interventional observational study looking at depressed patients and satisfaction with methadone maintenance treatment reported that patients with depression experienced more opioid withdrawal symptoms compared with nondepressed patients. This correlates well with other studies, such as those performed by Mitchell, et al., and Schreiber, et al., that show poorer outcomes with methadone maintenance therapy in depressed patients. These findings further emphasize the need to treat comorbid conditions such as depression for optimal patient outcomes. Antidepressants help with comitant depression, but many are now being used off-label to treat chronic pain. Incorporating appropriate antidepressants into an opioid dependent patient’s regimen may be an effective treatment strategy on multiple levels.

Negative emotional states may be strong predictors of relapse in opioid dependence. As such, addressing a patient’s coping
skills is important. A study by Chaney and Roszell examined an all-male veteran population on methadone for opioid dependence and found they had few coping skills and tended to utilize unsuitable strategies when coping with high-risk circumstances. The study group participated in a 12-week coping skills training program. After completing the training, 70% remained in the methadone treatment program, and depressive symptoms and avoidant (or maladaptive) coping diminished.

Relapse. Unfortunately, relapse is extremely common in treating opioid dependence. Continued use of opioids causes chemical changes in a person’s brain that cause negative emotions and cravings when a patient tries to stop using. During times of stress, a patient may relapse, especially if they do not have good coping skills. Relapse is particularly common among patients who abuse more than 1 substance. Remaining in treatment is important to success. Regrettably, only 1 in 10 patients with substance abuse receives treatment, and of those, only 1 in 7 complete a program, according to the Network for the Improvement of Addiction Treatment, a nonprofit agency. Interestingly, those who do complete treatment are often patients who have insurance that covers their treatment. (Figure 1)

Patients who are employed tend to be more compliant with treatment, as they may be motivated by having a supportive employer and a job to return to. Among employed people who sought help for opioid dependence, 93% said their employer knew of their treatment, 55% had an employee assistance program available to them, and 65% continued to work for the same employer 1 year after treatment, and about half abstained from substance abuse for more than a year. In a study of human resource professionals, 85% said their company would benefit from education programs in the workplace that would help them identify and help employees who are suffering from a substance abuse disorder.

Due in part to concerns about ramifications at work, employed persons with substance abuse disorders may not seek help. Employees need to know about assistance programs available to them, and that these programs must adhere to strict confidentiality guidelines. Missed days from work, changes in behavior, changes in work habits, and high accident rates are all signs that an employee may need some assistance. Employers, especially human resources departments, should be educated on identifying signs that an employee may need help with a substance abuse disorder and on how to assist employees in receiving the required help or health benefits in treating the disorder. Helping employees regain their ability to function in their jobs helps the employer; in addition to the costs associated with loss of productivity, the cost of firing that employee and replacing the position (including recruitment and training costs) can also be significant.

Conclusion

Patients who are opioid dependent utilize costly health care resources. An integrated approach to treatment is essential to reduce these costs and improve outcomes for these patients. Physicians should utilize contracts and monitoring policies for all their pain patients, as well as opioid-dependent patients. Risk stratification and assessing aberrant drug related behaviors are important and can be done with tools currently available to practitioners. Pain and opioid dependent patients must be provided with tools to enable them to cope with stressful situations and treatment for comorbid conditions, such as depression. Patients must be motivated to stay in therapy using integrated approaches to therapy including behavior modifications, employee assistance programs, and coverage of treatments by managed care organizations.

REFERENCES


The author acknowledges editorial assistance provided by Lance Nicholls, PharmD, and Lisa Bragaw, RPh, Lancer Solutions, LLC, New Milford, Connecticut; and Janet Cline, RPh, and Dana Frazier, Creative Educational Concepts, Inc, Lexington, Kentucky.

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The abstract is as follows:

**ABSTRACT**

BACKGROUND: Failure in treating opioid dependence is costly to the patient, the employer, managed care organizations, and the overall health care system. Opioid dependent patients tend to be less productive at work and in society and utilize a great many health care resources. Optimizing outcomes is essential.

OBJECTIVE: To introduce the benefit of integrated strategies and patient support in the treatment of opioid dependence.

SUMMARY: Health Analytics is currently studying the benefit of HereToHelp, a behavioral support program in which registered nurses or addiction treatment counselors with specialized training in addiction education provide information and encouragement to patients receiving pharmacologic treatment for opioid dependence. A total of 470 physicians in 41 states have been enlisted to participate in this patient support study. The study hypothesis is that patients who receive behavioral support and encouragement will be more compliant with their opioid replacement therapy, leading to better outcomes. Additional treatment strategies are also being developed to minimize the risk of abuse and diversion. Prodrugs and vaccines are also being investigated.

CONCLUSION: A coordinated team approach is essential in treating pain patients and opioid-dependent patients. Offering behavior modification in addition to pharmacotherapy and utilizing strategies such as prescription monitoring programs, pain contracts, and screening are all vital components necessary for positive outcomes.

**On the Horizon**

There are many new treatments and treatment strategies on the horizon for treating opioid dependence and designed to minimize misuse, abuse, and diversion of opioid analgesics.1,2 A long-acting, injectable form of naltrexone is being studied to be given monthly. It is currently approved for use in alcohol dependence. It is thought that cravings will be controlled by blocking...
neurotransmitters in the brain. Lofexidine hydrochloride (an antihypertensive drug similar to clonidine) is an agent that has been in use in the United Kingdom to lessen opioid withdrawal symptoms, and with less risk of hypotension when compared with clonidine. It is currently being evaluated in the United States and may be available in the next 5 years.

Aversive technologies are being utilized to prevent abuse and diversion. Adding opioid antagonists like naloxone to counter opioid effects if tablets are crushed is being considered for many opioids. Some examples include oxycodone immediate release plus naltrexone, oxycodone extended release plus naltrexone, and morphine sulfate plus naltrexone. Other aversion strategies being investigated include adding capsaicin to produce burning, ipecac to induce nausea and vomiting, or bitter-tasting agents to deter patients from misusing opioid analgesics.

Prodrugs that require first-pass metabolism are also in development; formulations of prodrugs would make it more undesirable to misuse or abuse these agents, as the release of drug and effect would be too slow. A prodrug of hydrocodone is currently being evaluated.

An opioid vaccine is being investigated that would theoretically prevent opioids from ever reaching the user's brain. Similar studies are already being tested in humans for a nicotine vaccine. Naltrexone implants that provide 8 to 10 weeks of opioid blockade are currently being studied in Russia and Norway. Long-term delivery of buprenorphine is also under investigation. An implant that is reported to deliver stable levels of buprenorphine over 6 months is currently being studied in humans.

The potential of NMDA (N-methyl-D-aspartate) receptor antagonists are being studied in rodents for preventing tolerance and dependence in rodents. Agents such as memantine, ketamine, phencyclidine, and dextromethorphan may be helpful in reducing cravings and could be used as an adjunct to other regimens used in treating opioid addiction.

Because corticotrophin-releasing hormone (CRH) is thought to be involved in response to stress and its action as a central nervous system modulator, researchers are looking into synthesizing selective CRH receptor antagonists to be used in the treatment of substance abuse, anxiety, and depression. It is believed that CRH antagonists can block conditioned aversion responses and attenuate withdrawal from opioids.

In order to address abuse and mismanagement of pain, novel strategies are being developed. Opioid diversion is a major problem. Prescription monitoring programs (PMPs) are being used to monitor and report on the utilization of controlled substances in many states. However, there are limitations due to different programs being used in each state that don’t interface with each other. Also, while PMPs can be useful tools, they may also be a barrier to care for some patients. They are often used to help law enforcement agencies to identify doctors who they feel are overprescribing and patients who are “doctor shoppers.” This creates a barrier for some physicians who are worried about legal ramifications when trying to manage difficult pain cases.

Conclusion

A coordinated approach to pain management is necessary. MCOs should evaluate difficult cases in an objective fashion, not just based on the costs generated by a member. Criteria should be based on whether the resources the patient is using are appropriate. Are patients being evaluated by a group of pain management specialists? If so, are they providing appropriate recommendations?

What is lacking? From the physicians’ perspective, MCOs and PBMs provide physicians with letters regarding members who are getting high doses of a prescription and only asking the physician to re-evaluate or reduce the dose. It would be beneficial if the physician was provided with support or recommendations and ways to help or correct issues identified by insurers looking at claims data and other sources. Some MCOs are developing internal programs in which pain management specialists review these cases quarterly and develop a customized treatment plan. That plan should be coordinated with the primary care provider (PCP) to provide that PCP support to better manage the patient. Many patients and prescribers alike don’t even understand the importance of having a contract if the patient is going to be taking chronic opioid pain relievers. For the safety of the practice, as well as the member, contracts must be developed. If prescribers do not have contracts in place, MCOs could provide sample contracts to offer additional support to these physicians.

The development of a pain management program needs to be a team approach. The patient is the primary stakeholder in the treatment. Physicians should implement and utilize guidelines and contracts to achieve successful outcomes. A team approach between the MCO and physician will allow patients to be better monitored and enabled to obtain more positive outcomes. If patients require more resources to achieve that, they should be identified and made available. Physicians must be educated on resources available in the treatment of opioid dependence, including tracking different opportunities.

REFERENCES


Opioid Dependence: Managing the High Cost of Treatment Failure

Physicians

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Creative Educational Concepts, Inc. (CEC) and Lancer Solutions, LLC, on behalf of AMCP Horizons, LLC. CEC is accredited by the ACCME to provide CME for physicians.

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Creative Educational Concepts, Inc. (CEC) is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

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Release Date: February 1, 2010
Expiration Date: January 31, 2011
Type of Activity: Knowledge-Based
Target Audience: Physicians and Pharmacists

Instructions for CE and CME Credit

To receive continuing education credit, the participant must complete the Posttest, Evaluation, and Credit Application for this activity (“Opioid Dependence: Managing the High Cost of Treatment Failure” online through the AMCP CE/CME Center at http://www.amcp.org [CE/CME Center]).

The posttest worksheet is provided to assist you in marking your answers prior to entering the online CE center for submission; these pages cannot be submitted for CE credits.

There is no fee to participate in this educational activity. To receive CE credit, you must receive a score of at least 70%. You will have 2 opportunities to pass the self-assessment posttest.

To complete this continuing education activity, go to www.amcp.org (CE/CME Center) to access the posttest and evaluation form.
1. The risk in developing an opiate addiction has been shown to be ______ according to a review of 24 studies on chronic pain patients.
   A. 3.3%
   B. 5.3%
   C. 8.3%
   D. 10.3%

2. Which of the following is NOT considered 1 of the 4 C's of addiction?
   A. Compulsive use
   B. Ability to Control the quantity used
   C. Craving the psychological drug effects
   D. Continued use of the drug despite its adverse effects

3. According to the National Survey on Drug Use and Health (NSDUH), what percentage of persons 12 and older were current nonmedical users of prescription pain relievers in 2007?
   A. 3.4%
   B. 1.8%
   C. 2.1%
   D. 4.7%

4. According to the National Survey on Drug Use and Health (NSDUH), of those people who were treated for substance abuse during 2007, ______ reported that they were being treated for prescription pain reliever abuse.
   A. 11.3%
   B. 13.6%
   C. 15.3%
   D. 17.3%

5. According to the study by White et al. (2005), opioid abusers are associated with ______ times higher mean annual direct health care cost than nonabusers.
   A. 5.4
   B. 8.7
   C. 9.8
   D. 11.3

6. Which of the following is no longer recommended by the American Psychiatric Association as a treatment modality for opioid dependence and withdrawal?
   A. Opioid substitution with methadone or buprenorphine, followed by a gradual taper
   B. Abrupt opioid discontinuation with the use of clonidine to suppress withdrawal symptoms.
   C. Clonidine-naltrexone detoxification
   D. Anesthesia-assisted rapid opioid detoxification

7. Physicians wishing to offer office-based opioid treatment must be certified to offer the service.
   A. True
   B. False

8. Aberrant drug-related behaviors can be better identified at higher rates using urine toxicology screenings than by patient observation.
   A. True
   B. False

9. According to the Network for the Improvement of Addiction Treatment, of those who receive substance abuse treatment, only 1 in ______ patients complete their treatment program.
   A. 3
   B. 5
   C. 7
   D. 10

10. Of employed people who sought help for opioid dependence, what percentage continued to work for the same employer 1 year after treatment?
    A. 32%
    B. 43%
    C. 54%
    D. 65%

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To complete this continuing education activity, go to www.amcp.org (CE/CME Center) to access the posttest and evaluation form.