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Phantom Limb Pain: Current Concepts and Treatment Strategies

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Abstract

Phantom limb syndrome is described as the perception of feelings originating from a limb that has been amputated or is otherwise absent. The pain associated with phantom limbs impacts millions of patients worldwide. It is estimated to occur in approximately 50-85% of patients that experience phantom limb syndrome. The exact mechanisms involving phantom limb pain are not yet fully understood. However, it is hypothesized to result from inadequate interchange between the peripheral and central nervous systems, including an abnormality concerning proprioceptive signals. The pain is characterized by the perception of pressure, burning, lacerating, and aching in a body part that is no longer present. Both pain varying intensity degrees and the associated decreased quality of life, combined with the complex nature of this neuropathic condition, represent a challenge for medical science. The diagnosis is primarily based on a complete medical history, physical examination, and neurologic assessments. Although there is no definitive cure for the disease, there are potential treatment options which include pharmacotherapy, adjuvant neuropsychological interventions, physical therapy, and different types of procedures. Commonly, a multimodal approach is required to manage these patients adequately. This review article aims to generate consensus regarding how to formulate more informed decisions when testing the efficacy of therapeutic interventions. We highlight advances in phantom limb pain concepts, pathophysiology, prevention, diagnosis, and therapeutic options.

Keywords: Phantom Limb; Pain; Phantom Limb Sensation; Brain stimulation; Chronic pain; Neuropathic pain

Abbreviations: PLS: Phantom limb syndrome, PLP: Phantom limb pain, MRI: Magnetic Resonance Imaging, TCAs: Tricyclic antidepressants, NSAIDs: non-steroidal anti-inflammatory drugs, AEDs: antiepileptic drugs, NMDA: N-methyl-D-aspartate, THC: tetrahydrocannabinol, CBD: cannabidiol, TENS: Transcutaneous electrical nerve stimulation, ECT: Electroconvulsive therapy, DBS: Deep brain stimulation, MCS: Motor cortex stimulation, SCS: Spinal cord stimulation, ASA: American Society of Anesthesiologists, CNS: Central nervous system.

Introduction

Phantom limb syndrome (PLS) is described as the perception of feelings originating from a limb that has been amputated or is otherwise absent [1]. Despite this physical absence, patients may experience various sensory and motor sensations as if the limb were still present. Phantom limb symptoms encompass a range of sensations, including the missing limb's presence, movements such as wiggling toes or opening and closing the hand, pressure,

tingling, itching, temperature changes, and pain [1-3]. Phantom limb pain (PLP) is commonly encountered in these patients, and it can vary in intensity, duration, and quality, ranging from throbbing or stabbing sensations to burning or cramping feelings. There is a high statistical heterogeneity across prevalence studies due to the different time windows assessed [4-10]. However, it is estimated that approximately 60-80% of individuals who have undergone limb amputation may experience phantom limb sensations, and around 50-85% of those individuals may also experience phantom limb pain [11,12]. Several factors have been identified as potential risk factors for developing this type of pain, including the level of amputation, pre-existing pain, post-amputation pain, chronic pain history, and psychological factors (i.e., anxiety, depression, post-traumatic stress disorder) [12,13].

It was first described in the 16th century by Antoine Paré; however, its origin remains unclear, and the exact mechanisms underlying PLP are not yet fully understood [14]. It is believed to result from complex interactions between the peripheral and central nervous systems (CNS), including changes in the brain's representation of the amputated limb, subcortical (thalamic) contributions, proprioceptive memory, and dissociation of vision and proprioception [15,16]. This condition can significantly impact an individual's quality of life, causing physical discomfort, emotional distress, and limitations in daily activities. The diagnosis of PLP is primarily based on a thorough clinical evaluation, a review of prior medical history, and the patient's reported symptoms [17]. Management often involves a multimodal approach, combining pharmacological (i.e., opioids, anticonvulsants, antidepressants, local anesthetics, etc.) and non-pharmacological interventions (i.e., physical therapy, massage, psychological interventions, biofeedback, neuromodulation techniques, mirror therapy, acupuncture, etc.) to alleviate pain and improve overall well-being and life quality [13,18-19]. This narrative review aims to provide an overview of the current literature concerning this complex and multifaceted neurological condition.

Epidemiology & Risk factors

Phantom pain is pain sensation to a limb, organ, or other tissue after amputation and/or nerve injury is included within a broad clinical spectrum and post-amputation phenomenon, which includes the sensation of phantom limb and residual limb pain. Several studies record trauma as the most frequent cause of amputation, followed by vascular disease associated with diabetes mellitus. The most common comorbidity is diabetes. Other underlying causes are given clinical considerations, such as cancer/malignancy and congenital conditions [20]. In the United States, 1.7 million people live with limb loss each year, and there are 185,000 new lower extremity amputations, which account for about 86% of the total amputations [21]. Reports agree that phantom limb pain affects 60%-85% of amputee patients [22].

Numerous factors associated with phantom pain have been described, including pain before the amputation, gender, dominance, and time elapsed since the amputation [21]. The short-term incidence of phantom pain is reported to be 72% in the immediate postoperative period and 67% 6 months after amputation [22,23]. In other words, 8 out of 10 people who lose a limb experience some degree of phantom pain [24]. PLP typically occurs within the first 6 months after losing a limb. However, its prevalence several years after surgery has been reported to be as high as 85%, and it can persist for years after surgical amputation [25].

Higher prevalence rates of PLP have been reported in people with lower limb amputations than those with upper limb amputations. Lower limb(s) amputations are performed chiefly to treat complications of diabetes and may be associated with risk factors for PLP, such as pre-amputation pain and depression. However, no clear hypothesis for these lower prevalence rates has been proposed. Further, it is unclear if the prevalence rates in developing countries are significantly lower than those in developed countries [26].

A study conducted in the Netherlands on 124 patients to find the prevalence and factors associated with phantom pain and phantom sensations in upper limb amputees showed a response rate of 80% [27]. The prevalence of phantom pain was 51%, of phantom sensations 76%, and of stump pain 49%; 48% of the subjects experienced phantom pain a few times per day or more; 64% experienced moderate to very much suffering from phantom pain. Diverse authors agree that there has been no evidence that the time since the amputation is associated with the prevalence or incidence of phantom pain [27].

The occurrence of phantom pain seems independent of age in adults, gender and level, or side of amputation [23]. Phantom pain is less frequent in young children and congenital amputees [20].

Physiopathology

Many theories surround the pathophysiology of phantom limb syndrome, and although this entity was first described in 1552, its mechanism is still poorly understood. Most theories, however, agree on the involvement of the central, peripheral, or both nervous systems. Both non painful and painful sensations characterize phantom limb syndrome. Nonpainful sensations can be divided into the perception of movement and the perception of external sensations (exteroception), including touch, temperature, pressure, vibration, and itch. Pain sensations range from burning and shooting pains to feelings of tingling "pins and needles." While phantom limb syndrome occurs only in amputees, phantom sensations may be perceived in people who have survived strokes but lost function of particular body parts or have spinal cord or peripheral nerve injury [28]. The hypothesized theories include the following:

Peripheral nerve changes: after nerve sectioning, there is retrograde degeneration and shortening of afferent neurons due to the injury, edema, and axon regeneration. This phenomenon

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is known as sprouting and gives rise to neuroma formation, i.e., expanded and disorganized A and C fiber-endings with ectopic firing that increases during the mechanical and chemical stimulus [29]. The nerves become hyper-excitable due to an increase in sodium channels and resulting in spontaneous discharges [30].

Spinal Cord Changes: spinal cord and thalamus are the other two reasonable accounts for PLP. In the spinal cord, a constant signal of inflammatory pain can lead to central sensitization, a change of synaptic function in the spinal dorsal horn. And after neuron injury during amputation, another similar process called central hyperexcitability frequently occurs along with phantom sensation and pain. Possible causes include decreasing inhibitory process in the spinal cord, increasing stimulation of the dorsal horn neurons, and the abnormality of Na+ channel expression in the thalamus and spinal cord pathways. Since the independence of thalamic hyperexcitability from the spinal cord, the thalamus can act as a pain generator and amplifier [31].

Brain Changes: over the past few years, significant research has been done into cortical reorganization, a commonly cited factor in phantom limb pain. During this process, the areas of the cortex that represent the amputated area are taken over by the neighboring regions in both the primary somatosensory and the motor cortex. Cortical reorganization partially explains why nociceptive stimulation of the nerves in the residual limb and surrounding area can cause pain and sensation in the missing limb. There is also a correlation between the extent of cortical reorganization and the patient's pain [30].

Proprioceptive memory: according to this view, proprioceptive memory stands for the internal awareness and memory of limbs and their positions. Such a three-dimensional scheme is relatively independent. Namely, it will not be affected by visual confirmation of an absent limb. This hypothesis is supported by the regional anesthesia study, in which patients reported that their limbs remained at the same site after being relocated during anesthesia. Therefore, it is highly possible that only the last input from the proprioceptive system will be accounted for by the memory, and the limb impression for amputees is maintained before the operation, leading to misrepresentation and continuous activities in nerves. Some symptoms, such as muscle cramping, can thus be explained by the impact of proprioceptive memory [31].

Clinical Presentation

Phantom limb pain presents as a painful or unpleasant sensation in the distribution of the lost or differentiated limb [32]. Symptoms range from neuropathic-type sensations (shooting, stabbing, or burning) to more nociceptive-specific such as sharp, aching, or throbbing pain, projecting to the distal end of the missing limb, with a frequency that ranges from every few days to multiple episodes per day, and a length variation from 1 minute to continuous pain [33].

Most patients develop phantom limb pain in the first days to weeks following amputation. However, onset is variable, with cases reported as early as within 4 hours following amputation to several decades later [34,35]. Triggers include environmental, emotional, and physical changes. It is expected for pain to decrease during the first six months after amputation, although up to ten percent of patients will report severe intensity after six months and beyond after surgery [36].

It is essential to distinguish between Phantom limb pain and residual limb pain. Both conditions can present in a patient, independently or concurrently, and differ in their pathophysiology. While phantom limb pain is attributed to changes in the peripheral and central nervous system that presents as pain referred to an absent limb, residual limb pain, also named stump pain, localizes to the remaining portion, which can have different causes such as ischemia, neuroma, faulty prosthesis, soft tissue or bone damage. Treatment will be targeted according to the source [37].

Diagnostic Approach

Phantom limb pain is a diagnosis of exclusion. History and physical examination are paramount in the appropriate identification of the condition. Diagnosis is based on the patient report and how the clinician conducts the evaluation, which presents a challenge due to subjectivity. Efforts have been made to establish a diagnostic process. A recent cross-sectional study revealed that asking patients directly about "pain" instead of an "unpleasant sensation" (which could be further characterized as movement, positioning, burning, tingling, cooling, pulsation, throbbing or shock-like perceptions) contributes to underdiagnosis of phantom limb pain, as patients tend to associate the former to nociceptive experiences that do not describe what they feel [38]. Education level, above-knee amputation, and prosthetic phase of rehabilitation are associated with more phantom limb pain descriptors being reported [38]. A proper physical examination is essential in diagnosis and allows the clinician to rule out other causes. A comprehensive inspection of the skin and soft tissues can identify pressure wounds developed due to bone spurs or heterotopic ossification. Laboratory analysis is often unnecessary, although a proper clinical indication could help rule out infection as a cause of pain. Ultrasound helps to study neuromas as a cause.

Different imaging modalities are used as complementing diagnostic tools but are more commonly applied in research. A recent literature review analyzed their role in phantom limb pain. The use of diffusion tensor imaging, functional MRI, electroencephalography, and magnetoencephalography was found to have different applications, such as structural change identification, surgical planning, and analysis of the effectiveness

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of therapy and response to stimulation. However, they had limitations such as accessibility, practicality, and reproducibility, which limited their clinical use [39].

Pharmacotherapy

Adequate management of phantom limb pain is challenging as this is a multifactorial condition with a wide range of features. Therefore, along with other therapeutic strategies, PLP often requires drug therapy to aid in handling the pain. Pharmaceutical treatment typically involves a combination of medications targeting different aspects of pain perception. Some commonly used drugs for PLP include tricyclic antidepressants (TCAs), non-steroidal anti-inflammatory drugs (NSAIDs), opioids, antiepileptic drugs (AEDs), N-methyl-D-aspartate (NMDA) receptor antagonists, and corticosteroids [40]. TCAs (i.e., amitriptyline, nortriptyline) function by blocking the reuptake of certain neurotransmitters, such as norepinephrine and serotonin, which can help modulate pain signals. The success rate varies among individuals, but studies have shown moderate effectiveness in reducing phantom limb pain. Success rates can range from 30% to 60% of patients experiencing partial or significant pain relief. However, adherence to TCAs can be challenging due to their side effects, such as drowsiness, dry mouth, constipation, blurred vision, and potential cardiac effects [41].

NSAIDs reduce inflammation and inhibit the production of prostaglandins, which can contribute to PLP. NSAIDs alone may not provide significant pain relief for phantom limb pain, but they may be used as part of a multimodal approach. However, their effectiveness may be limited, with success rates estimated to be lower than TCAs. Adverse effects may include gastric ulcers, bleeding, and potential kidney and cardiovascular complications [40,42]. Alternatively, opioids, such as morphine, oxycodone, and fentanyl, are potent pain relievers that can be used for patients with severe or unbearable phantom limb pain. They function by binding to opioid receptors in the brain, spinal cord, and other nerve endings, reducing the perception of pain [43]. Success rates can vary, but they may effectively provide partial or significant pain relief in a subset of patients. It should be stressed that opioids carry a high risk of dependence, tolerance, respiratory depression, constipation, sedation, and other adverse effects. Therefore, their long-term use for chronic pain conditions like PLP is generally avoided due to the potential for addiction and limited evidence supporting their effectiveness [43,44].

Certain antiepileptic drugs (AEDs), such as carbamazepine, lamotrigine, gabapentin, and pregabalin, have shown efficacy in managing neuropathic pain, including PLP [45]. AEDs modulate the activity of specific neurotransmitters involved in pain transmission, which can help stabilize overactive nerve cells. Success rates can range from 30% to 50%, with some patients experiencing partial or significant pain relief. Common adverse effects include dizziness, drowsiness, rash, and potential liver or blood-related complications [42,45]. Moreover, medications that target N-methyl-D-aspartate (NMDA) receptors (i.e., ketamine) have been studied for phantom limb pain since it is well-known that NMDA receptors play a significant role in the development and maintenance of chronic pain. NMDA receptor antagonists have shown promise in some cases of phantom limb pain, with success rates ranging from around 28% to 45% of patients experiencing partial or significant pain relief [46]. However, it is important to consider that these drugs include potentially harmful effects such as hallucinations, dissociation, increased heart rate, hypertension, and renal complications.

Other medications that have been researched for the management of PLP include local anesthetics, steroids, botulinum toxin, and cannabinoids. Corticosteroids have anti-inflammatory properties and may be used for reducing inflammation and PLP [41,47]. However, they are not recommended for long-term use due to their demonstrated low efficacy in neuropathic pain and their high risk of adverse effects, including weight gain, diabetes, mood changes, and osteoporosis. Botulinum toxin injections (Botox) can be injected into the residual limb to help alleviate muscle spasms or hyperactivity that may contribute to PLP [48]. The toxin acts by blocking the release of acetylcholine, which is involved in muscle contraction. Adverse effects are generally mild and temporary, including injection site pain and localized muscle weakness. Current data is limited regarding the effectiveness of Botox for PLP [42,48]. Finally, medical cannabinoids, such as tetrahydrocannabinol (THC) and cannabidiol (CBD), have shown potential for neuropathic pain conditions. These substances may exert their effects through interactions with the endocannabinoid system, which regulates pain perception. However, its long-term effects require further investigation [49].

As mentioned above, the success rates of medications for phantom limb pain can vary widely among individuals, and it's important to note that there is limited high-quality evidence specifically addressing success rates for each medication. Some patients may respond well to a particular medication, while others may experience little or no relief or significant adverse effects. While no specific medication has definitive evidence as the most effective for phantom limb pain, TCAs are often considered the first-line pharmacological option due to their moderate effectiveness and established use in neuropathic pain conditions [40-43,50]. However, the choice of medication should be individualized based on the patient's unique circumstances, medical history, and preferences. The cornerstone for treating PLP includes a multimodal approach combining medications, physical therapy, psychological interventions, and other modalities that may be necessary to manage phantom limb pain effectively.

Prevention Strategies

Preventing phantom limb pain is challenging as it can vary from person to person. Most preventive methods involve strategies to

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reduce the occurrence or severity of pain sensations experienced in a limb that is no longer present [51]. These measures can be broadly categorized into preoperative, intraoperative, and postoperative interventions.

Preoperative prevention includes patient education, psychological support, adequate pain management, and monitored physiotherapy. First, providing information about PLP before amputation can help manage patient expectations and alleviate anxiety [52,53]. This can help individuals to mentally prepare and comprehend the phenomenon. Also, education about potential risk factors and coping strategies can empower them to manage PLP effectively. Further, counseling, support groups, or psychological therapy sessions can assist patients in coping with emotional and cognitive challenges associated with limb loss, potentially reducing the risk of developing PLP [53]. In some cases, starting mirror therapy before amputation can help prepare the brain for the sensory changes that could occur after surgery. Another important preoperative strategy is the management of pain [53]. Controlling pre-existing pain conditions in the affected limb through medication or other therapeutic techniques can minimize the risk of PLP. If the limb scheduled for amputation is already experiencing pain, adequately managing that pain before surgery can minimize the likelihood of PLP [54,55]. Finally, performing gentle, controlled exercises with the affected limb (i.e, stretching, flexing, and relaxing) before and after surgery can help maintain the range of motion, promote circulation, and potentially reduce PLP [55].

Intraoperative prevention is mainly based on achieving adequate and complete control of pain. Administering nerve blocks or epidural anesthesia during the amputation procedure can reduce immediate postoperative pain and potentially inhibit the development of PLP. Moreover, utilizing a mirror box (mirror therapy) during surgery allows patients to view the reflection of their intact limb instead of the amputated one, helping to alleviate potential sensory conflicts [51,56].

Lastly, postoperative prevention may be obtained by a combination of strategies. For example, effective pain management immediately after surgery will reduce inflammation, stabilize neural activity, and potentially prevent or mitigate PLP [53,55]. Medications such as antidepressants, antiepileptic drugs, opioids, or NSAIDs can assist in managing symptoms [57]. Moreover, engaging in physical exercises and rehabilitation programs (i.e., desensitization techniques) can promote neural plasticity and optimal healing, reduce pain sensations, improve prosthetic use, and potentially reduce the likelihood and severity of PLP. After amputation, continued counseling, cognitive-behavioral therapy, or mindfulness-based techniques must also be maintained to address psychological aspects and enhance coping mechanisms [52,53,57]. Other helpful strategies for postoperative prevention and treatment might include the use of transcutaneous electrical nerve stimulation (TENS), virtual reality therapy, and neuromodulation techniques (i.e., spinal cord/peripheral nerve/deep brain stimulation) [51-54].

Adjuvant therapy

Phantom limb pain is a syndrome that can significantly impact an individual's quality of life. While no definitive cure exists, various adjuvant therapies can help manage the pain and improve overall well-being. Non-pharmacological adjuvant therapies commonly used include transcutaneous electrical nerve stimulation (TENS), mirror therapy, biofeedback, acupuncture and/or massages, and electroconvulsive therapy (ECT) [58].

TENS involves low-voltage electrical currents applied to the skin via electrodes. These electrical impulses help to disrupt pain signals and stimulate the release of endorphins, which function as the body's natural analgesics. Several studies have supported that TENS therapy can effectively reduce phantom limb pain and provide temporary relief. In addition, it has shown favorable results in managing acute pain flares. However, it may not eliminate the pain completely, and success rates vary. Some studies have reported significant reductions in pain intensity for a subset of patients [58,59]. Mirror therapy utilizes the reflection of the intact limb in a mirror to create the illusion of the missing limb's presence. The brain is tricked into perceiving movement in the phantom limb by performing symmetrical movements with the intact limb while observing it in the mirror. This can help alleviate pain by retraining the brain's neural pathways and reducing pain perception. Mirror therapy has shown promise in reducing phantom limb pain for many individuals. Studies have reported varying success rates, with some showing considerable pain reduction and improved functionality. However, the outcomes can be influenced by factors such as the individual's motivation, adherence to therapy, and duration of treatment [60]. Another adjuvant therapy is biofeedback, which is a technique that enables individuals to gain control over specific physiological processes by providing real-time feedback. In the case of the phantom limb, biofeedback can aid patients in recognizing and controlling physiological changes associated with pain, such as muscle tension or skin temperature. By learning to modulate these responses, patients may experience a reduction in pain intensity [61]. Biofeedback success rates can vary, but some individuals have reported improved self-regulation skills and decreased pain levels over a few weeks of therapy. However, further research is needed to establish the effectiveness of biofeedback specifically for phantom limb pain.

Other options for therapy include acupuncture and/or massaging techniques. Acupuncture is an ancient Chinese practice that involves the insertion of thin needles into specific points on the body. It is believed to balance the flow of energy and promote healing. Acupuncture has been explored as a potential therapy for phantom limb pain, and some individuals have reported reduced pain levels and improved overall well-being after acupuncture sessions [59,61]. The success rates of acupuncture vary among

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individuals. Some studies have reported positive outcomes, with individuals experiencing reduced pain levels and improved well-being. However, the evidence is mixed, and more research is needed to determine its effectiveness conclusively [62]. On the other hand, therapy with massages involves the manipulation of soft tissues to relieve tension, reduce pain, and promote relaxation. Targeted massage techniques can be applied to the residual limb, the surrounding muscles, and other body areas to help alleviate pain and discomfort. Massage therapy can improve circulation, reduce muscle stiffness, and promote well-being. Therefore, this therapy can temporarily relieve and promote relaxation in the phantom limb [63,64]. While it may not eliminate pain completely, many subjects report improved comfort and reduced muscle tension following massage sessions. Again, success rates can vary depending on the individual's response to treatment and the massage therapist's skill [64].

Finally, electroconvulsive therapy (ECT) is a procedure that involves the application of electric currents to the brain, inducing a controlled seizure. While typically used for psychiatric conditions, some studies have suggested that ECT may be beneficial in relieving chronic pain, including phantom limb pain [65]. However, ECT is considered a more invasive and controversial option, typically reserved for severe cases of pain that are unresponsive to other therapies. ECT is not a commonly used therapy for phantom limb pain, and its success rates in this context are not well-established. ECT is typically reserved for severe cases of pain that are unresponsive to other treatments [65,66]. It's important to note that ECT carries potential risks and side effects, and it is typically considered a last resort.

Determining the most effective therapy for phantom limb pain is challenging because individual responses to treatment can vary significantly. Therefore, what works well for one patient may not yield the same results for another. Additionally, the available research on the effectiveness of these therapies is limited, and there is no consensus on a single therapy being universally superior [64,66]. However, among the therapies mentioned, mirror therapy has shown promising results in multiple studies and is considered one of the most effective treatments for phantom limb pain. Mirror therapy can help alleviate pain, improve functional outcomes, and promote cortical reorganization [58,59,57]. Mirror therapy utilizes the brain's neuroplasticity to retrain neural pathways and reduce pain perception. However, it's important to note that individual responses to mirror therapy can still vary, and not everyone may experience the same benefit level. Therefore, each patient's unique circumstances and specific pain characteristics should be considered when determining the most appropriate treatment approach [60,67]. Additionally, combining therapies or a multimodal approach may be more effective than relying on a single therapy alone. Even though none of these therapies have been "officially approved" for managing phantom limb pain, numerous studies have reported positive outcomes as most of these techniques may aid in the reduction of pain intensity, improved range of motion, and increased overall functionality [58,62]. Moreover, they are non-invasive, relatively low-cost, and generally safe alternatives.

Surgical Interventions

Surgical treatment should be the last resource for patients with refractory phantom limb pain. Neuro-invasive treatments, including deep brain stimulation (DBS), are consecutively performed in subcortical areas by stereotactic stick lead implantation. There was limited evidence in a clinical trial where 56 patients had neuropathic or mixed nociceptive/neuropathic pain, and only 4 had phantom limb pain (PLP). Electrodes were placed in the somatosensory thalamus and the periventricular gray area. They used a double-blinded assessment before implanting the stimulation system to evaluate the effect of each electrode exclusively and the combined stimulation along numerous parameter settings. Only 2 of the 4 patients with PLP responded adequately with pain improvement [68]**.** Motor cortex stimulation (MCS), another surgical intervention, leads to subthreshold electrical cortex stimulation. MCS is classically used in patients with post-stroke pain or neuropathic trigeminal pain, whose outcomes constitute alternative pain management for patients suffering from phantom limb pain. A clinical trial in 2003 used MCS in PLP patients**.** MCS was performed in 19 patients with refractory neurogenic pain of different sources; 2 had PLP [68]. They tried to determine the best stimulation pain reliever area by placing the grid electrode in the subdural space and choosing the interhemispheric fissure, central sulcus, and precentral gyrus. Of the total, 14 patients had varying pain tolerance levels, and it was assumed that the best stimulation point for pain improvement was Brodman region 4 within the central sulcus.

Spinal cord stimulation (SCS) can be useful for long-term pain relief in patients with chronic pain. The procedure involves placing a device with a stimulating wire or "electrode" or connected to a control unit or "generator." Implanting a stimulating electrode over the spinal cord disrupts the pain signal from the spine to the brain [69]**.** SCS is a surgical therapy. However, it has a reversible trial time. Therefore, if the patient demonstrates good pain relief and functional improvement by the trial period, SCS implantation can be helpful for long-term treatment. In addition, SCS therapy likely reduces the PLP, showing better function and quality of life and partially decreasing the use of pain medications that can cause drug interactions and side effects [70].

Other techniques include the lumbar sympathetic block, which blocks nerve signals from the sympathetic chain to the lower extremities, corresponding to the treatment guidelines for chronic pain by the American Society of Anesthesiologists (ASA). This technique is helpful for the treatment of sympathetic-related pain; the procedure is done after adequate location and craniocaudal spread, and the medication (anesthetic bupivacaine

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0.5%, ethanol 96%, or botulinum toxin) is injected to complete the lumbar sympathetic blockade. In addition, some case studies have found lumbar sympathetic blocks to be secure and efficacious in relieving phantom limb pain [71].

Several reviews have reported that other surgical procedures, such as neurectomy, rhizotomy, sympathectomy, cordotomy, and myelotomy, have all been tried to treat patients with refractory phantom limb pain. However, no solid evidence was found for these surgical procedures [72]. In addition, Dorsal-Root Entry Zone lesioning is another studied neurosurgical procedure that involves getting into the spinal cord to cut off the damaged, painful areas of the signal nerve cells. Unfortunately, poor specificity and small sample size make it difficult to get an accurate conclusion about the outcomes of the Dorsal-Root Entry Zone on patients diagnosed with PLP [72].

In summary, surgical interventions are not usually recommended except when all medical and adjuvant therapies described above have been ineffective. However, other than the surgical procedures already discussed, which include CNS stimulation such as deep brain stimulation and spinal cord stimulation, are helpful in the surgical treatment and showed good response to relief of the phantom limb pain [69].

Conclusion

Phantom limb syndrome refers to the perception of sensations or symptoms associated with an amputated limb that no longer exists, such as pain. The exact mechanisms involved in phantom limb pain are not fully understood. However, it is estimated that 60-85% of people who have undergone limb amputation may develop it. PLP usually occurs within the first 6 months after surgery, regardless of age, gender, level, or side of amputation. There is more prevalence in the lower limbs than in the upper limbs. Given its multifactorial etiology and complex neurocognitive disturbance, pain is one of PLS's most frequent and challenging symptoms. Therefore, determining the most effective therapy for pain is difficult. Several treatment strategies (pharmacological and non-pharmacological) have been studied for PLP, but no therapy has been found to be completely effective for this type of pain. Among studied medications, tricyclic antidepressants have more scientific evidence as the most effective in PLP and are considered the first line. However, these are not always used alone, as success rates vary significantly among patients. Other beneficial therapies for PLP include psychotherapy, neuromodulation, central/peripheral neurostimulation, mirror therapy, and physiotherapy. Current evidence strongly supports that the multimodal combination of all these therapeutic strategies is the most appropriate direction to reduce the neuropathic pain caused by PLP and improve patients' life quality. However, it is evident that further large-scale prospective research studies are still required to understand this condition's physiopathology and to develop more effective treatment approaches.

References

1. Makin TR, Flor H (2020) Brain (re)organisation following amputation: Implications for phantom limb pain. Neuroimage 218: 116943.
2. Aternali A, Katz J (2019) Recent advances in understanding and managing phantom limb pain. F1000Res 8: F1000 Faculty Rev-1167.
3. Collins KL, Russell HG, Schumacher PJ, Robinson-Freeman KE, O'Conor EC, et al. (2018) A review of current theories and treatments for phantom limb pain. J Clin Invest 128(6): 2168-2176.
4. Balakhanlou E, Webster J, Borgia M, Resnik L (2021) Frequency and Severity of Phantom Limb Pain in Veterans with Major Upper Limb Amputation: Results of a National Survey. PM R 13(8): 827-835.
5. Bekrater-Bodmann R, Schredl M, Diers M, Reinhard I, Foell J, et al. (2015) Post-amputation pain is associated with the recall of an impaired body representation in dreams-results from a nation-wide survey on limb amputees. PLoS One 10(3): e0119552.
6. Morgan SJ, Friedly JL, Amtmann D, Salem R, Hafner BJ (2017) Cross-Sectional Assessment of Factors Related to Pain Intensity and Pain Interference in Lower Limb Prosthesis Users. Arch Phys Med Rehabil 98(1): 105-113.
7. Mioton LM, Dumanian GA, Fracol ME, Apkarian AV, Valerio IL, et al. (2020) Benchmarking Residual Limb Pain and Phantom Limb Pain in Amputees through a Patient-reported Outcomes Survey. Plast Reconstr Surg Glob Open 8(7): e2977.
8. Resnik L, Ekerholm S, Borgia M, Clark MA (2019) A national study of Veterans with major upper limb amputation: Survey methods, participants, and summary findings. PLoS One 14(3): e0213578.
9. Diers M, Krumm B, Fuchs X, Bekrater-Bodmann R, Milde C, et al. (2022) The Prevalence and Characteristics of Phantom Limb Pain and Non-Painful Phantom Phenomena in a Nationwide Survey of 3,374 Unilateral Limb Amputees. J Pain 23(3): 411-423.
10. Limakatso K, Bedwell GJ, Madden VJ, Parker R (2020) The prevalence and risk factors for phantom limb pain in people with amputations: A systematic review and meta-analysis. PLoS One 15(10): e0240431.
11. Flor H (2002) Phantom-limb pain: characteristics, causes, and treatment. Lancet Neurol 1(3): 182-189.
12. Collins KL, Russell HG, Schumacher PJ, Robinson-Freeman KE, O'Conor EC, et al. (2018) A review of current theories and treatments for phantom limb pain. J Clin Invest 128(6): 2168-2176.
13. Colmenero LH, Perez Marmol JM, Martí-García C, Querol Zaldivar MLÁ, Tapia Haro RM, et al. (2018) Effectiveness of mirror therapy, motor imagery, and virtual feedback on phantom limb pain following amputation: A systematic review. Prosthet Orthot Int 42(3): 288-298.
14. Finger S, Hustwit MP (2003) Five early accounts of phantom limb in context: Paré, Descartes, Lemos, Bell, and Mitchell. Neurosurgery 52(3): 675-686.
15. Modest JM, Raducha JE, Testa EJ, Eberson CP (2013) Management of Post-Amputation Pain. R I Med J 103(4): 19-22.
16. Collins KL, Russell HG, Schumacher PJ, Robinson-Freeman KE, O'Conor EC, et al. (2018) A review of current theories and treatments for phantom limb pain. J Clin Invest 128(6): 2168-2176.
17. Chahine L, Kanazi G (2007) Phantom limb syndrome: a review. Middle East J Anaesthesiol 19(2): 345-355.
18. Schone HR, Baker CI, Katz J, Nikolajsen L, Limakatso K, et al. (2022) Making sense of phantom limb pain. J Neurol Neurosurg Psychiatry 93(8): 833-843.

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19. Urits I, Seifert D, Seats A, Giacomazzi S, Kipp M, et al. (2019) Treatment Strategies and Effective Management of Phantom Limb-Associated Pain. Curr Pain Headache Rep 23(9): 64.

20. Ephraim PL, Wegener ST, MacKenzie EJ, Dillingham TR, Pezzin LE (2005) Phantom pain, residual limb pain, and back pain in amputees: results of a national survey. Arch Phys Med Rehabil 86(10): 1910-1919.

21. Dillingham TR, Pezzin LE, MacKenzie EJ (2002) Limb amputation and limb deficiencies: epidemiology and recent trends in the United States. South Med J 95(8): 875-883.

22. Jensen TS, Krebs B, Nielsen J, Rasmussen P (1983) Phantom limb, phantom pain and stump pain in amputees during the first 6 months following limb amputation Pain 17(3): 243-256.

23. Carlen PL, Wall PD, Nadvorna H, Steinbach T (1978) Phantom limbs and related phenomena in recent traumatic amputations Neurology 28(3): 211-217.

24. Owings MF, Kozak LJ (1998) Ambulatory and inpatient procedures in the United States, 1996. Vital Health Stat 13 139: 1-119.

25. Jensen TS, Krebs B, Nielsen J, Rasmussen P (1985) Immediate and long-term phantom limb pain in amputees. incidence, clinical characteristics and relationship to pre-amputation limb pain. Pain 21(3): 267-278.

26. Limakatso K, Bedwell GJ, Madden VJ, Parker R (2020) The prevalence and risk factors for phantom limb pain in people with amputations: A systematic review and meta-analysis. PLoS ONE 15(10): e0240431.

27. Kooijman C, Dijkstra P, Geertzen J, Elzinga A, Van der Schans C (2000) Phantom pain and phantom sensations in upper limb amputees: an epidemiological study Pain 87(1): 33-41.

28. (2023) Phantom limb syndrome | neurophysiology Phantom limb syndrome | neurophysiology.

29. Mayra Alejandra Malaveraa A, Sandra Carrillo V, Omar Fernando Gomezesec R, Ronald GG, Federico Arturo Silvaf S (2014) Pathophysiology and treatment of phantom limb pain. Colombian Journal of Anesthesiology 42(1): 40-46.

30. Hanyu-Deutmeyer A, Cascella M, Varacallo M Hanyu-Deutmeyer A, Cascella M, et al. (2022) Phantom Limb Pain. Statpearls Publishing.

31. Liu Y (2020) The Pathophysiology of Phantom Limb Pain, Advances in Social Science, Education and Humanities Research, Volume 496.

32. Hsu E, Cohen SP (2013) Postamputation pain: epidemiology, mechanisms, and treatment. J Pain Res 6: 121-36.v

33. Richardson C, Glenn S, Nurmikko T, Horgan M (2006) Incidence of phantom phenomena including phantom limb pain 6 months after major lower limb amputation in patients with peripheral vascular disease. Clin J Pain 22(4): 353-358.

34. Bornemann CH, Dorn C, Rumpold SG (2017) Early Onset and Treatment of Phantom Limb Pain Following Surgical Amputation. Pain Med 18(12): 2510-2512.

35. Rajbhandari SM, Jarett JA, Griffiths PD, Ward JD (1999) Diabetic neuropathic pain in a leg amputated 44 years previously. Pain 83(3): 627-629.

36. Erlenwein J, Diers M, Ernst J, Schulz F, Petzke F (2021) Clinical updates on phantom limb pain. Pain Rep 6(1): e888.

37. Stover G, Prahlow N (2020) Residual Limb Pain: An Evidence-based Review 47(3): 315-325.

38. Sugawara AT, Simis M, Fregni F, Battistella LR (2021) Characterisation of Phantom Limb Pain in Traumatic Lower-Limb Amputees. Pain Res Manag 2021: 2706731.

39. Browne JD, Fraiser R, Cai Y, Leung D, Leung A, et al. (2022) Unveiling the phantom: What neuroimaging has taught us about phantom limb pain. Brain Behav 12(3): e2509.

40. Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, et al. (2010) EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 17(9): 1113-e88.

41. Rowin J (2019) Integrative neuromuscular medicine: Neuropathy and neuropathic pain: Consider the alternatives. Muscle Nerve 60(2): 124-136.

42. Freo U (2022) Paracetamol for multimodal analgesia. Pain Manag 12(6): 737-750.

43. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. (2015) Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 14(2): 162-73.

44. Alles SRA, Smith PA (2018) Etiology and Pharmacology of Neuropathic Pain. Pharmacol Rev 70(2): 315-347.

45. Bouhassira D, Avez CJ, Alchaar H, Conradi S, Delmotte MH, et al. (2020) Pharmacological and non-pharmacological treatments for neuropathic pain: Systematic review and French recommendations. Rev Neurol (Paris). 176(5): 325-352.

46. Smith HS (2012) Opioids and neuropathic pain. Pain Physician 15(3 Suppl): ES93-110.

47. Attal N (2019) Pharmacological treatments of neuropathic pain: The latest recommendations. Rev Neurol (Paris) 175(1-2): 46-50.

48. Matak I, Bölcskei K, Bach RL, Helyes Z (2019) Mechanisms of Botulinum Toxin Type A Action on Pain. Toxins (Basel) 11(8): 459.v

49. Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W (2018) Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev 3(3): CD012182.

50. Bialer M (2012) Why are antiepileptic drugs used for nonepileptic conditions? Epilepsia 53 Suppl 7: 26-33.

51. Cai SB, Tran BNN, Ignatiuk A, Lee ES (2021) Surgical prevention of terminal neuroma and phantom limb pain: a literature review. Arch Plast Surg 48(3): 310-322.

52. Bloomquist T (2001) Amputation and phantom limb pain: a pain-prevention model. AANA J 69(3): 211-217.

53. Kuffler DP (2018) Coping with Phantom Limb Pain. Mol Neurobiol 55(1): 70-84.

54. Dunn J, Yeo E, Moghaddampour P, Chau B, Humbert S (2017) Virtual and augmented reality in the treatment of phantom limb pain: A literature review. NeuroRehabilitation 40(4): 595-601.

55. Ramchandran K, Hauser J (2010) Phantom limb pain #212. J Palliat Med 13(10): 1285-1286.

56. Anderson G, Kovoor M, Alsoof D, McDonald CL, Zhang AS, et al. (2022) Phantom limb syndrome: Assessment of psychiatric and medical comorbidities associated with Phantom pain in 44,028 below knee amputees. Injury 53(11): 3697-3701.

57. Larbig W, Andoh J, Huse E, Stahl CD, Montoya P, et al. (2018) Pre-and postoperative predictors of phantom limb pain. Neurosci Lett 702: 44-50.

58. Johnson MI, Mulvey MR, Bagnall AM (2015) Transcutaneous electrical nerve stimulation (TENS) for phantom pain and stump pain following amputation in adults. Cochrane Database Syst Rev 8(8): CD007264.

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59. Kannan P, Bello UM, Winser SJ (2022) Physiotherapy interventions may relieve pain in individuals with central neuropathic pain: a systematic review and meta-analysis of randomised controlled trials. Ther Adv Chronic Dis 13: 20406223221078672.

60. Barbin J, Seetha V, Casillas JM, Paysant J, Pérennou D (2016) The effects of mirror therapy on pain and motor control of phantom limb in amputees: A systematic review. Ann Phys Rehabil Med 59(4): 270-275.

61. Herrador CL, Perez MJM, Martí GC, Querol Zaldivar MLÁ, Tapia Haro RM, et al. (2018) Effectiveness of mirror therapy, motor imagery, and virtual feedback on phantom limb pain following amputation: A systematic review. Prosthet Orthot Int 42(3): 288-298.v

62. Moura VL, Faurot KR, Gaylord SA, Mann JD, Sill M, et al. (2012) Mind-body interventions for treatment of phantom limb pain in persons with amputation. Am J Phys Med Rehabil 91(8): 701-714.

63. Frischenschlager O, Pucher I (2002) Psychological management of pain. Disabil Rehabil 24(8): 416-422.

64. Batsford S, Ryan CG, Martin DJ (2017) Non-pharmacological conservative therapy for phantom limb pain: A systematic review of randomized controlled trials. Physiother Theory Pract 33(3): 173-183.

65. Garcia-Pallero MÁ, Cardona D, Rueda RL, Rodriguez AM, Roman P (2022) Central nervous system stimulation therapies in phantom limb pain: a systematic review of clinical trials. Neural Regen Res 17(1): 59-64.

66. Ferraro F, Jacopetti M, Spallone V, Padua L, Traballesi M, et al. (2016) Diagnosis and treatment of pain in plexopathy, radiculopathy, peripheral neuropathy and phantom limb pain. Evidence and recommendations from the Italian Consensus Conference on Pain on Neurorehabilitation. Eur J Phys Rehabil Med 52(6): 855-866.

67. Wolff A, Vanduynhoven E, van Kleef M, Huygen F, Pope JE, et al. (2011) 21. Phantom pain. Pain Pract 11(4): 403-413.

68. Garcia-Pallero MÁ, Cardona D, Rueda RL, Rodriguez AM, Roman P (2022) Central nervous system stimulation therapies in phantom limb pain: a systematic review of clinical trials. Neural Regen Res 17(1): 59-64.

69. Kaur A, Guan Y (2018) Phantom limb pain: A literature review. Chin J Traumatol 21(6): 366-368.

70. Barkin RL, Bhatia A, Gungor S (2017) A systematic review on the treatment of phantom limb pain with spinal cord stimulation. Pain Manag 7(1): 59-69.

71. Alexander CE, De Jesus O, Varacallo M (2023) Lumbar Sympathetic Block. 2023 Feb 12. In: StatPearls. Treasure Island (FL): StatPearls Publishing.

72. Richardson C, Kulkarni J (2017) A review of the management of phantom limb pain: challenges and solutions. J Pain Res 10: 1861-1870.

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