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Conversion from High-Dose Full-Opioid Agonists to Sublingual Buprenorphine Reduces Pain Scores and Improves Quality of Life for Chronic Pain Patients

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Abstract

Objective. This study aims to determine the effectiveness of converting patients from high doses of full-opioid agonists to sublingual (SL) buprenorphine.

Design. An observational report of outcomes assessment.

Setting. An interventional pain management practice setting in the United States.

Subjects. Thirty-five chronic pain patients (age 24–66) were previously treated with high-dose opioid-agonist drugs and converted to SL buprenorphine. Patients' daily morphine equivalents ranged from 200 mg to 1,370 mg preconversion, with a mean daily dose of 550 mg.

Methods. A retrospective chart analysis examined numerical pain levels and quality of life scores before and 2 months after conversion to SL buprenorphine.

Results. After continuation of SL buprenorphine therapy for 2 months, the mean pain score decreased from 7.2 to 3.5 ($P < 0.001$), with 34 of the 35 patients examined reporting a decrease in pain. This pain score decrease was robust with regard to initial pain score and preconversion morphine equivalent dosage. Quality of life scores improved from 6.1 to 7.1 ($P = 0.005$).

Conclusion. Average pain scores decreased from 7.2 to 3.5, and quality of life scores increased from 6.1 to 7.1 for 35 patients converted from high-dose full-opioid agonists to SL buprenorphine therapy for more than 60 days. Clinicians should consider buprenorphine SL conversion for all patients on high-dose opioids, particularly patients with severe pain (7–10) unrelieved by their current opioid regimen or patients for whom the clinician does not feel comfortable prescribing high-dose opioids.

Key Words. Buprenorphine; Sublingual Buprenorphine; Opioid Conversion; Opioid-Induced Hyperalgesia; Analgesia; Opioid Tolerance

Introduction

Analgesics that act at several sites along the pain pathway to diminish pain, opioids have been used to treat pain for thousands of years [1–3]. Today, some of the most commonly prescribed medications for severe pain

include opioids, despite their serious side effects and potential for abuse, addiction, and overdose [1,4,5].

Furthermore, prolonged use of opioids may result in physical consequences including opioid tolerance, opioid dependence, and opioid-induced hyperalgesia (OIH) [2–4]. Tolerance occurs when, after repeated use of opioid medication, patients need increased doses to maintain equipotent analgesia [6–8]. Tolerance reduces opioids' efficacy and may be the reason for dose escalation [3,6–8]. Prolonged opioid use may also have hormonal effects resulting in decreased fertility and libido, as well as immunosuppression [2]. Prolonged use of high doses of opioids is more likely to cause toxicity than short-term use of low doses [2].

Chronic pain is defined as pain associated that persists beyond the usual healing course of an injury and adversely affecting the function or well-being of the individual [1,3,9]. The efficacy of opioid therapy, especially high-dose opioid therapy, in treating chronic pain is in debate [1,3,10].

Doses of over 200 mg of morphine equivalents per day are considered high and may be excessive [2,11,12]. Nevertheless, clinicians frequently increase dosage when opioid patients complain of increased pain. Although progressively higher opioid doses may initially improve symptoms in some patients, repeated dose escalations may have limited utility because of adverse effects and other factors [2,12,13]. Clinicians should carefully reassess all patients on chronic opioid therapy who have repeated dose escalations, particularly to greater than 200 mg daily of morphine equivalents. Opioid treatment may require discontinuation or weaning if assessments indicate the presence of intolerable adverse effects, aberrant drug-related behaviors, decreased quality of life, decreased function and physical capacity, or decreased analgesia [2,13,14].

In addition, clinicians should be aware that opioid therapy, especially in high doses, may heighten pain sensitivity and aggravate preexisting pain, indicating OIH [2–4,13–20]. Research has shown certain opioids at high doses can produce allodynia and hyperalgesia, particularly during rapid dose escalation [2,4,13]. Several neuroplastic adaptations may underlie OIH, including: activation of the excitatory neurotransporter N-methyl-D-aspartate through the central glutaminergic system; increased levels of spinal dynorphins that cause the release of pro-nociceptive neuropeptides; and altered activation of descending pathways, such as the rostral ventromedial medulla, facilitating spinal nociceptive processing [4,6,14,15,18,21,22]. Clinically, OIH will increase the pain of preexisting nociceptive conditions, as well as produce diffuse pain that extends to areas beyond the preexisting nociception. Increasing opioid dose worsens OIH, whereas reducing opioid dose or utilizing alternate medications, such as sublingual (SL) buprenorphine, relieves OIH [8,15].

Buprenorphine, a semi-synthetic phenanthrene derived from thebaine, is a partial μ-agonist and κ-antagonist [3,8,23–26]. Buprenorphine is highly lipophilic and 96% protein-bound in systemic circulation [26,27]. It has a high affinity for the μ-opioid receptor with a slow dissociation, resulting in a long duration of action, and scientific literature supports the high therapeutic index of buprenorphine [25,27].

Buprenorphine's effects plateau at higher doses, limiting the maximal analgesic effect and respiratory depression [24]. The partial agonist ceiling and its high affinity at the μ-opioid receptor confer a high safety profile clinically and a low level of physical dependence [25].

In the 1970s, a parenteral buprenorphine dosage formulation indicated for treatment of pain was brought to the American market [15,25]. Since that time, a sublingual preparation, both alone and in combination with naloxone, has become available as a Schedule III, FDA-approved treatment of opioid dependency [15,25,27]. The Drug Enforcement Administration has acknowledged the legality of off-label of buprenorphine SL to treat pain in chronic pain patients [28]. In July 2010, the FDA approved transdermal buprenorphine for the treatment of moderate to severe chronic pain [29]. Transdermal buprenorphine has been available in Europe for several years, and studies have shown that the transdermal medication is well tolerated and effective in the treatment of chronic cancer and noncancer pain [28–30].

Studies have shown buprenorphine SL is useful for treatment of OIH, though other research has failed to demonstrate buprenorphine's efficacy in treating OIH, such that this proposed finding remains controversial [8,31–33]. A previous retrospective study by the authors demonstrated that conversion from full agonist opiates to buprenorphine SL led to a significant overall decrease in visual analog scale (VAS) of 2.3 points [34]. Significant decreases of pain occurred for all dosage ranges of patients on full agonist opioid medication (0–660 mg). However, the initial study showed lower buprenorphine SL efficacy at levels of >400 mg morphine equivalents, possibly due to a small sample size. Additionally, recent commentaries have questioned the prescription of high-dose opioids, with sublingual buprenorphine viewed as a "safety net" for patients needing to come off of these opioid regimens [35,36].

The purpose of this study was to evaluate the effectiveness of conversion to buprenorphine SL for patients with significant levels of persistent pain on high doses of full agonist opioid medications (200–1,370 mg morphine equivalents). One previous study to examine use of buprenorphine SL for pain management in chronic pain patients on high-dose opioid medication showed a beneficial effect of conversion off high-dose opioid medication onto ibuprofen alone, and even greater benefit after further conversion to buprenorphine SL [8]. This current study differs because of its greater sample size and outpatient setting. Another study found that 67% of patients hospitalized for buprenorphine conversion

reported moderate to dramatic improvements in pain and functional status [37]. This current study differs because of its outpatient setting. A third study showed 88% of patients experienced moderate to substantial pain relief and improved mood and functioning upon conversion to 2–20 mg (mean 8 mg) of buprenorphine SL [38]. This current study differs as patients were converted to significantly higher doses of buprenorphine (28.11 + 5.94 mg), owing to their high opioid doses preconversion.

Methods

Patient Selection

The study was conducted in a private practice setting at an interventional pain management practice in the United States. An electronic medical record system identified chronic pain patients on high-dose full agonist opioids converted to sublingual buprenorphine between July 2010 and April 2011. In order to be included for analysis, patients must have experienced continuous or worsening pain despite the use of opioid analgesics, must have been using at least 200 mg of morphine equivalents, and must have remained on buprenorphine SL after initial conversion for at least 60 days. Researchers obtained approval from an institutional review board that included authorization for a Health Insurance Portability and Accountability Act waiver, as the study was a retrospective chart review. Nonetheless, all patients were provided informed consent.

Patients were assessed initially from their history and physical examination. They were on a variety of full agonist opioids, including predominantly oxycodone (N = 12), hydromorphone (N = 4), oxymorphone (N = 2), fentanyl (N = 6), methadone (N = 5), and morphine (N = 6). Many patients were on combinations of different immediate release and sustained release combinations of opioid medication. Prior to conversion, a nurse practitioner provided patients information about the proper use and initiation of buprenorphine SL, the drug's risks, and its benefits in a 30-minute teaching session. Patients then completed conversions at their homes with phone access to the clinic if needed. The nurse practitioner, with backup from physicians trained in buprenorphine administration, supervised these conversions.

Table 1 shows preinduction morphine equivalent doses [34]. Of the 35 patients analyzed, 21 were male (60%) and 14 were female (40%). Patients averaged 49 years old, with a range of 24–66 years of age. The mean daily preinduction morphine equivalent dose of opioid was 550 mg. At the end of the study, average buprenorphine SL treatment duration was 6 months.

Data

Patients filled out a questionnaire to ascertain their current quality of life, via a validated Quality of Life (QOLS) scale, an 11-point numeral rating scale assessing function for people with pain, with 0 representing nonfunctioning and 10 representing normal quality of life [39]. Patients reported their numerical pain level via an 11-point numerical rating scale (NRS) [40]. Patient levels of withdrawal were evaluated with the Clinical Opiate Withdrawal Scale (COWS) score [41]. All data were abstracted from patient electronic medical records in a standardized manner. Patients were seen at 1-week intervals after home conversion until stable, and then on a monthly basis. For patients with multiple visits pre- and postconversion, this study considered the visit immediately prior to conversion for preconversion scores, and the visit closest to 60 days after conversion for postconversion scores.

Table 1 Equianalgesic dosage morphine equivalent conversion table

Drug	Dose (mg)
Morphine	30
Hydrocodone	30
Oxycodone	20
Oxymorphone	10
Fentanyl patch	12
Methadone	7.5
Hydromorphone	6

Patients' age, sex, diagnosis, medication history, preinduction medication, preinduction COWS, and morphine equivalent dosage were recorded. The most recent opioid prescription was used to define the type and amount of opioid medication. Sustained-release opioid medications were converted to morphine equivalents and added together with any immediate-release opioid medications to obtain a preinduction amount of morphine equivalents for each patient.

Table 1 shows the equianalgesic conversion doses of opioids utilized in the study. As there is no single established set of morphine conversion ratios, two of the authors generated a set of conversion values based upon published values and their clinical experience for a previous study [34]. For the sake of consistency, the same conversion values are used in this article.

The primary outcome evaluated was reduction in self-reported pain after conversion to buprenorphine SL, using a standard 11-point scale (0–10). The secondary outcome analyzed was change in patient QOL scale for patients with chronic pain. A two-tailed, paired Student's *t*-test assessed significance.

Drug Administration

All patients were detoxified from prescribed opioids by using buprenorphine SL in accordance with previously described protocols [34]. Patients received buprenorphine SL after they had discontinued all opioid medications for

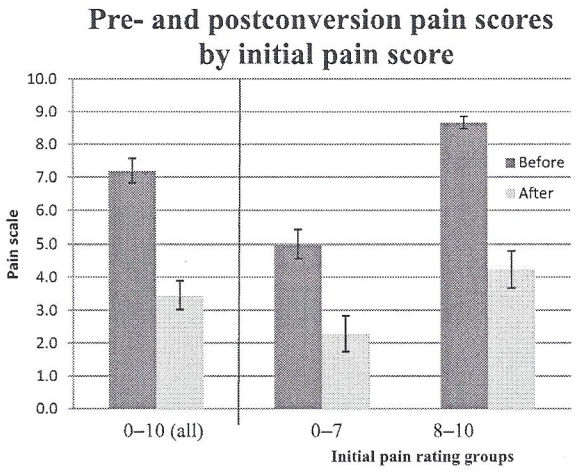

Figure 1 Pre- and postconversion pain scores with standard error for all patients (left) and patients grouped by initial pain ratings (right).

at least 24 hours (48–72 hours for methadone and transdermal fentanyl) and had achieved a COWS scale of at least 13. At conversion, patients were given 8 mg of buprenorphine sublingually and told to take an additional 8 mg dose 1 hour later if severe pain or significant withdrawal symptoms continued. Patients were instructed not to exceed 32 mg of buprenorphine SL daily. In addition, oral clonidine was offered during the first week of buprenorphine SL administration as all patients experienced withdrawal symptoms during that time. After 1 week, buprenorphine SL dose was adjusted based on reports of opioid abstinence symptoms, pain complaints, or side effects. Patients were then evaluated at least monthly.

Results

Overall, patients reported a 51% decrease in pain score before and after conversion to buprenorphine SL, from 7.2 to 3.5 points ($P < 0.001$), as shown in Figure 1, with 34 of 35 patients reporting decreased pain. Patients with initial pain ratings of 0–7 (N = 14) had a 54% average pain decrease (2.8 points), whereas patients with initial ratings of 8–10 (N = 21) had a 51% average pain decrease (4.4 points), an insignificant difference.

Patients' QOL scores, also assessed at baseline and after buprenorphine SL conversion, improved from 6.1 to 7.1 ($P = 0.005$). Furthermore, patients converting off higher opioid doses enjoyed a greater average improvement in quality of life score, as patients at or below the median dose (N = 18, range: 200–380 mg) saw average QOL improvement from 6.3 to 6.8 ($P = 0.020$), whereas patients above the median dose (N = 17, range: 405–1,370 mg) saw average QOL improvement from 6.0 to 7.4 ($P = 0.036$).

To assess whether the preinduction morphine equivalents dosage affected the reduction of patients' pain scores, patients were sorted into three groups. All groups showed a statistically significant reduction in pain of at least 40%, as Figure 2 shows. The 200–400 mg morphine equivalents group reported a 61% pain score decrease of 4.2 points from 6.8 to 2.6 ($P < 0.001$, N = 18). The 400–1,000 mg morphine equivalents group reported a 61% pain score decrease of 3.1 points from 7.2 to 4.1 ($P = 0.004$, N = 9). The >1,000 mg morphine equivalents group reported a 61% decrease of 3.5 points from 8.1 to 4.6 ($P < 0.001$, N = 8). Note that as morphine equivalents dosage increases by group, patients' pre- and postconversion pain scores increase as well.

The average dose of buprenorphine SL was 28.11 ± 5.94 mg. Fewer than 30% of patients did not complete the 60-day conversion to qualify for study inclusion.

Discussion

In this retrospective study, after clinicians converted patients taking high-dose opioids greater than 200 mg morphine equivalents onto buprenorphine SL, 34 of 35 patients studied experienced pain reduction. This result suggests that buprenorphine SL tablets can be an effective analgesic for patients who have not attained successful analgesia with traditional high-dose, full agonist opioid medications and that patients without severe pain (NRS 1–7) on high-dose opioid medication may improve analgesia with conversion to buprenorphine.

All the patients in this study underwent withdrawal upon cessation of the opioid medication, indicating physical dependence. This withdrawal, expected in such

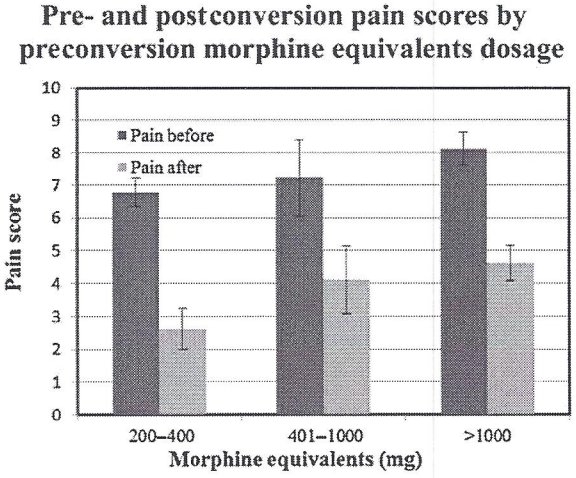

Figure 2 Pre- and postconversion pain scores with standard error for patients grouped by preconversion morphine equivalent dosages.

patients, included rebound pain and was adequately treated with buprenorphine SL and, if requested, oral clonidine.

Patients with the highest level of morphine equivalents had the highest initial pain score, suggesting tolerance and the presence of OIH [8]. Nonetheless, all groups of patients, regardless of initial morphine equivalent dosages, experienced significant reductions in pain. Furthermore, that patients with initially mild to moderate pain scores of 0–7 showed significant improved analgesia with conversion to buprenorphine suggests that decrease in OIH may not be not the only mechanism by which buprenorphine decreases pain.

This study builds on the authors' previous study, which showed an average decrease in pain of 2.3 points with conversion of 104 patients from 100 to 660 mg of morphine equivalents, but only a mild decrease in pain of 1.1 numerical points in patients taking over 400 mg of morphine equivalents, perhaps owing to a small sample of high-dose patients [34]. In this study, with 35 patients over 200 mg of morphine equivalents, results are more concordant with the hypothesis that OIH was present in patients on high-dose opioids with poor analgesia.

Although different morphine conversion ratios could reasonably have been applied, they would not affect the article's central findings: that after conversion to buprenorphine, patients reported a decrease in pain and quality of life scores. Furthermore, as 34 of the 35 study participants reported decreased pain, the decrease in pain scores would remain robust across preconversion morphine equivalent doses regardless of the exact conversion values used.

Indeed, and unlike in the authors' previous study, this study detected an improvement in QOL scores. An improvement in patient quality of life corresponds with the authors' clinical impressions, and patient reports of improved cognition, function, and pain score postconversion.

This study also shows similar results to the findings of Baron et al., who studied detoxification of 23 patients off high-dose opioid medication [8]. In that study, patients were converted from high-dose opioid medications onto either ibuprofen alone, or ibuprofen and buprenorphine. Both groups showed a highly significant decrease in pain, but the ibuprofen and buprenorphine group showed the greatest decrease in pain. Baron et al. reasoned that the underlying cause for improved pain was the elimination of OIH with detoxification and conversion to buprenorphine. They also believed that the same mechanisms that create OIH may reset after detoxification, thereby reducing pain sensitivity. This study shows similar results in an outpatient setting, which is more relevant to the treatment of chronic pain. Furthermore, this study enjoyed a larger sample than that of Baron et al.

Some patients on high-dose opioid medications attain excellent analgesia. Thus, the authors are not suggesting that all patients on high-dose opioid medication convert to buprenorphine. However, the authors believe that patients who exhibit tolerance and poor analgesia with increasing doses of opioids may be exhibiting OIH; this subset of patients does appear to respond well to detoxification off their high-dose opioid medication via conversion to buprenorphine. Furthermore, this study shows that patients taking high-dose opioids with pain scores in all ranges appear to improve with conversion to buprenorphine. There may be patients on very high doses of opioid medication who are relatively comfortable with NRS pain scores of 7 or less; if the clinician is not comfortable continuing to write for such high dosages, he or she may consider conversion to buprenorphine as well.

Limitations

A potential criticism of this study is that patients are simply switching from one high-dose opioid medication to another. Animal studies suggest that buprenorphine is 25–50 times as potent as morphine [42]. As the average postconversion dose of buprenorphine in this study was 28.11 mg, a direct conversion would imply a morphine dose as high as 700 mg. However, as a partial agonist, buprenorphine has a ceiling effect both on analgesia and side effects, rendering a direct dosage comparison between morphine and buprenorphine unrealistic.

Ultimately, however, due to the QOL improvement and the medication's inherent safety, the authors believe buprenorphine SL is a safer and better choice for analgesia. Furthermore, patients may be able to wean off buprenorphine SL more easily, given the drug's extremely long half-life. Indeed, it has been the authors' clinical impression that many patients can and do begin to decrease their dosage after 4–6 months of buprenorphine therapy.

Another limitation of this study was that it was an observational chart review with no control group. Chart reviews are advantageous in that easily accessible data allows for large sample sizes and are useful in identifying trends that can be examined in subsequent randomized controlled trials. Unfortunately, this study is limited because patient charts may be incomplete, missing, or unrecoverable; there may be difficulty interpreting information in patient charts; verification of past information may be difficult; and causality cannot be established as in a randomized controlled trial. In particular, the authors cannot rule out the possibility of selection bias, as patients who poorly tolerated conversion to buprenorphine may have switched back to opioids within 60 days of conversion and would not be included in this study's results. This issue is somewhat mitigated, as the outpatient clinic refused to switch patients back to opioids; however, some patients may have left the practice to seek high-dose opioids with different providers, potentially skewing results. Similarly, patients may have experienced similar improvement in pain and quality of life from weaning alone, given the high dosage of

opioids they were taking. Another limitation is that this study categorized only patients' total daily doses, leaving unexamined how frequently patients took buprenorphine SL each day and whether that affected analgesia.

Finally, clinical limitations and considerations also exist. Only clinicians with training and experience in working with buprenorphine should convert patients to buprenorphine SL. Untrained clinicians may take courses on utilizing buprenorphine SL but should note that though most courses are directed toward treatment of opioid addiction, a separate entity than buprenorphine conversion for high-dose opioid use. Although legal for clinicians to treat chronic pain patients with buprenorphine without certification, the authors recommend completing at least a standard 9-hour online course in buprenorphine administration. In addition, certain payors are reluctant to cover buprenorphine therapy for such cases, as it is an off-label use from the traditional labeled use of opiate dependence. In general, with preauthorization and discussion with insurance company medical directors, SL buprenorphine can be approved. If not authorized, then alternative formulations exist with generic SL buprenorphine pills, or even generic formulations of buprenorphine in troche gel form.

Conclusion

Patients converting from high-dose full-opioid agonists (200–1,370 mg of morphine equivalents) who continued buprenorphine SL therapy for more than 60 days reported a significant decrease in pain of >50% from 7.2 to 3.5 (3.7 points) and improvement in quality of life from 6.1 to 7.2 (1.1 points). The unique pharmacology of buprenorphine SL as a partial μ-agonist likely results in its therapeutic effects. The use of buprenorphine SL in this study was reasonably safe, effective, and well-tolerated. Buprenorphine SL is an excellent analgesic medication to treat many patients on high doses of opioid medication, and a useful tool for outpatient conversion of high-dose opioid patients within a traditional pain practice.

Based on the results of this study, clinicians should consider buprenorphine SL conversion for patients who initially present on high doses of opioid medication with limited pain control. Similarly, clinicians' own patients, who over time develop tolerance and need escalating doses of opioid medications with limited pain relief, would also likely respond well to conversion to SL buprenorphine. Buprenorphine SL has a better safety profile than traditional high dose opioids and should provide some QOL improvement. A clinician should also consider buprenorphine SL conversion if the clinician does not feel comfortable prescribing high-dose opioids to a given patient. Finally, recent clinical observation of utilizing transdermal buprenorphine demonstrates that transdermal buprenorphine may allow for conversion to SL buprenorphine without withdrawal symptoms, when applied in opioid-dependent pain patients as the initial exposure to buprenorphine [43]. This finding suggests a further simplification in the conversion from high-dose full agonist opioids to SL buprenorphine that may be recommended in the future.

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