

Use and misuse of buprenorphine in the management of opioid addiction

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ABSTRACT

Buprenorphine was approved in late 2004 for the treatment of opioid abuse and dependence in specially trained and certified physicians' offices. At the time of the approval, there was a regulatory concern that given the anticipated wide exposure there would be unexpectedly high levels of abuse in the high-risk population for which it was intended. To assess its abuse potential, the authors recruited more than 1,000 individuals seeking treatment for prescription opioid abuse from 100 stand-alone (ie, self-pay or insurance) drug abuse treatment programs around the country to determine whether they misused buprenorphine in the past 30 days to get high. The results indicate that there was a time-related increase in the number of subjects who used buprenorphine to get high, reaching 30-35 percent of individuals completing a questionnaire in the second quarter of 2006. At this time, it was equivalent to the misuse of methadone, both of which, however, were considerably lower than hydrocodone and oxycodone. Thereafter, the number of individuals using buprenorphine to get high dropped in a near linear fashion to less than 20 percent of those completing a questionnaire in the second quarter of 2007, significantly lower than that for methadone, oxycodone, and hydrocodone. The most likely interpretation of these data is that the polysubstance-abusing population, for whom buprenorphine is intended, experimented with this medication for its mood-altering effects for a period of time, but presumably because of its lack of euphorogenic properties, its use has now dissipated. Additionally, support for this conclusion is the very rare endorsement of buprenorphine as a primary drug (<3 percent of the total sample). Thus, the results indicate that it is unlikely that buprenorphine abuse will ever reach the epidemic that was feared by some regulatory groups and that its use in opioid detoxification and maintenance should continue.

Key words: buprenorphine abuse, buprenorphine misuse, prescription opioid abuse, treatment, opioid abuse

INTRODUCTION

Buprenorphine, in the form of Subutex (drug alone) and Suboxone (buprenorphine and naloxone), was approved in late 2004 for the treatment of opioid abuse and dependence in specially trained and certified physicians' offices.¹⁻³ The rationale for out-patient therapy in a standard physician's office was to remove the stigma associated with stand-alone methadone clinics and, as a result, facilitate the medical and pharmaceutical treatment of opioid addiction much as is done for all other medical disorders.¹⁻³ When buprenorphine was approved for use in opioid detoxification, it was placed in Schedule III of the Controlled Substances Act because of an established lack of strong abuse potential of prior formulations, which warranted such a schedule.⁴⁻⁸ However, there were concerns expressed by the Food and Drug Administration (FDA) and the Drug Enforcement Administration that this drug would have much greater abuse potential than predicted because of its use in very high-risk populations in which diversion of prescribed drugs is common. Consequently, an extensive risk-management program was mandated by the FDA to establish parameters for the use of buprenorphine and monitor abuse in a timely and proactive manner.⁹ This program consists of a number of elements, the most important of which are as follows: certification and training of physicians in the use of the drug; limits on the number of patients each physician can treat to 30 (recently, Congress amended this element by increasing the patient limit to 100); and the implementation of a proactive surveillance program for the detection of unexpectedly high abuse of buprenorphine.

To date, there has been very little published evidence of abuse of these new buprenorphine products. In a brief report,¹⁰ we found very low levels of abuse within a few months of the launch but cautioned that because of the very low-market penetration, as exposure to the drug grew, the abuse might grow. This cautionary note appears to have been appropriate because, in a subsequent publication,¹¹

we found that abuse of buprenorphine, expressed as cases of misuse to get high/1,000 persons filling prescriptions, was very high, ranking it as one of the most extensively abused opioid medications. In this report, we have examined in more detail the abuse of buprenorphine. We recruited more than 1,000 individuals seeking treatment for prescription opioid abuse from 100 stand-alone (ie, self-pay or insurance) drug abuse treatment programs around the country to determine whether they had used buprenorphine in the past 30 days to get high, and, if so, the reason for use. We elected to use self-pay or medically insured drug treatment programs for two reasons: first, to complement the Treatment Episode Data Set,¹² which gathers similar data only from publicly funded treatment centers; and second, given that buprenorphine is prescribed by a physician in his or her office, the individuals at most risk would likely be those with resources to pay for their care should drug abuse treatment abuse become necessary.

METHODS

Recruitment of subjects

As reported previously,^{11,13} subjects were recruited from 100 urban, suburban, and rural treatment centers

(Figure 1) that were self-pay or accepted health insurance to cover their costs and had very limited public support (<20 percent of public funding). Each of the treatment specialists was paid a stipend to recruit up to his or her next 50 consecutive patients/clients who used opioid analgesics nontherapeutically in the last 30 days to get high and had a diagnosis of opioid analgesic abuse using criteria based on the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*.¹⁴ The patients were asked to complete a detailed mail-in survey instrument covering demographics and licit and illicit drug use.

All of the completed questionnaires were identified solely by a unique case number and were sent directly to the Washington University School of Medicine. The treatment specialists did not see the detailed responses of their patients/clients. When completed questionnaires were received and processed, the treatment specialists were notified, and they in turn distributed \$25.00 gift certificates for a national or local retail chain (eg, Wal-Mart) to the individuals who had submitted the completed questionnaires.

Statistical analyses

Because much of our data were binary (yes/no), odds ratios were calculated using univariate logistic regression

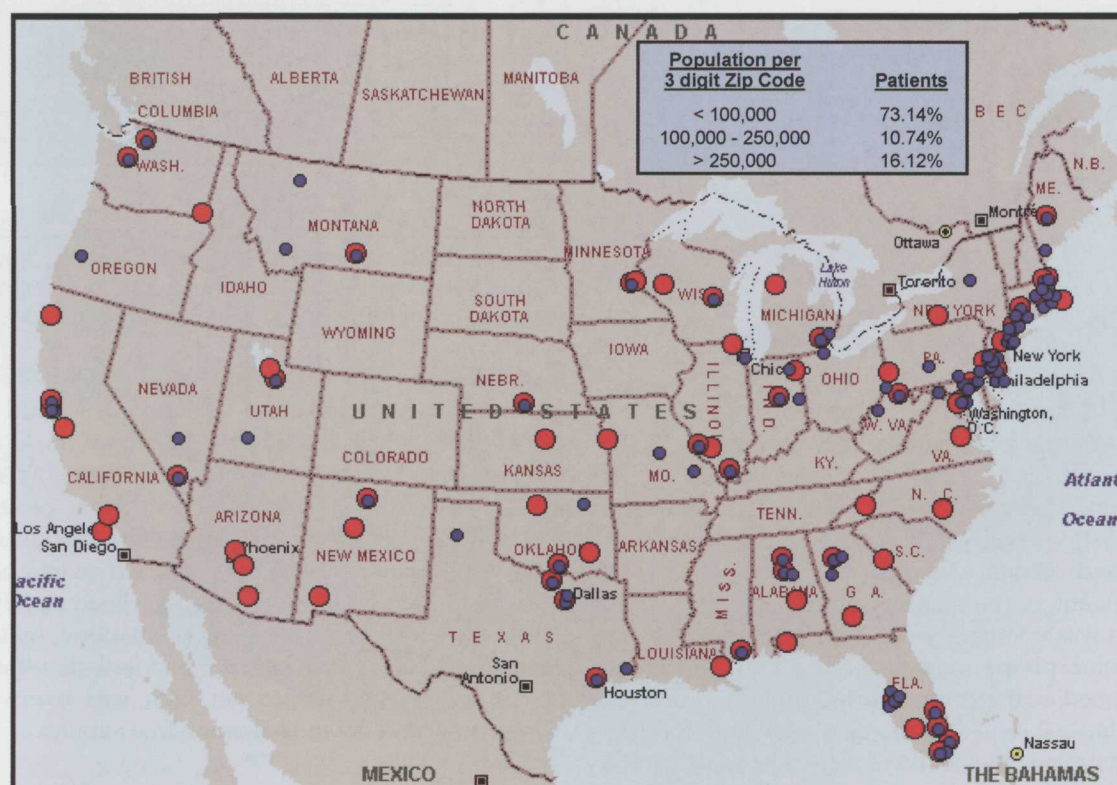


Figure 1. Location by three-digit zip code (first three digits) of the treatment centers (● red circles) and patients who used buprenorphine in the past 30 days or are currently enrolled in a buprenorphine treatment program (● blue circles). The inset shows the distribution of patients filling out questionnaires (n = 1,000) who used buprenorphine to get high stratified by the population of their residential zip code. Three-digit zip codes of key informants and buprenorphine users.

analyses to compare those who had used buprenorphine to get high in the 30 days before completing the survey instrument ($n = 264$) with those who had not ($n = 799$). For continuous variables, independent-sample *t*-tests were used to assess significant differences.

Persons filling prescriptions

The data regarding the number of persons filling a prescription for buprenorphine and the other study drugs for each of the three-digit zip codes in which patients completed questionnaires ($n = 233$ of 973) were purchased from Verispan Inc. (Yardley, PA). In this data base, individuals refilling existing prescriptions are excluded so that the number of persons filling a prescription are those filling a prescription for the first time.

Signal sites of disproportionately high buprenorphine abuse

As described elsewhere,¹¹ we defined “signal sites” in which buprenorphine abuse was disproportionately high relative to exposure by plotting the rate of buprenorphine misuse (cases of misuse to get high/1,000 persons filling a prescription) against the persons filling a prescription for buprenorphine in the same zip code. A “signal site” was a zip code that fell above the 97.5th percentile of the frequency distribution.

Patient/subject confidentiality

The protocol was approved by the Washington University Institutional Review Board.

RESULTS

Use of buprenorphine in prescription drug abusers seeking treatment

Figure 2 shows the percent of individuals who used the opioid analgesics listed in the past 30 days to get high, as well as the drugs they endorsed as their primary drug. It is clear that, first, polysubstance abuse is the norm in these individuals and, second, although buprenorphine was used by 20–25 percent, of our subjects in the last 30 days to get high, which was comparable with that observed for fentanyl, hydromorphone, morphine, and tramadol, it was rarely endorsed as the primary drug of choice. The data shown in Figure 2 represent the aggregate data for 2005–2007. To determine whether there were time-related trends in the use of buprenorphine to get high, Figure 3 shows the percent of individuals responding each quarter who used buprenorphine in the past 30 days to get high. As can be seen, the use of buprenorphine to get high increased markedly over the time course of this study, more than

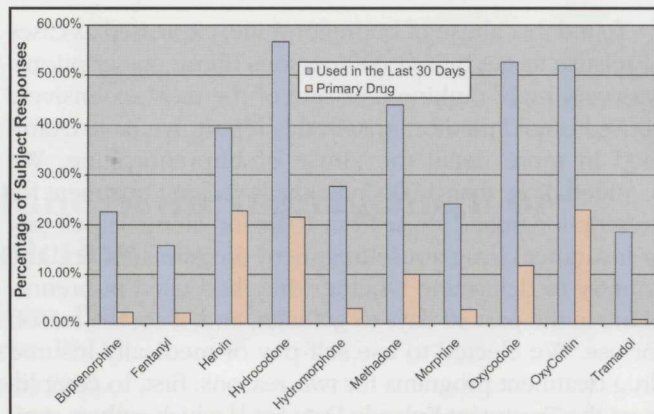


Figure 2. Percent of the 1,741 patients who indicated they had used the drugs shown to get high in the 30 days before completing the survey (blue bars); subjects were allowed to pick all the drugs they used so the percentages exceed 100. The yellow bars show the endorsement of a primary drug, defined as the drug they used most to get high in the past 30 days (only one drug could be selected so the totals equal 100 percent). Drugs used in the last 30 days to get high and primary drugs.

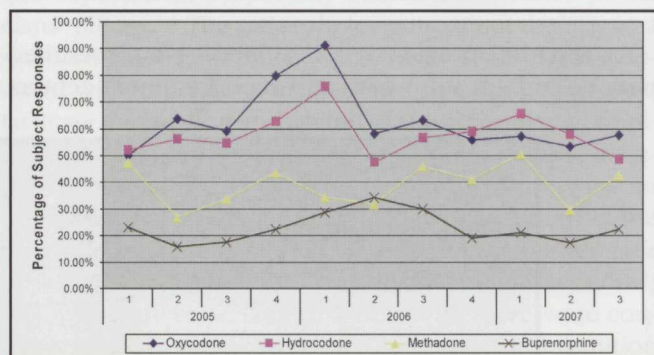


Figure 3. Percent of clients each calendar quarter who indicated they used oxycodone, hydrocodone, methadone, or buprenorphine to get high in the past 30 days.

doubling from the second quarter of 2005 (when buprenorphine was first marketed) through the second quarter of 2006 at which time about 35 percent of those answering the questionnaire reported use of buprenorphine to get high, which was comparable with that observed with methadone. However, during the last four quarters, from the third quarter of 2006 to the second quarter of 2007, the use of buprenorphine to get high declined rapidly such that it was significantly lower than methadone, hydrocodone, and oxycodone. It should be noted that the form of buprenorphine used to get high was overwhelmingly Suboxone and not the naloxone-free Subutex.

Comparison of buprenorphine users relative to other subjects

Table 1 provides the demographics of those who used buprenorphine in the past 30 days to get high

Table 1. Demographics of national opioid abusers

	Buprenorphine*, total (n = 264)	National†, total (n = 799)
Ethnic background		
White	92.05 percent	78.39 percent‡
African-American	1.52 percent	8.92 percent
Hispanic	3.79 percent	6.53 percent
Other	2.65 percent	6.16 percent
Age		
Average age	30.60 ± 0.65	34.63 ± 0.42‡
Education		
None	3.78 percent	10.58 percent
High school or GED	39.50 percent	46.20 percent
College	56.72 percent	43.22 percent‡
Employment Status		
Employed	54.41 percent	42.24 percent‡
Source		
Dealer	34.62 percent	73.96 percent‡
Friend	23.08 percent	64.43 percent‡
Doctor	56.67 percent	52.66 percent
Route of Administration		
Inject	6.06 percent	37.29 percent‡
Swallow	15.15 percent	66.33 percent‡
Sublingual	87.18 percent	13.79 percent‡
Chew	12.12 percent	33.50 percent§
Sniff	9.09 percent	44.83 percent‡
Smoke	3.03 percent	18.38 percent

*National sample does not include the buprenorphine sample.

†Buprenorphine sample includes only subjects who indicated they had used. Buprenorphine in the 30 days prior to survey completion.

‡significantly ($p < 0.01$) different than buprenorphine users.

§significantly ($p < 0.05$) different than buprenorphine users.

($n = 264$) compared with those who did not ($n = 799$). Buprenorphine users were much more heavily white ($OR = 3.19$, $p < 0.01$), much younger ($t = -4.88$, $p < 0.01$) when they sought treatment, more highly educated ($OR = 1.72$, $p < 0.01$), employed ($OR = 1.63$, $p < 0.01$) more often than all the other users, and lived in primarily suburban and rural areas (Figure 1). Doctor's prescriptions were the main source of buprenorphine, as was the case for all other prescription opioid abusers. Although a sizable number also got buprenorphine from friends, relatives, or a dealer, these sources were used much less frequently than those found in the general population (see Table 1). In contrast to other prescription opioid users, buprenorphine was taken primarily as directed—sublingual—with much smaller numbers using other routes.

Misuse corrected for exposure

To obtain some idea of the rate of misuse, which took into account the growing number of prescriptions for buprenorphine, we calculated the number of persons who used buprenorphine and comparable drugs to get high in the past 30 days divided by the number of persons filling prescriptions in their residential zip code. The results are shown in Figure 4. In the second quarter of 2005, it can be seen the use of buprenorphine to get high was three to four times higher than methadone and at least 10 times greater than oxycodone. Over time, as exposure increased and the number of cases of misuse remained constant or decreased, the rate has dropped progressively such that in the first and second quarters of 2007, the rates of abuse of buprenorphine were equivalent to those seen with methadone.

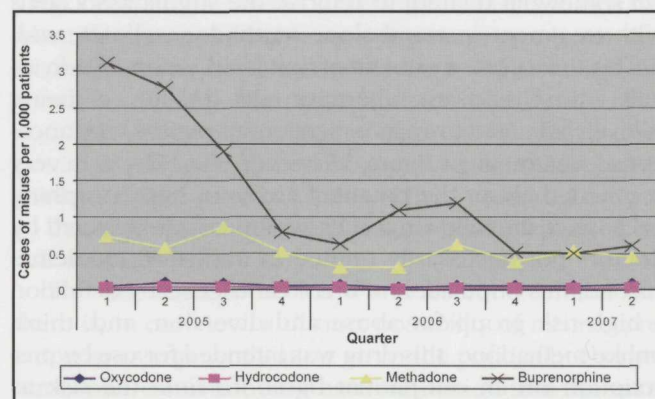


Figure 4. A: Rate of abuse of oxycodone, hydrocodone, methadone, and buprenorphine defined as cases of misuse to get high/1,000 patients filling a prescription in that calendar quarter.

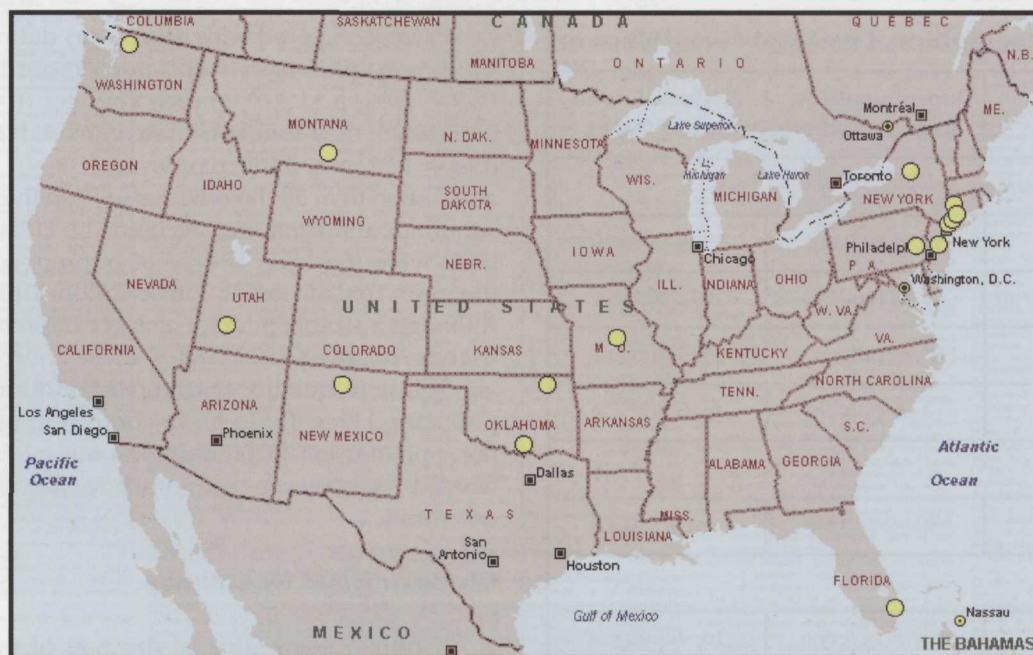


Figure 5. The location by three-digit zip codes of signals of buprenorphine misuse. A signal was defined as one above the 97.5th percentile of all cases of misuse plotted as a function of the patients filling a prescription in that zip code. Top 2.5 percent of buprenorphine signal sites.

Localization of buprenorphine signal sites

Figure 5 and Table 2 show those three-digit zip codes in which a signal site of buprenorphine was detected. It can be seen that the buprenorphine abuse was overrepresented in the suburban areas of the Northeast Corridor and in small urban and rural areas across the United States.

DISCUSSION

Buprenorphine was approved in 2004 for use in the treatment of opioid addiction in a trained physician's office setting for several reasons¹⁻³: (1) to place substance abuse in the same category as other medical disorders; (2) somewhat related, to remove the stigma associated with treatment in stand-alone methadone clinics; and, finally, to facilitate treatment of opioid addiction in individuals who would not otherwise take the step of being formally admitted to an in-patient or out-patient substance-abuse treatment program. However, the FDA was very concerned about the potential abuse of buprenorphine because of the following: (1) it was to be administered by doctors not necessarily trained in addiction medicine; second, this population of opioid abusers is by definition a high-risk group for abuse and diversion; and, third, unlike methadone, this drug was intended for use by prescription on an out-patient basis. To limit the risk as much as possible, the sponsor and the FDA agreed to the most comprehensive risk management program ever implemented for a newly approved drug.⁹ Key elements of the program were to require certification and training

Table 2. Signal sites of disproportionately high buprenorphine abuse

Zip	City	State
066	Bridgeport	CT
067	Waterbury	CT
069	Stamford	CT
086	Trenton	NJ
107	Yonkers	NY
133	Alder Creek	NY
195	Adamstown	PA
333	Ft. Lauderdale	FL
591	Billings	MT
650	Argyle	MO
734	Ardmore	OK
740	Stillwater	OK
847	Saint George	UT
875	Santa Fe	NM
982	Everett	WA

of physicians who wanted to use the drug; a limit of no more than 30 (now 100) patients treated per physician, and the implementation of a postmarketing surveillance program to detect regional or national outbreaks of abuse and diversion.

The studies described in this work, which are not a component of this risk-management program, indicate that there was a time-related increase in the number of subjects who used buprenorphine to get high after its launch date, reaching 30-35 percent of individuals completing a questionnaire in the second quarter of 2006. At this time, it was equivalent to the misuse of methadone, both of which, however, were considerably lower than hydrocodone and oxycodone. Thereafter, the number of individuals using buprenorphine to get high dropped in a near linear fashion to less than 20 percent of those completing a questionnaire in the second quarter of 2007, significantly lower than that for methadone, oxycodone, and hydrocodone. Interestingly, as mentioned in the results, most of our subjects used Suboxone in an effort to get high rather than the naloxone-free Subutex. The reason for this is not intuitively obvious except, as we have shown elsewhere,¹¹ abuse/misuse is directly proportional to availability. Because Suboxone is used almost exclusively in this country, the lack of exposure to Subutex is probably the main reason for its limited misuse.

One probable interpretation of these data is that the polysubstance-abusing population for whom buprenorphine is intended experimented with this medication for its mood-altering effects for a period of time. Such periods of experimentation are common with newly launched drugs. For example, in the mid-1990s, with the release of branded tramadol (Ultram), a spike in use and rates of abuse (cases/1,000 persons using a prescription) occurred as individuals apparently experimented with the new drug for its euphoric properties for 6-9 months after its release.^{15,16} This quickly dissipated, apparently because of the absence of highly reinforcing properties of tramadol, such that within 12-18 months, its use to get high dropped by over 80 percent. Moreover, the low euphorogenic properties of tramadol resulted in its rare endorsement as a primary drug of abuse as shown in the present studies and many others.^{15,16} Because we found very similar patterns with buprenorphine—apparent experimentation and very low endorsement as a primary drug—it seems highly likely that buprenorphine, such as tramadol, abuse will never reach the epidemic that was feared by some regulatory groups.

When expressed as a rate of abuse, defined by the number of patients using buprenorphine to get high divided by the number of persons filling a prescription in their zip code, the nontherapeutic use of buprenorphine was disproportionately high relative to methadone, oxycodone, and hydrocodone in the first 2 years after its introduction. Thereafter, the rate gradually declined such

that it was more comparable with methadone in the first and second quarters of 2007. We predict that with enhanced exposure and steady to lower numbers of patients using the drug to get high, these rates will ultimately drop further. Nonetheless, as we have reported previously,¹¹ the rates of abuse of methadone and buprenorphine are consistently higher than those of oxycodone and hydrocodone. These findings should not be surprising because both drugs are used in relatively small populations, which tends to inflate the rates of abuse, and most importantly, those for whom methadone and buprenorphine are intended have extensive substance abuse histories. Thus, this group consists of very-high-risk individuals who are more likely to divert medications for nontherapeutic purposes.

Our results in the United States seem to be consistent with the outcome of similar studies in other countries, in which buprenorphine has been used for opioid treatment for some time.¹⁷ Abuse and diversion from legitimate sources have been observed, particularly in France, where intravenous injection is common. There are major differences between France and the United States in terms of training in the use of buprenorphine and the form of buprenorphine used in both countries—buprenorphine only in France and buprenorphine + naloxone (Suboxone) in the United States—but nonetheless, it is clear that buprenorphine is certainly diverted and abused to some extent in all countries in which it has been used to treat opiate addiction. This would seem to serve as a reminder for those using buprenorphine to be mindful that, first, the population for which it is intended is likely to divert their medication, and second, buprenorphine has some abuse potential, which needs to be recognized and monitored.

In this study, we identified areas in which buprenorphine abuse was prevalent and was disproportionately high compared with the rest of the country. Interestingly, many of these areas are the same as those previously described for a number of other opioids such as OxyContin.^{13,15,18,19} In the spirit of the FDA-mandated risk identification and risk *management* program for buprenorphine, now that areas have been identified, we would encourage the program mandated by the FDA, and funded by the sponsor of buprenorphine, to carry out an assessment of the abuse problems in these areas, particularly the suburban areas of the Northeast Corridor, so that appropriate interventions can be implemented (ie, risk management).

The implications of our work are considerable and there is, in our view, a distinct possibility of misinterpretation or overgeneralization given the politically charged atmosphere surrounding harm reduction and the management of opioid addiction with pharmaceutical agents, particularly other opiates. What our results show is that in a very-high-risk group in which the use of many prescribed opioids is common, approximately 20 percent

have used buprenorphine to get high, which is similar to that observed for many other drugs with significant abuse potential. The misinterpretation of these data, or more properly, overextension of their significance, is that these data will be used as evidence that the initial fears of federal officials of an outbreak of buprenorphine abuse has been realized. Such a conclusion is premature, and the public health would not be well served by limiting its use in the treatment of opioid addiction, particularly since the period of experimentation with the drug to get high seems to be waning. The benefits of reducing the impact of illicit opioid abuse on individuals and society in our view offset an unfortunate side effect associated with its diversion. At this point, we believe that there is still a very favorable risk-benefit ratio and that the use of buprenorphine as a treatment for opioid addiction should continue. However, it seems equally clear that this needs to be objectively and systematically monitored to ensure that the risks do not override its obvious benefits.

There are many limitations in the approach we used in this study. Most notably, our sample reflects only those individuals who sought treatment for their abuse problems either because of self-recognition or referral by family or the legal system. Furthermore, most had the financial resources to pay for their care either with personal funds or some form of health insurance, and this no doubt impacts on the demographic profile we have observed. Moreover, our data shed no light on "recreational" users or those who do not opt for treatment, and, hence, are limited in this respect. Finally, our survey was completed by the patient and mailed to us and, thus, has all the limitations associated with such techniques.²⁰⁻²³

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