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HOT TOPICS IN PAIN AND HEADACHE (N ROSEN, SECTION EDITOR)

Treatment Strategies and Effective Management of Phantom Limb–Associated Pain

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Abstract

Purpose of Review Phantom sensations are incompletely understood phenomena which take place following an amputation or deafferentation of a limb. They can present as kinetic, kinesthetic, or exteroceptive perceptions. It is estimated that phantom limb pain (PLP) affects anywhere from 40 to 80% of amputees.

Recent Findings Psychiatric illnesses such as depression, anxiety, and mood disorders have higher prevalence in amputees than in the general population. Pharmacologic treatment has been used as first-line therapy for amputees suffering from PLP with agents including gabapentinoids, amitriptyline, and other tricyclic anti-depressants, opioids, and local anesthetics. Non-invasive treatment modalities exist for PLP including sensory motor training, mirror visual therapy, and non-invasive neuromodulation. Non-invasive neuromodulation includes interventions like transcutaneous electrical nerve stimulation (TENS) and transcranial magnetic stimulation.

Summary While many promising therapies for PLP exist, more clinical trials are required to determine the efficacy and protocols needed for maximum benefit in patients suffering from PLP.

Keywords Phantom limb · Phantom limb pain · PLP · Amputation · Pain management

Introduction

Limb amputation has been a part of medicine dating back 45,000 years ago [1•]. Its utility and prevalence have waxed and waned throughout history, becoming especially prevalent in times of war. Even today, amputation often proves the most definitive and safest option for many patients. In 2008, Ziegler-Graham et al. estimated 1 in 190 US citizens was living with limb loss and predicted that prevalence would double by 2050 [2]. Alongside the extensive history of amputation are reports of lingering pain or sensation in amputated limbs [1•].

During the American Civil war, Dr. Weir Mitchell reported an incidence as high as 90% among amputees and titled the condition "phantom limb pain" (PLP). In World War II, however, the condition's reported incidence dropped to less than 5%. This is suspected to be because of the attribution of PLP to psychiatric causes or malingering. Because of the inconsistencies of reported incidence and poor understanding of the pathophysiology itself, research on PLP has been slow to progress. At present, there has been a clearer understanding of PLP with several working theories as to mechanism coupled with more accurate reporting.

Recent studies estimate 50% of patients report PLP within the first 24 h post-amputation and 85% within 1 week [3]. This

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does not include the number of patients who report non-painful sensations associated with an amputated limb or pain derived from the stump of the amputated limb. The primary concern for PLP patients continues to be the chronic nature of the condition. The average reported pain intensity of PLP was 5.3 out of 10 with half of patients reporting an increase in intensity and half reporting no change in their pain long-term [4]. Descriptions of pain vary greatly. Some examples include cramping, burning, shooting, shocking, itching, or tingling [3, 5•].

The PLP patient population is obviously restricted to those who have undergone limb amputation. According to Ziegler-Graham et al., men have an amputation prevalence nearly twice that of women. Furthermore, 42% of patients living with limb amputations were found to be non-white and 42% were over 65 years old. These numbers are likely secondary to comorbidities ultimately necessitating amputation. Limb amputations in the USA are performed mostly secondarily to vascular disease (54%), trauma (45%), and malignancy of bone or joint (< 2%). Amputations secondary to vascular disease had a comorbidity of diabetes in roughly two-thirds of cases. Sixty-five percent of amputations reported are that of the lower extremity and more than half of those were classified as "major" (an example of minor being toe amputation). Of the upper limb, only 8% were considered major [2].

Prevention and appropriate management of conditions that predispose patients to amputation such as diabetes or vascular disease should aid in decreasing amputation and subsequently PLP incidence. Despite this, the practice of amputation and possible manifestation of PLP will continue to be prevalent, and as such cause significant detrimental impact on those affected with it. The following is a comprehensive review of phantom limb pain including patient presentation, diagnosis, pathophysiology, and treatment.

Diagnosis and Presentation

Phantom sensations are incompletely understood phenomena which take place following an amputation or deafferentation of a limb. It is specifically defined as the non-painful experience of feeling a missing limb as still present or persisting [1•, 6]. It is important to note that amputation of a body part is not an essential criterion. Phantom sensations have been reported in brachial plexus avulsions as well as after spinal cord injury [1•].

Phantom sensation is a general term for a wide variety of symptoms and symptom duration. They can present as kinetic, kinesthetic, or exteroceptive perceptions [1•]. Kinetic sensations describe perceived movements of the missing body part which are typically voluntary such as movement of fingers from an amputated hand. Kinesthetic sensations describe perceived changes in size, shape, or position of the missing extremity. This may manifest as feeling as if the hand is twisted or cramped in a specific position [1•]. Frozen phantom limbs, a type of kinesthetic sensation, have also been described in the literature. Frozen limbs may be stuck in a specific position for a variable amount of time but have been shown to diminish with time [6]. Exteroceptive sensations are those which are influenced by exterior sensations such as touch, temperature, pressure, itching, vibrations, or tingling. The sensations typically take place in regions with relatively larger cortical representations such as the hands and feet [1•].

Phantom limb pain is a type of phantom sensation in which pain is the primary complaint. Phantom limb pain is perhaps the most clinically relevant related to its distressing nature and chronic condition. More specifically, phantom limb pain can be described as painful sensations in the missing portion from a limb [7, 8, 9••]. The pain has variable onset, duration, severity, quality, and location which can make the management and treatment incredibly difficult. Phantom limb pain quality has been described as electric shocks, stabbing, burning, sharp, dull, cramping, or shooting [1•, 10]. The pain can begin soon after amputation or years later, often becoming a chronic condition. The pain has been shown to worsen with stress as well as during sleep, causing significant distress [11]. It is important to differentiate stump pain from phantom limb pain. Stump pain is defined by the International Association for the Study of Pain as pain perceived in the stump of the residual limb. Phantom limb pain has been described as localized to a small region of the missing limb or over the entire missing limb. The pain can also change through time [1•]. A commonly described pattern of the change has been from a sensation of exteroceptive-like pain to one of proprioceptive-like pain [1•].

Telescoping is a phenomenon described in 25–66% of major limb amputees [1•]. It is the perception of gradual shortening of an amputated limb. This results in the sensation that the distal limb shortens to become more proximal. A commonly described sensation is the hand becoming telescoped into the stump [10]. There has not been a significant connection between telescoping and phantom limb pain severity, however [12].

Most studies published have measured or confirmed phantom limb pain using a form of questionnaire regarding phantom pain combined with a more traditional questionnaire such as the McGill pain questionnaire [13, 14]. Table 1 summarizes key questions that most studies have used to identify phantom limb pain.

Clinical Implications

After amputation, patient frustrations emerge which can range from the loss of independence to financial and emotional strains. Table 2 summarizes recent studies evaluating the comorbidity of psychiatric conditions in patients with PLP. Experiencing additional pain in a phantom appendage could understandably cause psychiatric distress. It is not surprising

Table 1 Phantom phenomena questionnaire [13, 14]

Questions to identify phantom limb pain	Questions to identify general pain
• Do you ever have the sensation that your missing limb is still there? • If yes, does this trouble you at all? • Do you ever have pain in your missing limb? • Do you ever have pain at the site of your amputation?	• What does your pain feel like? • How does your pain change with time? • How strong is your pain?

that psychiatric illnesses such as depression, anxiety, and mood disorders have higher prevalence in amputees than in the general population [18]. Sahu et al. found elevated prevalence for major depressive disorder (71.2%), suicidality (30.5%), and posttraumatic stress disorder (20.3%) in amputees [15]. It logically follows that these comorbidities would further increase with PLP [16].

Padovani et al. found that patients who suffered from PLP rated their quality of life lower than those who did not experience PLP [16]. Additionally, they found increased anxiety among PLP patients ages 18–38 years and increased depression in 60–80 years old. Other research indicates less of a relationship between PLP and psychiatric illnesses. Desmond and MacLachlan found amputees had increased depressive symptoms, avoidance, and intrusions with either residual limb pain (RLP) or RLP with PLP. Yet these trends were not seen in patients with PLP alone [17]. This may suggest different psychiatric implications of PLP than those of other postamputation pains.

Fuchs et al. demonstrated no specific relationship between prevalence of anxiety and depression in PLP patients [18]. Yet Raichle et al. found greater PLP ratings in patients with higher preoperative anxiety [20]. Additionally, different maladaptive coping strategies such as catastrophizing have been shown to aggravate PLP [21•]. This creates an opportunity for PLP prevention and minimization of anxiety via the maximization of preoperative patient education.

The relationship between depression and PLP in patients is inconclusive [18]. One study described subjects who reported they were "extremely bothered" by PLP experienced depressive symptoms nearly three times that of subjects who reported they were "not bothered" by PLP [19]. Further literature seems to debate any relationship with PLP and depression at all. Another study asserted that PLP patients exhibited less depression and anxiety compared to patients with other neuropathic pain; notably, this excluded PLP [17].

Even fewer studies exist on anxiety and PLP. Desmond and MacLachlan showed anxiety was reported higher in PLP patients compared with pain-free amputees [17]. Yet these differences were within the ranges for anxiety prevalence in the general population. They hypothesize that because PLP itself does not significantly impair daily activities, there may be less implications than other chronic pain sources. Fuchs et al. point out that chronic pain in other scenarios causes significant distress as the patient conditions himself into a state of perpetual fear and anxiety [18]. PLP, of course, is not necessarily positional or easily provoked and thus does not elicit the same mental programming.

The inconsistencies of screening methods for psychiatric symptoms in literature remain a barrier to determining the relationship between depression and PLP [18]. Further, preventing this is the general paucity of studies with significant participants. Until more data is generated, there may not be a complete understanding of PLP's psychiatric implications on patients' lives.

Treatment

It is estimated that PLP affects anywhere from 40 to 80% of amputees, showing the importance of finding an optimal treatment [22, 23•]. Several modalities are effective, ranging from pharmacological, surgical, anesthetic, and psychological. However, the complexity of PLP, namely that the etiology still remains unclear, has led to treatment outcomes with mixed results and variable efficacy making a universal treatment hard to find. As such, some researchers suggest the need for combined therapy to target the multiple mechanisms suggested to underlie PLP [24, 25]. Most of the studies conducted aim at reducing PLP as the primary outcome; however, secondary outcomes of frequency and duration of pain, intrusion of pain into everyday life, and psychological impacts are often obtained [11]. Pharmacologic treatment has been used as a first choice for amputees suffering from PLP with agents such as gabapentin, amitriptyline, opioids, and local anesthetics [24, 26•]. However, many individuals' pain remains refractory to pharmacologic agents and requires either invasive or non-invasive options [27]. Table 3 provides a study of recent studies which evaluate the efficacy of various therapeutic modalities for the management of PLP.

Invasive options, mainly neuromodulation modalities, are often a last resort in patients who have failed other treatments for PLP [23•, 25]. Neuromodulation describes techniques where electrical stimulation of the nervous system is used in order to treat neurological conditions [27] and encompasses spinal cord stimulation (SCS), dorsal root ganglion stimulation (DRGS), and peripheral nerve stimulation (PNS). It has been theorized that neuromodulation works on the peripheral

Table 2 Clinical Implications

Author (year)	Groups studied	Intervention	Results and conclusions
Sahu et al. (2017) [15]	59 amputees within 6-month period from amputation	Interviewed on sociodemographic and amputation-related parameters. Psychiatrically assessed with Mini-International Neuropsychiatric Interview scale	Prevalence of major depressive disorder (71.2%), suicidality (30.5%), and posttraumatic stress disorder (20.3%)
Padovani et al. (2015) [16]	27 amputation patients over 18 years old with persistent postoperative pain	Quantitative approach to descriptive, exploratory, and cross-sectional study	Lower quality of life for physical and mental health components. Anxiety levels more prevalent in ages 18–38 years. Depression more prevalent in ages 60–80 years
Desmond and MacLachlan (2006) [17]	582 males with long-term limb amputations and members of the British Limbless Ex-Service Men's Association	Cross-sectional survey	Prevalence of significant depressive symptoms was 32.0%. 34.0% met the screening criterion for clinical anxiety. 24.6% reported significant posttraumatic psychological stress symptoms
Fuchs et al. (2018) [18]		Comprehensive review of emotional, motivational, cognitive, and perceptual factors in PLP	Emotional factors are less important in PLP than in other types of chronic pain. There are bidirectional relationships between stress and PLP. Catastrophizing seems to aggravate PLP. Body perception is altered in PLP
Darnall et al. (2005) [19]	914 amputees who contacted the Amputee Coalition of America from 1998 to 2000	Cross-sectional survey	Prevalence of 28.7% for depressive symptoms
Raichle et al. (2015) [20]	69 adults admitted for lower limb amputation	Monitored preoperative anxiety and pain. Recorded RLP, PLP, and analgesic medication 5 days postoperatively	Higher preoperative anxiety was significantly associated with greater ratings of average PLP
Vase et al. (2012) [21•]	18 upper limb amputees	Established spontaneous pain levels and thresholds to electrical stimulation.	Recorded EEG signals while non-painful electrical stimuli were applied to both affected and unaffected limbs.

nervous system by activating the large-diameter Aβ fibers, which mitigate the activity of the nociceptive Aδ and C fibers through inhibition of localized pathways in the spinal cord, ultimately causing an analgesic effect [27, 33].

SCS uses high-frequency electrical pulses delivered to the spinal column through an implanted electrode with a pulse generator positioned at the cervical or thoracic level for upper and lower limb pain respectively [27, 28, 34]. Twelve patients with implantable SCS devices were studied in a case series. Positive outcomes of patient-reported worthwhile benefit were experienced by 11/12 participants over the short term. However, of the 12, only five reported long-term benefit with

Table 3 Treatments for phantom limb pain

Author (year)	Number of participants	Intervention	Results
McAuley et al. (2013) [28]	12	SCS	11/12 patients reported worthwhile benefits short term. 5/12 reported long-term benefit averaging 11 years
Deng et al. (2018) [25]	1	SCS and anterior cingulomoty	90% decrease in PLP by NPRS and 80.6% reduction in depressive symptoms by HDS at 2-year follow-up
Eldabe et al. (2015) [23•]	8	DRGS	52% pain reduction
Cornish and Wall (2015) [29]	1	PNS	Pain free at 6-month follow-up
Ol et al. (2018) [30]	45	MT, TT, or MT and TT	50% reduction of PLP in all 3 interventions
Ortiz-Catalan et al. (2014) [36]	1	VR	Pain-free periods during sessions
Yanagisawa et al. (2018) [31]	1	MEG-BMI	Reduction in PLP during sessions
Malavera et al. (2016) [32]	54	rTMS	Greater reduction in PLP in active than in control group

an average of 11 years [28]. Deng et al. used a combined neuropsychiatric approach to SCS adding anterior cingulotomy to target depression. They found excellent pain relief with a decline of 90% by the Numerical Pain Rating Scale and significant improvement of depressive symptoms with a decline of 80.6% by the Hamilton Depression Scale at the 2-year follow-up with the combined treatment method [25]. While there has been patient-reported success in reducing PLP using SCS, more studies need to be conducted to refine the techniques used in SCS due to the need to revise placement of the electrodes over time as well as establish the efficacy.

DRGS has been suggested as an intervention for PLP due to the potential that ectopic firing of primary sensory neurons, including dorsal root ganglia may cause PLP [23•]. It is an appealing alternative form of neuromodulation to SCS due to the decreased likelihood of lead migration and need for revision [27]. In a retrospective chart review, eight patients were trialed with DRGS with the device leads placed near dorsal root ganglions based on the individual's pain distribution. The percentage of pain reduction was 52% on average, with five patients reporting good pain relief and one patient having complete pain relief [23•]. A novel approach to neuromodulation is the peripheral placement of leads, with the rationale that peripheral nerve blocks provided relief of PLP, suggesting that peripheral factors play a role in PLP [29]. In a case report by Cornish and Wall, the leads for neuromodulation were placed subcutaneously on either side of the patient's stump in attempt to relieve her PLP. The authors found a rapid decrease in the PLP over the 10-day trial that was sustained through the patient's 6-month follow-up [29]. While alternatives to SCS exist in DRGS and potentially PNS, more controlled trials need to be conducted to determine if their success can be replicated in more individuals.

Non-invasive treatment modalities exist for PLP including sensory motor training, mirror visual therapy, and non-invasive neuromodulation. One benefit of mirror therapy (MT) is that it is one of the least expensive options available [30]. MT works by placing a mirror at the observer's medial line and having them use the intact limb to produce voluntary movements. The reflection of the movements creates a visual illusion of non-painful movement of the phantom limb [35]. A recent study looking at MT for PLP in landmine amputees in Cambodia looked at 45 patients who underwent MT in combination with tactile therapy (TT) for 5 min twice/day for 4 weeks or monotherapy of either treatment. At the 3-month follow-up, all three interventions lead to a > 50% reduction of PLP based on the visual analogue scale with combined mirror-tactile treatment having the greatest effect on PLP [30]. While MT has had many positive outcomes, some patients actually experience aggravation of PLP or telescoping of the phantom limb towards the residual limb [35]. Virtual reality (VR) has been added as a more immersive experience than MT and allows for creation of a virtual image of the missing limb [36]. Recent studies have looked at myoelectric pattern recognition to predict phantom limb movement and then those movements are input into VR environments, allowing control over their motion [11, 36]. This intervention was successful in reducing one subject's pain by 18 weeks to completely pain-free periods during sessions [36]. Another approach to PLP treatment is using brain-machine interface based on real-time magnetoencephalography (MEG-BMI) signals in order to reconstruct hand movements using a robotic hand. It was noted the patient experienced less pain when the patient controlled the robotic hand by moving the phantom hand simultaneously with the intact hand [31]. Non-invasive neuromodulation includes interventions like transcutaneous electrical nerve stimulation (TENS) and transcranial magnetic stimulation. A recent study looked at repetitive transcranial magnetic stimulation (rTMS) as a treatment for PLP in landmine victims. The intervention was either real or sham rTMS of M1 contralateral to the amputated leg 20 min a day for 10 days. Those with the real intervention experienced a greater reduction in pain intensity up to 15 days post-intervention [32]. TENS works by stimulating the surface of the skin, activating Aβ afferents to impede transmission of pain signals to the brain. However, only partial relief has been noted and the efficacy for PLP remains questionable [27].

While many promising therapies for PLP exist, more clinical trials are required to determine the efficacy and protocols needed for maximum benefit. To date, many trials are small, have found a mix of results ranging from minimal to excellent pain reduction, and often are limited to short-term relief.

Conclusion

Pain without a tangible source may be one of the most daunting tasks to physicians. Without a clear starting point in managing this type of pain state, it is often difficult to treat, which is unfortunately the challenge regarding PLP. Diagnosis of PLP depends entirely on patient reports. Presentation and penetrance vary widely between individuals regarding onset, type of pain, severity, progression, and duration. Although the pain causes patients' distress, the exact psychiatric implications remain unclear. Some research shows increased prevalence of anxiety and depression among PLP patients while other deny it. Prevention of factors such as high preoperative anxiety and pain catastrophizing may reduce incidence of PLP.

Several mechanisms have been discussed regarding PLP's pathogenesis. Primary among them are cortical reorganization, reduced functional reactivity, and stochastic enlargement. Other theories such as peripheral nociception, sensory incongruence, and time to deafferentiation are less supported. Treatment for PLP is as varied as its pathogenesis, showing various reported efficacies. Non-invasive options include pharmacological training, sensory motor training, mirror therapy, and non-invasive neuromodulation. Refractory cases may require the more invasive approaches such as neuromodulation modalities including SCS and DRGS. In summary, PLP is an important and often difficult to treat component of conditions requiring amputation. Further research is needed to improve understanding and treatment of PLP in the future.

Compliance with Ethical Standards

Conflict of Interest Ivan Urits, Danica Seifert, Allison Seats, Stephen Giacomazzi, Michael Kipp, Vwaire Orhurhu, and Omar Viswanath declare no conflict of interest. Alan D. Kaye discloses that he is on the Speakers Bureau for Depomed, Inc. and Merck.

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