

Management of Post-Amputation Pain

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ABSTRACT

INTRODUCTION: The prevalence of amputation and post-amputation pain (PAP) is rising. There are two main types of PAP: residual limb pain (RLP) and phantom limb pain (PLP), with an estimated 95% of people with amputations experiencing one or both.

MEDICAL MANAGEMENT: The majority of chronic PAP is due to phantom limb pain, which is neurogenic in nature. Common medications used include tricyclic antidepressants, gabapentin, and opioids. Newer studies are evaluating alternative drugs such as ketamine and local anesthetics.

REHABILITATION MANAGEMENT: Mirror visual feedback and cognitive behavioral therapy are often effective adjunct therapies and have minimal adverse effects.

SURGICAL MANAGEMENT: Neuromodulatory treatment and surgery for neuromas have been found to help select patients with PAP.

CONCLUSION: PAP is a complex condition with mechanisms that can be located at the residual limb, spinal cord, and brain — or a combination. This complex pain can be difficult to treat. The mainstays of treatment are largely medical, but several surgical options are also being studied.

KEYWORDS: post-amputation pain, phantom limb pain, residual limb pain, amputation

INTRODUCTION

Limb amputations cause a major physical, economic, and psychological burden to patients and can result in chronic, often debilitating post-amputation pain (PAP). The most common causes of an amputation include diabetes, peripheral vascular disease, and trauma.¹ Amputation is a common operation; the prevalence of lower extremity amputation in the United States in 2005 was 1.6 million people, with projections of 3.6 million people by 2050.² Diabetic patients have an over thirty-fold increased risk of an amputation compared to non-diabetic patients, at a cost of \$4.3 billion annually in the U.S.³ While there are many detrimental effects of amputation including post-operative surgical site

infection, the need for revision amputation, economic cost, and physical disability, one of the most debilitating results is chronic PAP. Comorbid conditions such as fibromyalgia, migraines, irritable bowel syndrome, irritable bladder, and Raynaud syndrome have all been associated with chronic PAP.⁴ The management of PAP is primarily medical, but several surgical options also exist.

PATHOPHYSIOLOGY

There are several methods to categorize PAP. Acute post-amputation limb pain lasts less than two months and chronic post-amputation limb pain lasts more than two months.⁵ Residual limb pain (RLP), often unfortunately referred to as “stump” pain, is pain at the surgical site or proximal remaining extremity. Phantom limb pain (PLP) is described as pain localized distal to the amputation level.⁶ Ephraim et al. looked at 914 patients with limb loss and found that 95% had either RLP or PLP, and there was also a significant relationship with depression symptoms.⁷

While both types of pain may coexist, RLP is most common in the acute post-operative setting, while PLP may present later and with great chronicity. RLP is due to a variety of reasons including incisional pain, scar formation, poor prosthetic fit, or neuroma formation. While RLP has a more acute onset after surgery, it also improves more over time than PLP does.⁸

PLP is usually described as burning, aching, or stabbing and it can occur in the first postoperative week in as many as 25% of patients.⁵ A study of 96 people with upper limb amputations found that there were two peaks for the development of phantom limb pain: acutely within 1 month and at 12 months after amputation.⁸ Risk factors for phantom limb pain include female sex, upper extremity amputation, presence of pre-amputation pain, residual limb pain, and time after amputation.⁹

The mechanism for PLP is thought to be due to cortical reorganization of the somatosensory cortex that serves the sensation of the amputated limb. MRI studies of patients with hand amputations have shown that the cortical area corresponding to the amputated hand is activated and influenced by forearm movements.¹⁰ Another clear mechanism of pain is from nerve damage, as treatment with lidocaine injection or nerve stimulation has been effective in certain

cases. A confounding issue with many cases of PAP is that a significant percentage of patients with amputations have underlying diabetes and diabetic neuropathy.

MANAGEMENT OF POST-AMPUTATION PAIN

Initial and General Approach

After evaluating for anatomic, vascular, infectious, or other pathologic conditions of the residual limb, nonsurgical management is the preferred initial approach to treat PAP. A wide variety of strategies have been studied for the treatment of chronic phantom limb pain. Given that chronic PLP is a type of neuropathic pain, these investigated modalities are often similar to those used to treat other neuropathic pain conditions. These range from pharmacologic, behavioral and rehabilitative therapies to nerve stimulation. The evidence for favoring one medication or modality above another is lacking, and trial data for most studies are based on small numbers of patients. Treatment decisions are often based on patient characteristics and co-morbidities such as depression, as well as side effect profiles. Coupling pharmacologic therapy with other therapies is often practiced. Here, we will review the various non-operative strategies employed for the management of PAP.

PHARMACOLOGIC TREATMENTS

Several classes of medications have been explored as possible management options in chronic phantom limb pain, including antidepressants, anticonvulsants, N-methyl-D-Aspartate (NMDA) antagonists, calcitonin, calcium channel blockers, beta blockers, and local anesthetics. (Table 1)

Antidepressants are a commonly employed class of medications for the treatment of neuropathic pain. The tricyclic antidepressant amitriptyline has been evaluated in the treatment of phantom limb pain. A placebo-controlled study did not show any improvement in analgesia after six weeks of treatment, while a 2005 study reported positive results in controlling PAP with daily amitriptyline.^{11,12} However, amitriptyline was shown to produce undesirable side effects including drowsiness and dry mouth, making it a less desirable pharmacotherapeutic.¹¹ Urinary retention and weight gain are other problematic side effects of amitriptyline. Limited case reports and case series have also documented possible benefit with the use of mirtazapine and duloxetine. The advantages of duloxetine (Cymbalta) are that it is FDA-approved for both depression and neuropathic pain which are associated with diabetes.

Gabapentin is an anticonvulsant that is often used for the management of neuropathic pain, and it has also been

Table 1. Medical options for treating post-amputation pain

Medication	Mechanism of Action	Benefit	Adverse Effects
NMDA-antagonists			
Ketamine	Blocking hyperexcitability and sensitization via NMDA-receptors	Short-term benefit	Mood derangements, hallucinations, abusable
Dextromethorphan		Possible benefit, evidence insufficient	Well-tolerated; may cause abdominal symptoms, confusion
Memantine		Possible benefit, evidence insufficient	Well-tolerated
Antidepressants			
Amitriptyline	Serotonin and norepi-nephrine reuptake inhibitor	Possible benefit	Anti-cholinergic side effects: dry mouth, sedation
Opioids			
Morphine	Opioid receptor agonist	Beneficial	Dependency, respiratory depression
Injections			
Botulinum Toxin A	Transient focal nerve blockade	Short-term benefit	Low incidence of systemic toxicity, injection site reactions
Anticonvulsants			
Gabapentin	Voltage-dependent calcium ion channel inhibition	Likely beneficial	Good safety profile; may cause sedation
Hormone			
Salmon Calcitonin	Inhibition of centrally firing neurons	Possible benefit, evidence insufficient	Good safety profile; may cause nausea, abdominal pain, diarrhea
Antihypertensives			
Nifedipine	Calcium channel blocker	Possible benefit, evidence insufficient	Hypotension, flushing, peripheral edema
Propranolol	Beta blocker		Sedation, hypotension, bradycardia
Clonidine	Alpha2-adrenergic agonist		Sedation, syncope, hypotension, rebound hypertension

employed to control pain after amputations. The current literature is mixed as to the effectiveness of gabapentin in the treatment of PAP, and it has been associated with significant side effects in this population.¹²

The misuse of opioids continues to pose a nationwide problem, but they can be a useful tool in the management of acute pain, as they blunt the somatosensory cortical reorganization that is thought to lead to the phantom limb sensation.¹¹ Opioids such as high-dose morphine sulfate have shown a positive effect in improving PAP, but patients should be made aware of the risks of opioid dependence and tolerance.^{6,13} Opioids do not represent a long-term solution for patients with PAP wishing to return to their pre-amputation lifestyles. Consequently, they are best suited for the acute management of PAP, along with stool softeners to prevent constipation. Patients should be advised of their short-term use and ideally opioids should be tapered off in the acute hospital or inpatient rehabilitation setting.

NMDA receptor antagonists evaluated for PAP include ketamine, memantine, and the over-the-counter drug dextromethorphan. These medications are thought to block the hyper-excitability and sensitization mechanisms of PAP.^{14,15} Intravenous ketamine has been shown to improve such pain in the short-term, while a small case series has also demonstrated potential benefit for the use of oral ketamine.¹⁶ It is important to note that ketamine has side effects ranging from alterations in mood to hallucinations, and it is a highly abusable drug.

Several other classes of drugs have been explored in the treatment of post-amputation and phantom limb pain. Salmon calcitonin is a hormone that reduces blood calcium levels; it has also been studied as an analgesic due to its inhibition of the central activation of neurons when they are stimulated peripherally.⁶ Reports are mixed regarding calcitonin's ability to provide adequate analgesia in the setting of PAP. Calcium channel blockers such as nifedipine, beta blockers including propranolol, clonidine (an alpha 2-adrenergic agonist), and etanercept (tumor necrosis factor-inhibitor) are other possible treatments for PAP; however, the evidence to support the use of these agents is insufficient.^{6,17}

REHABILITATIVE AND PSYCHOLOGICAL TREATMENTS

As the pathophysiology of the chronic PAP pathway is proposed to have a significant cortical component, various psychological treatment including hypnosis, biofeedback, cognitive behavioral therapy (CBT), and guided imagery have been investigated.^{6,18} Other interesting interventions include eye movement reprocessing, mirror visual feedback (MVF), and the use of virtual reality.¹⁸ Most of the literature on these topics comes from case series, and larger, long-term studies are required to better evaluate their appropriateness for this indication. They are safe and generally well-tolerated,

however, and may help certain patient populations.

MVF utilizes the contralateral intact extremity to reflect an image in a position so that the patient perceives an intact limb, which may reverse the cortical reorganization proposed as a cause of PAP. This technique has shown short-term effectiveness for pain reduction in small studies.^{6,18}

Various forms of physical therapy including massage, taping, acupuncture and ultrasound have also shown modest relief of post-amputation pain. These low-risk, non-invasive treatment options should be offered before medications and invasive approaches.¹⁸

SURGICAL TREATMENTS

In general, the evidence supporting surgical management for the treatment of chronic PAP is limited, and surgery should only be performed if conservative management has failed. There are numerous procedures described in the literature, further emphasizing the lack of consensus for surgical treatment.^{6,19-21} There are two basic types of surgical intervention, neuromodulatory and reconstructive.

Neuromodulatory procedures target maladaptive neuroplastic changes and are represented by various implantable and transcutaneous stimulators. Transcutaneous electrical stimulation (TENS) is theorized to provide pain relief after amputations by increasing blood flow, reducing muscle spasms, and activating large afferent nerves to block nociceptor neurons in the spinal cord. While small series have demonstrated its value, a recent Cochrane review study reported no appropriate studies to judge its effectiveness.²² Other possible technologies include electric nerve block devices, myoelectric prostheses, residual limb covers, and laser systems.²¹

Deep brain, motor cortex, spinal or peripheral nerve stimulators attempt to modulate the neural pathways thought to be involved in chronic phantom limb pain. There are a few randomized controlled studies supporting their outcomes. As demonstrated by Corbett et al. in their systematic review, however, the evidence at best supports short-term benefits from repetitive transcranial magnetic or direct current stimulation.¹⁹ There is limited evidence for implantable stimulators to treat chronic phantom limb pain, even though spinal cord stimulators are reimbursed by Medicare for this specific purpose.

Reconstructive options include surgery for peripheral mechanisms of pain, e.g. residual limb pain caused by neuromas or heterotopic ossification, which can occur at rates as high as 80% and 63% respectively.⁶ There are many possible procedures for neuromas, but the general consensus is that after resection, the nerve end should be protected and implanted into soft tissues. Another surgical solution that has been investigated is upper extremity targeted muscle reinnervation (TMR), which transfers amputated nerves into remaining muscles in the residual limb in order to improve

myoelectric prosthesis control. A retrospective review showed that of the 15 patients who had post-amputation neuromas prior to the TMR, 14 had complete resolution of symptoms and the remaining patient experienced partial relief.²⁰ This evidence suggests that by altering the amputated nerve environment, perhaps neuroma prevention can produce better outcomes than treatment of problems that develop.

CONCLUSION

The number of people with amputations in the United States is increasing, and non-surgical practitioners will increasingly manage their chronic, residual limb and phantom pain. Post-amputation pain encompasses multiple complex pain syndromes after the amputation of an extremity. Currently, the specific pathophysiology is not well understood and is likely multifactorial, which explains the potential benefit of numerous non-operative and operative treatments. In general, approaches to treating chronic phantom limb pain are similar to those for other types of neuropathic pain, and there is no standard of care or strong evidence to support any particular method. However, there are several promising modalities, and further research on the mechanisms of PAP is likely to yield better evidence for some current treatments and new modalities.

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