

Sublingual Buprenorphine Is Effective in the Treatment of Chronic Pain Syndrome

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Many patients with chronic pain have less than optimal therapeutic outcomes after prolonged treatment with opiate analgesics. Worsening of pain perception, functional capacity, and mood often result. Medical detoxification is often undertaken in this situation. Ninety-five consecutive patients (49 men and 46 women; age range, 26–84) with chronic noncancer pain (maldynia) were referred by local pain clinics for detoxification from long-term opiate analgesic (LTOA) therapy. All patients had failed treatment as manifest by increasing pain levels, worsening functional capacity, and, in 8%, the emergence of opiate addiction. Length of prior LTOA therapy ranged from 1.5 to 27 years (mean, 8.8 years). After a minimum of 12 hours of abstinence from all opiate analgesics, patients were given low doses of sublingual (SL) buprenorphine or buprenorphine/naloxone (Reckitt Benckiser). Maintenance dosing was individualized to treat chronic pain. Daily SL dose of buprenorphine ranged from 4 to 16 mg (mean, 8 mg) in divided doses. Mean duration of treatment is 8.8 months (range, 2.4–16.6 months). At clinic appointments, patients were assessed for pain reports, functional capacity, and mood inventory. Eighty-six percent of patients experienced moderate to substantial relief of pain accompanied by both improved mood and functioning. Patient and family satisfaction was robust. Only 6 patients discontinued therapy secondary to side effects and/or exacerbation of pain. In this open-label study, SL buprenorphine and buprenorphine/naloxone were well tolerated and safe and appeared to be effective in the treatment of chronic pain patients refractory to LTOA.

Keywords: chronic pain, buprenorphine, treatment, detoxification

INTRODUCTION

When chronic pain progresses from a merely bothersome nuisance to becoming a profound affliction, the patient is said to have a chronic pain syndrome (CPS).¹ This is characterized by many of the same features of an addictive illness, including compulsive behaviors, obsessive thoughts, decreased functional capacity, cognitive impairment, and social isolation.^{2,3} Growing evidence from functional neuroimaging studies supports the concept that CPS, similar to the phenomena of

addiction, results from, and may cause neuroanatomical and neurochemical brain alterations, which may be permanent.^{4,5}

CPS consists of long-standing, localized or diffuse complaints of discomfort and pain that have persisted beyond the expected healing time (if resulting from injury) and have resisted more conservative and traditional health care intervention strategies.⁶ It is important to differentiate patients with CPS from those who experience chronic pain due to an unresolved or permanent localized injury. The Office of Disabilities of the Social Security Administration⁷ uses the following criteria to establish the diagnosis of CPS (patients must meet all the criteria): Any intractable pain of more than 6 months' duration; marked alteration in behavior with depression or anxiety; marked restriction in daily activities; excessive use of medication and frequent use of medical services; no clear relationship to organic disorder; and history of multiple, nonproductive tests,

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treatment, and surgeries. There is a high incidence of CPS in persons with a history of childhood abuse, borderline and narcissistic personality disorders, and lower income.^{8,9} Studies suggest that women are up to 4 times more affected than men.¹⁰

The treatment of CPS is difficult, often inadequate, and associated with high economic and psychological cost.^{1,2} The use of opioid analgesics for chronic non-malignant pain is gaining acceptance but remains controversial.¹¹ While opiate analgesics are now viewed as appropriate treatment of CPS, a recent review called into question their long-term efficacy.¹¹ The condition of opioid-induced hyperalgesia¹² may exacerbate the perception of pain in susceptible individuals. The presence of an addictive illness such as opiate or nicotine dependence appears to be a risk factor for failure of chronic opiate analgesic therapy in CPS.¹³

Buprenorphine, a derivative of thebaine, is classified as a partial μ -opioid agonist and κ -antagonist.^{14,15} It has a high affinity for the μ -opioid receptor, with slow dissociation, resulting in a long duration of action (6 hours).¹⁵ In lower doses, buprenorphine has an analgesic potency 25 to 40 times more potent than similar milligram doses of morphine.¹⁶ Because it is a partial agonist, its effects plateau at higher doses, and it begins to behave more like an antagonist. This antagonist property in higher doses limits the maximal analgesic effect and respiratory depression. The high-affinity blockade and the partial agonist ceiling confers a high safety profile clinically, a low level of physical dependence, and only mild withdrawal symptoms on cessation after prolonged administration. These qualities make it advantageous for the treatment of opioid dependence.¹⁶

Buprenorphine has low oral bioavailability (AUC)^{17,18} and is thus formulated in a sublingual preparation (Subutex) and in a sublingual formulation with naloxone (Suboxone). Naloxone has very poor sublingual bioavailability and is formulated with buprenorphine to prevent misuse via intravenous injection.

The FDA approved Suboxone/Subutex in 2002 as a treatment of opioid dependence. Sublingual buprenorphine has been successfully used for opioid detoxification and maintenance.¹⁹ It has a better pharmacotherapeutic safety profile than methadone.²⁰ A regimen of 8 to 12 mg/d sublingually has been used for 5 to 7 days for detoxification from opioids.²⁰ The slow release of buprenorphine from the μ_1 -receptor allows a relatively symptom-free withdrawal.

In the course of using buprenorphine in the detoxification of chronic pain patients from high-dose opiates, we observed significant changes in patient reports of pain and pain perception. We observed many patients on high doses of pure μ -opioid agonists begin

to experience significant decrease in pain, improved functional capacity, and improvement in their overall sense of well-being. This commences within days of detoxification from pure μ -agonist therapy. Until recently, there have been few reports in the literature citing or describing buprenorphine as a chronic pain management medicine.²¹

Because of its safety, unique agonist/antagonist activity at the μ_1 - and κ -opioid receptors, we began to employ this combination medication as a treatment of CPS patients. Patients referred for detoxification from long-term opiate analgesic (LTOA) therapy were treated with sublingual buprenorphine or buprenorphine/naloxone. Sublingual buprenorphine was with few exceptions associated with significantly lower pain scores, improved functional capacity, and improvement in mood/affect. Patient satisfaction was notable. Patients with comorbid addictive disorders showed stabilization and the same level of improvement as nonchemically dependent patients when both pain and addiction were addressed in a systematic fashion.

Side effects were tolerable and resulted in treatment termination in 6 of 95 patients (6.25%).

Buprenorphine is safe and effective and should be further studied as a treatment of chronic pain disorders.

METHODS

Patient selection

This was a single-center, open-label study in chronic pain patients referred from 3 local pain clinics. All patients had experienced worsening pain despite escalating doses of short- and long-acting opiate analgesics. Most had undergone prior surgeries. Patients were assessed with history/physical examination, blood and urine testing for renal function, liver function, and urine toxicology prior to initiating treatment. Between December 2003 and October 2004, 95 consecutive patients referred to our clinic for detoxification from high doses of opioids were treated with sublingual buprenorphine (see Table 1 for patient demographics).

All patients underwent multidimensional evaluation prior to treatment consisting of history/physical examination with particular attention to co-occurring psychiatric and addictive disorders. Addictive disorders were diagnosed by DSM-IV-TR criteria.²² All patients gave informed consent for detoxification/substitution with buprenorphine.

Nicotine cessation therapy was offered to all nicotine-dependent patients. Four patients did succeed in becoming abstinent from nicotine during the course of their treatment. The identification of other chemical

Table 1. Patient demographics.

	%	Mean	Range
Male	52		
Female	48		
Age, y		51.3	26–84
Employed	71		
Retired/unemployed	24		
Nicotine dependent	58		
Opiate dependent	8.42		
LTOA use range, y		8.8	1.5–27

dependencies either clinically or with urine toxicology prompted referral to a formal outpatient treatment program, attendance at 12-step meetings, and office-based counseling.

Initially, all patients were detoxified from prescribed opiates using sublingual buprenorphine according to previously published protocols.²³ All detoxification was office based and under the direct observation of the principal investigator (HLM).

Drug administration

All patients were required to discontinue their opiate analgesics at least 12 hours prior to instituting buprenorphine.²³ Patients were given an initial test dose of 1 mg Suboxone (1 mg buprenorphine/0.25 mg naloxone) sublingually and observed for signs of opiate withdrawal. Patients were then given 2 doses of 2 mg Suboxone at 45-minute intervals. Vital signs and symptom scoring were taken at 30-minute intervals. Patients were discharged from the clinic 2 to 2.5 hours after initiating buprenorphine treatment.

Following initial detoxification, patients were treated with varying doses of sublingual buprenorphine for pain. Daily doses ranged from 2 to 20 mg/d in divided doses (Table 2).

Patient assessment

Patients were seen in the clinic 3 to 5 days later and contacted by telephone. Patients were seen at least monthly. Dosing of buprenorphine was changed based on patient reports of opiate abstinence symptoms and pain complaints. A visual analogue scale (VAS) was employed for pain assessment at each clinic visit. This

Table 2. Buprenorphine dosing.

	Range	Mean
Daily dose (mg)	2–20	8
Duration of treatment (mo)	2.4–16.6	8.8

scale has 5 levels of visual discomfort ranging from no pain to severe misery.

Data abstraction

All data were abstracted from patients' medical records. To estimate the duration of CPS, we used historical statements from the patient recorded in the initial office evaluation by HLM. The numbers and types of other interventions including current prescriptions were recorded. The most recent opioid prescription was used to define the type and level of LTOA therapy.

Statistical analysis

The data variables are summarized as means \pm SD from the mean (SD).

RESULTS

No patient was hospitalized. Side effects including ataxia/lightheadedness, nausea, cephalgia, and diaphoresis were uncommon and resulted in 6 patients (6.25%) discontinuing treatment in the detoxification stage (Table 3). Pain reports as determined by VAS were improved in 86%. Patient and family satisfaction with therapy was robust. Many reported improved mood, diminished sleep disturbance, and improved sense of well-being. Pain relief was secondary to these other psychological improvements.

Tolerance to buprenorphine was not observed. Most patients remain on a stable maintenance dose. Aberrant behavior regarding buprenorphine was limited to 12 patients' self-escalating doses to treat worsening pain. No cases of return to Opiate Analgesics (OA) were identified in the average 8 months of follow-up.

DISCUSSION

We used sublingual buprenorphine (Subutex/Suboxone) in patients with chronic pain. All patients had failed conventional opiate therapy with increasing tolerance to high doses of short and long duration of action opiates, worsening pain perceptions and pain scores, lower functional capacity, and in some instances

Table 3. Responses to treatment with buprenorphine.

	Mean VAS
Before treatment	3.9 \pm 0.4
After treatment	2.2 \pm 0.5
Patients who reported substantial improvement	86%

Table 4. Adverse effects.

	No. (%)
Ataxia/lightheadedness	12 (12.6)
Nausea	9 (9.5)
Cephalgia	15 (15.8)
Discontinued therapy	6 (6.3)

(8%) the emergence of manifest addiction behaviors. Patients were seen in referral from local pain clinics and referred for opiate detoxification. Buprenorphine was administered to patients after they had discontinued all opioid medications at least 12 hours prior to their clinic visit. All patient were experiencing at least some symptoms of opioid abstinence syndrome prior to initiating sublingual buprenorphine. An initial test dose of 1 or 2 mg was given with physician supervisions. In all cases, this resulted in prompt relief of withdrawal symptoms. An additional dose of 1 or 2 mg was then given, with significant pain relief. Patients were then given an outpatient-specific dosing schedule based on age, prior specific opiate doses, and comorbid conditions. Other medications including neuromodulatory drugs (eg, antidepressants, anticonvulsants) were continued.

Within days to weeks, most patients reported improved pain levels, less distress, improved mood, and increased functional status and capacity. In many cases, patients report significant relief of the depression, anxiety and "misery" associated with their chronic pain, prompting us to undertake this study. Therapy

Table 5. Pharmacokinetics.

Absorption: Readily absorbed 55% (range, 15%–95%) after sublingual administration
Distribution: In rodent models, liver, brain, placenta, GI tract, liver. Parent and metabolite distributed in bile. $V_d \approx 97$ L
Plasma protein binding: 96% protein α and β globulins, not substantially to albumin
Elimination: Triphasic plasma concentration decline (distribution, redistribution, elimination phases)
$T_{1/2\alpha} = 37$ hours
Metabolism
Hepatic isoenzyme CYP450 3A4 substrate (n-dealkylation to norbuprenorphine- <i>N</i> -dealkylbuprenorphine, then phase II metabolism with conjugation to glucuronic acid)
First-pass gut metabolism (mucosal) additionally Enterohepatic recirculation; parent and metabolites excreted in feces via biliary elimination

Note: Metabolite norbuprenorphine has weak analgesic activity.

Table 6. Buprenorphine/naloxone side effects/adverse reactions.

Common: cephalgia, increased withdrawal symptoms, asthenia, insomnia, miosis, confusion, sedation, nausea, emesis, rigors, constipation, vasodilation
Less common but serious: Respiratory depression, bronchospasm, anaphylaxis, angioedema, hepatotoxicity, orthostatic hypotension
Pregnancy: category C

with buprenorphine was discontinued in 6 patients due to intolerable side effects including emesis and cephalgia. In most patients, side effects were tolerable and outweighed by the therapeutic effects on pain symptoms. No patient was hospitalized because of adverse events. There were no mortalities in the 95 patients treated.

Our results demonstrate the safety, efficacy, and simplicity of using sublingual buprenorphine to treat chronic nonmalignant pain refractory to LTOA therapy. In all cases, patients had previously failed LTOA therapy as demonstrated by increasing tolerance, worsening pain and mood, decreasing functional capacity, and, in some cases, the emergence of addictive illness. We observed that while pain control independently was often only fair, patients reported better tolerance of their pain, improved mood, and functional capacity. We hypothesize that Suboxone/Subutex effectively blocks the action of spinal dynorphin on κ -opiate receptors. This may result in lessening of perceived discomfort.²⁵

Buprenorphine is a partial agonist at the μ -opiate receptor, and an antagonist at the κ receptor. The unique pharmacology of buprenorphine at the μ -opioid receptor (ie, high affinity, low intrinsic activity, and slow dissociation) results in buprenorphine having a good safety profile, low physical dependence, and flexibility in dose scheduling. Buprenorphine as a synthetic opiate partial agonist analgesic has activity that occurs as μ -partial agonist in the central nervous system and peripheral tissues, with κ - and δ -receptor activity less defined; however, evidence of central κ -receptor antagonist exists with peripheral κ -receptor antagonism.^{26,27} Isomeric configuration may provide μ -opioid receptor binding in one configuration and μ -competitive antagonist activity in another configuration. Binding to μ -receptors is slow as is the complementary receptor dissociation accounting for its long duration of action and less physical dependency. Opiate agonist effects appear with up to 1 mg sublingually and doses of more than 1 mg have predominant antagonist activity; therefore, the agonist/antagonist effects are a linear

function of dose. Sublingual buprenorphine produces typical dose-related opiate agonist effects, which are limited by this ceiling effect and maximal at 8 to 16 mg.²³ The duration of analgesia is affected by age and duration and is prolonged in the elderly. Sublingual administration of buprenorphine/naloxone in fixed-dose combination was without naloxone-mediated pharmacologic effects, unlike those predictable effects if given parenterally.

The sublingual preparation approved in the United States, marketed under the brand name Suboxone (Reckitt Benckiser, Berkshire, UK) is available in 2- and 8-mg tablets combined with naloxone at 0.5 and 2 mg, respectively. Naloxone has no effect sublingually because of poor absorption but precipitates withdrawal symptoms if administered parenterally, thereby limiting diversion by opioid-dependent persons.^{25,28} The sublingual preparation of buprenorphine alone (Subutex) is also 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. Insurance coverage for Suboxone but not Subutex often dictated which preparation was prescribed for a given patient. Currently, sublingual buprenorphine is not approved by the FDA for the treatment of pain, although the parenteral formulation (Buprenex) has been approved since the 1980s. All patients were made aware of this off-label use of sublingual buprenorphine and gave informed consent.

This was a limited open-label study of nonrandomized patients receiving treatment via a single provider (HLM). As such, it can only suggest an effect of buprenorphine on chronic pain patients. All patients reported here had previously been treated with LTOA therapy with progression in pain symptoms, loss of function, and worsening mood. LTOA therapy is only one factor influencing pain perception in CPS. Emotional state, previous pain experiences, and cultural, environmental, and genetic factors are all known to be consequential.²⁹⁻³¹ Our study did not control for these factors. Responses to buprenorphine were not limited by gender, age, comorbid conditions including addiction, or the use of nonopiate analgesics.

Buprenorphine is subject to control under the Federal Controlled Substance Act of 1970 as a Schedule III drug. Under the Drug Addiction Treatment Act (DATA) of 2000, use of sublingual buprenorphine and buprenorphine/naloxone for treatment of opiate dependence is restricted to physicians who achieve certain qualifying criteria or requirements (Reckitt Benckiser Pharmaceuticals, Inc., information for pharmacists: Suboxone® [buprenorphine hydrochloride sublingual tablets]) and are required to have

notified the Secretary of the Department of Health and Human Services of their intention to prescribe these medications.³²

The use of buprenorphine and buprenorphine/naloxone to treat chronic pain patients refractory to LTOA therapy in this study was safe, effective, and well tolerated by these patients.

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