Review

Safety and health policy considerations related to the use of buprenorphine/naloxone as an office-based treatment for opiate dependence

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Abstract

Opiate dependence remains a fundamental challenge confronting health delivery systems and is often characterized as a social and moral issue. The impact of this disorder on healthcare policy is changing with the increased incidence of HIV, hepatitis C, and tuberculosis infections in opiate-dependent patients. These medical illnesses have substantial effect on escalating healthcare costs, and, therefore, also affect healthcare policy priorities, which are responsive to these costs. Pharmacological treatments for opiate dependence have had limited success; often the consequence of limited access to care. Hence, there is a need to develop new pharmacotherapies for opiate dependence that extend the range of clinical options, including new first-line treatment approaches. This paper will focus on the safety and health policy considerations related to the use of buprenorphine and buprenorphine/naloxone based on data derived from clinical trials and post-marketing surveillance that provide evidence for the use of the medications as first-line treatments in an office-based environment. The evaluation of this evidence formed the basis by the National Institute on Drug Abuse to support and pursue the evaluation and registration of buprenorphine/naloxone and buprenorphine in a public/private sector cooperative effort to become an office-based, first-line treatment for opiate dependence.

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1. Introduction

The subject of opiate dependence treatment elicits a powerful response in the general public as few other health issues do. While efforts to demonstrate that opiate dependence is a medical and biobehavioral disorder remain necessary, these efforts are making inroads in public opinion (National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction, 1998). Pharmacotherapeutic approaches to opiate dependence have shown success, but that success has been limited by many factors (Ball and Ross, 1990; Cooper, 1995; Rounsaville and Kosten, 2000). Opiate dependence, particularly on heroin, continues to be a problem in the United States and other parts of the world (Hartnoll, 1994; Hughes and Rieche, 1995; Knolle, 1997; Office of National Drug Control Policy, 1997; Harling, 1999). Moreover, disease transmission among and by injection drug users occurs by behaviors other than needle sharing. Transmission of HIV to children is primarily due to HIV-infected mothers resulting from injection use or from HIV-infected partners (Center for Disease Control and Prevention, 1998). Because supplies of heroin with greater purity have become more available and less expensive, there is...
now an increasing use of heroin by the smoking route (de la Fuente et al., 1997; Smyth et al., 2000). This shift will predictably extend the range of medical morbidity and mortality to include pulmonary disorders in addition to the increased prevalence of HIV, hepatitis C, and tuberculosis infections now present in the opiate-dependent population. Because changes in heroin supply characteristics may (and probably will) occur, the increasing use of smoked heroin, which may reduce injection-related transmission of diseases, may not continue at current levels. Thus, the epidemic of opiate dependence is a healthcare issue that can be expected to have considerable financial impact on healthcare policy (Zellweger et al., 1996).

Non-pharmacological treatment approaches to opiate dependence, principally medically supervised withdrawal from opiates, have shown an unacceptably high failure rate. The costs of treatment for these programs are substantial and reimbursement may be limited to one episode of withdrawal for the opiate-dependent person. Nonetheless, behavioral and psychosocial approaches are critical components of treatment for opiate dependence and for the achievement and maintenance of abstinence from illicit opiates (National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction, 1998).

Opiate-agonist pharmacotherapy has been shown to decrease illicit opiate use (Strain et al., 1993, 1994, 1999; Fudala, 1996; Fudala et al., 1997; Johnson et al., 2000), and to decrease the incidence of high-risk and unlawful behaviors associated with opiate dependence (French et al., 1993; Bates and Pemberton, 1996; Strain et al., 1996; Merrill et al., 1999). Methadone and levo-alpha-acetylmethadol (LAAM) are provided in a strictly regulated clinical environment, where the medication is typically taken under clinical observation, with significant restrictions placed upon take-home dosing (Code of Federal Regulations, 2001a,b). While mandated by concerns related to illicit diversion and abuse, these restrictions are known to discourage many individuals from seeking treatment, particularly, those who have only recently become dependent and may thus be ineligible for opiate-agonist therapy (Brown et al., 1989).

The recently opiate-dependent are the very individuals in whom early intervention could result in the delay or avoidance of exposure to the medical sequelae of opiate dependence. These medical conditions substantially increase the cost of medical care, as well as introduce further impediments to the return to an opiate-free condition. Moreover, even when eligibility criteria are met, there can be limited availability of treatment access (“treatment slots”) in many locales, leading to extended and extensive waiting lists (Brown et al., 1989; Schottenfeld et al., 1993; Friedman et al., 1994; Wenger and Rosenbaum, 1994; Stewart et al., 2000). Delay in access to treatment for individuals seeking therapy for opiate dependence results in continued exposure to the medical morbidity associated with opiate dependence. Office-based treatment for opiate dependence, if it were to increase treatment availability and utilization, would substantially reduce the burden of the disease. It must do so by also reducing the potential for diversion of licit treatment products to illicit use. A clinical product consistent with office-based treatment could represent an optimal first-line treatment for opiate dependence, expanding treatment to individuals not enrolled in an opiate-agonist pharmacotherapy program. To address these problems, buprenorphine and buprenorphine/naloxone have recently been approved for office-based, opiate dependence treatment in the United States.

The clinical pharmacology, pharmacokinetics, and efficacy of buprenorphine and the buprenorphine/naloxone combination have been discussed in other sections of this volume (see Chiang and Hawks, 2003; Ling and Wesson, 2003; Walsh and Eisenberg, 2003). Buprenorphine, and, in particular, buprenorphine/naloxone appear to be medications with considerable relevance for the office-based treatment of opiate dependence. This paper will focus on the safety and health considerations related to the use of buprenorphine and buprenorphine/naloxone based on data derived from clinical trials and post-marketing surveillance, and also provide evidence for the use of the medications as first-line treatments in an office-based environment. Such evidence supported the decision of the National Institute on Drug Abuse (NIDA) to pursue registration of buprenorphine/naloxone and buprenorphine under a Cooperative Research and Development Agreement with Reckitt-Benckiser Pharmaceuticals, Inc. that established a public/private sector collaboration to achieve this goal.

2. Buprenorphine safety

2.1. Clinical studies and trials

In the majority of clinical studies, experience with buprenorphine has been based on the use of a sublingual liquid formulation; fewer evaluations have been conducted using a sublingual tablet product and of buprenorphine/naloxone as a combination product. In aggregate, the pivotal trials and supportive studies document exposure of study participants to buprenorphine at doses up to 32 mg per day (sublingual liquid; 24 mg per day for the sublingual tablet formulation) for periods of up to 1 year. The demographic composition of these study populations has been consistent with the epidemiologic characteristics of individuals with opiate dependence. The majority of the studies relied on systematic classification of spontaneously reported ad-
verse events, and one study (Johnson et al., 1992) relied on directed inquiry about a subset of these adverse event terms believed to be the most relevant for the indication of the medication.

Only one study provided placebo-based contrast for safety evaluation of the sublingual liquid (Johnson et al., 1995). While there were more adverse events reported during the 2-week treatment period with buprenorphine compared with placebo (24% vs 5% of participants), the majority of these events were both anticipated and manageable (e.g., constipation, headache). Hence, the safety experience for this defined period of 2 weeks contrasted to placebo appeared to be acceptable. In this study and two non-placebo-controlled pivotal trials of buprenorphine (Johnson et al., 1992; Ling et al., 1998), safety data were available for doses up to 32 mg per day (sublingual liquid) for period up to 1 year. The most common adverse events appearing during exposure to buprenorphine included headache, pain (non-specific), insomnia, withdrawal syndrome, infection (non-specific), asthenia, back pain, sweating, anxiety, rhinitis, depression, nausea, abdominal pain, constipation, and flu-like syndromes. Given the known spectrum of adverse events associated with buprenorphine, these events were not unanticipated and would be expected to be manageable during treatment.

There were four deaths during the course of the above-described studies; none was considered related to the use of buprenorphine. The causes of death were reported as: (1) HIV-related sepsis, (2) coronary thrombosis with a study antecedent history of hypertension, (3) complications arising from an automobile accident, and (4) cocaine overdose occurring 4 days after patient discharge from the study. Serious adverse events in these three studies included, in decreasing the order of frequency: (1) elevated liver function tests (LFTs: 4.4%), (2) depression, including suicide thoughts or attempts (2.6%), (3) infection (1.0%), (4) accident (1.0%), (5) abscess (0.9%), (6) chest pain (0.6%), and (7) gastrointestinal problems (0.5%).

Elevated LFTs were studies defined to be concentrations more than eight times the upper limits of normal for the reporting lab. Of the 36 events, 8 occurred during baseline prior to initiation of treatment, 19 were related to hepatitis, and 8 had no identified etiology. Importantly, these elevations did not appear to be related to buprenorphine dose; moreover, only one participant with elevated LFTs was withdrawn from study participation. The cause of that elevation was later demonstrated to be hepatitis. With regard to other serious adverse events, the depression-related events were disproportionately present at one center (15 of 20 reported events). This suggests a site-specific rather than a treatment-related basis for this effect. As with the elevated LFTs, other serious adverse events did not result in study withdrawal or termination of patients secondary to medical concerns. Importantly, for safety assessment, the majority of study participants were treated with doses of study drug that resulted in greater serum concentrations than will likely occur with doses approved for treatment.

2.2. Post-marketing data

Buprenorphine has been approved for the treatment of opiate dependence in a number of countries, including Austria, Finland, France, Italy, and the United Kingdom. The first approval for this indication was in France in 1996, at approximately the same time that methadone was approved there. While buprenorphine was approved in France for use in an office-based setting, methadone was restricted to a regulated clinical environment somewhat similar to the procedures now in place in the United States (Thirion et al., 2002). Overall safety experience with buprenorphine in France has generally been satisfactory, though as documented (Reynaud et al., 1998; Tracqui et al., 1998; Gaulier et al., 2000; Kintz, 2001), there have been at least 20 deaths associated with buprenorphine overdose. Most of these deaths, perhaps all, were associated with parenteral misuse of the sublingual formulation, almost always in conjunction with evidence of use/abuse of other CNS depressants. While buprenorphine alone has been documented to demonstrate a ceiling to respiratory depressant effects in clinical pharmacological testing (Walsh et al., 1994), the interaction of buprenorphine with other CNS depressants such as benzodiazepines and alcohol may be potentially serious or lethal, and practitioners are advised to counsel their patients regarding such interactions.

In a recent analysis by Auriacombe et al. (2001), a contrast was made for buprenorphine- and methadone-related deaths in France for the period 1994–1998, surrounding the approval of these two products in that country. Because of the approval for office-based treatment with buprenorphine in France, it is not surprising to observe that the number of prescriptions for buprenorphine exceeds those for methadone by at least 10-fold. In contrast, the death rate associated with buprenorphine misuse was only 1.4 times that observed for methadone in the period studied. Fatal overdose with methadone alone is known to occur, and co-administration with other CNS depressants can magnify this risk. Finally, there is a suggestion in recent fatality reporting from France that the number of opiate-related deaths is decreasing (Auriacombe et al., 2001). This is promising and may reflect an increasing knowledge among opiate-dependent persons not in treatment that parenteral abuse of buprenorphine with other CNS depressants is dangerous. Interestingly, when buprenorphine was diverted to illicit use in Glasgow, a similar reduction of opiate-related overdose deaths was ob-
served (Hammersley et al., 1995). Based on these safety experiences, it is expected that buprenorphine/naloxone will be the first-line treatment for opiate dependence, which is consistent with the design of the pivotal clinical trial that formed the basis for the recent drug approval.

2.3. Drug–drug interactions and special populations

A limited number of drug interactions for buprenorphine have been identified. Obviously, increased respiratory and CNS depression may occur if buprenorphine is combined with other CNS depressants. Because of the metabolism of buprenorphine to norbuprenorphine by cytochrome P-450 3A4 (Iribarne et al., 1997, 1998a; Kobayashi et al., 1998), drugs which interfere with this system could reduce the formation of norbuprenorphine and result in increased levels of buprenorphine. Known inhibitors of this system include erythromycin, ketoconazole, and grapefruit juice; and HIV protease inhibitors such as ritonavir, saquinavir, and indinavir have been shown to inhibit the metabolism of buprenorphine (Iribarne et al., 1998b). Given the ceiling effects of buprenorphine for both safety and efficacy, this probably will not result in significant clinical problems, unless buprenorphine is abused parenterally with other CNS depressants. In contrast, inducers of cytochrome P-450 3A4 (e.g., phenobarbital, carbamazepine, phenytoin) could potentially lead to reduced levels of buprenorphine relative to usual doses within an individual. Such reductions might induce withdrawal signs and symptoms in buprenorphine-treated persons, if buprenorphine levels fall to levels that fail to provide sufficient opiate-agonist effects. Hence, co-administration of drugs in this group should be associated with increased clinical monitoring.

Information regarding special-group pharmacodynamic effects for buprenorphine are limited. Patients with hepatic disease, and to some extent, renal disease, should theoretically have reduced clearance of buprenorphine. However, the limited clinical data available would not suggest that a dosage adjustment would be required for these patients (Summerfield et al., 1985; Lasseter et al., 2001). In studies with buprenorphine, serious adverse events for individuals having substantial (up to eight times the upper limit of normal) hepatic enzyme activity levels, were not different from those without such hepatic abnormalities (Ling et al., 1998). Hepatic enzyme elevations are, however, common among opiate-dependent individuals.

3. Evidence for the use of buprenorphine as a first-line, office-based treatment

Based on a body of evidence that opiate-agonist pharmacotherapy, in conjunction with appropriate abstinence-based psychotherapy, is clinically efficacious for the treatment of opiate dependence, clinical investigators in the field of substance-abuse research have sought means by which treatment capacity for this indication can be expanded. This effort has gained further momentum as costly medical disorders have become more prevalent among injection drug abusers. Due to the nature of societal perceptions of opiate dependence, any approach to the expansion of treatment will, of necessity, require both clinical documentation of efficacy and safety, as well as regulatory and legal considerations.

A number of clinical studies have sought to document that clinical management in an office-based setting is both effective and safe for methadone (Brown et al., 1989; Friedman et al., 1994; Wenger and Rosenbaum, 1994; Fiellin et al., 2001a). These investigations have found that treatment in an office-based setting provides clinically acceptable therapy with regards to both safety and efficacy. To minimize the issue of potential diversion of medication supplies to illicit use, these studies have typically relied on participants who have had a long period of compliance in opiate pharmacotherapy programs. Hence, the potential for expanded treatment capacity would potentially be constrained to the limited population of demonstrably compliant patients who could be moved to treatment in an office-based setting. Their transfer, however, would free up traditional treatment capacity and thus reduce the waiting list phenomenon to some extent. Of course, applicants to these programs would be limited to those who qualify for treatment under current treatment regulations. While these approaches would be unquestionably helpful, the extent of their impact on addressing the public health priority of opiate dependence treatment would be limited in scope.

The potential advantages of an office-based, opioid dependence treatment environment are numerous. These include an increased availability of treatment, an opportunity to match services to individuals’ needs, minimization of the stigma associated with the disease and its treatment, and the limiting of patients’ contact with other substance-abusing individuals (Fiellin et al., 2001b; Fiellin and O’Connor, 2002). Additionally, the development of a medication that provides reduced diversion to illicit usage than a full opiate agonist for the treatment of opiate dependence would be one approach to address concerns that promulgated present regulatory restrictions. Further, a medication that provides a margin of safety regarding overdose would be preferable for use in an office-based practice. A study by O’Connor et al. (1998) indicated that in a limited sample (n = 23 per treatment arm), buprenorphine administered as a sublingual solution in an office-based treatment setting produced more favorable clinical outcomes than in a clinic-based setting. Another small
study (n = 14) also provided evidence for buprenorphine efficacy in a primary-care setting (Fiellin et al., 2002).

Buprenorphine, when formulated with the opiate antagonist naloxone, provides a medication that can reduce the likelihood of diversion to illicit usage. Naloxone combined with buprenorphine produces immediate opiate withdrawal signs and symptoms when used parenterally by opiate-dependent persons (Preston et al., 1988; Mendelson et al., 1996, 1999; Fudala et al., 1998; Stoller et al., 2001). Additionally, the pharmacological properties of partial opiate agonists are the basis for the observed ceiling effect for respiratory depression with increasing doses of buprenorphine. This ceiling effect provides a substantially preferable safety profile (compared with full agonists) for an office-based practice situation.

Clinical pharmacology studies indicate that the positive subjective effects of partial opiate agonists such as buprenorphine often do not equate to those seen with full opiate agonists (Jasinski et al., 1978; Mello et al., 1982; Nath et al., 1999). Moreover, there may be ceiling effects for both efficacy and safety parameters with partial agonists, such that increasing doses may not produce increasing clinical benefit or risk. Available data not only indicate clinically acceptable efficacy with buprenorphine, but also document that clinical failures occur. When treatment failure is observed, transfer to full opiate-agonist treatment may be warranted based on individual assessment and clinical judgment. Such a strategy was employed in a recently conducted study (Johnson et al., 2000), although the percentage of patients requiring therapeutic intervention was no greater in the buprenorphine treatment arm than in the high-dose methadone or LAAM arms.

4. Discussion

Concerns about safety, drug diversion, and illicit use of opiate-agonist pharmacotherapy have led to extensive control and regulation by state and national authorities. These controls can create considerable barriers to treatment for many opiate-dependent persons. Safety concerns are primarily focused on the respiratory depression associated with full, mu-opiate agonists. Even when formulated to minimize use by non-parenteral routes, such as by mixing methadone in orange juice, there are safety issues—as when children mistakenly consume this juice, occasionally with fatal outcomes. Abuse of opiate agonists by adults, particularly, when these drugs are combined with other respiratory depressants or when misused intravenously, can also be associated with fatal outcomes. Buprenorphine/naloxone, however, can expand treatment options since it provides for a reduced potential for misuse by the parenteral route due to the combination with naloxone, and an improved safety profile secondary to the mu-opiate, partial agonist properties of buprenorphine.

Buprenorphine (without naloxone) was approved as a treatment for opiate dependence in France in 1996. Deaths have been reported to be associated with the intravenous misuse of buprenorphine there, usually in association with other CNS depressants. While the incidence of these occurrences is decreasing over time, it can be anticipated that the presence of naloxone in the buprenorphine/naloxone combination will reduce the likelihood of diversion of this medication for intravenous misuse. Physicians can titrate buprenorphine/naloxone dosages to produce the optimal clinical response for each individual. The duration of buprenorphine/naloxone therapy will be a decision of the clinician and the patient. The reduced potential for diversion to misuse makes buprenorphine/naloxone more acceptable for office-based treatment settings than any other therapeutic option.

Buprenorphine/naloxone provides both a new and effective treatment agent and a vehicle to expand treatment environments to include office-based therapy. The anticipated increase in therapeutic capacity will benefit both the individual and the healthcare delivery systems. Office-based therapy can facilitate treatment of individuals earlier in their addiction history; optimally before substantial morbidity and mortality associated with parenteral drug abuse occurs.

Utilizing, in part, available evidence presented here, a public/private sector effort was mounted with NIDA’s leadership to evaluate the utility of buprenorphine/ naloxone as a first-line office-based pharmacotherapy for opiate dependence. This decision was based on properties of sublingual tablet buprenorphine/naloxone which include:

1) a reduced likelihood of diversion of the combination product for diversion to illicit parenteral misuse;
2) the established utility of the mono product for the treatment of opiate dependence; and
3) the preferable safety profile of a partial mu-opiate receptor agonist such as buprenorphine compared with that of a full mu-opiate receptor agonist.

Additionally, health policy issues that also formed the basis to pursue the evaluation and approval of buprenorphine/naloxone include the urgent need for expanded opiate dependence treatment capacity beyond those established to accommodate the regulatory requirements necessary to utilize full opiate agonists as pharmacotherapy for the treatment of opiate dependence.
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