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Addiction to Prescription Opioids: Characteristics of the Emerging Epidemic and Treatment With Buprenorphine

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Dependence on and abuse of prescription opioid drugs is now a major health problem, with initiation of prescription opioid abuse exceeding cocaine in young people. Coincident with the emergence of abuse and dependence on prescription opioids, there has been an increased emphasis on the treatment of pain. Pain is now the "5th vital sign" and physicians face disciplinary action for failure to adequately relieve pain. Thus, physicians are whipsawed between the imperative to treat pain with opioids and the fear of producing addiction in some patients. In this article, the authors characterize the emerging epidemic of prescription opioid abuse, discuss the utility of buprenorphine in the treatment of addiction to prescription opioids, and present illustrative case histories of successful treatment with buprenorphine.

Keywords: prescription, opioid, opiate, addiction, buprenorphine

Abuse of prescription opioid analgesics has emerged as a major public health problem in the United States (Zacny et al., 2003), with abuse of drugs such as OxyContin becoming "ubiquitous" (Cicero, Inciardi, & Munoz, 2005). Between 1990 and 2003, the rate at which young adults initiated abuse of prescription opioids (i.e., use not sanctioned by a physician) tripled, from 10.2/thousand person-years in 1990 to 31.6/thousand person-years in 2003 (see Figure 1) (U.S. Substance Abuse and Mental Health Services Administration [SAMHSA], 2004). Each year since 1999, more than 2 million adults started abusing prescription opioids in the U.S. (SAMHSA, 2006). In 2005, 2.4% of the U.S. population aged 18 to 25 (794,000 persons) initiated use of a pain reliever for a nonmedical purpose. Abuse of prescription opiates starts later than abuse of marijuana or alcohol: the average age of first nonmedical use of a pain reliever was 21.9 years, of marijuana 19.0 years, and of alcohol 16.6 years (SAMHSA, 2006a). "Generation Rx" is the popular name given by the Partnership for a Drug Free America for these young adult prescription opioid abusers. Young adults are much more likely to start abusing prescription opioids than they are to start abusing illegal opioids such as heroin, and initiation of prescription opioids abuse overtook that of cocaine abuse in 1996 (Compton, Darakjian, & Miotto, 1998).

Among all Americans 12 years and older in 2006, 13.6% (more than 33 million) reported a lifetime history of nonmedical use of prescription opioids. More than 12 million reported use in the prior year, and 5.2 million during the prior month. By comparison, 3.8 million reported ever using heroin (1.5%), 560,000 in the previous year and 338,000 in the prior month (SAMHSA, 2006b). Approximately 1.6 million Americans met *DSM–IV* criteria for abuse or dependence of prescription opioids in 2006 (SAMHSA, 2006c). Over five times more Americans abuse or are dependent on prescription pain relievers than abuse or are dependent on heroin. Dependence on or abuse of prescription opioids is now as common as dependence/abuse of cocaine, and more common than dependence/abuse of any other drug except marijuana (see Figure 2) (SAMHSA, 2006c).

Prescription opioids have more "street value" than marijuana and heroin, and are second only to cocaine in that regard, indicating that a market developed in illicit users (Parran, 1997). Because prescription opioids can be legally obtained through a physician, there may be a perception that nonmedical use of these drugs is less problematic than abuse of illicit substances. However, a parallel rise in the consequences of misuse belies this perception. U.S. college students abusing prescription opioids are over four times more likely to report frequent binge drinking, over three times more likely to drive after drinking alcohol, four times more likely to drive after binge drinking, and almost six times more likely to be a passenger in a car with a drunk driver (McCabe, Teter, Boyd, Knight, & Wechsler, 2005). Accord-

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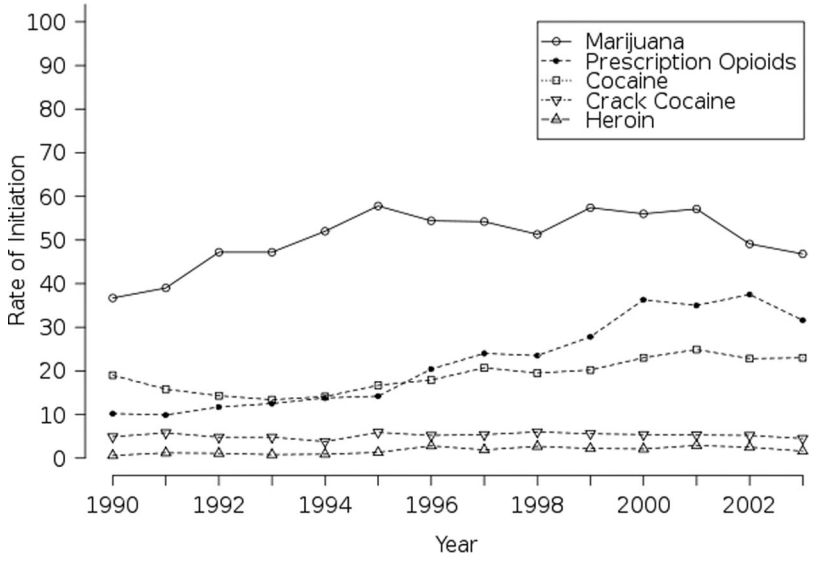

Figure 1. Rates of first use of select drugs in U.S. adults aged 18–25 (per 1,000 persons − years of exposure), 1990–2003). From the *National Survey on Drug Use and Health Detailed Tables—Tables 4.1a-4.4a and 4.10a*, SAMHSA, 2004.

ing to the Drug Abuse Warning Network (DAWN), the estimated number of emergency department (ED) visits involving opioid analgesic abuse in the U.S. more than doubled, from 90,232 to 196,225 visits, between 2001 and 2005 (DAWN, 2005). The prescription opioids hydrocodone and oxycodone (and their combination formulations) alone were involved in 6.5% of all drug abuse-related ED visits in 2005, and visits involving either hydrocodone or oxycodone formulations each accounted for more ED visits than methadone (DAWN, 2005). Indeed, the number of ED visits involving these two prescription drugs were more than half the total visits involving heroin. ED visits involving prescription opioids increased 24% between 2004 and 2005 alone, including a 92% increase for hydromorphone formulations (SAMHSA, 2006).

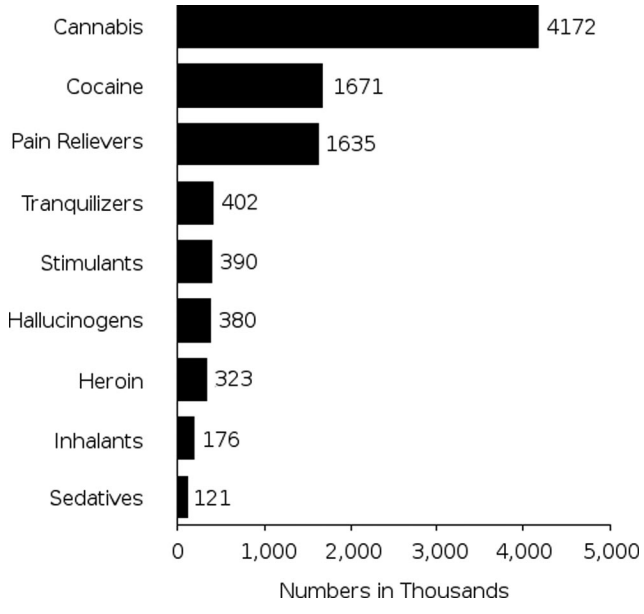

Figure 2. Dependence on or abuse of specific drugs in the past year in persons aged 12 or older. From the *National Survey on Drug Use and Health*, SAMHSA, 2005.

Persons misusing prescription opioids are not just presenting to emergency departments more frequently. According to surveillance data on the number of patients admitted for substance abuse treatment, such persons are also seeking treatment in record numbers. For the decade 1995 through 2005, admissions for the abuse of opioids other than heroin increased from 1% to 4%. Between 1995 and 2005, rates of treatment admissions involving opioid analgesics more than tripled, from 7 to 26 admissions per 100,000 persons aged 12 and over in the US. In the year 2005, there were more than 64,000 such admissions, and over 1,100 were of patients aged 12 through 17. While in about half of these visits, opioid analgesics were co-abused with another drug, in the other half an opioid analgesic was the only drug of abuse (U.S. Substance Abuse and Mental Health Services Administration [TEDS], 2005).

There are several differences between heroin abusers and prescription opioid abusers. Compared to heroin abusers, prescription opioid abusers are more likely to be White, be younger, have higher incomes, use less opioid per day, and not be injection drug users. Prescription opioid users seek treatment earlier, are more likely to be successfully induced into and complete treatment, and have better outcomes than patients using heroin. Prescription opioid users are also less likely to have hepatitis C infection, and have fewer episodes of drug treatment (Moore et al., 2007). Furthermore, prescription opioid abusers have fewer family and social problems, and report receiving less income from illegal sources (Sigmon, 2006).

Brands and co-workers in Toronto found that 83% of the patients presenting for methadone therapy were addicted to prescription opioids. Surprisingly, in 48% of these patients, prescription opioids were the primary source of opioids. There were 24% who used only prescription opioids and 24% started with prescription opioids and migrated to heroin later. In contrast, 35% were primary heroin addicts who also abused prescription opioids; only 17% used heroin exclusively (Brands, Blake, Sproule, Gourlay, & Busto, 2004). These prescription opioid addicts consumed enormous amounts of short-acting codeine and oxycodone formulations (23 ± 6 and 21 ± 3 tablets per day of codeine and oxycodone, respectively) equivalent to about 200 mg of morphine per day. About 80% of these patients started using opioids for the treatment of pain and they obtained almost all of their medications from physicians. It is important to note that most were on short-acting opioids that are usually combined with acetaminophen, aspirin, or ibuprofen. Consequently, these patients received enormous exposures to nephro- and hepatotoxic drugs and metabolites (e.g., 10–20 g per day of acetaminophen).

Why do people initially become involved with prescription opioids? Brands et al. found that most had started using opioids to relieve pain. It is estimated that more than 75 million Americans suffer from chronic, debilitating pain, hence the population at risk is enormous (National Pain Foundation, 2007). Becker et al. note that "undertreated chronic pain is a cause of low self-rated health status that may compel individuals to nonmedical use of prescription opioids" (Becker, Sullivan, Tetrault, Fiellen et al., 2008). Pain patients may be *psuedoaddicted*, appearing to abuse opioids secondary to addiction, but in fact trying to relieve undertreated pain (Longo, Parran, Johnson, & Kinsey, 2000).

Physicians, of course, are charged with relieving pain; "the fifth vital sign." We will discuss later how physician prescribing patterns for opioids may affect rates of misuse. However, most prescription opioid abusers obtain their drugs from family members, and not directly from physicians (see Figure 3) (Carise et al., 2007; Davis & Johnson, 2008; Rosenblum et al., 2007). For example, in one recent study 70% of the sample obtained prescription opioids (OxyContin) from friends and only 14% obtained them directly from physicians (Levy, 2007).

An increasing number of prescription opioid misusers are being referred for opioid substitution therapy with buprenorphine or methadone. Buprenorphine is marketed for this indication as a single agent, Subutex, and in combination with naloxone, Suboxone; the addition of naloxone is to deter parenteral abuse.

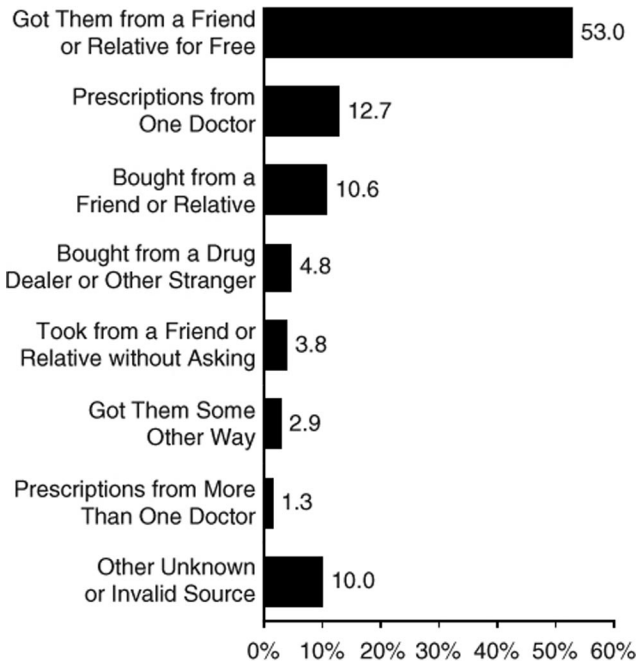

Figure 3. Percentages of reported method of obtaining prescription opioids for most recent nonmedical use in prior year, among persons aged 18–25. From "The NSDUH Report: How Young Adults Obtain Prescription Pain Relievers for Nonmedical Use," *National Survey on Drug Use and Health SAMHSA*, 2006.

Case Reports

AB is a 60-year-old information technology professional who presented with 6 months of escalating prescription analgesic abuse. Prescription opioids (Vicodin; hydrocodone 7.5 mg and acetaminophen 325 mg every 6 hours; 30 mg per day of hydrocodone) were initiated for pain control after oral surgery. Although pain control was adequate AB rapidly escalated hydrocodone dosing to approximately 150 mg per day, and decreasing or stopping hydrocodone resulted in classic opioid withdrawal symptoms. Hydrocodone was obtained from his physician, but as he increased the amount consumed he obtained drug from friends and later from the Internet. Before the oral surgery, there was no history of opioid dependence or abuse but there was a long history of alcoholism in remission (with 2 years sobriety). The medical history was notable for nicotine dependence (30 pack-years), moderate depression and a spontaneous pneumothorax at age 40. AB is employed, in a stable long-term relationship and has an advanced degree. Physical examination showed no evidence of intravenous drug use and HIV and hepatitis C serology were negative. Treatment options were discussed and he elected buprenorphine substitution therapy. Induction was uneventful and 1.5 years postinduction he is stable on 16 mg/day of sublingual Suboxone. Urine toxicology tests, obtained on each office visit, have showed no evidence of hydrocodone use. After 1 year of treatment he feels good, there are no significant adverse effects of treatment and he is not yet interested in tapering buprenorphine.

CD is a 35-year-old with a 10-year history of systemic lupus erythematosus (speckled antinuclear antibodies) with joint and skin involvement. About 1 year before consultation she was started on hydrocodone-acetaminophen combination analgesic for arthralgias and headache. Although the lupus flair resolved, she continued to use hydrocodone with the dose escalating to more than 200 mg/day (with an acetaminophen dose of approximately 7.5 g/day). Hydrocodone was obtained from friends and over the Internet. There was no history of nicotine, alcohol, or opioid abuse or

addiction. CD has a long history of depression and was in psychotherapy at presentation. She is married, has a daughter, and is employed in academia. The large hydrocodone dose made induction difficult but she eventually stabilized on Suboxone 40 mg/day. Three years later, despite attempts, she has not been able to decrease the dose but is not using any other opioids. Notably, despite family stresses (divorce in process, precipitated by her husband's alcoholism and depression), her depression is improved; she attributes this to buprenorphine.

Sublingual buprenorphine is approved in a dose range of 2 to 32 mg with some evidence that more than 98% of all μ-opiate receptors are occupied at doses of 32 mg/day (Greenwald et al., 2003). Buprenorphine has kappa opiate antagonists properties and kappa antagonists may have antidepressant effects (Shirayama et al., 2004; Zhang, Shi, Woods, Watson, & Ko, 2007). Both patients had depression, and perhaps the kappa antagonist-antidepressant properties of buprenorphine account for the higher than usual dose needed by CD.

These cases illustrate some of the challenges in treating iatrogenic dependence. Neither patient had a history of opioid abuse or dependence and the initial opioid pharmacotherapy for pain appears appropriate. Although depression was present in both patients it was not severe. Substantial dose escalation of analgesic opiates occurred over a relatively short period and stopping use resulted in withdrawal symptoms. Fortunately, the patients recognized the need for treatment, and induction on Suboxone was relatively easily achieved. On the downside, substitution treatment has lasted longer than the initial episode of opioid abuse. At present, the best dose and duration of substitution therapy with buprenorphine for prescription opiate addiction remains to be defined. These cases have some features that are commonly seen in our (JM) practice (initiation of opiates for pain with relatively rapid dose escalation) and that are atypical (the long period on substitution therapy and, for CD, the high buprenorphine dose). Thus, much remains to be learned about buprenorphine substitution therapy in prescription opioid addicts.

These cases raise two important issues that we discuss below. First, what is the contribution of opioid prescribing to the burden of addiction? Second, is there evidence of efficacy for opioid substitution therapy in prescription opioid addiction?

U.S. Trends in Ambulatory Care Opioid Prescribing From 1993 Through 2005

Opioid prescribing contributes to the supply of abusable opioids, but little is known about how opioid prescribing patterns have changed during this time. We (MP) have studied the contribution of physician prescribing to the rise in prescription opioid dependence. Pletcher evaluated the changes in opioid prescribing for pain by emergency departments using 13 years (1993–2005) of data from the National Hospital Ambulatory Medical Care Survey. Pain-related visits accounted for 156,729 of 374,891 (42%) emergency department visits. Opioid prescribing for pain-related visits increased from 23% (95% confidence interval [CI], 21–24%) in 1993 to 37% (95% CI, 34–39%) in 2005 ($p < .001$ for trend), and this trend was more pronounced in 2001 through 2005 ($p = .02$), most likely because of national quality improvement initiatives in the late 1990 stressing adequate treatment of pain (Pletcher, Kertesz, Kohn, & Gonzales, 2008). To estimate prescribing patterns in medical offices we used 10 years of survey data (from 1993–2003) from the National Ambulatory Medical Care Survey (a nationally representative stratified cluster sample of approximately 30,000 physician office visits per year) to estimate how many U.S. office visits included prescription of an opioid medication (an "opioid visit") to persons aged 12 and over. We calculated rates using U.S. Census denominators and categorized opioid visits by type of opioid to explain overall trends. Among the 272,983 evaluated visits we identified 11,327 opioid visits, representing ~32 million office opioid visits/year in the United States, an average rate of 0.142 opioid visits per person per year (95%CI: 0.134–0.149).

Two pronounced time trends were evident: a significant increase in the visit rate over the decade from 0.126 in 1993 to 0.166 in 2003, a 32% increase ($p < .001$ for trend) and a large shift in the types of opioids prescribed. Whereas codeine and propoxyphene visit rates declined (40% and 28%, respectively, paralleling a decline in DAWN mentions), visit rates for higher potency opioids such as hydrocodone and oxycodone increased (115% and 156%). Most of the increased opioid visit trend was explained by hydrocodone visits, which increased at a rate of ~1 million additional visits per year from 1993 through 2003 up to a total of 18 million hydrocodone visits in 2003 (95%CI: 14–22 million, 45% of all 2003 opioid visits). These data show that opioid prescribing patterns in ambulatory care have changed markedly in the last decade. Even if all opioid prescribing were appropriate, co-occurring increases in opioid abuse and prescribing suggest the possibility that emergency room and office visit prescribing are channels for the supply of abused opioids in the United States. Accordingly, methods that decrease the level of potentially harmful prescribing may have a large impact on prescription opioid dependence.

The recognition that opioid pain pharmacotherapy can lead to opioid addiction has fueled calls for increased regulation of opioid prescribing. The most common regulatory solution is to increase the DEA schedule category (from III, IV, and V to II) of commonly prescribed prescription opioids. Altering the DEA schedule obviously does not alter the pharmacologic effects of opioid analgesics, but can theoretically decrease the availability of prescription opioids by increasing the barriers to prescribing. However, one argument against a regulatory solution is that current schedule II medications include the oxycodone formulations, which continue to be widely abused. Although decreasing the legitimate supply of prescription opioids might diminish the numbers of new pain patients receiving opioid substitution therapy, many patients with chronic pain would be deprived of an essential medicine.

There has been difficulty quantifying the risk for iatrogenic addiction in patients on opioids (Wasan, Correll, Kissin, O'Shea, & Jamison, 2006). Strategies for minimizing such risk include careful patient evaluation, the use of standardized instruments (see, e.g., the Pain Assessment and Documentation Tool; Passik et al., 2004), maximizing other treatment options first, using goal directed therapy, maintaining careful documentation and written patient agreements, prescribing opioids as adjuncts where possible, monitoring pharmacies for opioid quantities used, and weaning and discontinuation if treatment goals are not met (Ballantyne & LaForge, 2007).

Treatments for Addiction to Prescription Opioids

Medications studied for prescription opioid dependence include methadone, naltrexone, levo-alpha-acetylmethadol (LAAM), and buprenorphine formulations. Although methadone has been a mainstay of opioid addiction treatment, in the U.S. this treatment may only be provided in specially licensed clinics, and these clinics can only treat a limited number of patients. By one estimate, treatment slots for methadone maintenance are available to only 20% of Americans with opioid addiction (Cunningham, Kunins, Roose, Elam, & Sohler, 2007). Methadone has not been available in some U.S. states (McCance-Katz, 2004), and communities often resist allowing methadone clinics to open or expand. Patients attending a clinic dedicated to treating a socially unpopular disease may feel stigmatized. Methadone medical maintenance, where methadone is prescribed in a medical setting and provides more take-home medication to stable patients, is one alternative to traditional methadone clinics. However, regulatory complexity and protocol development has limited expansion of this model (Merrill et al., 2005).

Naltrexone, an opioid antagonist, has little abuse potential, but treatment outcomes in studies have been mixed, and its use is inappropriate in abusers with chronic pain. There is also poor compliance and retention with its use (Minozzi et al., 2006), although better treatment retention has been reported with a naltrexone depot formulation (Comer et al., 2006).

LAAM is a pure opioid agonist and is approved for treatment of opioid dependence, although there are no studies of its use in prescription opioid abusers. Unfortunately, the U.S. Food and Drug Administration required a "black box" warning on the drug in 2001 after reports of QT interval prolongation and cases of torsades de pointes in patients treated with LAAM (United States Food & Drug Administration, 2001) and since 2004 LAAM has not been available in the United States.

In contrast to methadone, buprenorphine may be prescribed in a physician's office, and dosing is done not in the clinic but at home. When treatment is initiated in a physician's office, the concomitant physical and mental health issues that so often accompany opioid dependence can also be addressed. Offering office-based treatment with buprenorphine is associated with new types of patients entering treatment (Sullivan, Chawarski, O'Connor, Schottenfeld, & Fiellin, 2005). Buprenorphine appears less likely to produce an overdose because of a ceiling effect on respiratory depression (Dahan, 2006). Buprenorphine causes less QT prolongation than LAAM or methadone (Wedam, Bigelow, Johnson, Nuzzo, & Haigney, 2007). Like methadone, buprenorphine treatment may decrease risky behaviors, including drug-related HIV risk behaviors (Sullivan et al., 2007). Rapeli reported that buprenorphine-naloxone treatment is preferable to methadone treatment for preserving cognitive function in early treatment—an important benefit for prescription opioid addicts who are employed (Rapeli et al., 2007). Barry found that patients were satisfied with office-based buprenorphine treatment and expressed strong willingness to refer a substance-abusing friend for the same treatment (Barry et al., 2007).

Studies consistently show efficacy of buprenorphine treatment in opioid dependence, but most describe results in heroin users or mixed populations of heroin and prescription opioid users. A study of 99 patients treated with buprenorphine in four primary care clinics found 54% were sober at 6 months. Of the abstinent group, 40% were prescription opioid users, compared to 38% of the nonabstinent patients (Mintzer et al., 2007). The NIDA Clinical Trials Network Field Experience assessed buprenorphine for short-term opioid detoxification, and reported high compliance and treatment engagement, excellent safety, and a 68% completion rate. However, only 8% of that study population reported exclusive use of opioids other than heroin (Amass et al., 2004). Fiellin found reductions in the frequency of opioid use with three different patterns of buprenorphine dispensing and counseling in a treatment group that included 15% to 20% prescription opioid users (Fiellin et al., 2006). Caldiero reported that subjects maintained on buprenorphine (30% of whom were exclusively prescription opioid users) were more likely to initiate outpatient therapy and remained in outpatient treatment longer when compared to patients detoxified with tramadol (Caldiero, Parran, Adelman, & Piche, 2006). In another study of retention in primary care based buprenorphine treatment, 59% remained in treatment at 24 weeks. In this study 50% were heroin users, compared with 27% whose primary drug was another opioid, and heroin users were more likely to terminate treatment early. As previously noted, a study by Sullivan suggested that office based buprenorphine treatment expands access for patients who may not enroll in methadone clinics, and facilitates earlier access to treatment for patients who have more recently started opioid use (Sullivan et al., 2005). In that study, approximately 10% of subjects used a primary opioid other than heroin. The U.S. Substance Abuse and Mental Health Association (SAMHSA) evaluation of the buprenorphine waiver program in the United States, in which 40% of the subjects were prescription opioid-only misusers, found that treatment with buprenorphine was "clinically effective," "well accepted by patients," and "increased the availability of medication-assisted treatment for opioid addiction." There were minimal problems with diversion or adverse clinical events (Stanton et al., 2006).

The optimal duration of therapy with buprenorphine remains to be determined. The issue of termination of therapy is not trivial. In both clinical cases we presented above, the duration of therapy has exceeded the time spent abusing and there is no evidence-based data to suggest when or if substitution therapy can be discontinued. It appears that most

heroin dependent patients on methadone maintenance should be treated on an ongoing basis (Sorensen, Trier, Brummett, Gold, & Dumontet, 1992), but similar studies have not been conducted with prescription opioid dependent patients on buprenorphine.

Participants in a March 2003 conference on the U.S. national buprenorphine implementation program called for physicians to "move opioid addiction treatment into the mainstream of American medicine through office-based practice" by expanding use of buprenorphine-naloxone (Kosten & Fiellin, 2004). Education and experience should help this effort, but other barriers remain. Horgan et al. reported that about one third of insurance plans excluded buprenorphine from formularies, and if it was included, it was usually placed in the highest cost-sharing tier (Horgan, Reif, Hodgkin, Garnick, & Merrick, 2008). At the time of their study, retail prices for buprenorphine formulations (Subutex and Suboxone) were U.S. $170 to $274/month. Effective treatment of drug dependence can translate into public benefit, and there are advocates for additional public funding of opioid treatment to include buprenorphine therapy (Becker, Fiellin, Merrill, Schulman, Finkelstein et al., 2008).

Conclusions

Prescription opioids remain safe and effective pharmacotherapies for surgical, traumatic, and malignant pain, and although controversial, are widely prescribed for chronic nonmalignant pain. However, over the last decade marked increase in abuse of and addiction to prescription opioids has occurred. Opioid prescribing by physicians for pain has increased in medical offices and emergency rooms, and some of these appropriately treated patients develop addiction. Fortunately, for those who do develop addiction, opioid substitution with buprenorphine and medical management of iatrogenic addiction in office settings appears safe and efficacious.

Although the treatment of pain is better than the disease, the ethical imperatives of pain relief and therapeutic beneficence mandate development of analgesics with lower abuse liability, better methods to detect patients at risk for developing addiction, and improved treatments for patients who become addicted.

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