



## Buprenorphine for pain management physicians: A dilemma or a therapeutic alternative?

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The recent approval of office-based treatment for opioid addiction using buprenorphine expands treatment options for opioid addiction. However, the utility of this drug in controlling chronic pain in those suffering with chemical dependencies, although intuitively elegant, has yet to be fully explored. Buprenorphine's clinical efficacy results from its unique molecular structure: it is a partial  $\mu$  opioid agonist and a weak antagonist. Although it has a high affinity for the  $\mu$  receptor, with slow dissociation resulting in a long duration of action and an analgesic potency 25 to 40 times greater than morphine, most physicians outside the addictions field have yet to exploit buprenorphine as a therapeutic alternative, particularly in patients with a family history of addiction, or past history of opiate abuse or dependency. The primary reason to consider the drug in populations with addictive predisposition is that, at higher doses, its agonist effects plateau and antagonist effects predominate limiting the drug's desirability as a substance of abuse and decreasing the potential for respiratory depression resulting in a high safety profile. Even so, abstinence syndromes do develop and withdrawal symptoms, although mild constitutionally, can be as psychologically harrowing as with other narcotics. Thus, cessation after prolonged administration should be monitored. In conclusion, buprenorphine both structurally and clinically provides an elegant alternative to the dilemma of treating legitimate chronic pain in the patient with whom addictive predilections may be an issue. Physicians using the drug should consider getting the special DEA number to protect themselves in those cases where the fine line between treatment of chronic pain and management of opioid addiction is ambiguous.

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There are 980,000 long-term users of heroin in the United States, and the cost of heroin addiction to the health care system and to society in 1996 was conservatively estimated at \$5 billion and \$21.9 billion, respectively.<sup>1-3</sup> When abuse of narcotic pain medication is factored in, the number is much larger. Only 12% to 15% of opioid-dependent patients are actively enrolled in methadone maintenance.<sup>4</sup> Methadone maintenance has been found to be effective in curtailing drug use, reducing crime, enhancing social productivity, and preventing overdose deaths and the spread of infectious diseases.<sup>5</sup>

The Drug Enforcement Administration (DEA) and US Food and Drug Administration (FDA), having approved the

use of Buprenorphine in the office-based treatment for opioid addiction, expanded greatly the availability of opioid addiction treatment in the United States. Pain management physicians may now prescribe buprenorphine in the treatment of pain in patients with a history (documented or otherwise) of addiction, assuming that the etiology of the pain is well documented and the patient is not drug seeking in an attempt to maintain a habit. To be sure, pain management physicians will encounter buprenorphine, either as a current medication in patients who are maintained on the drug or in those patients who paradoxically deteriorate on escalating doses of traditional narcotic pain medication. When a history of addiction exists, or an occult dependency is suspected, it is important for physicians treating chronic pain to understand the unique pharmacology of buprenorphine and to develop informed treatment rationales. This can be accomplished via close communication with addic-

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tion medicine physicians or via patient referrals to physicians trained in addiction medicine who, by virtue of that training and certification, have special knowledge and privilege in relationship to the drug, or to psychiatrists with special certification in addictions who have received special training and a special DEA number allowing them to prescribe Buprenorphine in a maintenance regime. Any physician choosing to use Buprenorphine in clinical practice should consider taking a training course offered by the American Society of Addiction Medicine or by the American Association of Addiction Psychiatrists and apply for a special DEA number to protect them in those cases where the question of whether the physician is treating a chronic pain issue or is unwittingly maintaining a patient who may be in denial concerning an occult addiction.

## Policy

The Drug Addiction Treatment Act of 2000 expands the avenues for the treatment of opioid dependence in the United States from specially licensed methadone facilities to physicians' private offices, where schedule III to schedule V drugs can be prescribed.<sup>6-8</sup> The responsibility of methadone administration has historically been jointly shared by the FDA and the DEA. This organizational structure has created policies that isolate methadone therapy from the medical mainstream and limit the development of physician expertise and creativity.<sup>9</sup> Opioid substitution treatment will now be monitored by the Substance Abuse and Mental Health Administration and will allow the expansion of treatment to private practice, which will create opportunities to provide comprehensive care for addicted patients with AIDS, hepatitis, or other conditions that are complicated by opioid dependence. It is hoped that private treatment will reduce the stigma associated with the use of opioids and will bring addiction treatment into the mainstream of health care and that treatment may become similar to that of other chronically ill patients. In addition, this expansion could have substantial public health benefits by reducing heroin demand.

The act stipulates that physicians must use medications that have been approved by the FDA for maintenance and detoxification treatment of opioid dependence. It also requires that physicians notify the Department of Health and Human Services of their intent to prescribe these drugs for outpatient maintenance or detoxification by applying for a special DEA number. Physicians treating opioid-dependent patients must have specialized training, or, to be certified by the American Society of Addiction Medicine as an addictionist. The use of Buprenorphine by these physicians for maintenance of opiate addiction is expected to have substantial public health benefits by reducing demand for illicit opiates. Adverse societal outcomes, such as ease of diversion and unknown health care costs, to be sure, are possible, however, given the experience with methadone, the potential benefits far outweigh the potential risks.

On October 8, 2002, the FDA approved buprenorphine, a schedule III partial  $\mu$  agonist, for the treatment of opioid dependence. Physicians treating opioid-dependent patients

must have specialized training or experience, as well as have appropriate counseling and other services available.<sup>10</sup> A maximum of 30 patients can be treated per physician group.

## Pharmacology

Buprenorphine, a derivative of thebaine, is classified as a partial  $\mu$  opioid agonist and a weak antagonist.<sup>11</sup> It has a high affinity for the  $\mu$  receptor, with slow dissociation resulting in a long duration of action. In lower doses, buprenorphine has an analgesic potency 25 to 40 times more potent than similar milligram dosages of morphine.<sup>12</sup> Because it is a partial agonist, its effects plateau at higher doses, and it begins to behave more like an antagonist. This antagonistic property in higher doses limits the maximal analgesic effect and respiratory depression. The high-affinity blockade significantly limits the effect of subsequently administered opioid agonists or antagonists, and the "ceiling effect" provides a high safety profile clinically, a low level of physical dependence, and only mild withdrawal symptoms on cessation after prolonged administration. These qualities make buprenorphine advantageous for the treatment of opioid dependence. The ceiling effect may limit its usefulness in addicts who require higher doses of methadone. Buprenorphine is well absorbed sublingually, with 60% to 70% of the bioavailability of intravenous doses.<sup>13</sup> Buprenorphine is less well absorbed orally and is quickly metabolized by the liver. The drug is widely distributed, with a peak plasma concentration at approximately 90 minutes and a half-life of 4 to 5 hours. Buprenorphine is lipophilic, and thus brain tissue levels far exceed serum levels. It is highly bound to plasma protein and is inactivated by enzymatic transformation via N-dealkylation and conjugation. Buprenorphine is mainly metabolized to inactive conjugated metabolites (80% to 90%), but norbuprenorphine, a product of Ndealkylation by the cytochrome P-450 3A4 enzyme, has more potent respiratory depressive effects than the parent drug.<sup>14,15</sup> Drugs that interfere with the 3A4 enzyme, such as erythromycin, ketoconazole, and HIV protease inhibitors, could decrease the production of norbuprenorphine. Drugs that induce the 3A4 enzyme, such as phenobarbital, carbamazepine, and phenytoin, could increase the levels of norbuprenorphine.<sup>16,17</sup> The clinical effects of these interactions are unknown.

The sublingual preparation of buprenorphine alone (Buprenex), or in combination with naloxone (Subutex), is now available and is intended for use in the physician-supervised introduction of patients new to the drug to assess the dose effect and potential for withdrawal symptoms. Buprenex, the parenteral form of buprenorphine, has been available and used for pain control for decades.<sup>18,19</sup>

## Clinical use and addiction management

Buprenorphine is now used for opioid detoxification and maintenance by addiction medicine physicians and psychiatrists with special competency in addiction. It has a better

safety profile than methadone.<sup>20</sup> A variety of dosing regimens are being studied to optimize treatment and are more fully covered elsewhere. A regimen of 8 to 12 mg sublingual daily has been used for 5 to 7 days for detoxification from opioids.<sup>21</sup> The slow release of buprenorphine from the  $\mu$  receptor allows a relatively symptom-free withdrawal. Physical dependence to buprenorphine is considered milder than to methadone or heroin, and withdrawal signs and symptoms are limited making discontinuation less uncomfortable. However, in dependent individuals, the abstinence syndrome can be quite marked. Maintenance doses of 4 to 32 mg/d will suppress symptoms of withdrawal and reduce illicit opioid use.<sup>22-26</sup> Dosing can be extended to every 2 to 3 days. Physicians should be aware of the potential problem of precipitating withdrawal symptoms with the introduction of buprenorphine. In a patient with an active heroin or methadone effect, the antagonist effect of buprenorphine will prevail. An initial opioid-free period must elapse before the initial dose of buprenorphine without naloxone. The introduction of buprenorphine should be done in the presence of a physician.

### Pain management issues

It is not far fetched to wonder how many drug-seeking patients with variable response to narcotics are, in fact, suffering from an occult addiction and seeking maintenance when they enter the office of a pain management physician. Since the subjective perception of pain has become "the fourth vital sign," the frequency with which personal and family history of alcoholism or addiction is abbreviated, neglected, or ignored in patients is startling when viewed from the perspective of physicians who treat addiction and, by necessity, the aftermath of well-intentioned but ill informed pain management strategies. The United States Department of Health and Human Services Substance Abuse and Mental Health Services Administration (SAMHSA's) National Survey on Drug Use & Health [formerly called the National Household Survey on Drug Abuse (NHSDA)] is the primary source of information on the prevalence, patterns, and consequences of alcohol, tobacco, and illegal drug use and abuse in the general US civilian noninstitutionalized population, aged 12 and older. There was a significant increase in lifetime nonmedical use of pain relievers between 2002 and 2003 among persons aged 12 or older. The numbers increased from 29.6 million to 31.2 million, an average of 23.6% of the population. Specific pain relievers with statistically significant increases in lifetime use were Vicodin®, Lortab®, or Lorcet® (from 13.1 million to 15.7 million); Percocet®, Percodan®, or Tylox® (from 9.7 million to 10.8 million); Hydrocodone (from 4.5 million to 5.7 million); OxyContin® (from 1.9 million to 2.8 million); methadone (from 0.9 million to 1.2 million); and Tramadol (from 52,000 to 186,000).<sup>27</sup>

Data from SAMHSA's 2002 and 2003 National Survey on Drug Use and Health were also pooled to examine the patterns of illicit drug use among adults aged 21 or older that have used alcohol in their lifetime compared with adults who have never used alcohol in their lifetime. An estimated

88.2% of persons aged 21 or older (175.6 million) had used alcohol in their lifetime and 11.8% (23.5 million) had not used alcohol in their lifetime. Among those who had used alcohol, 52.7% had used one or more illicit drugs at some time in their life, whereas only 8% of the nondrinkers had used an illicit drug. Given statistics such as these, the likelihood that an average pain management practice has patients with addictive potential approaches one-third.

The introduction of buprenorphine management has the potential to greatly improve the treatment of chronic pain in patients with a history of addiction to opioids or with a family history of addictive disorders. Admittedly, the published clinical experience of treating acute and chronic pain in buprenorphine-maintained patients is limited, however, to the general principles of acute pain management, including intravenous administration of opioid analgesics and repeated and timely assessment of pain, blood pressure, and ventilation, should suffice in achieving pain control. In addition, patients maintained on methadone and buprenorphine will require higher doses of other opioids to achieve adequate pain relief in the setting of acute pain. For the patient with a history of chronic pain, it is important to note clinical and research evidence that suggests that persons maintained on long-acting opioid agonists have a lower sensitivity for a given pain stimulus.<sup>28</sup> Patients who are expected to require acute pain control in the near future should stop any further doses of their buprenorphine 1 to 2 days before the scheduled procedure. Because of the slow waning effect of buprenorphine throughout the next 12 to 24 hours, patient-controlled analgesia should be monitored carefully. Physicians can legally use buprenorphine for the inpatient treatment of opioid addiction without the special DEA number and training. The first dose of the buprenorphine without naloxone preparation should be administered at 4 to 8 mg sublingually and in the presence of a physician to monitor for signs of precipitated withdrawal. Oral buprenorphine can be used for acute pain management but has limited advantages over existing preparations. Its advantage in its use for chronic pain stem from the same characteristics that made it acceptable as maintenance.

### Intentional abuse and diversion

The sublingual preparation approved in the United States, marketed under the brand name Suboxone (Reckitt Benciser, Berkshire, United Kingdom), is available in 2-mg and 8-mg tablets combined with naloxone at 0.5 mg and 2 mg, respectively. Naloxone has no effect sublingually because of poor absorption but precipitates withdrawal symptoms if administered parenterally to an opioid-dependent person, thereby limiting diversion.

Although the experience in France and New Zealand has demonstrated that there is a potential for diversion of buprenorphine to intentional abuse by opioid addicts, the potential is much lower than the potential for misuse of methadone.<sup>29-32</sup> The clinical effects of intravenous buprenorphine were rated by addicts as comparable to equipotent doses of morphine; however, the ceiling effect makes the likelihood that an addict would continue to use buprenorphine lower than that of other synthetic narcotics.

A significant percentage (33%) of French buprenorphine patients reported intravenous use.<sup>33</sup> Diversion was also noted in New Zealand, but the addition of naloxone significantly decreased the buprenorphine and naloxone combination's monetary value and frequency of diversion.<sup>34</sup> The injection of a 4:1 combination of buprenorphine and naloxone has been demonstrated to result in acute withdrawal symptoms among heroin addicts. It is hoped that this combination will minimize the risk for diversion and intravenous use. There may still be concern of diversion to opioid-naïve users, particularly those with a family history of alcoholism or other addictions.

### Acute overdose management

Although buprenorphine has a salutary effect on decreasing deaths related to opioid overdose and has a better safety profile than methadone, cases of buprenorphine-related overdose deaths have been reported. There is little clinical experience with the acute overdose management of buprenorphine, but some inferences from clinical studies can be made.<sup>35-38</sup> The  $\mu$  receptor ceiling effect mentioned above should limit life-threatening respiratory depression, but it has been reported with both intravenous and sublingual doses of buprenorphine.<sup>39-42</sup> The intravenous administration of therapeutic doses of buprenorphine increased the diastolic blood pressure, slightly increased the pulse rate, and decreased pupil size for 24 hours. Oral administration results in a peak effect that is delayed several hours and can last 8 to 10 hours. Intravenous or subcutaneous administration of buprenorphine will demonstrate mild respiratory depression within 15 minutes and demonstrates a maximum effect at 45 minutes and duration of 6 hours. Hospital-based reporting of buprenorphine overdoses have demonstrated limited symptoms, including insomnia, vomiting, and pressure headache, without any respiratory depression.<sup>43</sup>

Cases of severe buprenorphine intravenous overdoses resulting in patient obtundation have been described in the literature and were characterized by the following: a Glasgow Coma Scale score of 8 or less, meiosis, and severe respiratory depression. Naloxone in doses of 0.4 mg to 0.8 mg caused rapid improvement in all of these patients. More than half of these patients had also concomitantly used alcohol or benzodiazepines. Supportive care and observation should be the major treatment modalities in suspected buprenorphine intoxication. Patients with significant symptoms related to buprenorphine should be admitted to the hospital for observation because symptoms will likely persist for 12 to 20 hours. The role of naloxone and the clinical presentation in this scenario needs to be determined by future studies.<sup>44</sup> Buprenorphine will not be detected on most random toxicological screens but will be detected when the specific test is requested.

### Conclusion

Pain management physicians will soon be routinely encountering patients undergoing detoxification or being main-

tained on outpatient buprenorphine. When referencing the data on the natural history of addictive disorders, it is not far fetched to consider that a full one-third of any pain management practice may involve patients with a history of or potential for developing an addictive disorder. Buprenorphine's unique pharmacology offers many practical advantages in the management of opioid addiction and the control of chronic pain in patients with a history of opioid addiction. To be sure, some distinct difficulties in the treatment of acute pain and the management of active addiction can be expected; however, the potential to identify and appropriately manage such a difficult problem as chronic pain and to do so against the back drop of an addictive history without activating or worsening an addiction is part of the promise of this unique medication. The United States, by repeating the experience of other countries that have implemented office-based buprenorphine management of opioid addiction, has already improved the plight of patients suffering from addictive disorders. By closely examining the utility of buprenorphine in the clinical pain management practice, the potential for significant decreases in pain-management related medical complications in a large portion of pain patients is, without doubt, worth the time and effort to safely, efficaciously, and legally add this drug to the pain management physician's armamentarium.

### References

1. Raisch DW, Fye CL, Boardman KD, et al: Opioid dependence treatment, including buprenorphine/naloxone. *Ann Pharmacother* 36:312-321, 2002
2. Merrill JO: Policy progress for physician treatment of opiate addiction. *J Gen Intern Med* 17:361-368, 2002
3. Mark TL, Woody GE, Juday T, et al: The economic costs of heroin addiction in the United States. *Drug Alcohol Depend* 61:195-206, 2001
4. Rounsaville BJ, Kosten TR: Treatment for opioid dependence: quality and access. *JAMA* 283:1337-1339, 2000
5. National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction: Effective medical treatment of opiate addiction. *JAMA* 280:1936-1943, 1998
6. Resnick RB: Food and Drug Administration approval of buprenorphine-naloxone for office treatment of addiction [letter]. *Ann Intern Med* 138:360, 2003
7. Fiellin DA, O'Connor PG: Clinical practice: office-based treatment of opioid-dependent patients. *N Engl J Med* 347:817-823, 2002
8. Jaffe JH, O'Keefe C: From morphine clinics to buprenorphine: regulating opioid agonist treatment of addiction in the United States. *Drug Alcohol Depend* 70:S3-S11, 2003
9. Fiellin DA, O'Connor PG: New federal initiatives to enhance the medical treatment of opioid dependence. *Ann Intern Med* 137:688-692, 2002
10. Buprenorphine training from SAMSHA [Substance Abuse and Mental Health Services Administration Web site]. Available at <http://buprenorphine.samhsa.gov>. Accessed October 30, 2003.
11. Ling W, Smith D: Buprenorphine: blending practice and research. *J Subst Abuse Treat* 23:87-92, 2002
12. Pickworth WB, Johnson RE, Holicky BA, et al: Subjective and physiologic effects of intravenous buprenorphine in humans. *Clin Pharmacol Ther* 53:570-576, 1993
13. Mendelson J, Upton RA, Everhart ET, et al: Bioavailability of sublingual buprenorphine. *J Clin Pharmacol* 37:31-37, 1997
14. Ohtani M, Kotaki H, Nishitani K, et al: Kinetics of respiratory depression in rats induced by buprenorphine and its metabolite, norbuprenorphine. *J Pharmacol Exp Ther* 281:428-433, 1997

15. Ohtani M, Kotaki H, Sawada Y, et al: Comparative analysis of buprenorphine- and norbuprenorphine-induced analgesic effects based on pharmacokinetic-pharmacodynamic modeling. *J Pharmacol Exp Ther* 272:505-510, 1995
16. Bridge TP, Fudala PJ, Herbert S, et al: Safety and health policy considerations related to the use of buprenorphine/naloxone as an office-based treatment for opiate dependence. *Drug Alcohol Depend* 70:S79-S85, 2003
17. Chiang CN, Hawks RL: Pharmacokinetics of the combination tablet of buprenorphine and naloxone. *Drug Alcohol Depend* 70:S39-S47, 2003
18. Mendelson J, Jones RT, Fernandez I, et al: Buprenorphine and naloxone interactions in opiate-dependent volunteers. *Clin Pharmacol Ther* 60:105-114, 1996
19. Mendelson J, Jones RT, Welm S, et al: Buprenorphine and naloxone combinations: the effects of three dose ratios in morphine-stabilized, opiate-dependent volunteers. *Psychopharmacology (Berl)* 141:37-46, 1999
20. Auriacombe M, Franques P, Tignol J: Deaths attributable to methadone vs buprenorphine in France [letter]. *JAMA* 285:45, 2001
21. Lintzeris N, Bell J, Bammer G, et al: A randomized controlled trial of buprenorphine in the management of short-term ambulatory heroin withdrawal. *Addiction* 97:1395-1404, 2002
22. Johnson RE, Eissenberg T, Stitzer ML, et al: A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence. *Drug Alcohol Depend* 40:17-25, 1995
23. Ling W, Charuvastra C, Collins JF, et al: Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction* 93:475-486, 1998
24. O'Connor PG, Oliveto AH, Shi JM, et al: A randomized trial of buprenorphine maintenance for heroin dependence in a primary care clinic for substance users versus a methadone clinic. *Am J Med* 105:100-105, 1998
25. Johnson RE, Chutuape MA, Strain EC, et al: A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med* 343:1290-1297, 2000
26. Fudala PJ, Bridge TP, Herbert S, et al: Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med* 349:949-958, 2003
27. The 2003 National Survey on Drug Use and Health, Department of Health and Human Services Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Available at: <http://www.oas.samhsa.gov/nhsda/>. Accessed September 27, 2005
28. Compton P, Charuvastra VC, Ling W: Pain intolerance in opioid-maintained former opiate addicts: effect of long-acting maintenance agent. *Drug Alcohol Depend* 63:139-146, 2001
29. Harper I: Temgesic abuse [letter]. *N Z Med J* 96:777, 1983
30. Rainey HB: Abuse of buprenorphine [letter]. *N Z Med J* 99:72, 1986
31. Tacke U: Abuse of buprenorphine by intravenous injection: the French connection [letter]. *Addiction* 97:1355, 2002
32. Quigley AJ, Bredemeyer DE, Seow SS: A case of buprenorphine abuse. *Med J Aust* 140:425-426, 1984
33. Obadia Y, Perrin V, Feroni I, et al: Injecting misuse of buprenorphine among French drug users. *Addiction* 96:267-272, 2001
34. Robinson GM, Dukes PD, Robinson BJ, et al: The misuse of buprenorphine and a buprenorphine-naloxone combination in Wellington, New Zealand. *Drug Alcohol Depend* 33:81-86, 1993
35. Tracqui A, Kintz P, Ludes B: Buprenorphine-related deaths among drug addicts in France: a report on 20 fatalities. *J Anal Toxicol* 22:430-434, 1998
36. Reynaud M, Petit G, Potard D, et al: Six deaths linked to concomitant use of buprenorphine and benzodiazepines. *Addiction* 93:1385-1392, 1998
37. Reynaud M, Tracqui A, Petit G, et al: Six deaths linked to misuse of buprenorphine-benzodiazepine combinations. *Am J Psychiatry* 155:448-449, 1998
38. Gaulier JM, Marquet P, Lacassie E, et al: Fatal intoxication following self-administration of a massive dose of buprenorphine. *J Forensic Sci* 45:226-228, 2000
39. Thorn SE, Rawal N, Wennhager M: Prolonged respiratory depression caused by sublingual buprenorphine. *Lancet* 1:179-180, 1988
40. Downing JW, Goodwin NM, Hicks J: The respiratory depressive effects of intravenous buprenorphine in patients in an intensive care unit. *S Afr Med J* 55:1023-1027, 1979
41. Schmidt JF, Chraemmer-Jorgensen B, Pedersen JE, et al: Postoperative pain relief with naloxone: severe respiratory depression and pain after high dose buprenorphine. *Anaesthesia* 40:583-586, 1985
42. Boyd J, Randell T, Luurila H, et al: Serious overdoses involving buprenorphine in Helsinki. *Acta Anaesthesiol Scand* 47:1031-1033, 2003
43. Banks CD: Overdosage of buprenorphine: case report. *N Z Med J* 89:255-257, 1979
44. Gal TJ: Naloxone reversal of buprenorphine-induced respiratory depression. *Clin Pharmacol Ther* 45:66-71, 1989