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Transdermal Buprenorphine, Opioid Rotation to Sublingual Buprenorphine, and the Avoidance of Precipitated Withdrawal: A Review of the Literature and Demonstration in Three Chronic Pain Patients Treated With Butrans

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Buprenorphine is an opioid, used in the United States and abroad for both analgesia and addiction, with unique opioid receptor binding properties. There are several pharmacological features of buprenorphine that make it an emerging option for the long-term treatment of chronic pain—its respiratory suppression ceiling effect, its efficacy in neuropathic pain and hyperalgesic states, and its decreased suppression of the immune and endocrine systems compared with other long-acting opioids. Previous studies have shown that high-dose sublingual buprenorphine is an effective treatment of chronic pain patients not responding to other opioids. Guidelines for the introduction of sublingual buprenorphine, termed buprenorphine induction, include an opioid-free "withdrawal" period of 12–48 hours to avoid an anticipated and accelerated opioid withdrawal, a syndrome described in this article as precipitated withdrawal. The requirement of a period of opioid abstinence before buprenorphine use may present a significant barrier to its adoption for chronic pain. We present a case series of a novel method of sublingual buprenorphine introduction without an induction period, using the recently Food and Drug Administration-approved low-dose transdermal buprenorphine (Butrans; Purdue Pharma L.P.) as a bridge medication. In these cases, buprenorphine was started in opioid-dependent chronic noncancer pain patients who had taken short-acting opioid medications within hours of the initiation of the rotation. This method avoids the painful abstinence period and did not result in precipitated withdrawal or other significant adverse effects.

Keywords: transdermal buprenorphine, sublingual buprenorphine, buprenorphine induction, full agonist opioids, pain management

INTRODUCTION

In recent years, the treatment of chronic pain, particularly noncancer pain, with opioids is being reexamined because of questions about the safety and effectiveness of this therapeutic strategy, particularly when the daily dose is high and the duration of use is long or indefinite. What has become characterized as a prescription drug epidemic has led to new scrutiny at both the US Food and Drug Administration (FDA) and the US Congress, as well as renewed emphasis on established guidelines for opiate use by professional organizations.[1,2] An alternative to the use of full agonist opioids for chronic pain is the partial agonist buprenorphine, which can be used as an effective substitute analgesic with a significantly improved safety profile.[3] Buprenorphine may also be used as a valuable tool for tapering a pain patient off of opioids altogether.[3,4] It is postulated that, because of buprenorphine's unusual

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pharmacologic properties, this "unique analgesic" demonstrates improved clinical outcomes in both addiction and chronic pain settings.[5,6] These properties include: (1) high potency and tight binding at the mμ-receptor, with partial agonism and slow dissociation; (2) antagonism at the kappa-receptor; (3) interaction with a distinct set of G proteins; (4) differential time frame for interaction with adenylate cyclase; (5) agonism at the ORL-1 receptor; and (6) associated increase in mμ-receptor expression on membrane surfaces.[5,6]

High-dose forms of sublingual buprenorphine were FDA approved in 2002 for the treatment of opioid dependency in the United States (Suboxone and Subutex; Reckitt Benckiser Pharmaceuticals, Inc., Richmond, VA) as part of a public health initiative for the management of both heroin and prescription opiate addiction in the setting of the primary care physician's and specialist's office. This use of buprenorphine requires a brief training, waivers from the regulations associated with methadone maintenance, and a modified Drug Enforcement Administration certificate. The US physicians, however, have used these sublingual forms for pain management, which requires only a general Drug Enforcement Administration certificate.[7] This is not surprising, as the parenteral form of buprenorphine has been FDA approved and continuously available for acute pain management in the United States since 1981.

Direct rotation of an opioid-dependent patient to the sublingual and parenteral forms of buprenorphine is often associated with an anticipated and accelerated opioid withdrawal, a syndrome described in this article as precipitated withdrawal. This is because of the tight binding of buprenorphine to the mu-opioid receptor and the rapid displacement of the full agonist opioid by the buprenorphine. To avoid this, the patient is usually required to be opiate free for an interval of time and to develop early symptoms of the abstinence syndrome before the administration of buprenorphine, a procedure known as buprenorphine induction. This induction period may be problematic in otherwise healthy addiction patients, because of withdrawal discomfort, and even more challenging in patients with chronic pain and other illnesses.

Although the emphasis of sublingual buprenorphine development has been on the treatment of addicts, a parallel development has occurred in Europe over the last decade with the study, approval, and dissemination of several buprenorphine transdermal systems for the treatment of pain.[8] Little noticed by addiction medicine clinicians in the United States have been findings that describe the introduction of the high-dose form of transdermal buprenorphine in opiate-dependent pain patients without an induction or waiting period and without reports of precipitated withdrawal. It is apparent that the gradual exposure of buprenorphine to the opioid receptors through the transdermal route is not associated with the precipitated withdrawal regularly seen with the sublingual preparation.

Following FDA approval of a low-dose buprenorphine transdermal system in the United States in 2010 (Butrans; Purdue Pharma L.P., Stamford, CT), we began to use this lower dose formulation in opioid-dependent pain patients to introduce buprenorphine without an opioid-free waiting period. This off-label use of Butrans was not associated with a precipitated opioid withdrawal syndrome that we otherwise would have expected had a sublingual form of buprenorphine been administered in this setting.

The rationale for this strategy can be understood after a review of the buprenorphine dose delivered by the different formulations. The low-dose transdermal buprenorphine patch, which is applied for a week, is available in 3 strengths, 5, 10, and 20 μg/h. The highest dose delivers 480 μg/d or slightly under 0.5 mg/d. Although this low-dose series can be an appropriate dose for a patient who is opioid naive or dependent on a low dose of full agonist opioids, many chronic pain patients have higher opioid tolerance and will need the higher daily doses only available with the sublingual preparations. These have been available in either 2 or 8 mg sizes. Suboxone also contains naloxone at one-fourth of the dose of buprenorphine, which serves as a disincentive for the preparation to be misused by the parenteral route, as the naloxone is active parenterally but minimally absorbed sublingually. Subutex was the original product of sublingual buprenorphine without naloxone. Reckitt Benckiser Pharmaceuticals has now discontinued this brand name, as there are a number of generic manufacturers who currently are producing these tablets at a considerably lower cost. Assuming the transdermal form of buprenorphine delivers the actual dose and the sublingual form delivers 50% of the dose, the bioequivalence of the highest dose of transdermal buprenorphine available in the United States is 1 mg of sublingual buprenorphine or half the dose of the 2 mg tablet. The higher dose transdermal buprenorphine patch, available in Europe since 1999, is available in 35, 52.5, and 70 μg/h and is applied for 3 days.

We present a review of the literature and 3 cases as examples of a novel method of opioid rotation of chronic pain patients from full agonist opioids to sublingual buprenorphine.

REVIEW OF THE LITERATURE

In 2005, Malinoff et al[9] reported on 95 consecutive patients, and in 2012, Daitch et al[10] reported on 104

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patients suffering from poorly controlled chronic pain on long-term opioid therapy who were rotated to sublingual buprenorphine, after a withdrawal period of 12 or more hours. These observational studies, which were subjected to statistical analysis, demonstrated a reduction in pain scores with a range of 2 or more points on a 0- to 10-point visual analog pain scale. The mean dose of sublingual buprenorphine in the study by Malinoff et al was 8 mg and the dose varied between 8 and 32 mg in the study by Daitch et al. Malinoff et al[9] reported that, overall, 86% of the patients experienced a significant benefit in analgesia and quality of life measures. Recent review articles and a nationally accepted clinical guideline also highlight the increasing relevance and importance of buprenorphine in the management of pain.[6,8,11]

Buprenorphine was first synthesized in 1966 in an opioid research laboratory established by Reckitt and Coleman, a home products company, in Hull, England. It represented the culmination of at least a generation of pre-molecular biology pharmacological research aimed toward the discovery of the "holy grail", an opioid-like substance with the analgesic power of morphine but devoid of its potent addictive and respiratory-depressant effects.[12] Buprenorphine was originally available in a parenteral form (0.3 mg/mL) and as a low-dose sublingual tablet (0.2 and 0.4 mg) and was thoroughly studied in the 1980s for acute, chronic, and cancer pain.[12] A decade later, the higher dose transdermal buprenorphine was evaluated and extensively prescribed for cancer and noncancer chronic pain in Europe, but neither the low-dose sublingual nor the higher dose transdermal buprenorphine has ever been available in the United States. The morphine equivalent of 0.3 mg of parenteral buprenorphine is 10 mg.[5]

As noted above, high-dose sublingual buprenorphine was FDA approved in 2002 for addiction and has been clinically available since 2003. In addition to the observational pain studies on this formulation mentioned above,[9,10] there have been other recent US reports published on its use for pain.[13,14] Buprenorphine, prescribed in this way, has been found to be particularly beneficial in opioid-induced hyperalgesia, neuropathic pain, and cancer pain.[15–17]

Several pharmacological features may make buprenorphine a preferable option for the long-term treatment of chronic pain in patients who have failed nonopioid therapies. It has an excellent safety profile with respect to overdose because of its so-called "ceiling effect" on respiratory depression.[18,19] Patients prescribed buprenorphine have a significantly lower risk of overdose than do those prescribed methadone, although studies confirming this have been largely evaluating those on opioid maintenance for addiction.[20,21] Buprenorphine is much less associated with the development of tolerance and with the experience of euphoria. The pharmacokinetics in terms of steady blood concentrations and ultrastable receptor occupancy reduces the highly variable effects of peaks and troughs observed in the blood concentrations of other opioids. Another benefit of buprenorphine is its antihyperalgesic effect.[15] Hyperalgesia, the increased sensitivity to painful stimuli, is particularly difficult to treat component of neuropathic pain. Additionally, opioids themselves have been demonstrated to increase sensitivity to pain. This condition is termed opioid-induced hyperalgesia.[22,23] Buprenorphine, because of this antihyperalgesic property, may reduce the incidence of this complication of opioid medication use.[6,8] Buprenorphine also has been found to be associated with decreased suppression of immune and endocrine function as compared with other evaluated full agonist opioids.[5,6,8]

As previously noted, buprenorphine is a high-potency partial mu-receptor agonist and kappa-receptor antagonist, with very high binding affinity for the mu-receptor. Consequently, if taken by a patient who is opioid dependent, sublingual buprenorphine is likely to precipitate an opiate withdrawal that is not reversed by adding more opioid medication.[24,25] If, however, sublingual buprenorphine is taken when the patient is already in withdrawal, it can treat the withdrawal and also treat any pain that might be present. For this reason, guidelines for buprenorphine induction in the context of opioid addiction treatment recommend that the buprenorphine only be started in patients who have remained abstinent for 12 or more hours from short-acting opiates, 24 or more hours from sustained release opioids, and up to 2 or more days from methadone, so that they are in a measurable symptomatic withdrawal at the time of their first buprenorphine dose.[26] There are currently no widely accepted guidelines on the process of high-dose sublingual buprenorphine induction for pain.

The requirement of a "withdrawal" or "abstinence day" before buprenorphine induction presents a significant barrier to the use of this unique and beneficial medication. The idea of a day or more of potentially severe withdrawal symptoms, as well as loss of needed analgesia, may be intimidating enough to deter opiate-dependent chronic pain patients from using this medication. Physicians' reluctance to start buprenorphine, because of both the time-consuming induction[27] and the potential discomfort for the patient, also presents a significant barrier to its use.

Higher dose transdermal buprenorphine was recently shown to eliminate severe withdrawal symptoms in addicts during rotation from doses of oral methadone that ranged from 60 to 100 mg/d.[28] More specifically, European studies with the buprenorphine patch have

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shown the feasibility of rapidly switching from full agonist opioids to transdermal buprenorphine in pain patients.[29,30] In the United States, Lanier et al[31] demonstrated the feasibility of a different proprietary transdermal buprenorphine technology for the detoxification of heroin addicts. Although they did not directly address the issue of the avoidance of precipitated withdrawal, it is notable from the protocol and published findings that precipitated withdrawal was not encountered.

Although it may be feasible to convert an opioid-dependent pain patient to longer-term transdermal buprenorphine, the transdermal formulations currently available in the United States (Butrans patch, at 5, 10, or 20 mcg/hr doses), as noted above, provide too little medication to sustain many patients who have been on higher doses of opioid therapy. Studies vary on the equipotent oral morphine dose to transdermal buprenorphine,[8,29,30,32] but the most generous estimate of the transdermal buprenorphine: oral morphine ratio is 1:115, giving a 24-hour morphine equivalent dose for the 20 μg/h patch of 55.2 mg, an inadequate daily amount of morphine for many opioid-dependent chronic pain patients.

We present a novel method of high-dose sublingual buprenorphine introduction using the slow-release low-dose patch as a bridge to prevent withdrawal. The patch, in this method, is applied on the day before beginning the higher dose sublingual tablets. Note that in 2 of the cases, for 1 or more days, a full agonist short half-life opioid (hydromorphone) was substituted for the long-acting full agonist regimen before the introduction of any buprenorphine.

CASE REPORTS

The following case reports are a selection of 3 patients treated for chronic pain at a private clinic specializing in pain and addictions. None of these cases met criteria for addictive disease. Opiate rotations were done supervised either in the clinic setting or at home with close telephone supervision and follow-up. Previous studies have confirmed the safety of at-home buprenorphine inductions.[33,34] Some incidental demographic information has been sufficiently altered to protect the patients' anonymity, without altering clinical implications.

Case 1

Patient A was a 38-year-old woman referred to our pain medicine practice because of intractable pain, severe insomnia, and suicidality. She had undergone multilevel lumbar reconstructive surgery several years earlier, including a fusion at one level and a total disc replacement at another. Her pain was being managed with sustained release oxycodone 80 mg/d, oxycodone/acetaminophen 7.5/500 mg twice a day pro re nata, transdermal lidocaine, diclofenac sodium topical gel, and celecoxib. She was also being treated with zolpidem or eszopiclone, cyclobenzaprine, and metaxalone. She had been on sustained release oxycodone for 2 years, except for a 3-month period off all opioids, which she did not tolerate because of pain. Her average pain severity was 8 on a 0 to 10 visual analogue scale (VAS).

Two days before the introduction of transdermal buprenorphine, both forms of oxycodone were discontinued, as was the zolpidem and eszopiclone. While under observation in the office or by her spouse at home, she was treated with hydromorphone and titrated to approximately 8 mg orally every 4 hours for analgesia. She was also treated with low-dose chlordiazepoxide.

On day 1 of the rotation, 20 μg/h of transdermal buprenorphine was applied and hydromorphone was reduced to approximately 4 mg every 4 hours. The patient reported reduced pain and anxiety. Her vital signs were normal and no signs of opioid withdrawal were noted. On day 2, the transdermal buprenorphine was removed and the patient was given sublingual buprenorphine 2 mg, approximately every 6 hours. There were no signs of precipitated withdrawal. The patient reported a lower level of pain and was able to eat and drink normally. Vital signs remained normal. On day 3, the sublingual buprenorphine was increased, the chlordiazepoxide reduced, and pregabalin was started. On day 5, the patient reported a pain score of 3 on the VAS. She was eventually titrated up to approximately 32 mg/d of sublingual buprenorphine. Her sleep and mood had improved significantly. There was no further suicidality.

Case 2

Patient B is a 72-year-old man with a 20-year history of severe burning neck pain radiating to his shoulders and limited mobility of the cervical spine. He reported persisting pain scores of 7 or more on the VAS, a severely restricted lifestyle, and escalating despair.

Imaging studies of the neck revealed prominent and diffuse calcifications of his ligamentous and cartilaginous soft tissues, widespread foraminal stenosis, and central canal stenosis from C3 to C7 but intact neural elements without evidence for compression. A prior epidural steroid injection had been unsuccessful. His pain was being managed with hydrocodone/acetaminophen 10/325 mg every 4 hours as needed, with an average daily dose of hydrocodone of 40 mg. He had also been treated for several months in the last year with sustained

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release oxycodone, 60 mg/d, but this was discontinued because of adverse effects on his mental status. He was also being treated with clonazepam and paroxetine for his tics and mood, 2 antihypertensive medications, and a bronchodilator. On initial examination, his blood pressure was 140/85, and his neck range of motion was severely limited because of stiffness and pain.

On the morning of transdermal buprenorphine introduction, day 1, patient B took his regular hydrocodone, antihypertensives, paroxetine, and a reduced dose of clonazepam with a low dose of chlordiazepoxide under supervision of his family. He was then placed on 20 μg/h of transdermal buprenorphine at home. When he was seen later that day in the office, he reported increasing pain severity. His blood pressure was 146/90, and he had decreased neck mobility from baseline. He took no further hydrocodone.

On day 2, the patient used his regular medications and removed the transdermal buprenorphine. That day he was treated with sublingual buprenorphine, 0.125 or 0.25 mg every 2–4 hours with a total dose of 0.875 mg. These doses were obtained from dividing gelatin troches of buprenorphine made by a compounding pharmacist. On examination, he had a blood pressure of 130/70 and appeared increasingly comfortable. By day 5, patient B's daily buprenorphine dose had stabilized at 0.75 mg, his clonazepam was restored to its usual dose, and the chlordiazepoxide was discontinued. He reported excellent analgesia and mood and felt "more alert than at any time in the past 10 years."

Case 3

Patient C is a 54-year-old man with intractable thigh pain, diagnosed as chronic regional pain syndrome after a large staphylococcal abscess he had developed 3 years before. In addition to an analgesic, his pain treatment has included transcutaneous electrical stimulation and physical therapy. For his pain, he was taking 15 mg of methadone and 15 mg of oxycodone daily, a 125 μg/h fentanyl patch every 48 hours, and transdermal lidocaine. He was also taking gabapentin, acetaminophen, low-dose aspirin, multiple laxatives including methylnaltrexone, and a statin. For insomnia, he took melatonin, lorazepam, eszopiclone, and doxepin. His pain and medications caused severe limitations on his ability to sit or drive, including sitting as a passenger. On initial examination, his blood pressure was 130/80, and no erythema or swelling was seen in the region of his thigh pain. He lay horizontally in the examination room for this entire encounter.

The patient's methadone, oxycodone, transdermal fentanyl, and eszopiclone were discontinued 3 days before the induction of transdermal buprenorphine. He was then given hydromorphone tablets to use for pain or withdrawal symptoms under the supervision of his family and our staff. Hydromorphone was titrated up to 8–12 mg orally every 4 hours for a daily average total over the 3 days of 80 mg/d. His lorazepam was reduced and cross-tapered with chlordiazepoxide. His pain level improved during this preinduction period, and he remained ambulatory with a good appetite.

On day 1, the patient's hydromorphone was continued at a reduced dose of 4–8 mg every 4 hours and a 20 μg/h transdermal buprenorphine patch was applied. No withdrawal symptoms were observed, and although the patient remained active, he reported an increase in pain that day. On induction day 2, sublingual buprenorphine was started at 2–4 mg every 4 hours for a total of 10 mg. The transdermal buprenorphine was left in place. No symptoms of withdrawal were observed and the patient's pain began to improve to the extent that the patient wanted to commence a road trip to visit a friend. Over the next few days, the patient's sublingual buprenorphine was titrated up to approximately 32 mg/d, and the hydromorphone was titrated down and eliminated. His vital signs and mental status remained stable during this entire time.

DISCUSSION

This case series discusses a novel use of the recently approved low-dose buprenorphine transdermal patch for 24 hours as a bridge to safely begin sublingual buprenorphine analgesia in opioid-dependent chronic pain patients without a period of withdrawal. It is our hope that this method of starting buprenorphine may make the switch to this potentially safer medication more feasible and tolerable to both pain patients and providers. At this point, several weaknesses of this case series should be acknowledged. First, because the treatment was carried out in part with the help of family members as has been studied in the addiction field[33,34] and because formal arrangements were not in place at the time in the clinic either, we do not have data for standardized objective measurements for withdrawal symptoms—such as the Clinical Opioid Withdrawal Scale—before and during buprenorphine introduction. Second, although each of the 3 cases represents a different anatomical pain syndrome, a case series such as this did not include the wider variety of conditions such as headache, fibromyalgia, or thoracic outlet syndrome that are often associated with chronic opioid therapy. Because of the increasingly recognized importance of safer opioid use for long-term analgesia, well-designed trials involving buprenorphine are needed, comparing opioid

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rotation with low-dose transdermal buprenorphine to the standard delayed induction.

The findings in this case series provide additional data to that presented by Hess et al[28] on the use of the higher dose buprenorphine transdermal formulation in addiction patients to ease the rotation from methadone to sublingual buprenorphine. Researchers and funding agencies, in both the pain and addiction medicine fields, should be encouraged to consider the favorable public health implications that a more formal set of data would provide on opioid rotations that use transdermal and sublingual buprenorphine.

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