Review article

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# Pharmacological and interventional treatment of phantom pain

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Phantom limb pain (PLP) is a common and debilitating form of neuropathic pain that occurs after limb amputation significantly impairing patients' quality of life.

The aim of this review is to summarize and analyze current data on pharmacological and interventional treatments for PLP, focusing on practical aspects of therapy to improve patients' quality of life and optimize treatment strategies for this complex condition.

A review of recent studies and clinical guidelines on PLP management was conducted, including pharmacological approaches (antidepressants, anticonvulsants, gabapentinoids, opioids, and NMDA receptor antagonists) and interventional methods (nerve blocks, radiofrequency procedures, neuromodulation).

Pharmacological treatment of PLP has shown variable outcomes. Gabapentinoids, anticonvulsants, and serotonin-norepinephrine reuptake inhibitors have demonstrated moderate efficacy in reducing pain intensity. Opioids may be used only in severe cases due to the risk of dependency and side effects. Interventional methods such as peripheral nerve blocks, radiofrequency ablation, and neuromodulation techniques (spinal cord stimulation, transcranial magnetic stimulation) provide long-term pain relief in refractory PLP cases with minimal side effects.

A personalized approach combining pharmacological and interventional methods appears to be the most effective in managing PLP. Further randomized controlled trials are needed to optimize therapeutic strategies. Given the increasing number of amputees due to military actions in Ukraine, the standardization of PLP treatment has become a priority for the medical community.

**Keywords:** *phantom limb pain; personalized approach; treatment methods; pharmacotherapy; interventional treatment*

## Introduction

Phantom limb pain (PLP) is a complex and debilitating pathological condition that arises after limb amputation and is characterized by pain sensation in the missing body part. This phenomenon is a form of neuropathic pain and remains a significant challenge for both patients and healthcare professionals due to its high prevalence and the complexity of treatment.

Current approaches to PLP management include both pharmacological methods (antidepressants, anticonvulsants, gabapentinoids, etc.) and interventional procedures (nerve blocks, radiofrequency techniques, neuromodulation). However, the effectiveness of many of these treatments remains controversial due to the limited number of high-quality clinical studies.

The aim of this review is to summarize and analyze contemporary data on pharmacological and interventional treatments for PLP, with a focus on practical therapeutic aspects to improve patients' quality of life and optimize treatment strategies for this complex condition.

## Epidemiology of phantom limb pain

The prevalence of PLP varies significantly across studies, ranging from 64% to 87% among amputees, depending on the study sample and assessment methods [1, 2]. Phantom pain occurs in both civilian and military populations, but its frequency and severity are disproportionately higher among military personnel due to the traumatic nature of their amputations. Globally, approximately 356 million limb amputations are performed annually, with the highest burden observed in low- and middle-income countries due to trauma and infections [3]. In the United States, approximately 185,000 amputations are performed each year, with the leading causes being vascular diseases (82.0%), trauma (16.4%), oncological conditions (0.9%), and congenital anomalies (0.8%) [4]. Among amputees, PLP is a persistent and often debilitating condition. The lifetime prevalence of PLP ranges from 64% to 87% [2]. A systematic review and meta-analysis conducted by Limakatso et al. (2020) [1] found that the prevalence of PLP is significantly higher in developed

countries (66.55%) compared to developing countries (53.98%), suggesting that access to medical care, surgical techniques, and postoperative management may influence PLP development. Approximately 82% of amputees experience PLP within the first year after amputation, and a substantial proportion continue to suffer from pain for years, indicating the chronic nature of the condition [3].

Several preoperative, perioperative, and postoperative risk factors contribute to the development of PLP.

*Preoperative risk factors*

1. Pre-amputation pain. Persistent pain prior to amputation is a strong predictor of PLP, as it may lead to central sensitization and maladaptive neuroplasticity [5].

2. Psychological factors. Anxiety, depression, and catastrophizing are associated with an increased likelihood of developing PLP [6].

3. Age and sex. Older age is linked to a higher risk of PLP, while sex-related differences remain inconclusive [3].

*Perioperative risk factors*

1. Surgical technique. Traditional traction neurectomy, in which the nerve is cut under tension, causing it to retract, may lead to neuroma formation, increasing the risk of PLP [7].

2. Advanced surgical techniques. Techniques such as targeted muscle reinnervation (TMR) and regenerative peripheral nerve interface (RPNI) have been shown to significantly reduce PLP incidence by improving nerve regeneration and minimizing neuroma formation [8].

*Postoperative risk factors*

1. Residual limb pain (stump pain). This strongly correlates with PLP, suggesting shared pathophysiological mechanisms [9].

2. Prosthesis use. Advanced prostheses with sensory feedback may alleviate PLP, whereas poorly fitted or purely cosmetic prostheses may exacerbate symptoms [10].

3. Acute postoperative pain. Uncontrolled pain persisting for weeks after surgery significantly increases the risk of chronic PLP [3].

**Phantom limb pain in military personnel**

Phantom limb pain (PLP) is a relevant issue in wartime conditions due to the high incidence of traumatic limb loss among military personnel. Studies have shown that amputee veterans experience more severe and persistent PLP compared to civilian amputees [11]. This can be attributed to several factors:

1. Nature of amputation: Combat-related amputations are often caused by high-energy blast or gunshot wounds, leading to more severe nerve damage and an increased risk of PLP [12].

2. Psychological stress factors: Military amputees exhibit higher rates of post-traumatic stress disorder (PTSD) and depression, both of which are closely linked to increased PLP severity [13].

3. Rehabilitation challenges: Delayed or inadequate rehabilitation, including limited access to specialized prosthetics and pain management programs, may exacerbate PLP in veterans [14].

**Pathophysiology of phantom limb pain**

Despite extensive research, the precise pathophysiological mechanisms underlying PLP remain incompletely understood. This chronic pathological condition is believed to result from a complex interplay of morphological, physiological, and chemical alterations within the peripheral and central nervous systems. Understanding the peripheral, spinal, and supraspinal mechanisms contributing to PLP is crucial for developing effective preventive and therapeutic strategies.

*Peripheral mechanisms.* PLP often arises due to the transection of peripheral nerves during amputation, leading to maladaptive changes in neurons. Key peripheral mechanisms include:

1. Neuroma formation – following nerve transection, damaged axons attempt to regenerate, frequently resulting in neuroma formation. Neuromas exhibit spontaneous ectopic activity and heightened excitability, leading to persistent pain [15, 16].

2. Ectopic discharges – hyperexcitability of injured nerve endings and dorsal root ganglia leads to spontaneous pain signals, which are interpreted as originating from the missing limb [3].

3. Inflammatory responses – post-amputation inflammation and immune cell activation may enhance nociceptive signal transmission, increasing peripheral nerve sensitization [15].

*Spinal mechanisms.* The spinal cord plays a pivotal role in amplifying and modulating pain signals following amputation. Several key processes are involved:

1. Central sensitization – increased excitability of dorsal horn neurons results in heightened pain transmission, causing persistent pain even in the absence of peripheral input [15, 16].

2. Disinhibition of pain pathways – reduced inhibitory neurotransmission, such as diminished GABAergic and glycinergic activity, enhances nociceptive signaling from the residual limb [1].

3. Neuroplastic changes – the loss of afferent input from the amputated limb leads to maladaptive plasticity in the dorsal horn, intensifying pain perception despite the absence of ongoing nociceptive stimuli [15].

*Supraspinal mechanisms.* The brain undergoes significant structural and functional changes following limb amputation, contributing to the development of PLP. These changes include:

1. Cortical reorganization – functional magnetic resonance imaging (fMRI) studies indicate that somatosensory cortical areas representing the amputated limb are taken over by adjacent body part representations. This remapping is associated with the perception of pain in the missing limb [1, 3].

2. Thalamic dysfunction – the thalamus, which processes sensory information, exhibits hyperactivity in PLP patients, likely due to the loss of afferent regulation [15].

3. Altered descending pain modulation – dysfunction of descending pain modulation pathways originating from the brainstem and limbic system contributes to persistent pain sensations [16].

**Pharmacological therapy of phantom pain**

Various pharmacological treatment strategies for PLP have been proposed; however, the administration of different classes of medications demonstrates variable outcomes. This review focuses on the efficacy of tricyclic antidepressants (TCAs), serotonin-norepinephrine

reuptake inhibitors (SNRIs), gabapentinoids (pregabalin and gabapentin), anticonvulsants (carbamazepine, oxcarbazepine, topiramate), opioids (tramadol, morphine, oxycodone), and additional pharmacological approaches, including NMDA receptor antagonists (ketamine) and botulinum neurotoxin.

*Tricyclic antidepressants.* Amitriptyline, a widely used TCA, has been investigated for its effectiveness in treating PLP. It is believed to exert its effects by enhancing serotonin and norepinephrine transmission in the central nervous system, thereby modulating pain perception. However, studies on its efficacy for PLP have yielded conflicting results. L.R. Robinson et al. (2004) conducted a randomized controlled trial comparing amitriptyline with placebo in patients with PLP and found no significant difference in pain reduction between the two groups [17]. Additionally, adverse effects of amitriptyline, such as sedation, dry mouth, and dizziness, may limit its use [18].

*Serotonin-norepinephrine reuptake inhibitors*. Duloxetine, the most well-known agent in this class, is recommended for the treatment of neuropathic pain, including painful diabetic neuropathy and fibromyalgia, based on findings from randomized placebo-controlled clinical trials. However, its potential in treating PLP has been less extensively studied, as large-scale trials evaluating duloxetine for this condition are lacking. Nevertheless, a meta-analysis of SNRIs for neuropathic pain management revealed that duloxetine significantly reduces pain scores in conditions similar to PLP [19]. Given the low prevalence of PLP in contemporary Western countries and the consequently lower number of randomized controlled trials on this condition compared to other neuropathic pain disorders, the standard practice is to apply general pharmacotherapy guidelines for neuropathic pain [20]. Notably, duloxetine's favorable side effect profile compared to TCAs makes it a promising option for patients intolerant to other medications [18].

The initial dose of duloxetine is 30 mg once daily, preferably in the morning. If tolerated, the dose may be increased to 60 mg after one week. In the management of pain disorders, this dosage is typically considered the maximum, as no clinical benefit has been observed from further titration up to 120 mg [21].

*Gabapentinoids.* Gabapentinoids, including gabapentin and pregabalin, are widely used for neuropathic pain disorders due to their ability to modulate calcium channels in the central nervous system. Studies have demonstrated that gabapentin reduces the intensity of phantom limb pain (PLP). In a randomized controlled trial conducted by D.G. Smith et al. (2005) [22], patients receiving gabapentin reported a significant pain relief. The daily dosage of gabapentin was gradually increased from 300 mg to 3600 mg. More than half of the patients experienced substantial pain relief with this medication, compared to one-fifth of participants in the control group. In another randomized, double-blind, placebo-controlled study [23], patients with post-amputation PLP were administered gabapentin, starting at a dose of 300 mg/day, which was gradually increased to 2400 mg or the maximum tolerated dose. After six weeks of monotherapy, patients receiving gabapentin reported a statistically significant reduction in pain intensity. However, other studies have yielded less favorable results in terms of pain reduction compared to placebo [19].

The initial dose of gabapentin is 100–300 mg, taken either at bedtime or divided into three doses throughout the day. The dosage is then gradually increased by 300–900 mg per day, depending on efficacy and tolerability. The maximum dose may reach 3600 mg.

Pregabalin is a structural analog of γ -aminobutyric acid (GABA). As a more potent gabapentinoid than gabapentin, pregabalin has demonstrated efficacy in various neuropathic pain disorders, including PLP treatment. Pregabalin binds to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, reducing the release of excitatory neurotransmitters such as glutamate, substance P, and norepinephrine. This mechanism underlies its efficacy in treating neuropathic pain disorders such as diabetic neuropathy and postherpetic neuralgia. Studies have confirmed the efficacy and safety of pregabalin administration. Given that PLP shares pathophysiological mechanisms with other neuropathic pain syndromes, pregabalin is considered an effective treatment for PLP [24].

Numerous studies have demonstrated the efficacy of pregabalin in patients with various types of neuropathic pain at daily doses of 300, 450, and 600 mg. A dose of 150 mg/day was largely ineffective [25]. Treatment is recommended to begin with 150 mg/day, divided into 2–3 doses. After one week, the daily dose should be increased to 300 mg. If necessary, further dose escalation to 450–600 mg may be considered after 2–3 weeks [21]. A flexible dosing regimen of pregabalin, allowing individualized dose adjustment within the range of 150–600 mg/day based on efficacy and tolerability, effectively alleviates pain and reduces the likelihood of treatment discontinuation [26].

There have been numerous reports on the successful use of pregabalin in PLP treatment [27–29]. However, a review of pharmacological therapy for PLP [30] noted that the number of high-quality studies on pregabalin for PLP is lower compared to other neuropathic disorders. In our opinion, this may be explained by the lower prevalence of PLP in developed countries compared to other chronic neuropathic pain conditions in peacetime, as well as its significantly lower prevalence relative to domestic data from wartime. Nonetheless, the authors of the aforementioned review consider the use of gabapentinoids, along with tricyclic antidepressants (TCAs), duloxetine, and opioids, to be justified for PLP management.

The predominant side effects of gabapentinoids include dizziness and drowsiness, as well as weight gain, which may limit their long-term use [31]. Dizziness and drowsiness typically occur within the first week of pregabalin administration, gradually diminishing over time and regressing in most cases within one month of treatment initiation [32]. There are simple recommendations that can significantly help to prevent the development of gabapentinoid-related adverse effects, particularly those of pregabalin. It is recommended to initiate pregabalin treatment with

an evening dose. Although the drug's instructions indicate that it can be taken with or without food, the initial dose is best administered during dinner (in the evening). In some cases, a single evening dose of 150 mg can effectively reduce pain and improve sleep quality with minimal adverse reactions. If morning pregabalin administration is associated with significant drowsiness and/or dizziness, asymmetric dosing—taking a higher dose in the evening—may be considered. This approach is also supported by pathophysiological reasoning, as there is an interdependence between sleep quality and chronic pain severity. Improved sleep following evening administration of higher pregabalin doses may reduce the need for significant daytime dosing. Numerous studies on the efficacy of pregabalin in chronic neuropathic pain have demonstrated that sleep improvement significantly contributes to pain intensity reduction [32, 33].

Due to patients' concerns and apprehensions regarding potential side effects of gabapentinoids, physicians may prescribe low, subtherapeutic doses, or patients may fail to adhere to the prescribed treatment regimen. Patient education regarding the necessity of adequate time for pain control and the potential for minimizing side effects through adherence to the aforementioned recommendations can help prevent suboptimal treatment outcomes. Over time, these adverse effects may regress [33, 34].

Since PLP is a debilitating pain disorder that, in some cases, responds poorly to treatment, the possibility of combination therapy with antineuropathic agents should be considered. D.R. Spiegel et al. [35] reported that combined administration of duloxetine once daily and pregabalin two to three times daily significantly reduced PLP intensity and gradually (within two weeks) allowed discontinuation of previously prescribed morphine sulfate. The daily doses were 60 mg of duloxetine and 450 mg of pregabalin. The titration regimen was as follows: from day 1, 30 mg of duloxetine in the morning and 50 mg of pregabalin three times daily; from day 4, 60 mg of duloxetine in the morning and 100 mg of pregabalin three times daily; from day 8 onward, 150 mg of pregabalin in the morning and 300 mg in the evening. A multinational, double-blind, parallel-group COMBO-DN study [36], involving 804 patients, demonstrated that combination therapy with moderate doses of duloxetine (60 mg/day) and pregabalin (300 mg/day) yielded slightly better outcomes in the treatment of peripheral neuropathic pain compared to monotherapy with these agents at their maximum daily doses (120 mg and 600 mg/day, respectively). According to the authors, combination therapy with duloxetine and pregabalin is effective, safe, well-tolerated, and allows for the avoidance of drug-related side effects in cases where monotherapy would require the maximum permissible doses.

*Anticonvulsants.* Antiseizure medications help alleviate neuropathic pain by stabilizing hyperexcitable neuronal membranes.

Carbamazepine, traditionally used for trigeminal neuralgia, has demonstrated potential in the treatment of PLP. Case reports and small-scale studies suggest that it may reduce pain intensity by modulating sodium channels in hyperexcitable neurons. However, its side effect profile—including dizziness, fatigue, and hepatotoxicity—limits its clinical utility [21].

Oxcarbazepine, a structural derivative of carbamazepine, exhibits a similar mechanism of action but with a more favorable side effect profile. It has been evaluated for the treatment of neuropathic pain, with some studies indicating benefits in PLP. However, high-quality randomized controlled trials remain lacking [21, 37].

Topiramate is widely used for migraine prophylaxis and epilepsy management. It has also been investigated for the treatment of neuropathic pain, including PLP. Its mechanism of action involves modulation of sodium and calcium channels, as well as enhancement of GABAergic transmission. Some studies indicate a reduction in PLP severity, but significant adverse effects—such as cognitive impairment and weight loss—may limit its clinical application [38].

*Opioids.* The use of strong opioids for PLP remains controversial due to concerns regarding tolerability, dependence, and long-term efficacy. Oxycodone, a potent μ-opioid receptor agonist, has been studied for its potential benefits in PLP. A Cochrane review reported that opioids, including oxycodone, provided pain relief but were associated with adverse effects such as constipation, drowsiness, and respiratory depression [19]. Morphine efficacy has also been investigated, demonstrating short-term analgesic effects; however, its potential for dependence and variable tolerability present significant challenges. Opioids should be considered only in severe cases of PLP when other treatment modalities prove ineffective.

Tramadol is an atypical analgesic that exerts its effects through two primary mechanisms: 1) an opioid effect, acting as a weak μ-opioid receptor agonist to provide analgesia; 2) neurotransmitter modulation, inhibiting serotonin and norepinephrine reuptake, which enhances antinociceptive effects and reduces neuropathic pain intensity. Due to these mechanisms, tramadol is considered a promising agent for the treatment of PLP, as it not only alleviates pain but also influences neuroplastic changes underlying pathological pain transmission. N.B. Finnerup et al. [31] demonstrated that tramadol provides moderate pain relief in neuropathic pain conditions, including PLP. It is generally preferred over stronger opioids due to a lower risk of dependence and fewer adverse effects, such as nausea and dizziness.

Studies evaluating the efficacy of tramadol in PLP have yielded the following findings:

- pharmacological treatment reviews of PLP identify tramadol as potentially effective in a subset of patients, particularly those with mixed pain components (nociceptive and neuropathic) [19,39].
- some clinical trials suggest that tramadol may help reduce pain intensity, though its efficacy is less pronounced compared to traditional opioids (e.g., morphine) or NMDA receptor antagonists [19].
- the combination of tramadol with anticonvulsants (e.g., gabapentin) or antidepressants may offer superior efficacy compared to monotherapy [39].

The standard tramadol dosage for chronic pain management is 50–100 mg every 6–8 hours, with a maximum daily dose of 400 mg. In PLP patients, it is recommended to start with the lowest possible dose and gradually titrate to assess efficacy and tolerability.

Common side effects include nausea, dizziness, dry mouth, and sedation.

*NMDA receptor antagonists (ketamine and memantine).* NMDA receptor antagonists, such as ketamine and memantine, have been investigated as potential treatments for PLP due to the role of these receptors in central sensitization. Intravenous ketamine has demonstrated analgesic effects in PLP patients; however, its clinical application is limited by significant psychotomimetic side effects, including hallucinations and sedation [19,30,39,40]. Memantine, an NMDA receptor antagonist primarily used for Alzheimer's disease treatment, has shown limited efficacy in PLP, with no significant pain relief compared to placebo [19]. Further studies are required to determine the long-term benefits and safety of NMDA receptor antagonists in PLP management.

*Botulinum neurotoxin type A (BoNT-A).* A review of BoNT-A potential in neuropathic pain management can be found in the second edition of the monograph "Botulinum Toxin Treatment of Pain Disorders" by Yale University professor Bahman Jabbari [41], as well as in the recently submitted "Ukrainian national consensus statement on botulinum toxin therapy for neuropathic pain". Those interested in the pathophysiological basis of this method, indications, technical details, and dosing of BoNT-A in PLP may refer to these sources.

**Interventional treatment of phantom limb pain**

A wide range of interventional techniques is available for the management of PLP. These methods can be particularly beneficial when pharmacological treatment proves insufficiently effective or is associated with intolerable adverse effects.

In cases where myofascial trigger points are present in the stump, their injection may provide significant pain relief. The underlying rationale is that *trigger point injections* alleviate myofascial pain by reducing muscle spasms, increasing the range of motion, and improving circulation. The core principle of this approach is the interruption of the spasm–pain–spasm cycle within the muscles. A study involving 21 patients reported a significant reduction in pain intensity, as measured by the visual analog scale (VAS), following local anesthetic injections into stump trigger points over a five-week period in most patients with post-amputation pain [42].

*Peripheral nerve blocks* are widely used to provide temporary pain relief in PLP. These procedures involve the administration of local anesthetics, often in combination with adjuncts such as clonidine or steroids, to block nociceptive signal transmission. Regional blocks of the sciatic and femoral nerves have been shown to provide temporary relief; however, their effects are typically short-lived, necessitating repeated injections to achieve sustained pain control. Another approach for limb PLP management is continuous peripheral nerve block. A study demonstrated that a six-day perineural infusion of ropivacaine could reduce PLP for at least one month, with some patients experiencing relief for 6–12 months [43].

Several minimally invasive interventions targeting stump neuromas have been proposed for refractory cases of PLP. One such technique is *chemical neurolysis*, which involves the ultrasound-guided injection of alcohol or phenol into stump neuromas to induce nerve tissue degeneration and subsequent pain relief. X. Zhang et al. (2017) investigated this technique and reported that 54% of patients experienced significant pain reduction after 1–3 alcohol injections. In patients unresponsive to this treatment, pain relief was achieved through radiofrequency ablation of neuromas [44]. The use of ultrasound-guided phenol injections was prospectively evaluated in 82 patients, all of whom demonstrated noticeable improvement, with 12% achieving complete pain resolution after 1–3 procedures. A distinguishing feature of this treatment was the low complication rate (5% minor and 1.3% major complications) [45]. Although neurolysis is effective, nerve regeneration may occur over time, potentially leading to pain recurrence.

*Radiofrequency Procedures.* Radiofrequency ablation (RFA) is a widely used interventional technique that delivers thermal energy to neural tissue to modulate pain transmission. Although the efficacy of RFA in treating various pain syndromes has been well established, the procedure may be associated with adverse effects and complications, including incomplete denervation of the pain-generating region, sensory and motor dysfunction, symptom exacerbation due to chaotic nerve regeneration, neuroma formation, and the development of deafferentation pain [46]. These complications can be mitigated by employing pulsed radiofrequency (PRF) treatment, which is referred to as "пульсове радіочастотне лікування (ПРЛ)" in the domestic literature. Unlike conventional thermal RFA, which destroys nerve fibers, PRF delivers energy in controlled bursts without causing permanent tissue damage.

PRF represents an advancement over traditional RFA, offering reduced tissue destruction while maintaining therapeutic efficacy. This method applies radiofrequency current at 500 kHz to the tip of the cannula in a sequence of discrete electrical bursts lasting 5–20 ms, repeated at a frequency of 2–5 Hz. Under this mode, the cannula temperature does not exceed 42°C, preventing thermocoagulation of nerve fiber proteins while preserving motor function and sensory integrity. The analgesic effect of PRF is attributed to its selective action on unmyelinated and thinly myelinated fibers, particularly through the modulation of synaptic transmission and excitability of C fibers, which are responsible for temperature and pain sensitivity and are implicated in the pathophysiology of most neuropathic pain syndromes [47–49].

Two literature reviews [46,50] have summarized the findings of numerous studies on the therapeutic mechanisms of PRF. These mechanisms include: microscopic alterations, such as selective damage to nociceptive C and Aδ fibers, with endoneurial edema observed for up to one week post-treatment; molecular changes, including microglial deactivation in the dorsal horn of the spinal cord, reduced levels of pro-inflammatory cytokines, increased mRNA production of endogenous opioid precursors, modulation of calcitonin gene-related peptide (CGRP) activity, and changes in ion channel function, notably increased $Na^+$/

$K^+$ channel expression; neuronal activity modulation, involving activation of descending antinociceptive serotonergic, noradrenergic, and GABAergic pathways, as well as inhibition of afferent C-fibers excitability; sustained pain signal suppression, with the analgesic effects of PRF persisting for several months.

Publications indicate positive outcomes of PRF therapy in cases of phantom limb pain (PLP) resistant to pharmacological treatment. A clinical case report describes the successful application of PRF in a 63-year-old female patient with severe PLP and residual limb pain following a below-knee amputation, persisting for four years [51]. The pain intensity ranged from 6 to 8 on the Numeric Pain Rating Scale (NPRS). After unsuccessful pharmacological management with gabapentin, pregabalin, hydrocodone, methadone, and morphine, PRF was applied to the sciatic nerve (two cycles of 120 seconds at 42°C, with a pulse duration of 20 ms and frequency of 2 pulses per second). The patient experienced complete pain relief, enabling the discontinuation of opioid analgesics. However, due to pain recurrence after four months, the procedure was repeated.

M. West and N. Wu (2010) [52] reported successful PRF application in four patients, in whom a radiofrequency cannula was placed under local anesthesia at the most tender neuroma site identified through palpation prior to the intervention. Following the procedure, all patients experienced significant reduction in residual limb pain, with effects lasting for six months. Additionally, two patients demonstrated substantial improvement in PLP. Patients reported enhanced functional status, improved prosthesis tolerance, and reduced oral analgesic consumption.

A. Kumar et al. (2024) [53] published a case series of 10 patients with refractory PLP following upper limb amputation. After a diagnostic nerve block, PRF of the stellate ganglion was performed. Marked reductions in PLP and functional improvement were observed at 1 week, 1 month, and 3 months post-procedure, without any side effects.

In a pilot study by S. Pu et al. (2020) [54], the efficacy of ultrasound-guided PRF for residual limb neuromas was investigated. The study found that 82.4% of patients with residual limb pain and 69.2% with PLP experienced significant pain relief, with no serious complications.

These findings suggest that radiofrequency-based techniques may represent a promising therapeutic option for patients with PLP, particularly those unresponsive to pharmacological interventions.

**Neuromodulation in the treatment of phantom limb pain**

Neuromodulation techniques—including spinal cord stimulation, peripheral nerve stimulation, transcranial magnetic stimulation, and deep brain stimulation — aim to modify neural activity at the spinal or cortical level to alleviate chronic pain.

*Spinal cord stimulation* (SCS) involves the implantation of electrodes in the epidural space to deliver electrical impulses to the dorsal columns of the spinal cord, modulating pain transmission. Studies have demonstrated that SCS can reduce PLP in certain patients. A systematic review by M. Corbett et al. (2018) [55] analyzed multiple studies on SCS and reported significant pain relief in patients with chronic PLP. The authors highlighted that the presence of residual limb pain is a strong predictor of SCS success, suggesting that SCS may be more effective in patients with both PLP and residual limb pain.

*Peripheral nerve stimulation* (PNS) is another promising approach, particularly for neuroma-related pain. This technique involves placing electrodes near the affected peripheral nerves to modulate pain perception. R. Pagan-Rosado et al. (2023) [56] demonstrated that PNS is a potentially effective neuromodulatory method for treating refractory chronic pain, including post-amputation pain.

Several studies have investigated both invasive and non-invasive brain stimulation techniques for PLP.

*Transcranial magnetic stimulation* (TMS) is a non-invasive technique that uses magnetic pulses to modulate cortical excitability. A meta-analysis by K. Pacheco-Barrios et al. (2020) [57] found that continuous current TMS applied to the primary motor cortex significantly reduces PLP symptoms, with effects lasting up to one week post-stimulation.

*Deep brain stimulation* (DBS) targets deep brain structures, such as the thalamus and periaqueductal gray matter, to modulate pain perception. A literature review by M. Corbett et al. (2018) [55] reported that DBS provided long-term pain relief in 73% of patients. However, the invasive nature of the procedure limits its widespread application.

*Motor cortex stimulation* (MCS) involves implanting electrodes over the motor cortex to disrupt pain-related neural activity. Studies suggest that MCS is effective in patients with treatment-resistant PLP; however, further research is needed to optimize stimulation parameters [57].

The presented data indicate that interventional techniques and neuromodulation approaches significantly expand the treatment options for PLP, particularly in patients unresponsive to pharmacological therapy. Radiofrequency techniques, especially pulsed radiofrequency (PRF), have demonstrated efficacy in reducing both PLP and residual limb pain, providing long-term relief with minimal invasiveness. Neuromodulation techniques, including SCS, TMS, DBS show promise in modulating pain pathways at both the spinal and cortical levels. However, despite encouraging results, further research is needed to establish standardized treatment protocols and optimize patient selection criteria. Large-scale randomized controlled trials are essential to confirm the efficacy of these approaches and explore multimodal treatment strategies that integrate pharmacological therapy, advanced rehabilitation techniques, and interventional or neurosurgical procedures to improve clinical outcomes.

**Conclusions**

PLP remains one of the most challenging forms of neuropathic pain, significantly impairing the quality of life of individuals with limb amputations. Despite extensive research, the pathophysiological mechanisms

of PLP are not yet fully understood, making effective treatment selection difficult. Current data suggest that a comprehensive approach combining pharmacological and interventional therapies is the most promising strategy.

Among pharmacological treatments, gabapentinoids, anticonvulsants, and serotonin-norepinephrine reuptake inhibitors have demonstrated moderate efficacy in reducing PLP intensity. Interventional techniques, such as peripheral nerve blocks, radiofrequency procedures, and neuromodulation, have shown high effectiveness in refractory pain cases, providing long-lasting relief with minimal side effects.

A personalized approach to PLP management, considering individual patient characteristics, pain patterns, and risk factors, is crucial to achieving optimal outcomes. Randomized controlled trials are needed to further elucidate the pathophysiology of PLP and determine the most effective treatment combinations.

Given the current reality and the increasing number of amputations due to military conflicts, the development of standardized PLP treatment protocols is a priority for the Ukrainian medical community. Conducting large-scale clinical studies and implementing innovative treatment approaches will significantly improve patients' quality of life and reduce the burden of this debilitating condition.

**Disclosure**

*Conflict of Interest*

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