Buprenorphine/Naloxone Therapy for Opioid Refractory Neuropathic Pain Following Traumatic Amputation: A Case Series

Lauren Licina, MD*; Carlyle Hamsher, MD*; Karl Lautenschager, MD†; Sandeep Dhanjal, MD†; Necia Williams, MD†; Christopher Spevak, MD, MPH, JD*

ABSTRACT
Phantom limb pain is a common consequence of limb amputation and is prevalent among the service members sustaining traumatic battlefield limb injuries during the conflicts in Iraq and Afghanistan. Current treatment to relieve phantom limb pain consists of physical, behavioral, and medical modalities including opioids and adjunct medications. Treatment failure resulting in persistent pain and disability may result. This case series describes four previously healthy service members who developed phantom limb pain following traumatic amputation successfully treated with buprenorphine/naloxone after failing traditional treatment. This is the first reported case series of patients expressing improved pain control with decreased frequency of phantom limb pain with the use of buprenorphine/naloxone instead of traditional opioid agonists.

INTRODUCTION

Phantom limb pain is a common consequence of amputation and is of particular interest in service members sustaining traumatic battlefield limb injuries. Standard pharmacologic treatment for phantom limb pain has involved opioids, anticonvulsants, and antidepressants; but efficacy rates remain unimpressive alone and also when combined with physical and behavioral modalities. Unfortunately, many of these patients will have less than optimal therapeutic outcomes after prolonged opioid analgesic therapy including worsening pain perception, deterioration of functional capacity, and depressed mood. Buprenorphine/naloxone, a mixed opioid agonist–antagonist, has been used for opioid addiction therapy and more recently as an alternative to opioid analgesics for acute or chronic pain in those wishing to decrease the side effect profile evident with pure opioid agonists. Buprenorphine is as a partial mu agonist and kappa and delta antagonist. Naloxone is a mu antagonist, however, has no oral bioavailability. It is combined with buprenorphine to prevent intravenous abuse as the naloxone will prevent the buprenorphine’s mu agonist euphoric effects. These characteristics allow for long-duration analgesia with limited physiological and subjective effects such as euphoria. We report 4 cases of buprenorphine/naloxone therapy in the setting of failed pharmacologic control of phantom limb pain with pure opioid agonists.

CASE DESCRIPTIONS

Case 1
A 31-year-old active duty male sustained a dismounted complex blast injury (DCBI) from an improvised explosive device (IED) resulting in substantial soft-tissue injuries, traumatic bilateral transfemoral amputations, and a transradial upper extremity amputation. His inpatient course consisted of standard multimodal pain regime including continuous sciatic and brachial plexus catheters, opioids, adjuvants, and behavioral and physical modalities including acupuncture. He was discharged with transdermal fentanyl 100 mcg every 72 hours, 15 mg immediate release morphine twice daily as needed, pregabalin 200 mg three times a day, and celecoxib 200 mg daily. Because of inadequate phantom pain control at a self-reported verbal analog score of 10/10 and side effects including sedation and constipation, the opioids were discontinued 6 months after sustaining his injuries, and he was converted to sublingual buprenorphine/naloxone 8 mg/2 mg with adequate control of both phantom and somatic pain. This was subsequently tapered to 2 mg/0.5 mg twice daily over a 4-month period.

The service member was readmitted because of symptomatic cholelithiasis 3 months later and underwent a laparoscopic cholecystectomy. During the perioperative period, his buprenorphine/naloxone was stopped and he was placed on intravenous hydromorphone with adequate pain control. He was discharged with 4-mg oral hydromorphone every 4 to 6 hours for pain control. He then immediately described an extreme increase in his phantom limb pain to an intensity level of 10/10, which he had not endured since his initial injuries. The patient stopped his oral opioid and reinstated sublingual buprenorphine/naloxone at 2 mg/0.5 mg twice daily with near complete resolution of the phantom pain over the next few days.

Case 2
A 26-year-old active duty male sustained a DCBI from an IED blast resulting in bilateral transfemoral amputations and severe perineal injuries. His inpatient course was complicated by multiple exploratory surgeries and wound washouts. Throughout the inpatient stay, the patient complained of...
phantom and somatic pain, which was controlled with continuous epidural analgesia as well as opioids, adjuvants, and physical and medical modalities including acupuncture and transcutaneous electrical nerve stimulation (TENS). He was discharged on transdermal fentanyl 100 mcg every 48 hours, oxycodone 15 mg every 4 hours as needed, nortriptyline 50 mg at night, and pregabalin 300 mg twice daily. The patient discontinued duloxetine as it did not help with the pain at a titrated dose of 60 mg. The patient complained of unrelenting phantom limb pain of 10/10 in his lower extremities bilaterally, which was not reduced with his multimodal pain regime preventing participation in amputee rehabilitation. Opioids were discontinued and buprenorphine/naloxone sublingual 8 mg/2 mg therapy was initiated, which reduced the patient’s pain to a tolerable level of 3/10 allowing increased participation in amputee care.

Case 3
A 20-year-old active duty male sustained a DCBI from an IED, resulting in bilateral transfemoral amputations and left severe upper extremity injuries requiring multiple extensive orthopedic and vascular procedures. Management of phantom limb pain during the inpatient course was achieved with opioids, adjuvants, low-dose ketamine infusion, physical and behavioral modalities as well as bilateral sciatic/femoral and brachial plexus continuous catheters. After discharge, the patient continued to experience unrelenting pain on long-acting oxycodone 20 mg three times per day, short acting oxycodone 15 mg up to every 4 hours as needed for pain, pregabalin 100 mg three times per day, acetaminophen 975 mg every 8 hours, and ibuprofen 800 mg every 8 hours. However, the patient stated that his phantom limb pain persisted at a level 8/10 and he did not wish to continue to take such frequent doses of oxycodone. The patient discontinued the opioids and started buprenorphine/naloxone 16 mg/4 mg, which reduced the pain severity to 4/10. The patient subsequently reduced the dose to 8 mg/2 mg daily. At follow-up visits, the patient stated that his pain was well controlled 2/10 with buprenorphine/naloxone and that he no longer experiences “cravings for medications.” The buprenorphine/naloxone dose was gradually reduced to 2 mg/0.5 mg daily.

Case 4
A 45-year-old active duty male sustained a DCBI from an IED resulting in a left lower extremity transfemoral amputation, right hip disarticulation, and right upper extremity fractures with soft-tissue injuries. The patient’s inpatient course consisted of multiple wound washouts before closures, including open reduction internal fixation of his right upper extremity. His phantom pain was treated with continuous nerve catheters as well as opioids, adjuvants, and physical and behavioral modalities. He was subsequently discharged with sustained release oxycodone 40 mg three times a day, short acting oxycodone 15 mg every 4 hours as needed, pregabalin 300 mg twice a day, and nortriptyline 75 mg at night. He continued to complain of phantom limb pain in his bilateral lower extremities described as sharp and similar in character to frostbite at a level 10/10. This pain was only partially relieved with his multimodal regime to 8/10. In an attempt to better control his pain, he was started on buprenorphine/naloxone 8 mg/2 mg therapy. Approximately 35 minutes after induction with sublingual buprenorphine/naloxone therapy, the patient experienced significant relief of his phantom pain for the first time. After 1 month of therapy, the patient was able to reduce buprenorphine/naloxone to 6 mg/1.5 mg, while still achieving complete pain relief. The patient subsequently developed purulent drainage from his right elbow after sustaining traumatic injury to his right upper extremity and required incision and drainage of the affected area. The buprenorphine/naloxone was stopped and replaced with intravenous/oral hydromorphone with return of the phantom pain. The patient resumed buprenorphine/naloxone therapy again with complete resolution of the phantom pain.

DISCUSSION
Buprenorphine/naloxone, a mixed opioid agonist–antagonist, has previously been described in the literature for use in both opioid-dependent individuals and acute pain management. However, its use for neuropathic pain and specifically phantom limb pain uncontrolled with opioid therapy has not been described. After sustaining traumatic injuries, the previously described patients developed phantom limb pain that was similar in context and character. All four patients developed phantom limb pain presenting as sharp, shooting, crushing, ripping, and tearing experienced distal to the residual limbs. In these cases, buprenorphine/naloxone appeared to be useful in controlling such pain, when many other modes of therapy were unable to do so. In addition, the equivalent dose of opioid used to control phantom pain was much less in the buprenorphine/naloxone form than pure opioid agonist medications. The combination of buprenorphine with naloxone instead of buprenorphine as a single agent was chosen because of its inherent abuse deterrent characteristics. These cases may represent a starting point for the utilization of mixed opioid agonist–antagonist medications not only as an appropriate alternative for pure opioids but rather a more appropriate therapy when opioids are not adequate to control neuropathic pain.

Phantom limb pain is a common consequence of amputation, occurring in 80% to 90% of cases. It must be differentiated from nonpainful phantom phenomena, residual limb pain, and nonpainful residual limb phenomena. Although peripheral and psychological factors may contribute to phantom limb pain, central changes seem to be a mainstay in the process. Phantom limb pain is a challenging condition to treat because of its underlying complex pathophysiology. The prevailing theory of etiology is that functional and structural changes occur both centrally (above and below the brainstem)
and peripherally that contribute to a state of chronic neuropathic pain that characterizes phantom limb pain.5 Moreover, severe preamputation pain is associated with phantom limb pain development in amputees. This is of particular interest for a patient population of soldiers with traumatic battlefield limb injuries.

Although standard pharmacological treatment for phantom limb pain can involve opioid analgesics, specific anti-convulsants, and various antidepressants, efficacy rates are unimpressive and in many cases, are only slightly higher than a placebo. There are also a plethora of nonpharmacological-based treatments such as deep brain stimulation, mirror therapy, TENS, vibration therapy, hypnosis, and acupuncture. The diversity in response to perceived effectiveness of the various treatments available highlights the necessity for individually tailored therapy.1

Because of the high rates of blast injuries sustained during operations in Iraq and Afghanistan, the number of soldiers returning with massive and multiple wounds is unprecedented.1 Although casualty survival rates have improved dramatically, the extent and impact of these wounds on soldiers' overall functional status pose unique challenges for their pain control and ultimate rehabilitation.2 The risk for opioid addiction or abuse is staggering. In addition, it is known that males, younger adults, and individuals with greater days supply of prescription opioids dispensed tend to develop opioid dependence and/or abuse.6 Although the use of opioid analgesics for the treatment of acute pain appears to be “generally benign,” extended use of opioids has been associated with clinically meaningful rates of addiction or abuse.7 Severe upper and lower extremity combat-related injuries are resulting in soldiers with two, three, and even four limb amputations suffering from neuropathic pain. The population of military patients subsequently developing phantom limb pain that is refractory to high-dose opioids and adjunctive pain medications is increasing steadily and necessitates another therapeutic option. The Warrior Clinic at Walter Reed National Military Medical Center treats combat-related injuries after the service member has been discharged from the inpatient service. The majority of amputees are managed by the primary care team with medical, physical, behavioral, and integrative modalities with success. The Pain Service assists the primary care team with treatment of refractory pain issues including traditional medication failure and as such generated these case reports. Although the number of amputees treated and the numbers of opioid failures would be of interest, the authors did not collect this data.

Buprenorphine/naloxone is designed for sublingual administration and is prepackaged in a 4:1 ratio of buprenorphine and naloxone. It is Food and Drug Administration approved to treat opioid dependence detoxification.8 Buprenorphine is a centrally acting partial mu agonist and a kappa and delta opioid receptor antagonist. Buprenorphine has a high affinity for the mu receptor but possesses lower intrinsic activity than seen with a full agonist at the mu opioid receptor.9,10 It appears that the mu agonist effect is most important for producing the drug’s analgesic results. Buprenorphine is associated with a long duration of action, 6 to 8 hours, which has been attributed to the slow dissociation of buprenorphine from the mu receptor. Unlike full mu-opioid agonists, at higher doses, buprenorphine’s physiological and subjective effects, including euphoria, reach a plateau.9 This ceiling may limit the abuse potential and may result in a wider safety margin. Furthermore, if the sublingual buprenorphine/naloxone form is tampered with or subsequently injected, naloxone will block the effects of buprenorphine and lead to withdrawal symptoms in a person with an opioid addiction who is attempting to misuse and abuse the medication.9 When administered sublingually as directed, naloxone will not affect the actions of buprenorphine. Prolonged use of buprenorphine can result in physical dependence. There are reported cases of withdrawal from buprenorphine, but the symptoms appear to be less intense than other opioids.11 Overdose events have been recorded when buprenorphine is combined inappropriately with other central nervous system depressants.11

Buprenorphine has been used for the treatment of acute and chronic pain, as a supplement to anesthesia, and for behavioral and psychiatric disorders including treatment for opioid addiction.9 Buprenorphine has been shown to provide adequate pain relief as well as improvements in pain intensity and duration of pain-free sleep. It is now considered a therapeutic option for the treatment of moderate to severe chronic pain.12 Buprenorphine is a mixed opioid agonist–antagonist in clinical use for over 25 years. Originally, buprenorphine was thought to be 25 to 50 times more potent by weight than morphine in an equivalent dose.9 However, the available literature on the equivalent dose of sublingual buprenorphine to other opioids is sparse. It has been shown that 0.4 mg sublingual buprenorphine had similar pain relief to 5 mg of intravenous morphine.13 In addition, this dose of buprenorphine also exhibited a similar safety profile. This data suggests that sublingual morphine is 12.5 times stronger than intravenous morphine.

Buprenorphine’s unique pharmacological profile has contributed to its usefulness in treatment of more than just opioid addiction. For example morphine, a typical mu opioid agonist, is not very sensitive in treating neuropathic pain. It has been suggested that the ineffectiveness of morphine in controlling neuropathic pain may be because of the downregulation of opioid receptors after nerve injury in the sensory neurons and in the spinal cord. In contrast, buprenorphine, a stronger opioid, has been shown to be effective in controlling neuropathic pain in rats and humans.14 It is known that some opioids have an N-methyl-D-aspartate (NMDA) receptor antagonist effect. Blocking the NMDA receptors is thought to prevent central sensitization of pain in both the spinal cord and brain. It has been shown that buprenorphine is one such opioid that can block NMDA receptors and reduce reflex facilitation and central sensitization.14

The cases presented here exhibit several unique features regarding buprenorphine/naloxone. As shown in all four cases,
phantom limb pain was not completely relieved with nortriptyline, pregabalin, gabapentin, toradol, acupuncture, TENS, and various opioid agonists. However, when buprenorphine/naloxone was administered, the patients finally received reduction of pain to a tolerable level. Of note, before patients began buprenorphine/naloxone therapy, all other opioids were discontinued and not resumed. The patients in cases 1 and 4 exhibit an even more convincing argument for buprenorphine/naloxone therapy. In these situations, the patients continued to experience phantom limb pain while using oxycodeone, pregabalin, and nortriptyline for pain control. On initiation of buprenorphine/naloxone therapy, the patients experienced significant pain relief. These two patients underwent cessation of buprenorphine/naloxone, during which their phantom limb pain returned, only to be resolved on restarting buprenorphine/naloxone. All four cases highlight that buprenorphine/naloxone achieved pain control is not successful with other modalities of pain management. In addition to alleviating phantom limb pain, the dose of opioid was much less in the buprenorphine/naloxone form. Table I displays the difference in total 24-hour opioid dose before and after replacement of conventional opioids with sublingual buprenorphine/naloxone. When calculating the 24-hour opioid dose, it was assumed as needed medications were taken and the sublingual buprenorphine equivalent dose was calculated based on a recent randomized controlled trial as discussed above.

As this is a case series, we are unable to provide an explanation of how this is possible. We can only speculate whether the therapeutic achievement is due to sublingual administration, or if the combination of buprenorphine and naloxone has some pharmacologic effect. Patient satisfaction in pain reduction is clear, and understanding the pathophysiology merits more attention. Although the number of amputees treated and the numbers of opioid failures would be of interest, the authors did not collect this data. We anticipate that this case series will stimulate discussion and interest in understanding the biophysical profile of why buprenorphine/naloxone has a different unique property of relieving phantom limb pain.

### REFERENCES


#### TABLE I. Morphine Equivalents Pre- and Post-Buprenorphine/Naloxone

<table>
<thead>
<tr>
<th></th>
<th>Pre (mg)</th>
<th>Post (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>230</td>
<td>150</td>
</tr>
<tr>
<td>Case 2</td>
<td>380</td>
<td>300</td>
</tr>
<tr>
<td>Case 3</td>
<td>300</td>
<td>75</td>
</tr>
<tr>
<td>Case 4</td>
<td>420</td>
<td>225</td>
</tr>
</tbody>
</table>