

Case Report

Methadone for Phantom Limb Pain

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Abstract:

Objective: The objective of this case series was to determine if severe phantom limb pain could be reduced with oral methadone.

Design: Four cases of phantom limb pain refractory to multiple treatment modalities were treated with oral methadone.

Setting: Pain clinic at a major university medical center.

Patients: Four patients with severe, intractable phantom limb pain.

Intervention: Oral methadone was administered, starting with a low dose of 2 to 5 mg twice a day or three times a day and slowly titrated upward to achieve pain relief.

Outcome Measures: Repeated administration of a visual analog scale for pain.

Results and Conclusions: Administration of oral methadone may be of value in the treatment of phantom limb pain; controlled clinical trials would be appropriate to verify this observation.

Key Words: Methadone—Phantom limb pain.

Phantom limb pain is referred neuropathic pain perceived to arise from the part of the body that was amputated. The mechanisms of phantom limb pain remain unknown; both peripheral and central factors seem to be important. Recently, Flor et al. postulated that a somatosensory pain memory and altered homonuclear structure in the somatosensory cortex may underlie phantom limb pain and that peripheral factors may sustain this memory.¹ Suggested therapies include administration of pharmacological agents (e.g., antidepressive drugs, anti-epileptic drugs, and calcitonin), behavioral interventions, transcutaneous electrical nerve stimulation, invasive techniques (e.g., epidural blockade, sympathectomies, dorsal root entry zone lesion, spinal cord stimulation, and motor cortex stimulation), and even electroconvulsive therapy.²⁻⁵ In a significant percentage of amputees, ad-

equating pain relief cannot be achieved, which makes the search for an effective therapy a priority. Not one of the many published treatments for phantom limb pain has been shown convincingly to be effective,⁴ necessitating the publication of even small case series. We report here on four patients with phantom limb pain refractory to multiple treatment strategies. The patients received methadone and all reported at least adequate relief of their phantom limb pain symptoms.

CASE REPORTS

Patient 1

This patient was a 49-year-old woman who had a right above-elbow amputation due to arterial vascular occlusion of the right arm. After the amputation she suffered stump pain, which subsided within a few days. Two weeks after surgery, the patient began complaining of phantom hand pain, which she described as feeling ice-cold and cramped. This pain increased in intensity over the following months despite treatment with transcutaneous electrical nerve stimulation and medication

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(nonsteroidal antiinflammatory drugs, opioids [oral slow-release morphine], carbamazepine, amitriptyline, and calcitonin).

Therapy with oral methadone was started 6 months after amputation. At that time, the patient rated her average phantom limb pain severity on a visual analog scale (VAS) as 7/10. Two days after she began treatment with 5 mg methadone twice a day, the pain intensity decreased to a VAS score of 4/10. After 4 weeks, during which time the methadone dose was gradually increased to 7.5 mg twice a day and 10 mg as needed, she reported no pain during the day and pain with a VAS score of 4/10 in the evening. On follow-up, 4 months after the start of therapy with methadone, the patient reported the absence of pain during the day and variable pain intensity in the evening, within a VAS score range of 4 to 8/10.

Patient 2

The second patient was a 47-year-old woman who had adenocarcinoma of unknown origin, with metastases to the right femur and to the brain. Because of the metastatic cancer in her right femur, her right upper leg was amputated.

Postoperatively the patient reported mild stump pain, which lasted for 2 days. After 1 week she began having phantom leg pain. The pain was treated medically, with opioids (intramuscular nicomorphine and transdermal fentanyl), amitriptyline, carbamazepine, valproic acid, and calcitonin.

Four weeks after amputation a course of oral methadone was started. She rated her phantom limb pain intensity at 6/10 before the start of this therapy. The initial dose of oral methadone (2 mg twice a day) was gradually increased to 6 mg twice a day and 8 mg as needed over a period of 3 months. At a 3-month follow-up, the patient reported substantial relief of the phantom limb pain, which she rated at 3/10.

Patient 3

The patient was a 21-year-old man who underwent a left above-the-knee amputation because of complex regional pain syndrome type 1 of the left lower leg and foot. Two days after surgery, the patient started suffering severe phantom limb pain, rating the intensity as 9 to 10/10 on a VAS. He also reported severe stump pain, rating it as 7/10. Initially the patient was treated with nonsteroidal anti-inflammatory drugs, tramadol, opioids (intramuscular nicomorphine, oral slow-release morphine, and transdermal fentanyl), amitriptyline, and gabapentin. Two weeks after amputation, therapy with oral methadone was started at a dosage of 2 mg three times a day. Within 3 days the patient reported dimin-

ished phantom limb pain but no relief of the stump pain. The dosage of methadone was increased to 5 mg four times a day over the next few days, and after 1 week the patient rated both his phantom pain and stump pain intensity at 4/10. At this time, other opioids and gabapentin were withdrawn, and the patient's condition was maintained with a methadone dosage of 5 mg four times a day until follow-up.

On follow-up 2 months later, the patient reported a VAS pain score of 4/10 for both phantom pain and stump pain.

Patient 4

This patient was a 27-year-old woman who had a right-upper-arm amputation because of recurrent upper-arm luxation due to Ehlers-Danlos syndrome. Immediately after the amputation she suffered severe phantom hand pain, which she described as a burning and cramping sensation. Stump pain was present for only the first 4 days postoperatively.

Medical treatment of her phantom limb pain consisted of administration of nonsteroidal anti-inflammatory drugs, opioids (oral slow-release morphine and transdermal fentanyl), amitriptyline, and carbamazepine, several injections of calcitonin, and a continuous intravenous infusion of a low-dose ketamine. After 4 weeks of ketamine treatment, the patient still rated her phantom limb pain as 8/10. Ketamine was withdrawn and oral methadone (4 mg three times a day) was started. After 2 days, the patient reported pain relief. Over a period of 2 weeks, the methadone dosage was gradually increased to 10 mg four times a day. At that time the patient reported a VAS score of 3/10.

Four months later, during which time the methadone administration was continued, she rated her phantom limb pain at 5/10. An attempt to reduce the methadone dosage failed because of a subsequent increase in the severity of her phantom limb pain.

DISCUSSION

Methadone is a drug that was developed more than 40 years ago. It is now mainly used both as a maintenance drug for opioid dependence and in the treatment of pain, mostly cancer pain.⁶ Some important characteristics of methadone are its lack of known metabolites, the long and unpredictable half-life, excellent absorption after oral and rectal administration, and its low cost. Because of its unpredictable half-life, methadone must be titrated carefully for each individual to avoid overdose.

Four cases have been presented in which methadone reduced phantom limb pain. In all cases other medication, including opioids, did not result in satisfactory pain

relief. No significant methadone-related side effects were noted in the four patients, a circumstance which we attribute to the low doses and the slow titration rate.

True phantom limb pain is a neuropathic pain⁷ in which the process of central sensitization may play an important role.⁸ The *N*-methyl-D-aspartic acid (NMDA) receptor-ion channel is thought to be important in the development of central sensitization,⁹ and substances that block this receptor can be effective in the treatment of pain.¹⁰

In animal studies methadone acts as an opioid agonist as well as an NMDA-receptor antagonist,¹¹ although it is not clear that the NMDA-receptor antagonist activity has any significance.¹² Still, a synergetic action between the opioid agonist activity and NMDA-receptor antagonist activity of methadone might contribute to its effectiveness in the treatment of phantom limb pain. In this respect it is remarkable that, in patient 4, the continuous infusion of ketamine did not produce any pain relief, whereas methadone dramatically decreased the phantom limb pain from an 8/10 score to a 3/10 score.

In addition to its effects at the μ -opioid receptor and the NMDA receptor, methadone appears to inhibit serotonin reuptake.¹³ It is known that serotonin plays a role in a variety of pain syndromes. The inhibition of serotonin reuptake may therefore contribute to the analgesic effect of methadone in phantom limb pain, although we must mention that other serotonin reuptake inhibitors failed to produce pain relief in our patients.

There are several limitations to the present case series. The series was nonrandomized, uncontrolled, and unblinded, and the follow-ups were limited to between 2 and 4 months. The possibility of a placebo response cannot be ruled out, but we think this is less likely since patients had been refractory to multiple other treatments. The limited follow-up times raise the possibility that the improvements we observed reflected the natural course of phantom limb pain, because the intensity and duration of phantom limb pain episodes appear to diminish during the first year after amputation.^{14,15}

Nevertheless, prospective studies show that the incidence of phantom limb pain is between 59% and 70% 1 to 2 years after amputation,^{14,15} and cross-sectional survey studies indicate that between 78% and 85% of amputees continue to experience significant phantom limb pain more than 25 years after amputation.⁴ Phantom limb pain occurs in the majority of amputees, and an effective treatment has yet to be found. We believe it is advisable to try treatment with oral methadone before considering invasive treatments. We realize that opioid therapy for chronic noncancer pain remains controversial because of

concerns about tolerance and addiction. We suggest starting with a low dose of methadone (e.g., 2–5 mg twice a day or three times a day, depending on the severity of the pain, body weight of the patient, and history of opioid use) and slowly titrating upward until satisfactory pain relief is reached or intolerable side effects are noted.

CONCLUSIONS

Oral methadone was effective in reducing the intensity of phantom limb pain in four patients. All patients had tried a variety of other analgesic agents without effect. Given the high incidence of phantom limb pain and the immense suffering the pain engenders, it is imperative that effective treatments be found. A prospective, controlled clinical trial evaluating the efficacy of methadone for phantom limb pain and addressing the issues of tolerance and addiction would be appropriate to verify our observations.

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