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Haunting of the phantom limb pain abolished by buprenorphine/naloxone

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SUMMARY

Neuropathic opioid refractory phantom limb pain (PLP) following amputation can be a life long debilitating chronic pain syndrome capable of completely destroying a patient's life. The pain, its associated depression and sleep deprivation can make many patients suicidal. Ever changing and relentless, it is notoriously unresponsive to traditional cocktails of strong opioids, adjuvant pain medications, antidepressants, local anaesthetics, nerve stimulators, hypnotics and psychotropics. Drug effects are seldom more effective than placebo. We describe a successful sustained rescue of a difficult 2-year-long PLP case with sublingual buprenorphine/naloxone using the drug's potent multimodal mechanisms of action: potent long-acting mu agonist/antagonist, kapa receptor antagonist, delta receptor antagonist and novel opioid receptor-like 1 (OR-L1) agonist effects. Traditional escalating pure mu-opioid receptor agonists and adjuvant neuropathic pain cocktails often have disappointing efficacy in the treatment of resistant PLP. We suggest introducing buprenorphine/naloxone as an early effective opioid choice in PLP management.

BACKGROUND

Phantom pain is a haunting, recurring pain so perfectly named as coming from a limb or body part that no longer exists. Horrified, the brain 'screams' to the sufferer that there is an absence or injury from a previous attack that otherwise, in nature, would have been an unsurvivable injury.[1 2] In the world of war, blast injuries, infections and trauma, the brain/mind does not discriminate. Up to 80% of amputee patients suffer daily chronic neuropathic phantom pain.[3 4] Current treatment consists of targeting complex central, peripheral and spinal origins of the pain[5] with success rates of only 20%–30%—barely above placebo.[6] Patients fail treatment and eventually disappear into the unproductive, dark world of angst and disability. This case describes a phantom limb pain score improvement from 8–10/10 to 0–2/10, which was sustained for 10 months. Supported by a recent case series in the military literature,[7] we describe a heroic, successful case of phantom limb pain resolution after traditional neuropathic pain multimodal treatment failure attempted both uninvasive and invasive methods for 2 years: (1) escalating opioids (Norco, oxycodone, hydromorphone), (2) gabapentin and pregabalin, (3) ketamine oral, nasal, sublingual, intravenous(4) antidepressants (Effexor, Cymbalta), (5) lidocaine (intravenous and patches), (6) mexiletine, (7) peripheral nerve stimulator in interscalene area for 30 days, (8) transcutaneous electrical nerve stimulation (TENS) unit, (9) cannabidiol oral oil and vaporising cigarette and (10) peripheral regional anaesthesia by interscalene catheter with ropivacaine. This would be a rare case report in the anaesthesia literature of sublingual buprenorphine/naloxone causing almost complete sustained remission of phantom limb pain following an arm disarticulation/amputation for necrotising fasciitis.

Phantom limb pain, a neuropathic pain syndrome, was once thought to be purely psychogenic but now is believed to be of multifactorial aetiology. Following amputation, lack of peripheral afferent sensory input may lead to spinal cord dorsal horn nerve reorganisation with resulting cortical brain reorganisation and cortical motor sensory dissociation.[5] The most recent Cochrane review of phantom limb pain treatments by Alviar *et al* concludes that pharmacologic and other therapies are largely ineffective: botulinum toxin A, opioids, N-methyl D-aspartate (NMDA) receptor antagonists (ketamine, memantine, dextromethorphan), anticonvulsants, antidepressants, calcitonin and local anaesthetics.[8] Buprenorphine, a derivative of thebaine, has long been discussed as a treatment for chronic neuropathic pain. Specific dosing for phantom limb pain has not been standardised. Several preparations of buprenorphine are currently available and are dosed according to the oral morphine milligram equivalents (MME) per day currently used by the patient on presentation. Butrans, approved in 2010, a transdermal buprenorphine patch preparation, can be used in maximal doses of less than or equal to 480 mcg/day of buprenorphine, in patients currently using doses of less than 80 MME of oral morphine per day. Belbuca, approved in 2015, a buccal dissolving preparation, can be used two times per day in a total daily dose of approximately 1.8 mg/day of buprenorphine, in patients currently using between 80 and 160 MME of oral morphine per day.[9–11] Finally, buprenorphine/naloxone sublingual film, approved in 2002 for outpatient treatment of opioid use disorder or addiction, has been used off label for chronic pain and may be the drug solution for patients on more than 160 MME of oral morphine per day or requiring more than 1.8 mg/day of buprenorphine.

CASE PRESENTATION

A 47-year-old previously healthy male executive deteriorated in 48 hours into life-threatening septic shock following ingestion of raw oysters at a 5-star restaurant. Just prior to hospital admission, he started to report left elbow soreness, where a clean scratch from his desktop 10 days earlier was healing.

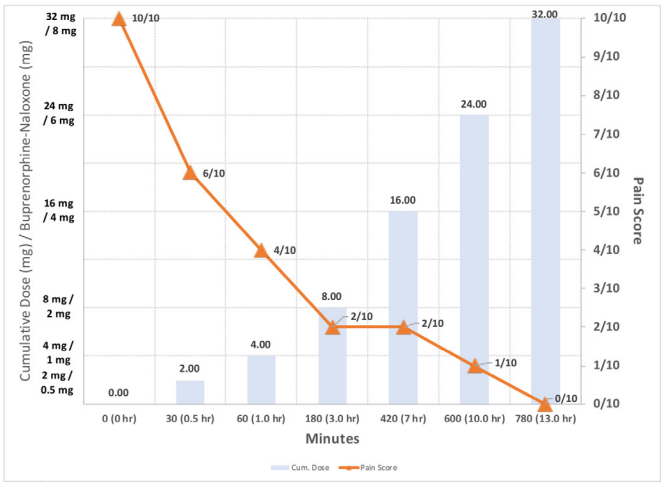

Figure 1 Induction sequence with buprenorphine/naloxone and pain scores for phantom limb pain of left upper extremity.

Surgical wound exploration revealed a polymicrobial necrotising fasciitis of pseudomonas species (by DNA PCR) and Streptococcus A pyogenes (intraoperative gram stain, DNA PCR). He received a left arm disarticulation/amputation to provide source control of the Streptococcus A infection as well as multiple antibiotics to control the severe sepsis. The working diagnosis was marine toxin (pseudomonas sp) ingestion (second most common bacteria in oysters next to Vibrio vulnificus) from raw old oysters causing sepsis, followed by severe immune-depressing consequences, causing a local pre-existing elbow wound with Streptococcus A to expand rapidly and cause a secondary infection. The patient survived and was discharged 1 month later.

Following his amputation, the neuropathic phantom pain began as burning, cramping and electrical shocks in the phantom hand and peaked at 8–10/10 daily.

The medications of greatest efficacy were the hydromorphone combined with ketamine, but the escalating doses of ketamine orally reached such high levels that the pain doctors were no longer comfortable prescribing this as an outpatient. Fear of drug dependence and tolerance grew. Despite every intervention, the phantom pain persisted. Treatments that were used included: (1) escalating opioids (Norco, oxycodone, hydromorphone 24–40 mg/day (160–280 MME oral morphine) orally, intravenous), adjuvant medications, (2) gabapentin 1200 mg orally three times a day, pregabalin, muscle relaxants, (3) antidepressants (Effexor, Cymbalta), local anaesthetics, (4) lidocaine (patches, intravenous), mexiletine, (5) ketamine (intravenous inpatient 0.5 mg/kg/hour for 5–7 days, sublingual, oral 400–600 mg per day), (6)TENS unit, (7) temporary implantable peripheral nerve stimulator in the interscalene region x 30 days,[12] (8) regional anaesthesia with catheter and ropivacaine local anaesthetic (successful once, failure once) and (9) cannabinoid oil oral and vaporised. In the second year, he was hospitalised five times as the pain transformed and escalated.

Because he planned future arm reconstruction requiring nerve preservation, more invasive treatments for phantom pain such as cryoneurolysis[13] and spinal cord stimulators were not options.

Hospitalised three times in 6 months, he received intravenous ketamine and hydromorphone, which provided short-lived improvements and then failed when he was discharged to outpatient maintenance. At this time, his drug regimen consisted of: (1) hydromorphone 24–40 mg orally per day (160–280 MME oral morphine per day), (2) ketamine 300–600 mg orally per day, (3) Effexor daily and (4) mexiletine orally per day. Pain was still 8-10/10 day and night. Exhausted and desperate the patient and providers were lost. The providers suggested psychoactive tetrahydrocannabinol cannabinoids and magic mushrooms. These drugs were not an option for the executive as he travelled internationally where these drugs were not legal.

Patient (Health Insurance Portability and Accountability Act of the USA) consent was obtained.

Treatment

At this point, the patient and his wife decided to seek help from a private addiction medicine/emergency medicine physician specialist hoping to try some other longer acting opioids and possibly wean the hydromorphone and ketamine. This doctor prescribed sublingual buprenorphine/naloxone (Suboxone) over a day and stopped hydromorphone, ketamine, antidepressants and all other adjuvant medications. He titrated it over a day to 24–32 mg buprenorphine per day (see figure 1).

The induction sequence with buprenorphine/naloxone sublingual (Suboxone) strips was:

1. Stopped hydromorphone last dose by 10 pm the night before and did not administer any for 12 hours. The patient arrived in opioid withdrawal, as expected.
2. After12 hours buprenorphine/naloxone sublingual strips in outpatient office setting is initiated .
   a. Gave 2 mg buprenorphine/0.5 mg naloxone, waited 30 min, pain score was from 10/10 to 6/10
   b. Gave an additional 2 mg buprenorphine/0.5 mg naloxone, waited 30 min, pain score was from 6/10 to 4/10. Total buprenorphine 4 mg at 1 hour. Withdrawal symptoms were subsided.
   c. Gave an additional 4 mg buprenorphine/1 mg naloxone, waited 1–2 hours, pain score was from 4/10 to 2/10.
   d. Gave an additional 8 mg buprenorphine/2 mg naloxone, waited 2–4 hours, pain score 2/10 to 2/10. Total buprenorphine now 16 mg.
   e. Gave an additional 8 mg buprenorphine/2 mg naloxone. Waited 2–4 hours, pain score was from 2/10 to 1/10. Total buprenorphine now was 24 mg.
   f. Gave an additional 8 mg buprenorphine/2 mg naloxone. Waited 2–4 hours, pain score was from 1/10 to 0/10. Total buprenorphine now 32 mg/day.

At 32 mg buprenorphine/8 mg naloxone sublingual, the patient's opioid receptors will be 85% occupied by the long-acting opioid.[9] No need to escalate the dose as this is the maximum dose administered to both addiction patients and chronic pain patients. It is also the maximum dose per day dispensed and covered by insurance as an outpatient prescription.

Outcome and follow-up

That day, the patient's pain decreased from 10/10 to 0-2/10 over 12 hours and has remained at 0–2/10 per day for 10 months. Unpredictably, the phantom pain surges will occur to 4/10 on occasion with psychological stress, prolonged physical exertion or sleep deprivation. He had his oral ketamine for breakthrough (ketamine 100 mg orally per dose) but only had to use it three times in the first 3 months. The patient's mood is improved, sleep is corrected, and he is working in his profession! He is very technologically savvy and uses all known devices and software to overcome his disability. He has travelled to and from Asia independently successfully without incident. His medication is legal and covered by insurance. Without question, his doctors and family are thrilled and grateful for his response to buprenorphine/

naloxone. The future will hold many more operations for reconstruction and a smart robotic myoelectric prosthetic that will be the first of its kind. There will also likely be perioperative pain management challenges ahead. Once completed, the plan is to wean the buprenorphine/naloxone down to the minimum amount necessary for phantom pain control. The myoelectric prosthetic itself will provide electrical afferent input to the brain via the brachial plexus and in itself relieve some of the peripheral component of his phantom pain.

DISCUSSION

Severe opioid refractory neuropathic phantom limb pain may require doses of buprenorphine not typically used to manage chronic nonmalignant pain as an outpatient. The phantom limb pain coupled with opioid tolerance, opioid-induced hyperalgesia and drug dependence may require buprenorphine doses typically used in opioid use disorder/addiction management.[14 15] Opioid-induced hyperalgesia can be reduced by the anti-kappa receptor effects unique to buprenorphine and its resultant decreases in spinal dynorphin.[15] Spinal dynorphin is typically upregulated and mu opioid receptors are downregulated by large doses of pure mu opioid agonists.[15]

Managing phantom pain may be described as shooting at a moving target. The overall pain experience has multiple points of input: (1) 'deafferentation of the severed peripheral nerve' (growth of a stump neuroma from the injured axons can result in random electrical discharges and upregulation of Na^+ channels), (2) 'central spinal cord sensitisation and hyperexcitability' (permanent synaptic changes in the dorsal root ganglion can cause this via the NMDA receptor, OR-L1 receptor, destruction of inhibitory spinal interneurons, downregulation of mu opioid receptors and 'opioid-induced hyperalgesia' via upregulation of spinal dynorphin) and (3) 'central brain functional and structural changes' (reorganisation of the primary somatosensory cortex).[5] As these pathologic pain targets work in orchestra, it may be challenging to hit each target accurately while the phantom pain evolves in a single patient. Thus, the generic approach to treating phantom pain with multimodal analgesics for neuropathic pain may fail depending on which aspect of the pain is most prominent (peripheral, central spinal and central brain) at any point of time. The authors think that the central spinal component of this patient's phantom pain was the most prominent at his treatment failure point. Intravenous ketamine bolus of 1 mg/kg over 30 min was able to eliminate the phantom limb pain in our patient from 10/10 to 0/10, but the effects were time limited to 8–12 hours and were not reproducible as an outpatient. Therapy must be individualised and changed over time.

Buprenorphine/naloxone sublingual film appears to be a more ideal drug for severe opioid resistant phantom limb pain as compared with a pure mu opioid receptor drug (hydromorphone) due to its multimodal mechanism of action.[7 16] A combined mu opioid agonist-antagonist, kappa-antagonist, delta-antagonist, it is USA Food and Drug Administration approved for opioid dependence detoxification and used 'off label' for chronic pain.[17] Buprenorphine has 30 times the potency of morphine, long duration of action (6–8 hours), euphoric effects that plateau and ceiling effects on respiratory depression. Although pain doctors do not need a special Drug Enforcement Administration (DEA) waiver to prescribe buprenorphine, prescribing physicians of buprenorphine/naloxone (Suboxone) need a DATA 2000 DEA waiver along with additional Continuing Medical Education training in addiction medicine. Thus, it is evident that buprenorphine/naloxone is an underutilised but incredibly useful treatment as it sits on the interface between specialties: addiction medicine and pain management. The potent, long-acting mu receptor binding results in its antihyperalgesic opioid effects.[18] Its kappa-antagonist effect improves accompanying

Patient's perspective

If there is a fate worse than death, it is living with agonising chronic neuropathic pain that reminds you day and night of the fateful day when you became unwell.

This was my experience of the phantom limb pain that came on a number of days after my arm was taken from me in exchange for my life 3 years ago.

For 2 days after eating raw oysters at a 5-star restaurant on the Pacific West Coast of USA, I suffered from food poisoning symptoms including diarrhoea and fever. Then, while starting to get better, I suddenly got worse and went to the hospital following a fainting spell. On arrival, I was diagnosed with septic shock unresponsive to fluids and drugs. My elbow became sore while at the hospital where I had a small scratch 10 days before. Then, I went to surgery in order to investigate the elbow pain and came out to critical care without my left arm. I remember nothing for a number of days until I awoke alive and in disbelief of what had happened. I had ingested a marine toxin via the raw oysters called pseudomonas and then developed a Group A Strep Pyogenes secondary bacterial infection in my arm due to the immunosuppression by the pseudomonas bacteria gram-negative sepsis. This was discovered on DNA PCR 16s genetic testing.

I spent the next 2 years battling the phantom pain in my arm which progressively escalated to 8-10/10 day and night. My doctor had me on every pain medication and adjuvant pain medication in addition to a peripheral nerve stimulator and regional nerve blocks. As my pain intensified and evolved it was crampy, electrical, crushing and burning. It was so severe I could think of nothing but pain relief. Oral hydromorphone became ineffective and ketamine doses increased providing only temporary relief. I had to stop my high gabapentin dose (1200 mg three times per day) due to severe ringing in my ears. Oral ketamine at 600 mg per day gave me bladder spasms and blood in my urine. I was in and out of the ER and hospital for pain surges and need for intravenous pain medication. I rarely slept but was always in bed. I planned reconstruction of my arm, so any invasive nerve treatments were not an option and reconstruction was also not an option until the phantom pain subsided. I was at an impasse.

Then a specialist doctor tried buprenorphine /naloxone (Suboxone) and in 1 day he transitioned me to one drug plus ketamine for breakthrough pain. I stopped hydromorphone, regular oral ketamine, pregabalin, mexiletine, duloxetine, Effexor and a peripheral nerve stimulator. Suddenly, I stopped sweating, crying and using daily ketamine. I started to sleep peacefully, my mood improved, and I began working again 8–10 hours per day without napping. I got my life back! My wife says I am not irritable and angry, and my kids want to play with me. This effect has been sustained for 10 months and I only had to take my ketamine three times in the first 3 months for pain surges. I am forever grateful and thankful for my response to buprenorphine/naloxone. I am so thankful to all the doctors and my family for accompanying me on my unexpected journey thus far. In future, I hope to be fortunate during the surgeries required for my new myoelectric 'smart' prosthetic arm.

Learning points

- Phantom limb pain is a complex neuropathic pain disease composed of peripheral nerve and central (spinal cord and brain) components that evolve over time. Many treatments seldom relieve pain more than placebo.
- Early institution of buprenorphine in the neuropathic pain cocktail may be a better choice than a pure mu opioid receptor agonist like morphine or hydromorphone. This might prevent 'opioid-induced hyperalgesia' and decrease the daily requirement of buprenorphine needed to successfully manage the phantom limb pain. Patients do not need to fail pure mu opioid treatment to benefit from buprenorphine. If the patient's morphine milligram equivalents of oral morphine are more than 160 mg per day, then buprenorphine/naloxone sublingual may be a safer and more potent formulation for outpatient phantom limb pain management.
- The pharmacology of buprenorphine (multimodal mechanism of action): (1) partial mu opioid receptor agonist/antagonist, (2) kappa receptor antagonist (3) delta receptor antagonist and (4) opioid receptor-like 1 (OR-L1) agonist may make it an ideal opioid for phantom limb pain treatment. Also, it may allow the patient to take fewer medications with more favourable results and less side effects.
- Buprenorphine/naloxone sublingual, well known in the addiction medicine world, is now permeating the chronic pain world. Anaesthesia physicians as well as perioperative physicians should understand the special drug considerations of buprenorphine/naloxone (Suboxone) and anaesthetics.

depression,[19] mood disorder, chronic sleep deprivation and consequent cognitive effects. It's anti-kappa effects and OR-L1 receptor effects at the central spinal cord level are likely critical in phantom pain management and prevention of opioid induced hyperalgesia. Intravenous ketamine, an NMDA receptor antagonist, is well known to be extremely effective in phantom pain treatment, but it is not useful for outpatient management.[20] Oral ketamine has only a 15%–30% efficacy as compared with the intravenous dose. Intravenous ketamine can cause psychosis at larger cumulative doses and should be used cautiously with other central nervous system stimulants like lidocaine and gabapentin.

The naloxone component of the drug duo is there to deter the addicted user from dissolving the buprenorphine and naloxone and injecting it intavenous to get a 'high'. When taken sublingual or orally, naloxone has no effect.[7]

A recently published case series in the military literature describes a similar effect of buprenorphine/naloxone rescue for patients having one or multiple limb amputations following blast injuries and severe opioid refractory phantom limb pain.[7]

Thus, some phantom pain can be treated and maintained with buprenorphine/naloxone alone. It can be weaned to a minimum effective dose; however, the phantom pain may return when it is discontinued. Occasionally, the patient may need future surgeries, which may require that the dose of buprenorphine be adjusted prior to larger operations to open up the mu receptors in the perioperative period.[18] Then, buprenorphine/naloxone can be increased and reinstated in the recovery/discharge period in consultation with the buprenorphine prescribing physician.[21 22]

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REFERENCES

1 Arias Vázquez PI, Castillo Avila RG, Dominguez Zentella MDC, *et al*. Prevalence and correlations between suicide attempt, depression, substance use, and functionality among patients with limb amputations. *Int J Rehabil Res* 2018;41:52–6. Vol.
2 Gudin J, Fudin J. A narrative pharmacological review of buprenorphine: a unique opioid for the treatment of chronic pain. *Pain Ther* 2020;9:41–54.
3 Jensen TS, Nikolajsen L. Phantom pain and other phenomena after amputation. In: Wall PD, Melzack RA, eds. *Textbook of Pain*. *4*th Ed.. Edinburgh: Churchill Livingstone, 1999: 799–814.
4 Ketz AK. The experience of phantom limb pain in patients with combat-related traumatic amputations. *Arch Phys Med Rehabil* 2008;89:1127–32.
5 Flor H. Phantom-Limb pain: characteristics, causes, and treatment. *Lancet Neurol* 2002;1:182–9.
6 Sherman RA, Sherman CJ, Gall NG. A survey of current phantom limb pain treatment in the United States. *Pain* 1980;8:85–9.
7 Licina L, Hamsher C, Lautenschager K, *et al*. Buprenorphine/naloxone therapy for opioid refractory neuropathic pain following traumatic amputation: a case series. *Mil Med* 2013;178:e858.
8 Alviar MJM, Hale T, Dungca M. Pharmacologic interventions for treating phantom limb pain. *Cochrane Database Syst Rev* 2016;10:CD006380.
9 Webster L, Gudin J, Raffa RB, *et al*. Understanding buprenorphine for use in chronic pain: expert opinion. *Pain Med* 2020;21:714–23.
10 Purdue Pharma LP. *Butrans (buprenorphine transdermal system) [package insert]*. Stamford CT, 2019Oct.
11 BioDelivery Sciences International Inc. *Belbuca (buprenorphine buccal film) [prescribing information]*. Raleigh, NC, 2019December.
12 Gilmore CA, Ilfeld BM, Rosenow JM, *et al*. Percutaneous 60-day peripheral nerve stimulation implant provides sustained relief of chronic pain following amputation: 12-month follow-up of a randomized, double-blind, placebo-controlled trial. *Reg Anesth Pain Med* 2019;0:1–8.
13 Gabriel RA, Finneran JJ IV, Trescot AM. Ultrasound-Guided percutaneous Cryoneurolysis for postoperative analgesia after limb amputation: a case series. *A&A Practice* 2019;12:231–4.
14 Fishman MA, Kim PS. Buprenorphine for chronic pain: a systemic review. *Current Pain and Headache Reports* 2018;22:83.
15 Chen KY, Chen L, Mao J. Buprenorphine-Naloxone therapy in pain management. *Anesthesiology* 2014;120:1262–74.
16 Omote K, Ohmori H, Kawamata M. Intrathecal buprenorphine in the treatment of phantom limb pain. *Anesth Analg* 1995;80:1030–2.
17 Heit HA, Gourlay DL. Buprenorphine: new tricks with an old molecule for pain management. *Clin J Pain* 2008;24:93–7.
18 Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Ann Inter Med* 2006;144:127–34.
19 Lalanne L, Ayranci G, Kieffer BL. The kappa opioid receptor: from addiction to depression, and back. *Front Psychiatry* 2014;5:170.
20 Nikolajsen L, Hansen CL, Nielsen J. The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input. *Pain* 1996;67:69–77.
21 Anderson TA, Quaye A, Ward E. To stop or not, that is the question: acute pain management for the patient on chronic buprenorphine. *Anesthesiology* 2017;126:1180–6.
22 Rudolf GD. Buprenorphine in the treatment of chronic pain. *Phys Med Rehabil Clin N Am* 2020;31:195–204.