Narrative Review

Current Understanding of Phantom Pain and its Treatment

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Background: Phantom limb pain (PLP), defined as a painful sensation in a portion of the body that has been amputated, occurs in upwards of 80% of limb amputees and can significantly impact a patient's quality of life. First hypothesized in 1551, the disease has been poorly understood for much of this time. Still today, the exact etiology of the condition is yet to be elucidated. In the periphery, PLP resembles the neuronal changes seen in other neuropathic pain conditions. However, in the central nervous system (CNS), imaging studies suggest changes unique to PLP, such as cortical reorganization. Despite a growing understanding of its underpinnings, a mechanism-based treatment is not yet available. Rather, a plethora of treatment methodologies are available with varying levels of supporting evidence and many treatments being utilized based on efficacy seen in non-PLP patients.

Objectives: In this review, we provide a thorough summary of the current literature regarding PLP's etiology, diagnosis, treatment, and attempts to prevent the development of PLP following amputation.

Study Design: A narrative review.

Methods: This was a narrative review conducted after an extensive and thorough review of available literature on the topic from a variety of sources.

Results: Current evidence supports a central reorganization process with potential amplification of aberrant peripheral inputs as the etiology of PLP. This conclusion is supported by functional neuroimaging as well as the failure of peripherally focused treatments. Treatment of PLP remains difficult due to varying response rates to therapies. Nonetheless, there are several treatment modalities that have proven effective in the majority of patients tested, ranging from noninvasive systemic pharmacotherapy to more invasive neuromodulation, such as spinal cord stimulation. While opioid therapy remains the most evidence-based treatment, the newer neuromodulation techniques appear to be superior in symptom reduction with minimal side effects.

Limitations: Evidence for the treatment of PLP is largely restricted to uncontrolled case reports and/or small single-site uncontrolled case series. Some research is further hampered by the presence of confounding factors such as concurrent treatment regimens.

Conclusions: While PLP remains a difficult-to-treat condition, practitioners can greatly improve the quality of life of patients suffering from the condition with a wide range of developing treatments. For pain intractable to traditional pharmacologic treatment, neuromodulation therapies have proven to be highly effective with minimal side effect profiles.

Key words: Phantom Limb Pain, Neuropathic, Mirror Therapy, Deafferentation, Cortical Reorganization

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Phantom limb pain (PLP) is defined as pain sensation to a limb, organ, or other tissue after amputation and/or removal. Patients with phantom pain often report the sensation as a feeling of burning, stinging, aching, and piercing. This contrasts with the phantom sensation, which is the non-painful feeling of a lost body

part after surgical removal or amputation (1). PLP must be further differentiated from sensations in the remaining portion of the amputated limb, which is referred to as stump pain or residual pain. While phantom pain has been found to occur after the removal of internal organs and other non-limb body parts, the phenomenon is most prevalent following limb amputation (2).

Ambroise Pare, a French military surgeon, first theorized the existence of phantom pain and believed a combination of both central and peripheral factors to be the cause. The specific term "phantom limb pain" is most often attributed to Silas Weir Mitchell, who published a study in 1872 using the term after his experience with traumatic amputation patients in the United States Civil War (3). The close relationship between the military and the study of PLP remains today. Recent military activities in the Middle East, specifically in Iraq and Afghanistan, have led to a dramatic increase in the number of limb amputations (4).

While popularly associated with these traumatic amputations, PLP is also seen in other amputees, such as cancer patients. Overall, in the United States, an estimated 1.7 million people live with at least a single amputation, and another 215,000 amputations are performed each year, 86% of which are lower limb amputations (5,6). The leading cause of amputation in the United States is trauma with diabetes and following vascular disease (7).

Of these amputations, it is estimated that 65% will develop PLP within one month of amputation, 82% within one year, and 87% throughout their lifetime (8). Therefore, the treatment of phantom pain is an important topic for all physicians who may encounter amputees. Likewise, possible prevention of the disease through a better understanding of its etiology has the potential to dramatically increase the quality of life for a large population of patients.

Differentiation of Phantom Limb Pain (PLP) and Residual Limb (Stump) Pain

Proper understanding and study of PLP require that it be differentiated from other post-amputation pain conditions such as residual limb pain (RLP). At the most basic level, the 2 conditions are clearly demarcated by the location of the pain. RLP originates from the remaining portion of an amputated limb, whether that be the proximal portion of an arm, leg, or simply the stump resulting from the amputation. For this reason, RLP may also be referred to as stump pain. The most common cause of RLP is prosthogenic, typically originating from a poorly fitted or poorly padded prosthetic. Nearly all cases of RLP have identifiable causes, including open/unhealed wounds, infection, bony abnormalities, nerve entrapment, neuromas, and compromised skin.

In contrast to this, phantom pain feels to the patient as if it originates from the amputated portion of the body. Although phantom pain has been observed in non-limb portions of the body, such as internal organs, for this article, we will focus only on PLP as literature is more widely available (2). Causes of PLP are discussed in greater detail later in this article, but there is no single identifiable cause, as is often the case in RLP.

Disease course may also help distinguish PLP from RLP. RLP typically occurs immediately after surgery and will typically resolve as the underlying cause is treated Although PLP also shows high incidence within one month of amputation, it is typically unresponsive to standard treatments, and its severity does not correlate with the healing of surgical wounds (8).

It is also important to consider that the 2 conditions can exist concurrently; that is, a patient may experience RLP and PLP. In fact, almost half of people with PLP have or have had RLP occurring at the same time, and RLP itself has been identified as a risk factor for the development of PLP (9,10).

Etiology of Phantom Limb Pain

The exact etiology of PLP remains unknown and is often debated by clinicians. Most theories involve a combination of both the central nervous system (CNS) and peripheral nervous system (PNS). While the PNS is clearly involved due to the severing of both afferent and efferent innervation of the amputated limb, CNS involvement is also likely due to the loss of peripheral inputs, which play a role in plasticity and modulation. For ease of discussion, the following section has been split between mechanisms that take in the CNS and the PNS. It is important to note that no single theory has yet to prove adequate in fully explaining PLP, and it is likely that a myriad of CNS and PNS changes occur simultaneously.

Central Nervous System Involvement

Melzack's Neuromatrix

One of the most often cited causes of PLP are changes to the neuromatrix. The neuromatrix is a term coined by Ronald Melzack, a Canadian psychologist best known for his development of the gate control theory of pain. Indeed, it was the observance of several patients suffering from PLP that led Melzack to

evolve his gate control theory into the neuromatrix theory (11). In this theory, the "experience of self as the point of orientation in the surrounding environment is produced by central neural processes is …'built-in' by genetic specification...and modified by experience," which may be termed one's neurosignature (11). In the neuromatrix, pain is a central pattern of nerve impulses in the brain which may be stimulated by peripheral inputs but can also be generated internally independent of any peripheral inputs (12).

Melzack and others have explained that an amputation would create a drastic change to the neuromatrix as the deafferented/amputated limb is no longer providing inputs to its corresponding cortical areas. If this exceeds the capacity of the genetically determined neurosignature to change, there may be maladaptive alterations in these cortical areas capable of producing these internally generated patterns of pain, which are then localized to the amputated limb (13).

While the neuromatrix theory is inherently difficult to test due to its complexity, perhaps the strongest evidence in its favor is that cordotomy targeting the spinothalamic tract and, therefore, all peripheral pain input from a limb, is not effective in treating phantom pains or several other neuropathic pain conditions (14,15).

Cortical Remapping

Another leading theory indicating CNS changes in the etiology of PLP is the cortical remapping theory (CRT). The CRT postulates that deafferentation of the amputated limb results in somatosensory and primary motor cortical areas that previously corresponded to this limb being infringed upon by neurons from nearby cortical areas. This infringement then results in the cortical area originally attributed to the amputated limb now reacting to stimulation from the areas nearby in the cortex that have newly innervated this region.

The cortical remapping theory is often traced back to a set of studies that took place using adult owl monkeys by Dr. Merzenich in which amputation of digits resulted in an invasion of adjacent areas into the previous cortical representation of the deafferented digit. However, at the time, it was unclear the magnitude to which cortical remapping could occur. Dr. Merzenich's study only showed a remapping equivalent to a few millimeters within the somatosensory cortex, a finding which by itself was not likely to explain PLP. However, this study was soon followed by another, which demonstrated cortical remapping an order of magnitude greater in adult monkeys who had undergone dorsal rhizotomy 12 years earlier (16).

In humans, the cortical remapping theory has been the most studied regarding upper limb amputations. In one study, fMRI was used to demonstrate that following upper-limb amputation, patients experienced a shift in somatosensory and primary motor representation (detected as an increase in blood flow) of the lip into the area associated with the hand and fingers in healthy controls (17). This agrees with predictions that would be made using the idea of nearby somatosensory areas invading into the deafferented limb's cortical area. The results of one such fMRI study can be seen in Fig. 1.

Of particular interest, multiple studies have demonstrated that the degree to which cortical remapping occurs is positively associated with the severity and occurrence of PLP (17,18).

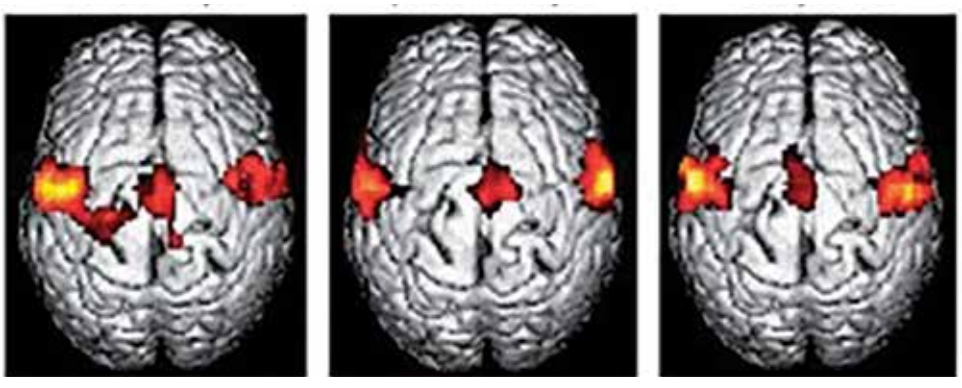

Fig. 1. *fMRI images from 7 amputee patients with PLP, 7 amputees w/o PLP, and 7 healthy controls taken while patients were instructed to purse their lips. In the PLP group, the motor cortex activation associated with lip pursing extends into motor cortex areas that usually represent the hand an arm. This cortex extension is not seen in amputees w/o PLP whose activation regions closely resemble the controls (17).*

Thalamic Involvement

In a manner similar to cortical somatosensory remapping, it has also been proposed that the thalamic circuitry may undergo significant reorganization following an amputation (19). It is unclear if this process occurs independently of cortical remapping or if the 2 are interconnected (20). Regardless, there is evidence that sub-cortical involvement may also play an important role in phantom sensations.

Following amputation, thalamic representation to a deafferented limb is enlarged compared to healthy controls. Additionally, stimulation of these areas can produce pains and sensations that are subjectively the same as PLP and phantom limb sensations (21).

Dr. Dostrovsky showed in a study that areas of the thalamus have at least 2 receptive fields or inputs. The first is a primary receptive field, which can be mapped in a manner similar to the homunculus of the cortex, and whose inputs are dominant in magnitude to a second subliminal receptive field. When input from the primary receptive field is diminished or absent, as is the case in amputation and some anesthesia procedures, this subliminal receptive field can strengthen and become the dominant signal (22).

Previously subliminal thalamic inputs becoming dominant is hypothesized as one of the ways in which the thalamic representation is enlarged for areas proximal to amputations. When these enlarged thalamic representations are no longer in synchrony with the patient's previously learned somatotropic map, phantom pain and/or sensations may occur (22).

Proprioceptive Memory

A large number of patients suffering from PLP report being able to either detect the presence of the phantom limb undergoing volitional movement; for example, patients report being able to wave goodbye or shake a hand with their phantom limb. Other patients report the sensation that the limb is not able to undergo movement but do report the sensation that the limb is "stuck" in a certain position. Of interest, oftentimes, the position of the frozen phantom limb resembles the patient's last memory of the amputated limb's position (23). This phenomenon is also seen in anesthetized patients who report being able to feel as if the limb is still occupying the same position as immediately before the limb was anesthetized, even if the limb has been significantly moved under anesthesia (24).

This has led some to propose that there is the existence of what is coined "proprioceptive memories" stored somewhere within the CNS. This is supported by the everyday experience of learning repetitive tasks. When a task is performed repeatedly, it becomes almost automatic. One way by which this could occur is if the basic movements and expected proprioceptive feedback required for an activity are stored in the proprioceptive memory of an individual and can be easily accessed without conscious effort (23).

Within this proprioceptive memory, it is also hypothesized that "pain memories" could be an important evolutionary tool. "Pain memories" are essentially subconscious memories of painful joint/limb positions which have occurred in the past; hyperextension is given as an example (23,25). Normally, when a pain memory is triggered, the subject will act to end the painful state, and proprioceptive and visual feedback will confirm that this has been accomplished, ending the pain memory (23).

For an amputee, it is possible that specific and long-lasting proprioceptive pain memories are created during the amputation process. As a result, when the amputee later performs certain movements and/or postures that are associated with these memories, an episode of PLP may occur. Additionally, since the amputee lacks the visual feedback to confirm that the limb is not in a painful position, these episodes may persist (23).

Psychological Theories

Early in the history of PLP, it was often believed that the pain was the result of unresolved stress caused by the amputation. With no physical indication of what could be causing the pain, the condition of PLP was assumed to be psychological for some time. However, psychological explanations of PLP are no longer favored as several studies have demonstrated that PLP patients have psychological profiles similar to the general public (26,27).

However, this is not to discount all psychological contributions to the pain, as it has also been shown that stress can exacerbate PLP episodes, perhaps by excessive stimulation of the sympathetic nervous system. This feature is not unique to PLP and is seen in many chronic pain states.

Peripheral Nervous System Involvement

Formation of Neuromas

When the peripheral nerves innervating an amputated limb are amputated, the remaining axons will attempt to innervate the "missing" portion of the limb via a mechanism of neuronal sprouting and growth.

However, due to the total absence of the amputated portion of the limb, this growth can quickly become disorganized due to a lack of proper growth targeting signals. Once this growth has become disorganized, the remaining axons are at risk of forming an unorganized collection of nerve fibers. When in a neuroma, these fibers tend to increase their expression of and accumulate novel sodium channels for as-of-yet unknown reasons. This accumulation results in hyperexcitability of the nerve fibers accumulated in the neuroma and increased nociceptive transmission to the spinal cord (28-30).

This hyperexcitability can be exacerbated by exposure to stimulation, such pressure from prosthetics and/or temperature extremes. The repetitive firing of these neurons was initially one of the leading theories for the cause of PLP. However, recent studies showing an inconsistent but mostly short-term benefit of nerve blocks have caused this theory to fall out of favor with most researchers (31-34).

Abnormal Dorsal Root Ganglion Activity

In addition to axonal changes following nerve transection via amputation, the dorsal root ganglion (DRG) soma themselves have also been demonstrated to undergo significant change in the post-injury state. Some studies have found the alterations of DRG soma to be so dramatic that it has been termed a "phenotypic change," which includes gene transcription and protein expression alterations in a time course as short as a few minutes within injury (35).

In all types of DRG neurons, there has been evidence of increased excitability following axonal transection. These changes include decreased excitation threshold, prolonged action potentials, and alterations of input resistance. Furthermore, animal models of neuronal injuries showed an increase in spontaneous electrical discharges from the DRG cells, which may themselves be enough to increase nociceptive transmission (35). In addition to these structural and electrical changes in the DRG, soma have also been shown to change the number and distribution of cell-surface receptors in response to injury, which may play some role in increasing nociceptive transmission (36).

While increased electrical activity from these DRG neurons could theoretically be an explanation for PNS involvement in phantom pain that is at least partially resistant to more distal peripheral nerve blocks, it is likely just one of several factors contributing to the cortical reorganization and CNS changes that are now the favored etiology.

Treatment of Phantom Limb Pain

Pharmacologic Treatment Options

Pharmacologic treatment options are often favored for their noninvasive nature and the option to discontinue the medication if the desired effect is not achieved. However, in many pain conditions, pharmacology alone is not able to treat the underlying cause of the disease and is instead effective only as symptomatic treatment. This is complicated by the fact that agents may have undesired systemic effects. A review of identified studies investigating pharmaceutical treatments and their results can be found in Table 1. A more in-depth review of each potential treatment is provided in the subsections below.

Opioids

As with many chronic pain conditions, opioids are one of the many options available to physicians trying to treat PLP. Oral morphine was shown to be effective in reducing pain scores in 42% of patients in a crossover study compared to placebo. The minimum dose used

Table 1. *A summary table of pharmacologic treatments for Phantom Limb Pain.*

Authors	Study Type	Sample Size	Treatment Protocol	Results	Comments
Opioids					
Huse et al 2001	Double-blind placebo-controlled crossover	12	Oral Morphine Sulfate ranging from 70-300 mg/day	Oral morphine produced significant pain reduction from baseline VAS scores that was not seen during placebo treatment.	25% of morphine treatment group demonstrated fMRI imaging suggestive of partial reversal or cortical reorganization
Wu et al 2002	Double-blind active-placebo-controlled crossover	31	IV Morphine, .05 mg/kg bolus + .2 mg/kg bolus over 4 hours	IV Morphine significantly reduced both stump and phantom pain compared to active placebo diphenhydramine.	Lidocaine treatment was also effective in significantly reducing stump pain but failed to reduce phantom pain.

Table 1 cont. *A summary table of pharmacologic treatments for Phantom Limb Pain.*

Licina et al 2013	Case series	4	Buprenorphine/ Naloxone at 8 mg/ 2 mg, one patient reduced to 6 mg/1.5 mg	Buprenorphine/Naloxone provided adequate pain relief in all 4 patients. One patient reported total pain relief at 8/2 mg and maintained this relief after reducing dosage to 6/1.5 mg.	All 4 patient had previously failed trials of more traditional treatments including opioids, adjuvants, physical and behavioral therapies.
NMDA-Receptor Antagonists					
Maier et al 2003	Randomized-double blinded placebo-controlled	36	Memantine, 30 mg/ day orally	Oral Memantine 30 mg/day failed to significantly reduce PLP compared to placebo.	Placebo affect likely present in study as memantine and placebo equally reduced PLP.
Schwenkreis et al 2003	Randomized double-blind placebo-controlled	16	Memantine, starting a 5 mg/day ramping to 30 mg/ day in 6 days	Oral Memantine failed to significantly reduce PLP when compared to a placebo group.	Memantine group demonstrated increased Intracortical inhibition and decreased intracortical facilitation.
Wiech et al 2004	Randomized double-blind placebo-controlled crossover	8	Memantine, 30 mg/ day orally	Oral Memantine failed to produce significant PLP pain reduction at any time point.	Memantine also shown to have no effect on cortical organization via neuromagnetic imaging.
Nikolajsen et al 1996	Randomized double-blind placebo-controlled crossover	11	Ketamine, .5 mg/kg infusion	All 11 patients experienced decreased stump and phantom limb pain with ketamine treatment. Ketamine also significantly increased pressure-pain thresholds.	Side effects of discomfort, feelings of insobriety, and elevated mood reported.
Eichenberger et al 2008	Randomized double-blind placebo-controlled crossover	20	Ketamine .4 mg/kg infusion	4 IV infusions of Ketamine .4 mg/kg significantly reduced phantom limb pain and increased pain thresholds compared to placebo.	A combination ketamine/ calcitonin infusion provided no benefit over ketamine infusion alone.
Anti-depressive Agents					
Robinson et al 2004	Randomized active- placebo-controlled	39	Amitriptyline titrated to 125 mg/ day oral.	Oral amitriptyline failed to produce any significant phantom limb pain difference compared to placebo.	Patients noted anti-cholinergic side effects including dry-mouth, constipation, drowsiness.
Wilder-Smith et al 2005	Randomized open label-trial	94	Amitriptyline mean dose 55 mg/day oral	All 40 patients determine to be responsive to Amitriptyline treatment reported complete resolution of PLP.	Majority of patients switched to open-label amitriptyline trial after failing tramadol or placebo treatment.
Anticonvulsants					
Bone et al 2002	Randomized double-blind placebo-controlled crossover	19	Gabapentin 2400 mg daily or maximum tolerated	Pain intensity was significantly decreased in the gabapentin treatment arm compared to the placebo treatment.	Gabapentin group did not report increased sleep interference or difficulty with ADLs.
Nikolajsen et al 2006	Randomized double-blind placebo-controlled	46	Gabapentin 2400 mg daily	Gabapentin failed to significantly reduce phantom and residual limb pain compared to placebo.	Administration of Gabapentin began immediately following amputation for 30 days.
Smith et al 2005	Randomized Double-Blind Placebo-Controlled Crossover	24	Gabapentin 3600 mg daily	Gabapentin failed to significantly reduce pain intensity or pain interference scores.	Gabapentin also had no effect on depression, life satisfaction, and daily functioning scores.
Cannabinoids					
Mücke et al 2018	Meta-analysis Cochrane Review	1750	Various	Cannabinoids found to significantly increase number of neuropathic pain patients experiencing 30% pain relief.	CBD-treated groups exhibited higher prevalence of psychiatric conditions.

was 70 mg/day, while a maximum of 300 mg/day was used by at least one patient. Of significant note in the study was MRI data which suggested that in 25% of patients, the morphine treatment showed preliminary evidence of reduced cortical reorganization corresponding to reduced pain score. These findings may hint at morphine actually reversing one of the underlying causes of PLP and not just treating the symptomatic pain (37).

These findings were supported by another study using morphine intravenously at 0.2 mg/kg, which again reported reduced pain scores compared to placebo. In this second study, morphine was found effective in reducing stump and PLP, while a lidocaine infusion was only effective at reducing stump pain. This may be due to morphine's more central acting mechanism compared to lidocaine (38).

Buprenorphine, a partial opioid agonist, has also been effective in reducing PLP in at least 4 military amputees, as documented in a case report (39). Buprenorphine may have benefits due to its higher affinity to the opioid receptor, although its intrinsic activity and, therefore, efficacy at the receptor is noted to be lower than that of morphine and many other opioids. While buprenorphine has some evidence of efficacy, it requires considerably more research and literature supporting its use in PLP before it can be considered mainstream.

NMDA Receptor Antagonists

In recent literature, N-methyl-D-aspartate (NMDA) receptor antagonists, specifically ketamine, have been shown effective in managing and reducing several types of chronic pain, including neuropathic and neoplastic-associated pains. Ketamine is proposed to work by reducing the process of central sensitization and therefore reducing hyperalgesia and allodynia (40). Seeing as central changes are believed to be at least partially at fault for phantom pains, there is hope that NMDA receptor antagonists may show benefit in PLP.

In 3 different studies comparing the effectiveness of 30 mg/day of memantine, a drug most commonly associated with Alzheimer's treatment, found no treatment effect in reducing PLP versus a placebo control (41-43).

In contrast, 2 different studies have indicated successful treatment of PLP with another NMDA receptor antagonist: ketamine. In the first study, an intravenous infusion of 0.5 mg/kg ketamine provided a statistically significant decrease in pain intensity of all 11 patients within the treatment population (44). In the second study, ketamine at a dose of 0.4 mg/kg was again effective in reducing phantom pain both when administered alone and in combination with 200 IE of calcitonin. Of note, the ketamine-only infusion was equally as effective as the combination infusion in regard to pain relief (45).

Although the rate of adverse events was not directly reported in all of the studies cited above, they included: hallucination, nausea, fatigue, headache, and agitation (44,45).

Anti-depressive Agents

In the only 2 studies that could be found investigating the use of tricyclic antidepressants (TCAs), specifically amitriptyline, for the treatment of phantom pain, there were conflicting results. The first study found no significant difference between an amitriptyline treatment group (maximum dose of 125 mg/day) and an active placebo group. The treatment group did report an increased incidence of anti-cholinergic side effects such as dry mouth, drowsiness, constipation, and urinary retention (46).

In the second study, all 40 patients who were initially unresponsive to tramadol and subsequently switched to amitriptyline in an open trial reported a 0 pain score at a mean amitriptyline dose of 55 mg/day. These patients also reported typical anti-cholinergic side effects, although at comparable rates to the tramadol group. While this trial appears to show the efficacy of amitriptyline in treating phantom pain, patients and providers were not blinded, which leaves the possibility of treatment bias in this group (47).

Anticonvulsants

Gabapentin, a favorite drug of choice for controlling neuropathic pain, has been studied in at least 3 different studies of phantom pain. The initial study by Bone et al was completed in 2002 and showed a significant difference in pain score reduction in a group treated with gabapentin for 6 weeks of up to 2,400 mg daily when compared to placebo. While gabapentin was effective in treating the phantom pain, Bone et al noted no difference between treatment groups in secondary outcomes of sleep interference, anxiety, and depression, or functional independence. The study also noted no increased incidence of adverse events in the gabapentin group (48).

Spurred on by the promising results of the previous study, gabapentin was later used in 2 more studies, although both included patients with RLP and PLP. Neither

study found a benefit to gabapentin treatment when compared to placebo in regard to pain intensity and/or reduction. Nikolajsen et al repeated the dosing of the Bone et al study at 2,400 mg per day, while the Smith et al study used a greater dosage of 3,600 mg per day (49,50).

While evidence is very limited, there are case reports suggesting that other anticonvulsants such as topiramate, pregabalin, and carbamazepine are also effective in treating PLP (51-53). However, no high-quality randomized study could be identified using any of these drugs, and judgement on their efficacy at this point in time may be hampered by publication bias.

Cannabinoids (CBD)

Cannabinoids (CBD) are one of 2 chemicals of medical significance identified in leaves of the Cannabis genus of plants, the other being tetrahydrocannabinol (THC). Cannabinoids are also found within the animal kingdom in the form of endogenous cannabinoids (endocannabinoids), which have at least 3 known functions within mammals. These functions are broad: control intake and utilization of food, respond to stress and return the body to homeostasis, and modulate inflammatory responses (54).

CBD achieves these affects by binding to the CB1 and CB2 cannabinoid receptors throughout the body. CB1 receptors are more commonly found in the CNS, while CB2 receptors are more common in the PNS. In the PNS, stimulation of CB2 receptors by endocannabinoids is believed to play a role in tempering the inflammatory response that is responsible for some neuropathic pains. In the CNS, the distribution of CB1 receptors focused in the frontal-limbic area suggests cannabinoids may alter cognitive and autonomic processing of affective qualities of pain (55-57).

Due to CBD's derivative plant, marijuana, being the topic of hot public policy debate, trials with it are highly limited, even more so than its psychoactive THC counterpart. As such, trials testing CBD treatment specifically on phantom pain patients were not available. However, there is a Cochrane review for the use of CBD treatment in neuropathic pain conditions and PLP falls under the umbrella.

In the review mentioned above, a total of 16 studies with 1750 patients were examined. Cannabis-based medicines were found highly effective in neuropathic pain conditions. They were found to significantly increase the number of people achieving 50% pain reduction (primary outcome) and to significantly increase the number of people achieving 30% pain reduction (secondary outcome). However, more adverse events were found in the cannabis-treated groups than in the placebo. While data could not determine if this was significant, an increase in psychiatric conditions from 5% in placebo to 17% in the treatment group is likely the greatest concern (58).

Cannabis-derived products with low THC content, such as CBD oils, are often available over the counter without a prescription; however, the unregulated market of these products makes the concentration of CBDs and efficacy of products a near-guessing game for patients. If brought up by the physician or patient during the course of treatment, patients should be informed of the current literature supporting CBD use but also cautioned about the potential adverse effects (58).

Peripheral Nerve Blocks

Due to the known abnormal peripheral signaling that occurs as a result of limb amputation, peripheral nerve blocks which can prevent peripheral neural impulses from reaching the CNS have been attempted as a treatment option. These nerve blocks are similar to those performed via injection for local surgeries; however, for repetitive administration of an anesthetic, a peripheral perineural catheter is often placed. The anesthetic agents used most often are lidocaine, bupivacaine, and ropivacaine.

In a large multi-centered randomized controlled trial (RCT) study examining the use of a 6-day infusion of ropivacaine vs. normal saline in 144 patients suffering from PLP, the ropivacaine-treated group was found to have a significantly lower visual analog scale (VAS) pain score at 4-weeks posttreatment. The decreased VAS scores remained significantly lower for the treatment group at 6 months posttreatment but were no longer significant at 12 months posttreatment. The ropivacaine-treated group also reported an improved global impression of change and less physical and emotional dysfunction. However, rates of depression were not significantly different between groups (31).

Similar findings were found in case studies investigating the use of a lumbar plexus block for lower limb PLP using bupivacaine and ropivacaine for bilateral upper limb PLP (59,60). Crossover studies have also demonstrated no pain relief in sham treatments which makes the likelihood of a placebo effect low (61).

At this point in time, the evidence seems to support a rapid and long-lasting relief from PLP using ambulatory infusions of local anesthetic agents without severe side effects.

Neuromodulation Therapies

Transcutaneous Electrical Nerve Stimulation (TENS)

Transcutaneous electrical nerve stimulation (TENS) therapy has been proven in a wide array of peripheral pain conditions. TENS is most commonly applied in acute pain conditions such as soft muscle sprains and strains; however, it has also seen attempts at treatment for more chronic conditions. TENS therapy involves passing small electrical stimulation currents across the surface of the skin. This stimulation is targeted at activating Aβ afferent nerve fibers, which are proposed to decrease pain signaling through the gate theory of pain (62). Its noninvasive nature contributes to its trial in many patients.

Several studies exist suggesting the benefit of TENS in PLP, including a single-blinded study by Tilak et al which involved 26 patients and demonstrated significant pain relief using TENS therapy that was equal to that seen with mirror therapy (63). Another study also found significant pain reduction using TENS in 10 patients suffering from PLP (64). The previous studies all included TENS stimulation on the ipsilateral side as amputation, typically at the most distal point available. However, case reports also suggest that contralateral application of TENS may also help alleviate PLP (65-67).

The largest single publication found regarding TENS in phantom pain was a Cochrane review which found "mixed evidence" for the use of TENS in PLP. The primary issue disallowing a more definitive conclusion is the low availability of high-quality studies (68).

Scrambler Therapy

Another noninvasive neural modulation technique used to treat chronic pain conditions is scrambler therapy (ST). ST is similar to TENS in that it requires the placement of superficial electrodes on the patient's skin, but the nerve fibers targeted and the theoretical basis behind the therapy are in direct contrast to TENS.

Unlike TENS therapy which is based on the Gate Control Theory of Pain and is concerned with the quantity of signals conducted by various nerve fibers, ST is based on what many call the Active Principle of Information. This is a pain theory concerned with the qualitative characteristics of a signal transmitted by nociceptors such as frequency and how these qualities enable the coding of "pain" vs. "non-pain." More directly, TENS attempts to stimulate Aβ, which is theorized to "close" the gate for transmission of chronic pain signals in smaller C fibers. In contrast, ST attempts to transform the "pain" signals being transmitted via C fibers into "non-pain" signals via stimulation of the C fibers themselves using impulses with varying geometries and duration (69).

ST is relatively new and gained FDA approval through the 510(k)-clearance pathway, which limited the amount of clinical trial information required before approval. The therapy also requires specialized equipment and training, which have continued to limit its use, and therefore published clinical data is rather scarce.

The largest study of ST was a multicenter case series involving 201 patients with varying chronic pain etiologies, including post-herpetic neuralgia, chronic low back pain, and peripheral neuropathy. The study revealed high efficacy rates, with > 80% of patients experiencing > 50% pain reduction. All 9 centers reported at least 50% of patients experiencing this benchmark. The authors noted that success rate of ST was correlated with achieving pain elimination rather than just pain reduction when optimizing electrode placement. Physicians with considerable experience also had markedly higher success rates when compared to less-experienced individuals (70).

Other clinical reports of ST are largely limited to case series and/or single case reports. There have been reported successes of ST in chemotherapy-induced neuropathy, chronic back pains, and central pain (71-73). Additionally, there is at least one case report of ST being used to treat a PLP patient, which resulted in the elimination of pain for over 2 months from an initial VAS score of 7/10, which was intractable to other treatment modalities (74).

Spinal Cord Stimulation

The mechanism of spinal cord stimulation (SCS) is still not fully understood. The leading theory for its effectiveness focuses on the gate control theory that proposes that constantly stimulating the large and myelinated columns found within the dorsal column of the spinal cord results in the inhibition of pain signals originating from the small unmyelinated fibers. The procedure includes a laminectomy in the appropriate region (cervical spine for upper limb phantom pain and thoracodorsal for lower limb PLP) and subsequent placement of stimulating electrodes either epidurally or in the DRG, which is now the preferred location due to more precise targeting of the dorsal columns (75).

Due to the invasive nature of the procedure, it is typically reserved for patients with pain that is intractable to medical management and which interferes

with daily life. Additionally, a trial run of SCS is usually attempted using less invasive and temporary percutaneous stimulators to test for response to therapy (75).

SCS has been attempted in PLP treatment since at least the 1970s and has been proven effective in several studies (76). An Italian multicenter study that is commonly cited for evidence of SCS's effectiveness in chronic pain conditions had PLP patients as 14% of its cohort, 74% of whom underwent permanent stimulator implantation due to adequate pain control with the percutaneous trial (77).

Another study demonstrated further success of spinal cord stimulation in 36 out of 49 patients suffering from deafferentation nerve injuries, including amputation, nerve root avulsion, and chronic regional pain syndrome. Over half of these patients (57%) reported a > 75% reduction in total pain score. While this study is not solely focused on PLP patients, the mechanism of injury in all conditions included, including deafferentation, is identical to that seen in amputations (78).

Katayama et al found SCS to be successful in reducing long-term pain by > 80% in 6 out of 19 (32%) phantom pain patients. The remaining patients were assigned to either deep brain stimulation (DBS) or motor cortex stimulation (MCS). Of note in the Katayama et al study is that some of their patients had prolonged pain-free intervals with continued use of SCS and therefore required less frequent use of their stimulators (79).

Finally, a trial of SCS in 4 PLP patients at MD Anderson Cancer Center from 2003-2006 demonstrated > 80% reduction of pain in all 4 patients, with 3 out of the 4 patients stating that they would undergo SCS implantation again and the fourth being equivocal to the placement. Complications in this study were mostly surgically related and included an infection and allergic dermatitis after placement of the stimulator (80).

Repetitive Transcranial Magnetic Stimulation (rTMS)

Transcranial magnetic stimulation is a proposed treatment modality for chronic, refractory neuropathic pain that is hypothesized to work by preventing cortical reorganization via stimulation of the affected neurons in the brain using a magnetic field. Repetitive transcranial magnetic stimulation (rTMS) is favored over some other methodologies of stimulating the CNS, such as SCS, MCS, and DBS, due to its noninvasive nature. rTMS requires no surgical interventions and simply involves placing an electromagnetic coil on the scalp, typically in the form of a cap (81).

This treatment modality is quite common in the treatment of medically refractory major depressive disorder (MDD) and is authorized by the US FDA for this indication. The response rate to rTMS in MDD is estimated to be in the range of 50-55%. In depression, the targeted region is the dorsolateral prefrontal cortex, a region of the brain responsible for mood regulation (81).

In PLP, the target of rTMS is an area of the brain which has been affected by the deafferentation of a limb and lack of subsequent neuronal feedback. In the studies identified below, the most frequent target is the contralateral (in relation to amputation) primary motor cortex, also called M1 (82).

The largest of the available studies, including 54 patients with PLP, found a statistically significant difference in the number of patients experiencing > 30% pain reduction compared to a sham rTMS treatment group. However, this effect was only short-term and had disappeared by one-month posttreatment (82).

Another study by Ahmed et al found that a 5-day course of rTMS resulted in a significantly greater reduction in VAS pain score and Leeds assessment of neuropathic symptoms and signs (LANSS) at one month and 2 months compared to a sham treatment group. This study also found that serum beta-endorphin levels were significantly increased following rTMS treatment compared to no change for the shame treatment (83). This indicates that rTMS may trigger a release of beta-endorphins that could be responsible for the antalgic effect.

The third identified trial found no difference in pain score reduction immediately following rTMS vs. sham rTMS treatment. However, this was the smallest of the trials (14 patients). Additionally, since the pain scores were taken immediately following treatment, it is possible that any significant pain reduction would have taken place over a longer time course than detected in this trial (84).

A systematic review of rTMS for the treatment of neuropathic pain conditions in general found that the treatment is generally effective, although great heterogeneity exists in response to therapy and pain reduction between studies. Out of 24 studies regarding rTMS for neuropathic pain, 18 found a statistically significant effect. Additionally, based on pooling across studies, it was found that a positive treatment response to rTMS can be used as a relatively strong predictor of response to the more invasive MCS (85).

Transcranial Direct Current Stimulations (tDCS)

Another treatment modality that operates on the same therapeutic principle as rTMS is Transcranial direct current stimulation (tDCS). The key difference is in how microcurrents are induced within the brain cortex. In rTMS, application of a magnetic field via a coil induces the microcurrents in the cortex via electromagnetic interactions. In contrast, tDCS directly applies a current (direct current) using the placement of 2 electrodes across which a voltage is applied. While theoretically similar, less data currently exists regarding the efficacy of tDCS across many conditions, and unlike rTMS, tDCS has yet to gain FDA approval for any indications and is, as such, still regarded as an experimental treatment (86). For PLP treatment, tDCS often targets the motor cortex as was done in rTMS, although cerebellar targets have also been attempted (87,88).

An initial study examining a 5-day course of tDCS for the treatment of PLP involving 8 single-limb amputees suffering from PLP found a significant decrease in PLP immediately after tDCS treatment with an average decrease in background PLP VAS score of 41%. This pain reduction was found to persist until at least one week after receiving the final tDCS treatment. Patients also reported a 33% decrease in painful PLP paroxysms after tDCS treatment. Finally, several patients reported a subjectively increased ability to "move" their phantom limb in the tDCS group compared to a sham treatment which was unable to be directly correlated with pain reduction but may be a significant finding showing central changes induced by tDCS (87).

Another study also investigated tDCS for the treatment of PLP, although in this study, tDCS was tested as an adjunct treatment paired with mirror therapy for 29 patients with PLP. Patients underwent 2 weeks of either mirror therapy, mirror therapy + tDCS, or mirror therapy + sham tDCS. The study revealed a significant decrease in PLP numeric pain sScore (NPS) in the mirror + tDCS therapy as compared to both the mirror therapy and mirror therapy + sham tDCS treatment groups beginning at 2 weeks after treatment initiation. This significant decrease was also seen in the secondary outcome measures of the Short Form McGill Pain Questionnaire and Brief Pain Inventory scores beginning at 2 weeks. These significant differences remained at one week, one month, and 3 months posttreatment, indicating that a combination of mirror therapy and tDCS provides at least 3 months of pain relief to PLP patients (89).

At least one study refutes the efficacy of tDCS in the treatment of PLP, although the authors of this study chose to target the cerebellum with tDCS rather than the more widely accepted primary MCS seen in other tDCS and rTMS studies. This illustrates that treatment modality is not the only determinant of treatment efficacy, and the selection of the proper target cortical areas is necessary (88).

Based on these studies, the evidence seems to support the efficacy of tDCS targeting the primary motor cortex for the treatment of PLP, while there is not yet enough evidence to make a conclusion regarding tDCS regarding the cerebellum.

Motor Cortex Stimulation (MCS)

MCS is a procedure in which a series of electrodes are placed intracranially, usually just outside the dura mater overlying the M1 motor cortex area. The goals of treatment and theories behind its benefit are similar to rTMS described above, although the stimulation is provided with an electrical current rather than a magnetic field. MCS is also significantly more invasive than rTMS due to the requirement for craniotomy and placement of internal hardware. The pulse generator for MCS is generally located in the subclavian space or a subcutaneous abdominal space depending on the exact device and placement techniques used (90).

MCS has been shown to regularly activate sites of the brain remote from the stimulation, such as the thalamus. The brain areas activated by stimulation, as well as the efficacy of treatment, have been shown to be greatly dependent on the placement of electrodes and the stimulation pattern applied. Due to these highly variable parameters, the comparison of MCS efficacy across treatment sites and pain conditions is difficult (90). Regardless, evidence exists for the successful use of MCS in recalcitrant pain conditions.

In 3 phantom pain patients treated with MCS aided by computer and image-guided placement of electrodes, all 3 patients reported initial resolution of PLP following placement. Two out of the 3 patients reported stable pain reduction > 80% at one-year post-placement while also reporting a significant increase in Activity of Daily Living (ADL) score. The third patient reported a pain reduction of 40% at one year post-placement but noted that the pain reduction had been decreasing for 4 months following his MCS placement (91).

Another trial of MCS found that only 5 out of 10 patients suffering from neuropathic pains experienced pain relief after the implantation of MCS electrodes.

However, out of the 5 patients that responded to the therapy, the pain reduction ranged from 50-90%, and the duration of pain relief for 4 of the patients was > 21 months. Also of note is that 2 out of 3 phantom pain patients included in the study were long-term responders to therapy (92).

Finally, another study showed 6 out of 8 patients treated with MCS had significant pain reduction following device implantation and optimization using various applied frequencies and voltages. Two out of these 6 patients responsive to therapy were suffering from PLP. In contrast to the correlation between rTMS success and MCS response, the researchers found no correlation between effective pharmacologic treatments and response to MCS (93).

As discussed previously, the precise placement of electrodes and various amplitudes, frequencies, and patterns of stimulations available to physicians make direct study-to-study comparisons hard. However, the above evidence clearly shows that a substantial portion of PLP patients who have been unable to gain adequate control via medications may benefit from MCS treatment.

Deep Brain Stimulation (DBS)

DBS is similar to MCS in that electric current is applied to targeted brain regions in an invasive manner using intracranial electrodes. However, in comparison to MCS, DBS targets much deeper areas of the brain and therefore requires the use of long and penetrating electrodes. DBS targets were first identified via a combination of animal experiments and surgical ablations in humans. The most promising targets and, therefore, the most frequently used today were shown to be the periventricular and periaqueductal grey regions and ventral posterior lateral (VPL) and ventral posterior medial (VPM) thalamic nuclei (94).

In one study involving 85 DBS trials and 74 subsequent implantations for various etiologies, over 66% of those who were followed long-term reported significant pain reduction following DBS implantation. Of those reporting pain improvements were, 8 out of 9 (88%) PLP patients included in the trial. The trial noted varying rates and lengths of efficacy based on pain etiology, but at least 14 patients reported continued pain improvements 4 years post-implant. The DBS targets for this trial were either the PVG, VPL/VPM, or both, based on which selection provided the best pain reduction during the surgical trial (94).

Another 2-center study focusing solely on the use of VPL in phantom pain and brachial plexus avulsion (BPA) patients found that 11 out of 12 patients (91.6%) had significant pain reduction one year post-DBS implantation. In the PLP group, average pain scores (via VAS) were reduced by 90%, while in the BPA group, average pain scores were reduced by 52%. Similar reductions were seen in the University of Washington Neuropathic Pain Score (UWNPS), which was reduced by an average of 80.4% in the PLP group and 26.2% in the BPA group. This study is also of interest because it reports specific DBS signal profiles being used, with the average being a 2.5 V Potential applied for 213 microseconds at a frequency of 25 Hz (95).

These findings are confirmed in several other studies and case reports which find that near to or > 50% of PLP patients are at least moderately responsive to DBs treatment in regard to pain reduction. Additionally, the pain reduction seen in PLP patients seems to be comparatively greater than in several other neuropathic pain conditions (96-99).

Other Treatment Options

Mirror Therapy and Motor Imagery

The use of mirror therapy (MT) as a treatment for chronic PLP first arose in the 1990s theories and writings of Dr. Vilayanur Ramachandran. Ramachandran proposed that by placing a patient's healthy limb in a box with a mirror in the centerline, a patient would be able to arrange the "healthy" limb into the perceived position of the now amputated and painful limb. Once the patient had matched this position, they could then perform movements with the healthy limb. The reflection in the mirror would provide visual feedback as if both the healthy and amputated limbs were performing these movements. In this way, it was hoped that a patient could "move" the proprioceptive position of the painful limb out of potentially painful positions (100).

Motor imagery (MI) therapy is closely related to MT and involves many of the same procedures, with the absence of a mirror or mirror box being the key difference. In MI, the patient is simply asked to imagine moving the amputated limb. Depending on the exact form of this technique, the patient may or may not be asked to perform symmetric movements with the intact limb if available (100,101).

The latest available systematic review of MT and MI shows that it is generally effective. In 12 out of 12 of the identified studies, the treatment group reported

a significant reduction in pain intensity. Some studies were uncontrolled, while others formed control groups by covering the mirror with a cloth or other material. In general, the authors noted that MT and some virtual reality techniques were more effective at reducing pain scores than MI techniques. It is proposed that this may be due to a lack of visual feedback, which may play an important role in reversing cortical changes (101).

Unfortunately, the availability of high-quality controlled clinical trials is lacking due to the limited number of patients and complex pain-control regimens typically used for these patients. Before a strong and definitive recommendation can be made on MT for PLP, a large-scale, well-funded, and long-term study is needed.

Technological advancement has also made virtual and augmented reality an option for patients who may find MT difficult or who may not have an intact limb remaining. It is yet to be determined if augmented reality can fully replace the visual feedback provided by MT, but this is surely an area to be explored in the near future.

Attempts at Preventing PLP

Pre-emptive Analgesia

Due to the high prevalence of phantom pain and its potentially debilitating long-term effects, there has always been considerable interest in preventing the development of PLP in situations where amputation is non-emergent. In these situations, physicians would have ample time and resources to take action to prevent PLP. Actions taken during this time to reduce long-term pain have come to be known as pre-emptive analgesia.

Pre-emptive analgesia as a whole remains a somewhat controversial field with unclear and contradictory evidence resulting from several studies into the practice. Several studies have demonstrated an apparent pre-emptive benefit to ketamine treatments in both animal and human pain models (102-104). However, these studies are complicated by ketamine's known effect in reducing and even reversing opioid-induced hyperalgesia (OIH) which could be misinterpreted as preventing the development of a higher level of pain (40).

A study by Bach et al showed a pre-emptive analgesic effect in PLP patients via a 72-hour lumbar epidural blockade. In this study, all 11 patients (100%) who received a lumbar epidural blockade remained pain-free for 12 months in comparison to 11/14 patients (80%) in the control group (105). Unfortunately, several attempts to repeat this preemptive analgesic effect, including with ketamine, have failed. A systematic review of 11 studies investigating preemptive analgesia found that some are effective in reducing immediate perioperative pain but that no methodology could consistently produce a significant difference in the occurrence of PLP (106).

Targeted Muscle Reinnervation

Targeted muscle reinnervation (TMR) is a surgical technique that uses a redundant or physiological non-functional muscle in order to provide the EMG signals and sensory feedback which previously would have originated from muscles in the amputated limb. To achieve this, the donor muscle (redundant muscle) has its original nerves severed and ligated to prevent regrowth. The remaining proximal nerves from the amputated limb are then grafted to the donor's muscle. The procedure can include both sensory and motor nerves or just one type. TMR of motor nerves allows EMG signals to be sampled from the donor's muscle and used to control the prosthesis. TMR of sensory nerves allows amputees to receive biofeedback from a properly equipped prosthetic which essentially provides a sense of touch to the prosthesis. TMR of sensory nerves is also hypothesized to restore normal sensory feedback from the amputated limb and potentially prevent the development of PLP (107).

A large multicenter cohort study involving 58 patients undergoing TMR and 438 controls conducted from 2012-2018 found that TMR at the time of amputation resulted in a lower incidence of both PLP and residual limb pain when compared to a group of untreated controls. Furthermore, immediate TMR resulted in a lower "worst pain in 24 hours," patient-reported outcome measurement information system (PROMIS) score, and pain interference score. TMR was found to correlate with > 3x odds of reducing PLP and RLP pain scores when compared to standard treatment (108).

Results are also promising for secondary TMR, which occurs well after amputation, in regards to eliminating PLP that may have already developed. McNamara et al found that secondary TMR resulted in complete resolution of PLP in 90% of patients across 4 studies (109).

Unfortunately, despite its proven success, TMR remains available to only a select few patients due to a lack of knowledge and/or training. In a survey of

Canadian providers, nearly 71% reported that they were familiar with TMR for the treatment of peripheral neuromas; however nearly half (45%) were not aware that the same treatment could be applied to PLP. Only 8 out of 66 respondents had incorporated TMR into their treatment of phantom pain, highlighting the limited availability of this potential treatment to patients (110).

Limitationss

While PLP has been recognized for several centuries, its relatively limited prevalence has long-hampered research into the condition. This has led to limited high-quality literature on the topic. Instead, much of the information that is available on PLP is held within case reports and/or case series with relatively small sample sizes.

Unfortunately, these facts provide us with limited power to determine the true efficacy of several treatment modalities in treating PLP. Heavy reliance on case reports also leads to the possibility of placebo effect, as few of these reports make use of placebo or non-active controls. These shortfalls make it evident that more large-scale placebo-controlled clinical trials are necessary before being able to make a statistically strong conclusion on the most effective treatments for PLP.

Confounding variables may also be present in many of the studies due to the large number of medications/treatments patients are often placed on to treat PLP. Many of the novel therapies such as SCS, DBS, and tDCS {AU: This sentence is incomplete.}

Discussion

In this article, we present PLP as a significant challenge to the medical community in that it is a condition affecting over half of all amputees whose etiology and clinical management remain incompletely understood. While previously thought to affect a small portion of amputees, more comprehensive studies and better identification have identified PLP as a common sequelae of amputation. Although much research has been dedicated to treating the condition, there as of yet remains no single therapeutic regimen accepted as the gold standard of treatment.

While many pain conditions, including residual limb pain, have well-understood etiologies, the mechanisms underlying PLP have yet to be identified. Initial theories treated PLP as a standard neuropathic pain arising from injury of peripheral nerves. However, subsequent studies demonstrated that blocking PNS input to the CNS failed to ameliorate the condition. This fact revealed that at least some of PLP's etiology lied within changes to the CNS. Currently, the most widely supported theory is that of cortical reorganization, postulating that inappropriate activation of the somatosensory cortex previously corresponding to the amputated limb results in the painful sensations of PLP.

While numerous treatment options have been discussed in this article, their response rates are highly variable, and predicting which modalities will work for any given patient is near impossible. Pharmacologically, PLP is treated much like any other neuropathic pain condition. Unfortunately, standard pharmacologic treatments have widespread systemic effects and may come with a plethora of adverse effects. For example, the TCA amitriptyline, which is one of the most commonly prescribed medications, comes with known complications of anti-cholinergic toxicity and QTc prolongation, which may contraindicate its use in older populations.

Non-pharmacologic treatments, including several neuromodulation techniques, have also proven effective in reducing pain levels associated with PLP. In these instances, treatment should begin conservatively and with the least invasive option available to the treatment team. If treatment fails, a more aggressive and/or invasive option may be chosen. However, it is important to inform patients that a more invasive treatment does not mean a higher likelihood of success and may come with significant risks.

Conclusion

While the current evidence is unable to designate any single treatment as the most effective for PLP, this article has elucidated a plethora of treatment options that can be explored for any given patient. Physicians who desire to use an evidence-based approach in the treatment of PLP may utilize the references included above but should be mindful that the treatment of PLP is rapidly evolving, and new studies may be useful, especially regarding more recent treatments such as artificial and/or augmented reality.

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