

# Transdermal Buprenorphine for Treating Nociceptive and Neuropathic Pain: Four Case Studies

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The use of opioids for treating neuropathic pain is controversial, and some studies have indicated that neuropathic pain may be relatively insensitive to typical  $\mu$ -opioid analgesics such as morphine. However, it is becoming clear that different opioids produce analgesia by affecting different pain pathways. We present two cases of neuropathic pain and two cases

of nociceptive pain with a significant neuropathic component that were treated with transdermal buprenorphine. In each case, sufficient pain relief was obtained and no problems were encountered in switching from prior analgesic therapy with larger doses of other opioids.

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**N**europathic pain may be defined as lancinating, shooting, or burning pain that is poorly responsive to conventional analgesics and that often occurs in areas of altered sensation (1,2). The cause is either injury or chronic changes to peripheral or central nerve pathways. Patients often have an exaggerated sensitivity to nociceptive stimuli (hyperalgesia) or may perceive normal stimuli as painful (allodynia) (3), and the areas involved may lie outside the distribution of the affected nerve. The use of opioids in the treatment of neuropathic pain has generated intense debate (4,5). Nevertheless, there is an increasing amount of evidence that opioids are effective in peripheral and central neuropathic pain conditions (6–9). There is, however, a considerable rate of variation in response rates depending on the type of pain, the type of opioid and the route of its administration, and other patient-related factors (compliance, predisposition to side effects). Studies have indicated that neuropathic pain may be relatively insensitive to typical  $\mu$ -opioid analgesics such as morphine (10). Inconsistencies in the professional literature may be related to the lack of well-conducted prospective clinical trials.

Buprenorphine is a long-acting opioid with both agonist and antagonist properties. It binds to  $\mu$ -opioid,  $\kappa$ -opioid,  $\delta$ -opioid, and nociceptin (ORL-1)

receptors. Its actions at these receptors have not been completely characterized, but buprenorphine is regarded as a partial agonist at  $\mu$ -opioid and as antagonist at  $\kappa$ -opioid and  $\delta$ -opioid receptors (11).

McCormack (12) argued that because of the manner by which buprenorphine interferes with signal transduction processes in neuropathic pain, buprenorphine may be one of the most promising opioids for the treatment of neuropathic pain. In rats with peripheral nerve or spinal cord injury, systemic buprenorphine markedly alleviated neuropathic pain-related behaviors, including mechanical and cold allodynia and hyperalgesia, at doses which were comparable to those producing antinociception (13). In a double-blind, randomized study, long-term neuropathic pain which developed in patients after thoracotomy was adequately controlled by IV buprenorphine, although the dose was significantly larger than that required to relieve short-term postoperative pain (14). Intrathecal buprenorphine has also been shown to produce complete and long-lasting relief from pain in patients suffering from postamputation phantom limb pain (15).

We present two cases of neuropathic pain and two cases of nociceptive pain with a significant neuropathic component in which patients were treated with the new transdermal formulation (TDS) of buprenorphine (16). In each case, TDS buprenorphine provided sufficient relief from pain. No problems were encountered in switching from prior analgesic therapy with other opioids. Furthermore, compared with previous opioid use, dose reductions of up to 30% were achieved without any limitation in analgesic efficacy, but the incidence and severity of side

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effects were reduced and patient safety and comfort were enhanced.

## Case Reports

### Case 1

An 83-yr-old man presented with peripheral arterial occlusive disease in his left leg. Three years earlier he had undergone aorto-femoral bypass surgery, but for 2 yr he had complained of burning pain in the sole and toes of his left foot. The diagnosis was neuropathic pain. His analgesic therapy at that time included transdermal fentanyl (TTS) 75  $\mu\text{g}/\text{h}$ , dexibuprofen, and diclofenac extended release as required, plus a combination product of acetaminophen 250 mg and propyphenazon 250 mg and caffeine 50 mg on demand. This regimen provided effective pain relief; on a visual analog 10 cm continuous self-rating (VAS) scale (0 = no pain and 10 = the worst possible pain), the patient scored his pain as 2. However, since commencing therapy with fentanyl TTS, he had experienced hyperhidrosis (excessive sweating), which he described as intolerable.

After efforts to treat the patient's sweating with sage tea had failed, therapy was switched from fentanyl to hydromorphone extended release (8 mg twice daily) plus immediate release hydromorphone (2.6 mg) for breakthrough pain, with slow release amitriptyline (25 mg) in the evening. His sweating was reduced, but 1 wk later his pain worsened and it was necessary to increase the dose of hydromorphone to 12 mg twice daily. Hyperhidrosis returned to previous levels and the VAS score increased to 5–6 of 10.

Two weeks later, because of the side effects and unsatisfactory pain relief, the patient's therapy was changed again to buprenorphine TDS. We chose buprenorphine because it is a safe and potent analgesic, and we knew from previous experience that sweating is notably reduced, although not completely abolished, with buprenorphine. In addition, its new transdermal formulation offers the attractive possibility to reduce the overall amount of oral medication. We therefore provided the patient with buprenorphine TDS (70  $\mu\text{g}/\text{h}$ ) and sublingual buprenorphine (0.2 mg) as required. The evening dose of amitriptyline was retained and it was recommended that the patient apply capsaicin ointment locally. Three days later he experienced very good pain relief; the VAS pain intensity score decreased to 2 of 10, and sweating had diminished by 25% according to his subjective reporting and observation by the physician. After another 2 wk, pain was experienced only at night. Although sweating did not completely disappear, it decreased by 70% after a period of 4 mo. The patient has now been maintained on this regimen for 2 yr. Sweating remains at 30% of the previous level, and he has had no other side effects. In addition to buprenorphine TDS and amitriptyline, he takes one sublingual buprenorphine tablet (0.2 mg) approximately once every 6 days.

In summary, TDS buprenorphine led to good therapeutic success in this case of neuropathic pain and showed a favorable side effect profile. By changing from other opioids to buprenorphine TDS, it was possible to reduce the dose by 30% according to currently used conversion tables (in this case reduction from fentanyl TTS 75  $\mu\text{g}/\text{h}$  in premedication therapy to buprenorphine TDS 70  $\mu\text{g}/\text{h}$ ).

### Case 2

A 57-yr-old female with right side, third branch trigeminal neuralgia had a history of poorly controlled pain. After conventional treatment had failed, microvascular decompression of the trigeminal nerve (17) was performed and she remained pain-free for 3 mo, after which her pain returned. She described the pain as having a lancinating quality and it persisted episodically for 2–3 h at a time. Two years later, thermocoagulation of the Gasserian ganglion (17) was performed twice but brought only weak pain relief. Two months after the second thermocoagulation, the patient had experienced further episodes of pain and was referred to the pain unit. Severe pain could be elicited by eating, chewing, or touching; on a VAS the patient scored her pain as 7–8 of 10. At this point she was receiving 15 mL of liquid carbamazepine (300 mg) 4 times daily, amitriptyline extended release (25 mg) in the evening, gabapentin (300 mg) twice daily, and fentanyl TTS (25  $\mu\text{g}/\text{h}$ ).

A ganglion-specific local opioid application was performed by administering buprenorphine (0.6 mg) directly to the superior cervical ganglion (18). This intervention eliminated the patient's pain for 2 days. Over the next month she underwent 10 further ganglion-specific local opioid applications and her family doctor increased the dose of fentanyl TTS to 75  $\mu\text{g}/\text{h}$ . This resulted in 90% pain relief, enabling the patient to eat and speak normally, but episodes of persistent burning pain still occurred. Four months later, only one ganglion-specific local opioid application per month was necessary and the dose of gabapentin was changed to 600 mg in the morning, 300 mg at noon, and 600 mg in the evening. Carbamazepine was discontinued.

After another 4 mo fentanyl TTS (75  $\mu\text{g}/\text{h}$ ) was switched to buprenorphine TDS (35  $\mu\text{g}/\text{h}$ ) because of intermittent pain attacks of a burning character. The gabapentin medication scheme was maintained. No withdrawal symptoms were observed after the change of opioid. Three days later, the patient experienced a profound improvement in her condition. Since then she has had no episodic pain and rates the pain experienced as VAS 2 of 10. In this patient, opioids were effective in controlling persistent, lancinating neuropathic pain. A change from fentanyl to buprenorphine allowed a dose reduction in the sense of equipotency. There were no problems encountered in switching directly from fentanyl to buprenorphine.

### Case 3

A 49-yr-old woman had suffered for 6–7 yr from stabbing, tearing, burning pain in her small finger joints, shoulder, neck, hip, knee joints, spine, and cervical vertebrae, the latter of which radiated into her arms and was independent of physical strain or the time of day. The diagnosis was nociceptive pain with neuropathic components, psoriatic arthropathy, and prolapsed intervertebral discs at C5-6. Her medications consisted of dihydrocodeine (90 mg twice daily), paroxetine (20 mg), mianserin (30 mg), and flunitrazepam (2 mg), as well as IV infusions with non-opioid analgesics and muscle relaxants, and physiotherapy. Despite this regimen, she rated her pain at VAS 8–10.

On referral to the pain clinic she was prescribed slow release tramadol (150 mg, twice daily), tramadol drops (20 drops/50 mg) as required for breakthrough pain, naproxen (550 mg twice daily), and amitriptyline (25 mg) instead of mianserin. Flunitrazepam was discontinued.

Drug therapy was supplemented by biofeedback therapy and acupuncture. Pain relief was satisfactory after 2 mo, as indicated by a VAS of 3–4/10, but a year later this had increased to 7 of 10 again. Therefore, diclofenac 75 mg/cyprostitol 200  $\mu$ g twice daily was added to her medication because she had experienced gastrointestinal side effects. Furthermore, the tramadol extended release dose was increased to 150 mg in the morning and 300 mg in the evening, tramadol drops (20 drops/50 mg) for pain attacks and paroxetine (20 mg) were maintained, and the dose of amitriptyline was increased to 50 mg. This regimen provided the patient with satisfactory pain relief (VAS 3–4 of 10).

Six months later the patient relapsed again and her pain increased to VAS 7 of 10. A morphine test was performed with IV morphine (50 mg in 500 mL vehicle, infused at 240 mL/h). As the patient's pain score became worse (VAS 9 of 10), a buprenorphine test was performed with a buprenorphine dose of 1.5 mg per 500 mL NaCl and an infusion rate of 240 mL/h. As the pain score decreased from VAS 7 to 3, the patient was provided with buprenorphine TDS 70  $\mu$ g/h, supplemented by sublingual buprenorphine (0.2 mg) on demand, biofeedback, and transcutaneous electrical nerve stimulation. Two weeks later, the VAS decreased to 3 of 10 and the patient experienced satisfactory pain relief, but, as the burning component of her pain continued, the dose of amitriptyline was increased to 100 mg. Effective pain relief was finally achieved with the following therapy: diclofenac 75 mg/cyprostitol 200  $\mu$ g twice daily, paroxetine (20 mg), amitriptyline (100 mg), buprenorphine TDS (70  $\mu$ g/h), and sublingual buprenorphine (0.4 mg, 1–2 tablets per day). Transcutaneous electrical nerve stimulation therapy was also successful. The patient has not experienced any opioid-specific side effects. This case illustrates the importance of opioid testing to determine the correct opioid for the individual patient and pain condition. It further demonstrates that different opioids act differently in individual patients, with buprenorphine being a valuable therapeutic option in nociceptive and neuropathic pain.

#### Case 4

A 38-yr-old woman presented with postlaminectomy syndrome after a left laminotomy at L4-5 in 1979 and a laminectomy at L5-S1 and a discectomy at L4-5 in 1980, also on the left side. Spondylodesis stabilization had been performed on the lumbar spine in 1980, followed by plate removal in 1987. She was suffering from cervical and lumbar pain and, since 1994, had experienced burning pain radiating to both legs, which she rated at 5–6 on a 10-cm VAS. Computer axial tomography revealed osteochondrosis at C4-7, but no evidence of a recent disk lesion, and spondylodesis at L3 to S1 after the laminotomy. A peridural surgical scar could be seen on the left side at L5 and lumbosacral disk degeneration was present. For the previous 6 mo she had been taking dihydrocodeine (120 mg twice daily). Other treatments included physiotherapy, neural blockade, and infusion therapy.

In June 1998, the patient was enrolled in the preliminary phase of a clinical trial of buprenorphine TDS. For the next week she received sublingual buprenorphine (mean daily dose 1.2 mg) and sustained release amitriptyline (25 mg). She was then randomized into the placebo group for 2 patch cycles (6 days). Good pain relief was achieved with sublingual buprenorphine (5–6 tablets of 0.2 mg per day). On being enrolled into the 5-mo follow-up study the patient

received buprenorphine TDS (35  $\mu$ g/h, equivalent to a daily dose of 0.8 mg) and was very satisfied with the level of analgesia obtained. Her overall quality of life was much improved by the reduction in pain, longer periods of sleep, lack of side effects, and ease of use of the TDS patches.

#### Discussion

Buprenorphine is a semi-synthetic, highly lipophilic opioid that is derived from thebaine. *In vitro* data characterize buprenorphine as a partial agonist at the  $\mu$ -opioid receptors and as an antagonist at the  $\delta$ - and kappa receptors (11,19,20). The systemic potency of buprenorphine is 20–40 times that of morphine (21,22). *In vivo*, when the measured response is analgesia, it has been shown to behave as a full agonist in the analgesic dose range, with the ability to induce long-lasting analgesia (23). The longer duration of analgesia produced by buprenorphine compared with other lipophilic opioids is attributed to its high affinity for the  $\mu$ -opioid receptor (24).

As mentioned earlier, different opioids induce analgesia within different pathways (12). In a new paradigm of centrally-originating neuropathic pain, the intrathecal administration of the toxin produced by *Bordetella pertussis* bacteria (PTX) alters receptor binding affinity, causing hyperalgesia and allodynia that appear similar to the symptoms reported by patients suffering from neuropathic pain. In animal studies, the antinociceptive action of opioids in this model was attenuated by PTX, with the exception of buprenorphine (25–27). In addition to the induction of PTX-insensitive analgesia, buprenorphine also demonstrates atypical receptor binding (28), is uniquely sensitive to the effects of adenosine triphosphate-sensitive potassium channel openers and blockers (29), and is significantly more potent than other opioids in the rat neonate formalin test (30). These findings support the existence of a mechanistically discrete pain transmission pathway for buprenorphine analgesia that is not accessible to other opioids and that may prove to be of considerable therapeutic importance.

The physico-chemical properties of buprenorphine make it an ideal candidate for transdermal delivery: it is highly lipophilic, has a low molecular weight, and its high potency means that only 1–2 mg per day are required for therapeutic efficacy. The recently introduced buprenorphine TDS uses a matrix-type patch. The drug is homogeneously incorporated into an adhesive polymer matrix that also controls its release by a matrix diffusion system, with the backing layer acting as an occluding foil. Release of the drug does not depend on a rate-controlling membrane, as in reservoir-type patches, so in the case of damage to the patch there is no risk of excessive overdose, or "dose-dumping." Three different release rates are

available (35  $\mu\text{g/h}$ , 52.5  $\mu\text{g/h}$ , and 70  $\mu\text{g/h}$ ), achieved simply by increasing the active area of the patch, with each providing a steady plasma concentration for 3 days.

The case reports presented here demonstrate the therapeutic success of buprenorphine TDS in two cases of neuropathic pain and two cases of nociceptive pain with a neuropathic component. Patients experienced long-lasting pain relief, pain intensity was reduced as measured by self-rating scales, and breakthrough pain episodes were fewer. All four patients had previously received other opioids (hydromorphone, fentanyl, tramadol, or dihydrocodeine) and the switch to buprenorphine was uncomplicated and did not produce any withdrawal symptoms. This confirms the findings of a clinical trial on buprenorphine TDS where it was applied after tramadol and morphine (16). In fact, withdrawal symptoms precipitated by buprenorphine are not to be expected in the clinical setting, as buprenorphine behaves as a full  $\mu$  agonist at smaller dosages (23,31,32), which were also used in the present cases (from 0.8 to maximal 2.8 mg) and which correspond to the analgesic dose range of buprenorphine (0.1–10 mg). In other words, although buprenorphine might replace other opioids from  $\mu$ -opioid receptors because of its higher affinity, in the doses used for analgesia, it exerts  $\mu$ -agonistic intrinsic activity just like the full  $\mu$  agonists morphine or fentanyl.

Remarkably, the effective dosages of buprenorphine used were in each case smaller as per current equipotency tables. This might also have an impact on the safety of the compound. In fact, in the present cases, patients did not experience opioid-specific side effects such as nausea, vomiting, constipation, or drowsiness. Of course, it should be kept in mind that the patients presented here were not opioid-naïve patients and they probably had already adapted to opioid-specific side effects.

Initiating treatment with buprenorphine TDS was simply a case of applying the patch to an area of dry, nonirritated skin on the upper torso, making it easy for the patients to manage while avoiding unpleasant invasive procedures.

In conclusion, buprenorphine TDS was effective in cases of neuropathic pain or in pain having a strong neuropathic component when other opioids failed. Furthermore, patients were satisfied with buprenorphine TDS and compliance to therapy was good. It is hoped that the promising results from these case reports will stimulate further research into the use of buprenorphine TDS in the treatment of neuropathic pain. There is a need for randomized controlled trials with longer follow-up times and larger and more homogenous cohorts of patients suffering from neuropathic pain.

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